ISSN 2220-3141 (online)

World Journal of

Critical Care Medicine

World J Crit Care Med 2023 January 9; 12(1): 1-40



Published by Baishideng Publishing Group Inc

World Journal of Critical Care Medicine

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Bimonthly Volume 12 Number 1 January 9, 2023

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World Journal of Critical Care Medicine

Bimonthly Volume 12 Number 1 January 9, 2023

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INDEXING/ABSTRACTING

The *WJCCM* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Li-Li Wang*.

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Hua-Dong Wang

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

PUBLICATION DATE
January 9, 2023

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https://www.wjgnet.com/bpg/gerinfo/208

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https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

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World Journal of Critical Care Medicine

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World J Crit Care Med 2023 January 9; 12(1): 1-9

DOI: 10.5492/wjccm.v12.i1.1

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Observational Study

Role of cerebrospinal fluid lactate in diagnosing meningitis in critically ill patients

Devraj Yadav, Omender Singh, Deven Juneja, Amit Goel, Sahil Kataria, Anisha Beniwal

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Jha P, United States; Lai Z, China

Received: November 7, 2022
Peer-review started: November 7, 2022
First decision: November 25, 2022
Revised: November 30, 2022
Accepted: December 23, 2022
Article in press: December 23, 2022
Published online: January 9, 2023

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Abstract

BACKGROUND

Meningitis is a life-threatening clinical condition associated with high mortality and morbidity. Early diagnosis and specific treatment may improve outcomes. Lack of specific clinical signs or tests make the diagnosis challenging.

AIM

To assess the efficacy of cerebrospinal fluid (CSF) lactate in diagnosing meningitis in critically ill patients.

METHODS

A prospective, observational cohort study was carried out in a neuro-medical intensive care unit (ICU) over a 22 mo period. Adult patients, with suspected meningitis admitted in ICU, were serially recruited. Patients who refused consent, those with peripheral sensorineural deficit, or with any contraindication to lumber puncture were excluded. CSF cytology, bio-chemistry, lactates, culture and polymerase chain reaction based meningo-encephalitis panel were evaluated. Patients were divided in two groups based on clinical diagnosis of meningitis. The efficacy of CSF lactate in diagnosing meningitis was evaluated and compared with other tests.

RESULTS

Seventy-one patients were included and 23 were diagnosed with meningitis. The mean values of CSF total leucocyte count (TLC), proteins and lactates were significantly higher in meningitis group. There was a significant correlation of CSF lactate levels with CSF cultures and meningo-encephalitis panel. CSF lactate (> 2.72 mmol/L) showed good accuracy in diagnosing meningitis with an area under the curve of 0.81 (95% confidence interval: 0.69-0.93), sensitivity of 82.6%, and specificity 72.9%. These values were comparable to those of CSF TLC and protein. Twelve patients with bacterial meningitis had significantly higher CSF lactate (8.9 ± 4.7 mmol/L) than those with non-bacterial meningitis (4.2 ± 3.8

mmol/L), $P = 0.006$.

CONCLUSION

CSF lactate may be used to aid in our diagnosis of meningitis in ICU patients. CSF lactate (> 2.72 mmol/L) showed good accuracy, sensitivity, and specificity in diagnosing meningitis and may also help to differentiate between bacterial and non-bacterial meningitis.

Key Words: Encephalitis; Cerebrospinal fluid; Critically ill; CSF lactates; Meningitis

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Core Tip: We conducted a prospective, observational cohort study to assess the efficacy of cerebrospinal fluid (CSF) lactate in diagnosing meningitis in critically ill patients. 71 patients were included and 23 were diagnosed with meningitis. There was a significant correlation of CSF lactate levels with CSF cultures and meningo-encephalitis panel. CSF lactate (> 2.72 mmol/L) showed good accuracy in diagnosing meningitis with an area under the curve (AUC) of 0.81, sensitivity 82.6%, and specificity 72.9%. These values were comparable to those of CSF total leucocyte count (TLC) and protein. Twelve patients with bacterial meningitis had significantly higher CSF lactate (8.9 ± 4.7 mmol/L) than those with non-bacterial meningitis (4.2 ± 3.8 mmol/L), $P = 0.006$. To conclude, CSF lactate may be used to aid in our diagnosis of meningitis in critically ill patients.

Citation: Yadav D, Singh O, Juneja D, Goel A, Kataria S, Beniwal A. Role of cerebrospinal fluid lactate in diagnosing meningitis in critically ill patients. *World J Crit Care Med* 2023; 12(1): 1-9
URL: https://www.wjgnet.com/2220-3141/full/v12/i1/1.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i1.1

INTRODUCTION

Meningitis is a life-threatening condition associated with high mortality and morbidity and may affect any patient's age group[1]. Patients with meningitis may present with headache, photophobia, and neck stiffness and may develop confusion and coma in the later stages[2]. Older patients are more prone to have altered mental status and focal neurologic deficits rather than neck stiffness and headache[3,4]. However, these are non-specific; hence, a high index of suspicion is required to make the correct diagnosis. As early diagnosis and specific treatment may improve outcomes, every attempt must be made to make an early etiological diagnosis to institute specific therapy[5].

The most common form of meningitis is aseptic meningitis. These cases are primarily viral, and enterovirus is the most common etiological organism reported in immune-competent individuals[6,7]. Aseptic and bacterial meningitis are similar in clinical presentation, but patients with bacterial meningitis appear more ill clinically. All patients with symptoms suggestive of meningitis should undergo lumbar puncture (LP) at the earliest and cerebrospinal fluid (CSF) assessment for definitive diagnosis and appropriate treatment. On cytological and biochemical analysis of CSF, lymphocytic pleocytosis with normal glucose level and a normal to slightly elevated protein level are seen in aseptic meningitis. Whereas bacterial meningitis characteristically has an elevated and predominantly neutrophilic pleocytosis with low glucose level, decreased CSF/serum glucose ratio (< 0.4), and a high protein level. The reported sensitivity and specificity of CSF total leucocyte count (TLC), proteins, and sugars for diagnosing meningitis are 80%, 89%; 97%, 85%; 93%, and 49%, respectively[8].

CSF Gram and acid-fast bacilli stains are quick methods of detecting the organism, but they lack sensitivity (50% to 80%). CSF cultures, which are positive in, at best, 80% of cases of bacterial meningitis, have a long turn-around time of 48 h and may be falsely negative in patients already on antibiotics. The sensitivity of CSF Gram stain and cultures is less than 50% in such patients[9]. A real-time polymerase chain reaction (rt-PCR) based meningoencephalitis panel is useful for the etiological diagnosis of meningitis. Even though it has good sensitivity and specificity, its application is restricted due to its limited availability and high cost. Hence, there is a need for a readily available test that is easy to apply and can diagnose meningitis and differentiate between bacterial and non-bacterial causes of meningitis.

Blood lactate is tested in almost all critically ill patients in intensive care units (ICUs) and has been used to guide treatment and predict prognosis. In contrast, CSF lactate is rarely tested. Normal CSF lactate levels are 1.2-2.1 mmol/L, but they may range from 0.6-3.1 mmol/L[10]. Anaerobic glycolysis of brain tissue due to decreased cerebral blood flow and oxygen uptake may increase lactate concentration in CSF patients with meningitis[11]. Hence, CSF lactate has been suggested as an excellent marker to diagnose meningitis and may be a better marker than CSF TLC, sugar, and proteins[12,13]. In addition,

it is inexpensive, has high test-retest reliability and is also readily available even in the resource-poor world, where neurological imaging may be difficult to obtain. However, most of the studies have been done on post-neurosurgical and brain trauma patients, and there is a dearth of data regarding its accuracy in critically ill medical patients with suspected meningitis.

MATERIALS AND METHODS

A prospective, observational cohort study was carried out in a neuro-medical ICU of a tertiary care hospital in India from December 2019 to October 2021. Institutional Human Ethics Committee approval was obtained before the commencement of the study (Reference number: TS/MSSH/MHIL/SKT-1/MHEC/CC/20-17). After explaining the study protocol, written informed consent was obtained from all the participants. Those patients fulfilling inclusion criteria, patients older than 18 years, admitted with suspected meningitis in ICU, were serially recruited. Patients who refused to consent to the study, those with a peripheral sensorineural deficit, and those with any contraindication to the LP procedure were excluded. Trained intensivists performed LP with full aseptic precautions per the clinical protocols, and samples were sent immediately to the hospital laboratory in sterile containers. CSF cytology, biochemical parameters, culture and polymerase chain reaction (PCR) -based meningoencephalitis panel, were evaluated. CSF lactate levels were measured in all the patients. The final diagnosis of meningitis was made based on the clinical picture, CSF analysis, culture and PCR reports. The sensitivity, specificity, and positive and negative predictive value of CSF lactate, to diagnose meningitis were calculated. The efficacy of CSF lactates was compared with other commonly employed tests like CSF TLC, proteins, and sugar levels. Correlation of CSF lactate with CSF culture and PCR was also performed. CSF lactates were also compared in patients with bacterial *vs* non-bacterial causes of meningitis. Hospital and ICU length of stay (LOS), need for invasive mechanical ventilation, and ICU mortality were also recorded.

Statistical analysis

Statistical analysis was performed by the SPSS program for Windows, version 17.0 (SPSS, Chicago, IL, United States). Normally distributed continuous variables were compared using the unpaired t test, whereas the Mann-Whitney U test was used for those variables that were not normally distributed. Categorical variables were analyzed using either the chi square test or Fisher's exact test, as appropriate. Area under receiver operating characteristics (AUROC) analysis was calculated to determine optimal cut-off values for CSF TLC, protein and sugar and lactate levels. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

RESULTS

Seventy-one patients, who fulfilled the inclusion criteria were included in the final analysis and divided in two groups, meningitis and non-meningitis groups, based on the clinical diagnosis of meningitis. Their basic characteristics, clinical parameters and hospital course are given in the Table 1.

The mean values of CSF TLC, proteins and lactates were significantly higher in meningitis group whereas mean value sugar levels were significantly higher in non-meningitis groups (Table 2). There was a significant correlation of CSF lactate levels with CSF cultures; meningo-encephalitis PCR based panel, and a combination of both (CSF cultures and meningo-encephalitis panel) with P value < 0.05.

As shown in Table 3, CSF lactate cut-off point for the diagnosis of meningitis, obtained by analyzing the ROC curve, was > 2.7 mmol/L with AUC of 0.81 (95% confidence interval: 0.69-0.93). Sensitivity was 82.6%, specificity 72.9%, positive predictive value 59.4%, negative predictive value 89.7% and accuracy 76.1%.

Causes of meningitis and the final diagnosis of patients in the non-meningitis group is given in Table 4. Out of 23 patients of meningitis patients, 12 patients had bacterial meningitis and 11 patients had non-bacterial meningitis. CSF lactate levels were significantly higher in bacterial meningitis (8.9 ± 4.7) than non-bacterial meningitis (4.2 ± 3.8), P = 0.006.

DISCUSSION

Even though central nervous system (CNS) infections account for only 2.9% of infections in ICU, they are associated with high morbidity and mortality, ranging from 17%-40%[14,15]. These patients' outcomes depend on the etiological organism and the kind of care provided[15]. Hence, making an early diagnosis and initiating specific treatment measures is imperative. In the present prospective cohort study, we found that CSF lactate had good accuracy, sensitivity and specificity in diagnosing meningitis and showed a good correlation with CSF cultures and RT-PCR-based panels. In addition, it may also aid

Table 1 Basic characteristics, clinical parameters and hospital course

Patient parameters	Overall (*n* = 71), %	Meningitis group (*n* = 23) , %	Non-Meningitis Group (*n* = 48), %	*P* value
Age, yr	58.1 ± 16	57.8 ± 15.4	58.9 ± 17.3	0.820
Males	23 (32.4)	10 (43.5)	13 (27.1)	0.167
Clinical parameters				
Headache	25 (35.2)	11 (47.8)	14 (29.2)	0.123
Seizures	46 (64.8)	17 (73.9)	29 (60.4)	0.265
Fever	50 (70.4)	16 (69.6)	34 (70.8)	0.871
Altered sensorium	70 (98.6)	23 (100)	47 (97.9)	0.486
Photophobia	5 (7)	3 (13)	2 (4)	0.171
Coma	24 (33.8)	9 (39.1)	15 (31.3)	0.511
Antibiotic exposure before CSF analysis	65 (91.5)	22 (95.7)	43 (89.6)	0.39
Traumatic brain injury	2 (3)	0 (0)	2 (4)	0.321
Neurosurgical intervention	4 (5.6)	3 (13)	1 (2)	0.061
Neurosurgical device in-situ	4 (5.6)	3 (13)	1 (2)	0.061
Glasgow coma scale	9.5 ± 4	9 ± 4	9.7 ± 4	0.508
Neck stiffness	4 (5.6)	4 (17.4)	0 (0)	0.003[a]
Focal neurological deficit	14 (19.7)	5 (21.7)	9 (18.8)	0.767
Length of stay in hospital	21.1 ± 16	21.9 ± 8.9	21 ± 18.2	0.053
Length of stay in ICU	10.4 + 8.9	12.1 ± 6.3	9.6 ± 9.8	0.005[a]
Need for any surgical intervention	20 (28.2)	10 (43.5)	10 (20.8)	0.047[a]
Need for invasive mechanical ventilation	27 (38)	13 (56.5)	14 (29.2)	0.026[a]
ICU mortality	20 (28.2)	10 (43.5)	10 (20.8)	0.047[a]

[a]*P* value statistically significant.
CSF: Cerebrospinal fluid; ICU: Intensive care unit.

Table 2 Comparison of cerebrospinal fluid analysis between meningitis and non-meningitis groups

CSF parameters	Meningitis group (*n* = 23)	Non-meningitis group (*n* = 48)	*P* value
TLC (mean ± SD)	1223.4 ± 2611	8.1 ± 12.6	< 0.001[a]
Protein (mean ± SD)	177.1 ± 204.2	69.3 ± 61.5	0.002[a]
Sugar mg/dL (mean ± SD)	90.1 ± 98.4	102.1 ± 41	0.011[a]
Lactate levels mg/dL (mean ± SD)	60 ± 43.9	23.6 ± 11.1	< 0.001[a]
Lactate levels mmol/L (mean ± SD)	6.6 ± 4.8	2.6 ± 1.2	< 0.001[a]
Positive CSF cultures	17 (74)	0 (0)	< 0.001[a]
Positive meningo-encephalitis panel	7 (30)	0 (0)	0.001[a]
Positive CSF cultures or meningo-encephalitis panel	23 (100)	0 (0)	< 0.001[a]

[a]*P* value statistically significant.
CSF: Cerebrospinal fluid; SD: Standard deviation.

in differentiating between bacterial and non-bacterial causes of infective meningitis.

In critically ill patients, there could be several differential diagnoses that may mimic meningitis symptoms. These include acute stroke, tumours, toxins, autoimmune and paraneoplastic diseases and cerebral or epidural abscesses. In addition, several metabolic derangements like sepsis and electrolyte disturbances may also present similarly. In the present study, these factors were the most common

Table 3 Comparison of various cerebrospinal fluid parameters for diagnosing meningitis

CSF Parameters	Cut-off	Sensitivity, %	Specificity, %	NPV, %	PPV, %	Accuracy, %	AUC	CI	*P* value
TLC (Cell/mm^3)	> 55	73.9	100	100	88.9	91.5	0.92	0.84-1	< 0.001[a]
Lactate levels (mmol/L)	> 2.7	82.6	72.9	59.4	89.7	76.1	0.81	0.7-0.9	< 0.001[a]
Protein (mg/dL)	> 104.4	56.5	87.5	68.4	80.8	77.5	0.73	0.6-0.9	0.002[a]
Sugar (mg/dL)	> 63	56.5	83.3	61.9	80.0	74.6	0.7	0.6-0.9	0.006[a]

[a]*P* value statistically significant.
CSF: Cerebrospinal fluid; AUC: Area under the curve; CI: Confidence interval; NPV: Negative predictive value; PPV: Positive predictive value; TLC: Total leucocyte count.

Table 4 Etiological causes of patients in meningitis and non-meningitis groups

Meningitis group (*n* = 23), %		
Bacterial (*n* = 12)	Streptococcus pyogenes	5 (41.7)
	Staphylococcus aureus	2 (16.7)
	Haemophilus influenzae	2 (16.7)
	Enterococcus faecium	2 (16.7)
	Escherichia coli	1 (8.4)
Viral (*n* = 6)	Varicella zoster virus	3 (27.3)
	Herpes simplex virus	2 (18.2)
	Measles virus	1 (9.1)
Fungal (*n* = 2)	Candida tropicalis	1 (9.1)
	Cryptococcus neoformans	1 (9.1)
Tubercular (*n* = 3)	Mycobacterium tuberculosis complex	3 (27.3)
Non-meningitis group (*n* = 48)		
Septic and metabolic encephalopathy		34 (70.8)
Hypoxic brain injury		3 (6.3)
Guillain barre syndrome		2 (4.2)
Autoimmune encephalitis		2 (4.2)
Metastatic brain involvement		2 (4.2)
Post-ictal confusion		2 (2.1)
Hypoglycaemic coma		1 (2.1)
Demyelinating disorder		1 (2.1)
Unknown		1 (2.1)

causes of neurological derangement in the non-meningitis group. The typically described triad of headache, fever and neck rigidity is present in less than 50% of patients with meningitis; hence a high degree of suspicion is required[3].

CSF analysis remains the cornerstone for diagnosing meningitis and making the etiological diagnosis. The etiological organism causing meningitis depends on several patient conditions, including age, immunocompromised status, sinusitis or endocarditis, and any traumatic brain injury, neurosurgery or indwelling neurological devices or catheters. Streptococcus pneumoniae has been reported to be the commonest cause of bacterial meningitis, similar to the results of our study. Haemophilus influenza and Staphylococcus aureus are rare causes of meningitis in adult patients and are generally secondary to other underlying clinical conditions like sinusitis and endocarditis[16]. The reported incidence of Mycobacterium tuberculosis as a cause of acute meningitis is around 5%, but it may be higher in countries with a higher prevalence of tuberculosis[17]. Among the viral causes, the Varicella-zoster virus is most commonly implicated in immunocompromised patients and the Herpes simplex virus in

immunocompetent adults[17].

Presently, there is a need for a definitive test to enable rapid and accurate diagnosis, and hence the search for an ideal test continues. Apart from the routinely employed tests, several other CSF markers have been tested for their efficacy in diagnosing meningitis. Tests like CSF adenosine deaminase and cortisol have explicitly been evaluated for the diagnosis of tubercular meningitis, and specific other markers like CSF TNF-alpha, IL-6, IL-8 and IL-17 Levels have been tested for the diagnosis of nosocomial meningitis, with varied success[18-20].

CSF culture is still the gold standard for diagnosing bacterial meningitis, with a reported sensitivity of up to 80%. However, its efficacy in diagnosing other causes of infective meningitis is limited[21,22]. Its clinical application is also limited by a long turn-around of 48 h, thus delaying the initiation of appropriate early treatment. Moreover, its efficacy is further hampered in patients who have already received antibiotics.

Newer tests like RT-PCR-based meningitis-encephalitis panel (FilmArray PCR), a qualitative multiplex nucleic acid-based in-vitro diagnostic test, have been developed and are being increasingly used to diagnose meningitis[23]. This test has several advantages, including rapid turn-around time, good sensitivity and specificity (above 90%) and minimal effect of previous antibiotic exposure[24]. In addition, this test may help diagnose non-bacterial causes of meningitis, including viral and fungal meningitis and culture-negative cases[23]. This panel is capable of simultaneous identification of 14 different organisms, including multiple bacterial (Escherichia Coli, H. Influenzae, L. Monocytogenes, N. meningitides, Strepto. agalactiae, Strepto. pneumoniae), viral (Cytomegalovirus, Enterovirus, HSV 1; HSV 2; HHV 6, VZV) and fungal/yeast (Cryptococcus neoformans/gatti) nucleic acid directly from CSF specimen and may help diagnose complex cases too[25].

CSF lactate is now recognized as a valuable marker for diagnosing acute meningitis. It has shown to be a helpful marker in diagnosing nosocomial meningitis and has shown up to 100% sensitivity for diagnosing bacterial meningitis[19]. As it is a rapid, inexpensive and readily available tool, it may guide physicians in making an early diagnosis of acute meningitis and differentiating bacterial from other causes of meningitis. Nevertheless, it cannot be used as a standalone test but may be helpful to our routine CSF analysis. The value of CSF lactates does not depend on the serum lactate levels as ionized lactate crosses the blood-brain barrier very slowly, eliminating the need for simultaneous measurement of blood lactate levels[11]. CSF lactates have also been used for prognostication, with rapidly falling levels shown to be associated with positive outcomes[26]. It is generally advised to obtain CSF for lactate measurement before administering antibiotics, as antibiotic exposure may reduce its sensitivity [27]. However, in our patient cohort, more than 90% of patients had already received antibiotics still the sensitivity and specificity of CSF lactate remained good.

The cut-off for CSF lactate still needs to be clarified, with different authors using different cut-offs ranging from 2-3 mmol/L[28,29]. Our study observed that CSF lactates had the best accuracy at the cut-off of 2.7 mmol/L, within the generally accepted range. Moreover, it is agreed that the higher the CSF lactates, the higher the chances of it being caused by bacterial meningitis. A meta-analysis by Huy *et al* [26] reported that a CSF lactate of ≥ 3.5 mmol/L was associated with a high sensitivity ranging from 96%-99% and specificity ranging from 88-94% in diagnosing bacterial meningitis. In our study, CSF lactate levels were also significantly higher in bacterial (8.85 ± 4.66 mmol/L) *vs* non-bacterial causes of meningitis (4.15 ± 3.84 mmol/L).

There are several strengths to our study. It was a nicely designed prospective study, and we included all the available measures, including CSF cultures and PCR-based panels, to reach a diagnosis. Moreover, our study had primarily medically ill patients and was the first to show the correlation of CSF lactates with modern diagnostic techniques like PCR-based panels. The limitation of our study was that it was a monocentric study with a relatively small number of patients. Hence, it is imperative to conduct a larger multi-centre trial to improve the generalizability of our results.

CONCLUSION

CSF lactate may be used as an add-on marker to aid our clinical diagnosis of meningitis in critically ill patients. CSF lactate cut-off value above 2.72 mmol/L showed good accuracy, sensitivity, and specificity in diagnosing meningitis. High CSF lactates also help us to differentiate between bacterial and non-bacterial causes of meningitis and show a good correlation with CSF cultures and PCR-based meningo-encephalitis panel for the diagnosis of meningitis.

ARTICLE HIGHLIGHTS

Research background

Meningitis is a life-threatening clinical condition associated with high mortality and morbidity. Early diagnosis and specific treatment may improve outcomes. Lack of specific clinical signs or tests make the

diagnosis challenging, especially in critically ill patients.

Research motivation

Cerebrospinal fluid (CSF) lactate has been used to diagnose meningitis in post-operative neurosurgical patients. However, there is a dearth of data from neuro-medical patients regarding its role in diagnosing meningitis.

Research objectives

To assess the efficacy of CSF lactate in diagnosing meningitis in critically ill patients.

Research methods

A prospective, observational cohort study was carried out in a neuro-medical intensive care unit (ICU). CSF cytology, bio-chemistry, lactates, culture and polymerase chain reaction based meningo-encephalitis panel were evaluated. Patients were divided in two groups based on clinical diagnosis of meningitis. The efficacy of CSF lactate in diagnosing meningitis was evaluated and compared with other tests.

Research results

Seventy-one patients were included and 23 were diagnosed with meningitis. The mean values of CSF total leucocyte count, proteins and lactates were significantly higher in meningitis group. There was a significant correlation of CSF lactate levels with CSF cultures and meningo-encephalitis panel. CSF lactate (> 2.72 mmol/L) showed good accuracy in diagnosing meningitis with an area under the curve of 0.81 (95% confidence interval: 0.69-0.93), sensitivity 82.6%, and specificity 72.9%. Patients with bacterial meningitis had significantly higher CSF lactate (8.9 ± 4.7 mmol/L) than those with non-bacterial meningitis (4.2 ± 3.8 mmol/L), $P = 0.006$.

Research conclusions

CSF lactate may be used to aid in our diagnosis of meningitis in ICU patients. CSF lactate (> 2.72 mmol/L) showed good accuracy, sensitivity, and specificity in diagnosing meningitis and may also help to differentiate between bacterial and non-bacterial meningitis.

Research perspectives

Larger trials may assess the utility of CSF lactate in differentiating various infective meningitis like those secondary to bacterial, fungal, viral and tubercular bacilli.

FOOTNOTES

Author contributions: Yadav D, Singh O, and Juneja D designed the study. Yadav D, Kataria S, and Beniwal A collected the data, and analyzed the results. Yadav D, and Juneja D performed majority of the writing, and prepared the tables; Singh O, Goel A, Kataria S and Beniwal A provided the inputs in writing the paper and reviewed the manuscript.

Institutional review board statement: The study was reviewed and approved by the Max Super Speciality Hospital, Saket, New Delhi, Institutional Review Board *via* letter no. TS/MSSH/MHIL/SKT-1/MHEC/CC/20-17.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 January 9; 12(1): 10-17

DOI: 10.5492/wjccm.v12.i1.10

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Prospective Study

Bedside ultrasonography of optic nerve sheath diameter for detection of raised intracranial pressure in nontraumatic neuro-critically ill patients

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Fülöp T, United States; Pandey S, India

Received: November 4, 2022
Peer-review started: November 4, 2022
First decision: November 30, 2022
Revised: December 5, 2022
Accepted: December 23, 2022
Article in press: December 23, 2022
Published online: January 9, 2023

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Abstract

BACKGROUND

Delay in treatment of raised intracranial pressure (ICP) leads to poor clinical outcomes. Optic nerve sheath diameter (ONSD) by ultrasonography (US-ONSD) has shown good accuracy in traumatic brain injury and neurosurgical patients to diagnose raised ICP. However, there is a dearth of data in neuro-medical intensive care unit (ICU) where the spectrum of disease is different.

AIM

To validate the diagnostic accuracy of ONSD in non-traumatic neuro-critically ill patients.

METHODS

We prospectively enrolled 114 patients who had clinically suspected raised ICP due to non-traumatic causes admitted in neuro-medical ICU. US-ONSD was performed according to ALARA principles. A cut-off more than 5.7 mm was taken as significantly raised. Raised ONSD was corelated with raised ICP on radiological imaging. Clinical history, general and systemic examination findings, SOFA and APACHE 2 score and patient outcomes were recorded.

RESULTS

There was significant association between raised ONSD and raised ICP on imaging ($P < 0.001$). The sensitivity, specificity, positive and negative predictive value at this cut-off was 77.55%, 89.06%, 84.44% and 83.82% respectively. The positive and negative likelihood ratio was 7.09 and 0.25. The area under the receiver operating characteristic curves was 0.844. Using Youden's index the best cut off value for ONSD was 5.75 mm. Raised ONSD was associated with lower age ($P = 0.007$), poorer Glasgow Coma Scale ($P = 0.009$) and greater need for surgical intervention ($P = 0.006$) whereas no statistically significant association

was found between raised ONSD and SOFA score, APACHE II score or ICU mortality. Our limitations were that it was a single centre study and we did not perform serial measurements or ONSD pre- and post-treatment or procedures for raised ICP.

CONCLUSION

ONSD can be used as a screening a test to detect raised ICP in a medical ICU and as a trigger to initiate further management of raised ICP. ONSD can be beneficial in ruling out a diagnosis in a low-prevalence population and rule in a diagnosis in a high-prevalence population.

Key Words: Intracranial pressure; Intensive care unit; Neuro-critical care; Optic nerve sheath diameter; Ultrasonography

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Core Tip: Raised intracranial pressure (ICP) maybe present in a significant proportion of neuro-critically ill patients and any delay in its management may lead to poor outcomes. Even though the gold standard for measuring raised ICP is the intraventricular catheter, it is invasive, not widely available, requires expertise in insertion and maintenance and may be associated with many risks. Hence, non-invasive methods like computed tomography scan or magnetic resonance imaging are being increasingly used to diagnose raised ICP. However, their utility is also restricted by logistical issues and have limited repeatability. Bedside ultrasonography measuring optic nerve sheath diameter (ONSD) can be used as a screening test to detect raised ICP and as a trigger to initiate further management. ONSD can also be beneficial in ruling out a diagnosis in a low-prevalence population and rule in a diagnosis in a high-prevalence population.

Citation: Bhide M, Singh O, Juneja D, Goel A. Bedside ultrasonography of optic nerve sheath diameter for detection of raised intracranial pressure in nontraumatic neuro-critically ill patients. *World J Crit Care Med* 2023; 12(1): 10-17

URL: https://www.wjgnet.com/2220-3141/full/v12/i1/10.htm

DOI: https://dx.doi.org/10.5492/wjccm.v12.i1.10

INTRODUCTION

Raised intracranial pressure (ICP) is a dreaded complication in the intensive care unit (ICU) which may occur either as a result of a primary neurological disorder or as a secondary complication in patients admitted due to other causes. A delay in detecting raised ICP can lead to poor clinical outcomes and increased mortality. The latest Brain Trauma Foundation guidelines now recommend a cut off 22 mmHg to initiate ICP-lowering therapies[1]. Gold standard for measuring raised ICP is the intraventricular catheter. However, it is not widely available, requires expertise in insertion and maintenance and may be associated with many risks like infection, collapse of ventricles and haemorrhage[2]. Hence, non-invasive methods like computed tomography (CT) scan or magnetic resonance imaging (MRI) are increasingly used to diagnose raised ICP. However, they are associated with transport risk and radiation exposure, in the case of CT scans, leading to logistical issues and limited repeatability.

Determination of optic nerve sheath diameter by ultrasonography (US-ONSD) is a simple bedside test with a rapid learning curve, low intra and interobserver variation and good repeatability[3,4]. Studies have shown good accuracy even when performed by non-radiologists[5]. In modern ICUs, bedside ultrasonography is integrated into routine clinical examination and is readily available. Optic nerve sheath diameter (ONSD) is frequently used across neuro-surgical ICUs as a tool for ICP monitoring and is particularly useful in patients in whom invasive ICP monitoring criteria are not met or are contraindicated. However, the spectrum of disease and comorbidities of patients admitted to neuro-medical ICUs are distinct from neurosurgical ICUs. There need to be more practical bedside screening tools to detect raised ICP in neuro-medical ICUs timely; hence, we aimed to validate ONSD in neuro-medical ICU patients.

MATERIALS AND METHODS

We conducted this study to determine the diagnostic accuracy of ONSD in adult non-traumatic neuro-critically ill patients after approval from the institutional ethics committee (TS/MSSH/MHIL/SKT/-

MHEC/CC/20-16). Our inclusion criteria were patients older than 18 years admitted to the neuro-medical ICU with signs and symptoms suggestive of raised ICP. Our exclusion criteria were previously known history of neurological conditions like chronic hydrocephalus, in situ ventriculoperitoneal shunt, known ocular mass, ocular trauma, conjunctival oedema, orbital oedema, cavernous sinus pathology or arachnoid cysts, and patients having optic nerve disease. Additionally, patients in whom CT/MRI could not be performed within 24 hours of US-ONSD were excluded from the analysis.

For the prospective study, the sample size required was calculated according to the following formula: $Z\alpha 2 \times SN \times (1 - SN)$, $n = 2 \times P$. Where, n = required sample size Z = SNV at α = 5% = 1.96. S.N.SN = Anticipated Sensitivity. d = Absolute precision desired on either side P = Expected prevalence in the population or based on the previous/pilot studies.

For this study, a 95% confidence level with an appropriate effect size and a statistical power of 80% was taken. In a previous study by Salahuddin *et al*[6], the expected prevalence of non-traumatic raised ICP in a medical ICU was 30.4%[6]. The pooled sensitivity of ONSD to determine raised ICP was 90%, as determined by a systematic review and metanalysis by Dubourg *et al*[3]. Keeping these values for the calculation of the sample size, our required sample size was 114.

We serially enrolled patients who fulfilled the inclusion criteria. After written informed consent was obtained, ocular USG was done by critical care specialists trained in critical care ultrasonography, using a 7-15 MHz ultrasound probe in B mode to determine the ONSD three mm distal to the optic disc in both eyes. A fibrous trabecular network connects the optic nerve and its sheath. Studies have shown a greater degree of mesh 6 to 12 mm behind the globe, whereas there is a lesser degree of mesh 3 mm behind the globe. Therefore, 3 mm behind the globe expands to a greater degree than 6 to 12 mm behind the globe, with the maximum expansion dependent on the individual's trabecular density[7]. Hansen *et al*[8] first validated ONSD and standardized the method to document it by B mode ultrasonography by measuring it 3 mm behind the globe. Two readings were taken for each eye, and a mean value was calculated to represent the final ONSD. ONSD more than 5.7 mm was taken as a threshold for determining raised ICP[3]. CT/MRI scans of the brain were done within 24 h of US-ONSD, and the images were reviewed for signs of raised ICP. Raised ICP or non-traumatic radiographic cerebral oedema [NTRCE] was defined on imaging as significant brain oedema, midline shift, compression of basal cisterns or ventricles, effacement of sulci, insufficient grey/white differentiation and transalpine herniation. Clinical history, general and systemic examination findings, SOFA and APACHE 2 scores and patient outcomes were recorded.

Statistical analysis

The collected data were transformed into variables, coded and entered in Microsoft Excel. Data were analyzed and statistically evaluated using the SPSS-PC-25 version. Quantitative data were expressed in mean ± standard deviation or median with interquartile range, and depending upon normality distribution, the difference between two comparable groups was tested by student's *t*-test (unpaired) or Mann Whitney 'U' test. Qualitative data were expressed in percentages, and statistical differences between the proportions were tested by the chi-square or Fisher's exact test, as appropriate. For all statistical tests, a *P* value less than 0.05 was taken as valid evidence for the statistical significance of the data.

The performance of the diagnostic tests was estimated using 2 × 2 contingency tables to calculate sensitivity, specificity, overall diagnostic accuracy, positive and negative predictive value, likelihood ratios (LRs) and 95% confidence intervals (CI). Post-test probability was determined using Bayes's nomogram. Discrimination was tested using the receiver operating characteristic (ROC) curves. The best cut-off value for ONSD was calculated by using Youden's index.

RESULTS

114 patients with signs and symptoms suggestive of raised ICP were included in the analysis. Out of these, raised ONSD (> 5.7 mm) was found in 45 (39.5%) patients. The mean age of patients in our study cohort was 64.05 (± 16.80) years, with a predominantly male population (59.3%). Table 1 shows that the patient comorbidities, clinical symptoms and signs, except Glasgow Coma Scale (GCS), on admission were comparable across both groups. Lower GCS was significantly associated with raised ICP (P = 0.009). Raised ICP on imaging was seen in 49 patients (43%). The most common feature of raised ICP on imaging was diffuse cerebral oedema (38.1%) followed by effacement of sulci (32.7%), insufficient grey/white differentiation (30.1%), compression of ventricles (21.2%), midline shift (20.4%) and transfalcine herniation (1.8%).

There was a statistically significant correlation between raised ONSD and increased ICP features on CT/MRI scans (P < 0.001). As shown in Table 2, the sensitivity, specificity, and positive and negative predictive values at this cut-off were 77.55%, 89.06%, 84.44% and 83.82%, respectively. The AUROC was 0.844. The best cut-off value for ONSD calculated using Youden's index was 5.75 mm.

The commonest diagnosis was septic/metabolic encephalopathies (27.4%). Other diagnoses were acute intracranial bleeding (21.2%), acute ischaemic stroke (20.4%), meningoencephalitis (13.3%), super

Table 1 Patient comorbidities and clinical features on admission

	Variables	Overall (*n* = 114), %	Normal ONSD (*n* = 69), %	Raised ONSD (*n* = 45), %	*P* value
Comorbidities	Hypertension	54 (47.8)	37 (68.5)	17 (31.5)	0.083
	T2DM	35 (31.0)	21 (60.0)	14 (40.0)	0.979
	CKD	20 (17.7)	14 (70.0)	6 (30.0)	0.323
	CAD	10 (8.8)	4 (40.0)	6 (60.0)	0.193
	OAD	8 (7.1)	7 (87.5)	1 (12.5)	0.142
	Malignancy	7 (15.0)	12 (70.6)	5 (29.4)	0.341
	Others	30 (26.5)	19 (63.3)	11 (36.7)	0.680
	No comorbidities	26 (23.0)	12 (46.2)	14 (53.8)	0.096
Symptoms on admission	Headache	30 (26.5)	18 (60.0)	12 (40.0)	0.982
	Vomiting	19 (16.8)	12 (63.2)	7 (36.8)	0.771
	Blurring of vision	10 (8.8)	4 (40.0)	6 (60.0)	0.193
	Seizures	30 (26.5)	18 (60.0)	12 (40.0)	0.982
	Altered sensorium	103 (91.2)	60 (58.3)	43 (41.7)	0.311
General examination	GCS, mean ± SD	9.39 ± 4.09	10.21 ± 3.97	8.16 ± 3.99	0.009[a]
	Bradycardia	34 (30.1)	18 (52.9)	16 (47.1)	0.303
	Hypertension	31 (27.4)	19 (61.3)	12 (38.7)	0.882
	Neck stiffness	33 (29.2)	20 (60.6)	13 (39.4)	0.952
	Focal neurological deficit	70 (61.9)	41 (58.6)	29 (41.4)	0.656

[a]Denotes Statistical significance

CAD: Coronary artery disease; CKD: Chronic kidney disease; GCS: Glasgow coma scale; OAD: Obstructive airway disease; SD: Standard deviation; T2DM: Type 2 diabetes mellitus.

Table 2 Accuracy of optic nerve sheath diameter at cut-off of 5.7 mm with raised raised intracranial pressure on brain imaging

	Values	95%CI
Sensitivity	77.55	63.38-88.23
Specificity	89.06	78.75-95.49
Positive likelihood ratio	7.09	3.47-14.50
Negative likelihood ratio	0.25	0.15-0.43
Disease prevalence	43.36	34.07-53.01
Positive predictive value	84.44	72.64-91.73
Negative predictive value	83.82	75.36-89.78
Accuracy	84.07	76.00-90.28

refractory status epilepticus (4.4%), newly diagnosed space-occupying lesion (1.8%), cerebral venous sinus thrombosis (CVST) (1.7%) and hypoxic-ischaemic encephalopathy (1.7%). Of the 31 patients presenting with septic/metabolic encephalopathy, 26 (83.9%) had a normal ONSD.

Patient outcomes, including ICU length of stay (LOS) and ICU mortality, were comparable across both groups, as shown in Table 3. Raised ONSD had a statistically higher requirement of surgical intervention (P = 0.006). The surgical procedures were decompressive craniotomy in 6 patients, ventriculoperitoneal shunt (VP shunt) in 3 patients and extra-ventricular drain (EVD) insertion in 2 patients. One patient underwent EVD followed by a VP shunt with Omaya reservoir.

Table 3 Hospital course across normal and raised optic nerve sheath diameter groups

		Overall (*n* = 114)	Normal ONSD (*n* = 69)	Raised ONSD (*n* = 45)	*P* value
Hospital course	SOFA, median [IQR]	5 [3-8]	5 [3-8]	5 [3-8]	0.409
	APACHE II score, median [IQR]	20 [14-26]	21 [14-26]	20 [14-26]	0.569
	Hospital LOS, median [IQR]	17 [7-27.5]	15 [7-28]	18 [8-25]	0.688
	ICU LOS, median [IQR]	10 [5-21]	10 [5-20]	10 [5-21]	0.609
Surgical intervention	Yes	11 (9.7)	2 (18.2)	9 (81.8)	0.006[1]
	No	102 (90.3)	66 (64.7)	36 (35.3)	
Discharged or Death	Discharged	64 (56.6)	41 (64.1)	23 (35.9)	0.335
	Death	49 (43.4)	27 (55.1)	22 (44.9)	

[1]Denotes statistical significance.

APACHE: Acute physiology and chronic health evaluation; IQR: Inter quartile range; LOS: Length of stay; ONSD: Optic nerve sheath diameter; SOFA: Sequential organ failure assessment.

DISCUSSION

Invasive ICP monitoring is not widely available across the ICUs, especially in resource-limited settings. An internet-based survey of critical care physicians in India in 2013 showed that only 36.42% had access to exclusive neurocritical care units, and 63.4% of consultants did not monitor ICP. Amongst the physicians who monitored for raised ICP, 60.32% used CT/MRI scans, 28.57% intraventricular catheter with external transducer, and 11.11% used Codman microsensor[9]. This shows the extent of the deficit in terms of advanced neuro-monitoring facilities across ICUs in resource-limited settings. US-ONSD provides a lucrative alternative to the available methods for ICP monitoring. We conducted a prospective study with the primary objective of validating ONSD by bedside ultrasound compared to features of raised ICP on the CT/MRI brain. Our study found a significant association between raised ONSD (> 5.7 mm) and findings of raised ICP on imaging. The sensitivity and specificity, at this cut-off, were 77.55% and 89.06%, with an AUROC were 0.844. The positive and negative predictive values were 84.44% and 83.82%, respectively. The best cut-off value for ONSD determined by Youden's index was 5.75 mm.

Physical findings of raised ICP are nonspecific and lack accuracy in diagnosing raised ICP. Diagnosis of raised ICP is essential as it may be associated with poor clinical outcomes. Early intervention using osmotherapy with hypertonic saline or mannitol has been shown to be effective in lowering ICP[10-12]. GCS is commonly used for monitoring neuro-critically ill patients. Poor motor performance has been associated with raised ICP and poor prognosis[13]. In our study, the most common symptom in patients with suspected raised ICP was altered mental status, and poor GCS score was significantly associated with raised ONSD. This was in accordance with a study of patients with traumatic brain injury where raised ONSD was compared to three groups of GCS 3-5, 6-8, > 8 and a statistical significance was found between poor GCS and raised ONSD[14]. In patients whose GCS cannot be assessed due to ongoing sedatives or paralytic agents, raised ONSD can be used as an indicator for raised ICP warranting further evaluation. However, further studies are required to establish any linear relationship between deteriorating GCS and increasing ONSD.

Out of our entire study population, 49 patients (42.98%) showed the presence of NTRCE. In a study in general medical ICU by Salahuddin *et al*[6], NTRCE was found in 30.4%[9]. Higher prevalence of NTRCE in our study can be explained by the fact that it was done in neuro-medical ICU patients with suspected raised ICP, as opposed to the study mentioned above, which was done in a general medical ICU.

For over 10 years, the upper limit of normal for US-ONSD was considered to be 4.5 to 5.0 mm. However, recent studies have shown a higher threshold. Geeraerts *et al*[15] reported that an ONSD cut-off of 5.7 to 5.8 mm could exclude raised ICP with sensitivity and a negative predictive value of > 90%. If the ONSD was < 5.7 mm, the probability of ICP above 20 mmHg was less than 5%. Another study on 100 stroke patients with mass effect compared US-ONSD with signs suggestive of raised ICP on a brain CT scan and showed that an ONSD cut-off of > 5.7 mm positively correlated with CT scan findings[14]. In the present study, we found the best cut-off for ONSD using Youden's index as 5.75 mm, per the recent data[16].

Our study found a statistically significant association between raised ONSD (> 5.7 mm) and raised ICP on CT/MRI brain. Raised US-ONSD was a good screening tool for raised ICP with a sensitivity and specificity of 77.55% and 89.06%, respectively, and AUROC was 0.844. However, the terms sensitivity and specificity do not account for disease prevalence and are more applicable at a population level. LRs

depend on disease prevalence and can be used to quantify the probability of disease in an individual patient. In our study, the positive and negative LR was 7.09 and 0.25, respectively. The disease prevalence (raised ICP) in our study was 43%. Baye's nomogram suggests that if ONSD is more than 5.7 mm, there is an 84% probability of a patient having raised ICP. On the other hand, if ONSD is less than 5.7 mm, the probability of raised ICP is only 16% (CI: 10%-24%). Hence, in neuro-medical ICUs where raised ICP has a high prevalence, ONSD is a good screening test to detect raised ICP but may need to be more accurate to rule out raised ICP. When the same LRs are applied to a low prevalence population, like in a study by Tayal *et al*[5] where raised ICP was found to be prevalent in only 14% of patients presenting to the emergency department with a suspected acute head injury requiring CT, the positive post-test possibility was 54%, and negative post-test probability was less than 4%. Therefore, in a population with a low prevalence of raised ICP, the ONSD may be good for ruling out the diagnosis of raised ICP.

Most studies on ICP monitoring and US-ONSD have been conducted in neurosurgical ICUs, where trauma and strokes form the bulk of the disease. Primary pathology of neurocritical illness is different in medical ICUs[3,4]. A previous study of ONSD in a medical ICU found that the common causes of coma were septic or metabolic encephalopathy (25.4%) followed by new intracranial vascular event (17.6%), anoxic brain injury (4.9%), hepatic encephalopathy (21.5%), intracranial malignancy (8.8%) and others (intracranial infection, reversible posterior leukoencephalopathy syndrome, subclinical seizures) in 21.5%[9]. Similarly, our study also found septic/metabolic encephalopathy to be the commonest cause, with the majority (83.9%) of these patients having a normal ONSD. As septic/metabolic encephalopathy forms a large cohort of patients with altered sensorium in a medical ICU, it would be worthwhile to conduct an adequately powered study to validate ONSD in these patients. This gives an insight into the spectrum of diseases causing signs and symptoms of raised ICP in a neuromedical ICU.

There was no statistically significant difference between raised ONSD and SOFA scores and APACHE II scores. The severity of the disease seems to have no impact on ONSD. The hospital LOS, ICU LOS, and ICU mortality did not show any statistical correlation with ONSD. Hence, ONSD may not be a good test for prognostication in a neuro-medical ICU. However, patients with raised ONSD had a statistically higher rate of surgeries in our study and raised ONSD may indicate a greater likelihood for surgical intervention.

There are several strengths in our study. We included a reasonably large number of patients. This was a prospective study with a well-defined study protocol. The study was done in a single centre, so the ICU admission protocol and management strategies were uniform and standardized. We used CT/MRI brain as the gold standard for comparison with US-ONSD. We acknowledge the inferiority of CT/MRI to invasive gold standard measures of raised ICP. However, as invasive ICP monitoring is not readily available, CT/MRI shows a more real-life situation and may have better external validity, especially in resource-poor settings. Limitations were that all data were obtained from a single centre database, which may result in concerns regarding the generalization of the conclusions. We did not perform serial ONSD measurements or ONSD pre and post-treatment or procedures undertaken for raised ICP. Hence, the effect of therapeutic strategies on delta ONSD is not available.

CONCLUSION

Given the good sensitivity, positive LR and AUROC, ONSD can be used as a screening test to detect raised ICP in a medical ICU and future potential as a threshold trigger to escalate the management of raised ICP. This can help decrease the time gap between the episode of raised ICP and the initiation of treatment.

ARTICLE HIGHLIGHTS

Research background

Delay in treatment of raised intracranial pressure (ICP) leads to poor clinical outcomes.

Research motivation

Optic nerve sheath diameter (ONSD) by ultrasonography (US-ONSD) has shown good accuracy in traumatic brain injury and neurosurgical patients to diagnose raised ICP. However, there is a dearth of data in neuro-medical intensive care unit (ICU) where the spectrum of disease is different.

Research objectives

We conducted this study to validate the diagnostic accuracy of ONSD in non-traumatic neuro-critically ill patients.

Research methods

We prospectively enrolled 114 patients who had clinically suspected raised ICP due to non-traumatic causes admitted in neuro-medical ICU. US-ONSD was performed according to ALARA principles. A cut-off more than 5.7 mm was taken as significantly raised. Raised ONSD was correlated with raised ICP on radiological imaging. Clinical history, general and systemic examination findings, SOFA and APACHE 2 score and patient outcomes were recorded.

Research results

There was significant association between raised ONSD and raised ICP on imaging ($P < 0.001$). The sensitivity, specificity, positive and negative predictive value at this cut-off was 77.55%, 89.06%, 84.44% and 83.82%, respectively. The positive and negative likelihood ratio was 7.09 and 0.25. The AUROC was 0.844. Using Youden's index the best cut off value for ONSD was 5.75 mm. Raised ONSD was associated with lower age ($P = 0.007$), poorer GCS ($P = 0.009$) and greater need for surgical intervention ($P = 0.006$) whereas, no statistically significant association was found between raised ONSD and SOFA score, APACHE II score or ICU mortality. Our limitations were that it was a single centre study and we did not perform serial measurements or ONSD pre- and post-treatment or procedures for raised ICP.

Research conclusions

ONSD can be used as a screening a test to detect raised ICP in a medical ICU and as a trigger to initiate further management of raised ICP. ONSD can be beneficial in ruling out a diagnosis in a low-prevalence population and rule in a diagnosis in a high-prevalence population.

Research perspectives

Large scale studies need to be performed to assess the utility of ONSD in specific sub-groups of critically ill patients with neurological derrangements.

FOOTNOTES

Author contributions: Bhide M and Juneja D designed the study. Bhide M and Goel A collected the data. Bhide M and Juneja D analysed the results, performed the majority of the writing, and prepared the tables; Singh O, and Goel A provided the inputs in writing the paper and reviewed the manuscript.

Institutional review board statement: The study was approved by the institutional review board of Max Super Speciality Hospital, Saket (TS/MSSH/MHIL/SKT/MHEC/CC/20-16).

Informed consent statement: All study participants, or their legal guardian, provided written consent prior to study enrollment.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

Data sharing statement: There is no additional data available.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 January 9; 12(1): 18-28

DOI: 10.5492/wjccm.v12.i1.18

ISSN 2220-3141 (online)

SYSTEMATIC REVIEWS

Clonidine use during dexmedetomidine weaning: A systematic review

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Arslan M, Turkey; Karim HMR, India

Received: September 13, 2022
Peer-review started: September 13, 2022
First decision: October 21, 2022
Revised: November 15, 2022
Accepted: November 30, 2022
Article in press: November 30, 2022
Published online: January 9, 2023

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Abstract

BACKGROUND

Dexmedetomidine is a centrally acting alpha-2A adrenergic agonist that is commonly used as a sedative and anxiolytic in the intensive care unit (ICU), with prolonged use increasing risk of withdrawal symptoms upon sudden discontinuation. As clonidine is an enterally available alpha-2A adrenergic agonist, it may be a suitable agent to taper off dexmedetomidine and reduce withdrawal syndromes. The appropriate dosing and conversion strategies for using enteral clonidine in this context are not known. The objective of this systematic review is to summarize the evidence of enteral clonidine application during dexmedetomidine weaning for prevention of withdrawal symptoms.

AIM

To systematically review the practice, dosing schema, and outcomes of enteral clonidine use during dexmedetomidine weaning in critically ill adults.

METHODS

This was a systematic review of enteral clonidine used during dexmedetomidine weaning in critically ill adults (≥ 18 years). Randomized controlled trials, prospective cohorts, and retrospective cohorts evaluating the use of clonidine to

wean patients from dexmedetomidine in the critically ill were included. The primary outcomes of interest were dosing and titration schema of enteral clonidine and dexmedetomidine and risk factors for dexmedetomidine withdrawal. Other secondary outcomes included prevalence of adverse events associated with enteral clonidine use, re-initiation of dexmedetomidine, duration of mechanical ventilation, and ICU length of stay.

RESULTS

A total of 3427 studies were screened for inclusion with three meeting inclusion criteria with a total of 88 patients. All three studies were observational, two being prospective and one retrospective. In all included studies, the choice to start enteral clonidine to wean off dexmedetomidine was made at the discretion of the physician. Weaning time ranged from 13 to 167 h on average. Enteral clonidine was started in the prospective studies in a similar protocolized method, with 0.3 mg every 6 h. After starting clonidine, patients remained on dexmedetomidine for a median of 1-28 h. Following the termination of dexmedetomidine, two trials tapered enteral clonidine by increasing the interval every 24 h from 6 h to 8h, 12h, and 24 h, followed by clonidine discontinuation. For indicators of enteral clonidine withdrawal, the previously tolerable dosage was reinstated for several days before resuming the taper on the same protocol. The adverse events associated with enteral clonidine use were higher than patients on dexmedetomidine taper alone with increased agitation. The re-initiation of dexmedetomidine was not documented in any study. Only 17 (37%) patients were mechanically ventilated with median duration of 3.5 d for 13 patients in one of the 2 studies. ICU lengths of stay were similar.

CONCLUSION

Enteral clonidine is a strategy to wean critically ill patients from dexmedetomidine. There is an association of increased withdrawal symptoms and agitation with the use of a clonidine taper.

Key Words: Clonidine; Dexmedetomidine; Intensive care unit; Withdrawal; Weaning

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Core Tip: In this systematic review of enteral clonidine use during dexmedetomidine weaning in critically ill patients, an association of increased withdrawal symptoms and agitation with the use of a clonidine taper and no difference in intensive care unit length of stay with or without clonidine taper was observed. However, varied techniques and a small total sample size restrict utility of the findings.

Citation: Rajendraprasad S, Wheeler M, Wieruszewski E, Gottwald J, Wallace LA, Gerberi D, Wieruszewski PM, Smischney NJ. Clonidine use during dexmedetomidine weaning: A systematic review. *World J Crit Care Med* 2023; 12(1): 18-28

URL: https://www.wjgnet.com/2220-3141/full/v12/i1/18.htm

DOI: https://dx.doi.org/10.5492/wjccm.v12.i1.18

INTRODUCTION

In critically ill patients, agitation and delirium lead to poor clinical outcomes, such as prolonged mechanical ventilation, intensive care unit (ICU), and hospital length of stay (LOS)[1,2]. To optimize outcomes related to sedation in ICU patients, the 2018 Society of Critical Care Medicine practice recommendations suggest avoiding benzodiazepines[3]. Dexmedetomidine and propofol are the most commonly used sedatives in this group[3]. They have resulted in a shorter duration of mechanical ventilation as compared to benzodiazepines[3-6].

Dexmedetomidine, an intravenous (IV) alpha-2A adrenergic agonist provides cooperative sedation, sympatholysis, and analgesic-sparing effects without inducing respiratory depression and is frequently used in critically ill patients to treat pain, agitation, and delirium[7,8]. Due to a lack of central depression, dexmedetomidine is an attractive sedative clinically for weaning from mechanical ventilation and awake sedation in non-intubated patients. Dexmedetomidine was licensed by the Food and Drug Administration as a sedative with a 24-h time limit; however, studies have shown that it is safe and effective for up to 5 d with bradycardia and hypotension being the most commonly reported adverse effects[4,9-11]. Other drawbacks have included the cost of drug acquisition and availability only in an IV formulation[12-14]. Sudden cessation of the drug can lead to withdrawal symptoms such as agitation, tachycardia, hypertension, and other hypersympathetic conditions[15]. Clonidine, a

structurally comparable alpha-2A that is widely used as an antihypertensive, sedative, and sympatholytic, could be an alternate enteral medication for patients transitioning from dexmedetomidine[16].

The use of enteral clonidine may be a potential strategy for weaning from dexmedetomidine to prevent withdrawal syndromes[17,18]. However, dexmedetomidine has an eight-fold higher affinity for central alpha-2A receptors than clonidine; as a result, the best dosing and conversion strategies for clonidine in this context are unknown[8]. The purpose of this systematic review was to summarize the available evidence regarding the use of enteral clonidine to prevent withdrawal symptoms during dexmedetomidine weaning.

MATERIALS AND METHODS

This was a systematic review designed to assess the use of enteral clonidine to prevent withdrawal syndromes in critically ill adults weaning from dexmedetomidine. The study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 guidelines[19]. The protocol was *a priori* registered in the PROSPERO database (No. CRD42022330666).

Data sources and eligibility criteria

The systematic search was designed and executed by a skilled medical librarian (DJG). We searched for the concepts of enteral clonidine and dexmedetomidine combined with variant keywords and standardized index terms. The search was performed in April 2022 and included the electronic databases Ovid Evidence-Based Medicine Reviews, Ovid Embase, Ovid Medline, Scopus, and Web of Science Core Collection. The search was limited to the English language and did not include animals or pediatrics. The full search strategy is detailed in the Supplementary Table 1.

Eligible studies to be included were those that reported randomized-, crossover-, or parallel-designed clinical trials, prospective and retrospective longitudinal (cohort) studies, and cross-sectional studies (non-longitudinal studies) that reported on the use of enteral clonidine specifically for the purposes of weaning from dexmedetomidine to avoid withdrawal syndromes. Studies were excluded if they reported on pediatric patients (age < 18 years), animal or other non-clinical experiments, case reports, case series, review articles, editorial, and book chapters. Studies using intravenous clonidine or oral alpha-2A agonists other than clonidine were also excluded. No restrictions were placed on date of publication. In addition, a relevant search was performed by Reference Citation Analysis database (https://www.referencecitationanalysis.com/) to supplement and improve the highlights of the latest cutting-edge research results.

Article selection and data extraction

Article titles and abstracts were screened by two independent reviewers (SSR, MEW) for inclusion based on the pre-defined inclusion and exclusion criteria. Discrepancies between reviewers were adjudicated by a third independent reviewer (EDW) with consultation of a senior investigator (PMW) if necessary. The full text files of the candidate articles were randomly assigned to the two independent reviewers (SSR, MEW) to screen for final inclusion. Discrepancies between reviewers were adjudicated by a third independent reviewer (EDW) with consultation of a senior investigator (PMW) if necessary. All article screening was performed using Covidence software (Melbourne, Australia).

The data from the final articles meeting inclusion criteria were abstracted from full-text documents by two independent abstractors (JAG, LAW). Disagreements were adjudicated by discussion between the abstractors, and consultation of an adjudicator (EDW) when agreement was unattainable with consultation of a senior investigator (PMW) if necessary. The data abstracted included details regarding the publication information, study design, demographic data, details regarding the dosing schema and protocols, and outcomes information.

Risk of bias assessment

The Risk of Bias in Non-randomized Studies of Interventions tool was used to assess for risk of bias[20]. The tool was applied by two independent assessors (JAG, LAW) and disagreements were adjudicated by the senior investigators (PMW, NJS). The risk of bias information was summarized using R version 4.2.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2022) and the robvis version 0.3.0 package[21].

Outcomes and data analysis

The primary outcomes of interest were the dosing and titration schema of enteral clonidine and dexmedetomidine. Secondary outcomes included risk factors for dexmedetomidine withdrawal, incidence of adverse events associated with enteral clonidine use, re-initiation of dexmedetomidine, duration of mechanical ventilation, and ICU LOS. The data were summarized in descriptive format. No inferential analysis was performed.

RESULTS

Trial inclusion

The initial search identified 3427 studies. Following removal of duplicates and excluded records, 29 full-text articles were assessed for eligibility. Three (10.3%) of these met the inclusion criteria and were included in the analysis[22-24]. The results of the systematic search are summarized in Figure 1.

Trial and patient characteristics

Two of the included studies were prospective with one double cohort observational study and the other an observational pilot study[22,23]. The third was a retrospective observational study[24]. A total of 88 participants were included across the 3 studies. All studies were performed in the United States, and publication dates spanned from 2015 to 2020. Characteristics of all the studies included are detailed in Table 1. Males outnumbered females in all studies, with the most common initial diagnosis on admission being respiratory or heart disease, followed by sepsis, gastrointestinal disorders, trauma, neurological issues, and substance abuse. Indications of dexmedetomidine and enteral clonidine taper use were agitation, delirium, substance abuse, post procedural and intolerance of other sedatives.

Dosing and titration schema

The decision to initiate enteral clonidine to wean dexmedetomidine was per clinician discretion in all included studies (Table 2). Bhatt *et al*[22] required at least 72 h of dexmedetomidine prior to enteral clonidine initiation for study inclusion with a median of 167 h [interquartile range (IQR) 115-217.1]; over the entire dexmedetomidine course patients received a mean dose of 0.9 mcg/kg/h and standard deviation of 0.3. Patients in the Gagnon *et al*[23] study had shorter median dexmedetomidine duration prior to enteral clonidine initiation of 33 h (IQR 21-47.5) at a median rate of 1 mcg/kg/h (IQR 0.7-1.2). Dexmedetomidine duration prior to enteral clonidine was shortest in the Terry *et al*[24] study with a median of 24 h (IQR 14.5-39) for patients who had dexmedetomidine discontinued within 8 h of clonidine initiation with a median dose at time of clonidine initiation of 0 mcg/kg/h (IQR 0-0.25). The group requiring more than 8 h of enteral clonidine to wean dexmedetomidine received a median of 13 h (IQR 4-32) of dexmedetomidine at a rate of 0.7 mcg/kg/h (IQR 0.45-0.7). Enteral clonidine was initiated in a similar protocolized fashion by Gagnon *et al*[23] and Bhatt *et al*[22], starting with 0.3 mg every 6 h. Patients with a dexmedetomidine rate < 0.7 mcg/kg/h, weight < 100 kg, or age > 65 years were initiated on 0.2 mg at the same interval. The doses were reduced by 0.1 mg for bradycardia and hypotension and increased by 0.1 mg for agitation. Dexmedetomidine dose was weaned by 25% every 6 h if no agitation requiring rescue medications had occurred. Terry *et al*[24] initiated enteral clonidine at 0.1 mg with non-protocolized uptitration every 6-8 h until the Richmond Agitation-Sedation Scale (RASS) goal was met, or hemodynamics prohibited further uptitration. Dexmedetomidine was weaned as soon as patients responded to clonidine as assessed by RASS, Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), and hemodynamics without a defined protocol.

Patients spent a median of 19 h (IQR 9.5-23) on dexmedetomidine after enteral clonidine initiation in the Bhatt *et al*[22] study. Dexmedetomidine was utilized for a median of 23 h (IQR 2-53) for patients in the Gagnon *et al*[23] study after enteral clonidine was started. Terry *et al*[24] separately evaluated patients able to wean off dexmedetomidine within 8 h of enteral clonidine initiation from those requiring more than 8 h. Of 26 patients included, 17 (65%) were weaned off dexmedetomidine within 8 h with a median transition time of 1 h (IQR 0.5-4.25). Patients requiring more than 8 h to wean off dexmedetomidine after clonidine initiation had a median transition time of 28 h (IQR 20-56.5).

After dexmedetomidine discontinuation, Bhatt *et al*[22] tapered enteral clonidine by increasing the interval every 24 h from 6 h to 8h, then 12h, then 24 h, followed by clonidine discontinuation without any individual dose reduction. Gagnon *et al*[23] also increased the dosing interval in the same manner every 24-48 h without dose reduction. For signs of clonidine withdrawal, the previously tolerated dose was reinitiated for several days and then an attempted taper resumed on the same protocol. Terry *et al*[24] did not describe any subsequent enteral clonidine taper.

Outcomes

Dexmedetomidine re-initiation: No patients had dexmedetomidine restarted for documented enteral clonidine failure, albeit transition failure was identified as inability to wean dexmedetomidine after 8 h (Table 3)[24]. Failed transition had a median transition time of 28 h (IQR = 20-56.5). Patients who failed transition had alcohol withdrawal, septic shock, endocarditis, lung transplant and aortic valve replacement[24]. None of the patients were restarted on dexmedetomidine in the observation pilot trial [23]. Bhatt *et al*[22] showed 93% of patients were able to stop dexmedetomidine within 24 h of enteral clonidine initiation. No explicit details on re-initiation were provided.

Duration of mechanical ventilation: Seventeen (37%) patients were mechanically ventilated of the 2 studies that reported this data[23,24]. Gagnon *et al*[23] reported duration of mechanical ventilation of 3.5 d (IQR 0-10.5) and mechanical ventilation free days of 24.5 (IQR 15.3, 28)[23]. One study, despite having the bulk of its patients admitted with respiratory diagnosis to the ICU, did not provide data regarding

Table 1 Trial characteristics

Ref.	Type of study	Study dates	Total patients studied	ICU	Admitting diagnosis	Mechanical ventilation	Age (yr)	Sex	Weight (kg)	BMI (kg/m²)	APACHE score
Terry *et al* [24], 2015	Single-center, retrospective, observational study	February 1, 2013-February 28, 2014	26	Cardiac surgery 21 (80.7%), thoracic 3 (11.5%), neurology 1 (3.8%), surgical 1 (3.8%)	Respiratory 4 (15.4%), cardiac 20 (76.9%), trauma 1 (3.8%), substance abuse 1 (3.8%)	4 (14.8%)	54.4 ± 16.9[1]	Male: 17 (63%), female: 9 (37%)	NR	32 ± 3.1[1]	18 (14-22)[2]
Gagnon *et al*[23], 2015	Single-center prospective observational pilot study	January, 2014-March, 2014	20	Mixed medical, surgical, neuro ICU	Respiratory 12 (60%), neurologic 1 (5%), trauma 2 (10%), substance abuse 2 (10%), other 3 (15%)	13 (65%)	62 (54-73)[2]	Male: 13 (65%), female: 7 (35%)	NR	29.9 (26.5-33.1)[2]	62 (54-80)[2]
Bhatt *et al* [22], 2020	Single-center, prospective, double cohort observational study	November, 2017-December, 2018	42	Medical-surgical 10 (67%) *vs* 13 (48%), cardiothoracic 3 (20%) *vs* 8 (30%), neurosurgical 2 (13%) *vs* 6 (22%)	Respiratory 16 (38.1%), cardiac 12 (28.6%), gastroenterological 5 (11.9%), neurologic 2 (4.8%), trauma 1 (2.4%), sepsis/shock 6 (14.3%)	NR	Clonidine taper: 58 (43-66[2] *vs* no taper: 54 (45-66)[2] (P = 0.93)	Male: 27 (64%), female: 15 (36%)	Clonidine taper: 86.9 (67.3-94.1)[2] *vs* no taper 91.6 (78.9-101.1)[2] (P = 0.19)	NR	NR

[1]Data reported as mean ± SD.

[2]Data reported as median (interquartile range).

NR: Not reported; ICU: Intensive care unit; BMI: Body mass index, APACHE: Acute physiology and chronic health evaluation.

the need for supplemental oxygenation or ventilation[22].

ICU LOS: All three studies reported ICU LOS; two of the studies appear to have similar ICU LOS in patients that had weaning protocol with no comparison[23,24]. Only one study specifically evaluated and found no statistically significant difference in ICU LOS between enteral clonidine taper *vs* no taper (22.7 d *vs* 17 d; P = 0.3) and time to discharge after dexmedetomidine wean in either group (7.2 d *vs* 7 d; P = 0.69)[22].

Adverse events: Terry *et al*[24] did not specify symptoms associated with enteral clonidine withdrawal. Gagnon *et al*[23] discovered that only one patient met withdrawal criteria (blood pressure > 180/120 mmHg) after stopping enteral clonidine despite a 6-d taper; this patient was also tapering off methadone and clonazepam. Bhatt *et al*[22] provided significant withdrawal data as defined by ³2 of: heart rate > 90, CAM positive, RASS > 1, systolic blood pressure > 140, or Withdrawal Assessment Tool Version 1 (WAT-1) > 2. Patients who experienced at least two withdrawal symptoms from dexmedetomidine during a single assessment during the wean period were not significantly different between the two groups (73% for patients who were given an enteral clonidine taper and 59% for patients who were weaned off dexmedetomidine alone; P = 0.27). The most common symptoms reported by both groups on the WAT-1 were loose stools, fever, and agitation. Those on enteral clonidine taper had more withdrawal symptoms, notably agitation (RASS > 1), than patients on

Table 2 Dosing schemes reported in study methods

Ref.	Formal protocol	Dexmedetomidine indication	Threshold for clonidine use	Initial clonidine dose	Dexmedetomidine wean	Clonidine taper
Terry *et al*[24], 2015	No	Primarily for sedation after cardiac surgery	No standard	No standard. 0.1 mg three times daily commonly used	No standard	No standard
Gagnon *et al*[23], 2015	Yes	Agitation: 12 (60%); Alcohol withdrawal: 3 (15%); Delirium: 2 (10%); Intolerance to other sedatives: 3 (15%)	Hemodynamically stable patients; Favorable response to DEX for 12-24 h	0.2-0.5 mg every 6 h; Start at 0.2 mg with DEX doses of < 0.7 μg/kg/h, weight < 100 kg or age > 65 yr; Start with 0.5 mg every 6 h for all other patients	Decrease DEX dose by 25% of baseline within 6 h of clonidine administration (as long as no rescue meds were needed for agitation)	Extend the dosing interval to every 8, 12 and 24 h every 1-2 d as tolerated until discontinuation
Bhatt *et al*[22], 2020	Yes	No clear selection criteria; patients with substance withdrawal were excluded	Variable; Clonidine taper and DEX wean started together	0.3 or 0.2 mg every 6 h; Start at 0.2 mg with DEX < 0.7 μg/kg/h, weight < 100 kg, age > 65 yr old; Start with 0.3 mg every 6 h for all other patients	Decrease DEX dose by 25% of baseline from 0 h to 6 h, and continue dose reduction by 25% every 6 h while on clonidine	Extend the dosing interval to every 8, 12 and 24 h every 1-2 d as tolerated until discontinuation

DEX: Dexmedetomidine.

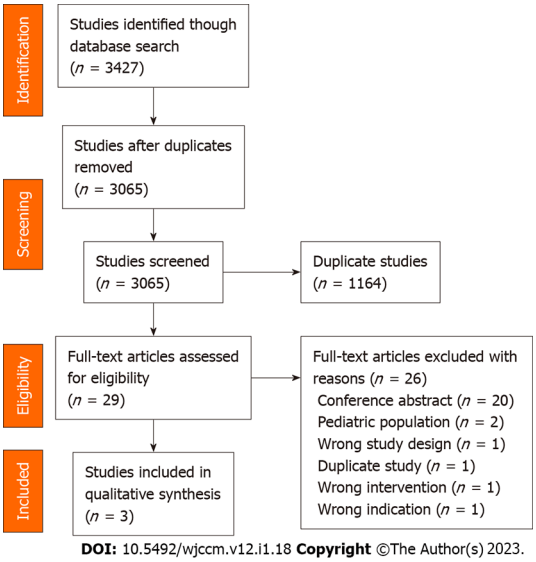


Figure 1 Study flow diagram.

dexmedetomidine taper (40% *vs* 11%; $P = 0.05$). During the weaning period, there was no difference in the use of propofol, antipsychotics, benzodiazepines, or ketamine between groups. Patients on enteral clonidine taper had a higher average daily dexmedetomidine rate (mcg/kg/h) than patients on a dexmedetomidine alone taper, although the total infusion dose in g/h was not significantly different between groups[22].

Socioeconomic factors: Gagnon *et al*[23] reported an estimated $15360-$52140 cost reduction with enteral clonidine usage based on drug acquisition cost alone assuming a minimum of 24 h of enteral clonidine in place of dexmedetomidine per patient and a maximum of substituting the entire enteral clonidine course with continuous dexmedetomidine[23]. Bhatt *et al*[22] reported an average cost savings of $1553 per patient, also based solely on drug acquisition costs. Gagnon *et al*[23] reported 25% (5/20) of the patients were discharged on enteral clonidine with 20% (4/20) receiving instructions to taper off the medication. Terry *et al*[24] discovered 54% (14/26) of patients were continued on enteral clonidine at ICU transfer with 23% (6/26) of patients being discharged home on clonidine unintentionally.

Risk of bias: In the risk of bias assessment, two studies[22,23] were deemed to be moderate risk and one study[24] was deemed to be serious risk (Figure 2). The primary reasons for a serious risk of bias were

Table 3 Outcomes data

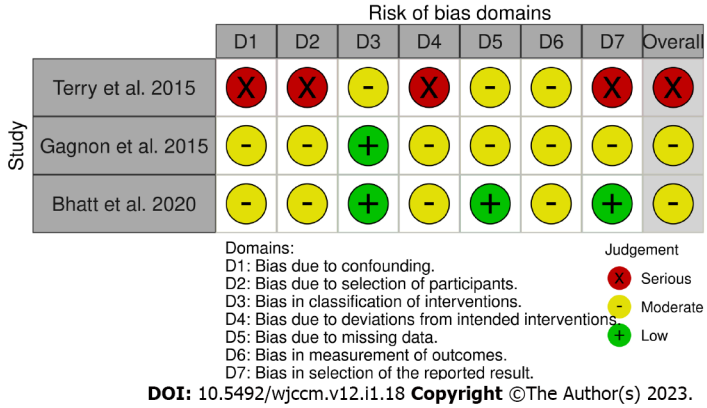
Outcomes data	Terry *et al*[24], 2015	Gagnon *et al*[23], 2015	Bhatt *et al*[22], 2020
Breakthrough withdrawal	NR	1[1]	Taper 11 (73%); No taper 16 (59%)[2]
Discharged on clonidine	Out of ICU: 14 (54%); Out of hospital: 6 (23%)	5 (25%)	NR
Use of other agents			
Propofol	NR	No individual data	Taper: 5 (33%); No taper: 8 (30%)
Ketamine	NR	NR	Taper: 1 (6.7%); No taper: 6 (22.2%)
Benzodiazepines	Clonidine: 2 (22%); No clonidine: 5 (29%)	No individual data	Taper: 3 (20%); No taper: 3 (11%)
Antipsychotics	Clonidine: 4 (44%); No clonidine: 3 (18%)	DEX maintenance dose	Taper: 9 (60%); No taper: 10 (37%) (P = 0.2)
Opioids	Clonidine: 7 (78%); No clonidine: 13 (76%)	No individual data	No individual data
Hemodynamic changes			
Tachycardia	NR	NR	Taper: 12 (80%); No taper: 20 (74%)
Hypertension	NR	DEX maintenance dose: 0; Transition: 0; Clonidine maintenance: 0; Clonidine taper final day: 0; Post clonidine: 1 (6%)	Taper: 6 (40%); No taper: 8 (30%)
Bradycardia	NR	DEX maintenance dose: 0; Transition: 0; Clonidine maintenance: 1 (5%); Clonidine taper final day: 1 (6%); Post clonidine: 0	0
Hypotension	Clonidine: 4 (44%); No clonidine: 6 (35%)	DEX maintenance dose: 8 (40%); Transition: 7 (35%); Clonidine maintenance: 4 (20%); Clonidine taper final day: 2 (12%); Post clonidine: 2 (25%)	0
Sedation assessment score	RASS; Clonidine: 0 (-2 to 2); No clonidine: 0 (0-2)	SAS Score outside the goal of 3-4; DEX maintenance: 10 (50%); Transition: 10 (50%); Clonidine maintenance: 9 (45%); Clonidine taper final day 13 (76%); Post clonidine: 2 (25%)	NR
CAM ICU	Clonidine: 4 (44%); No clonidine: 3 (18%), P = 0.036	DEX maintenance: 10 (50%); Transition: 11 (55%); Clonidine maintenance: 9 (45%); Clonidine taper final day: 13 (76%); Post clonidine: 3 (38%)	Taper: 11 (73%); No taper: 17 (63%)
Duration of mechanical ventilation (d), median (IQR)	NR	3.5 (0, 10.5)	NR
Hospital length of stay (d), median (IQR)	8 (4, 10.5)	16.5 (10.5, 29.5)	NR
ICU length of stay (d), median (IQR)	12.5 (7, 28)	9.5 (5, 16.5)	Taper: 22.7; No taper: 17
Mortality	0	2 (10%)	NR

[1]Systolic blood pressure (SPB) > 180/120 after stopping despite 6-d taper, but was also tapering off methadone and clonazepam so causality if not clear.
[2]Significant withdrawal as defined by paper (≥ 2 heart rate > 90, Confusion Assessment Method positive, Richmond Agitation-Sedation Scale > 1, SBP > 140, Withdrawal Assessment Tool Version 1 > 2).
DEX: Dexmedetomidine; NR: Not reported; SAS: Sedation-Agitation scale.

confounding, participant selection, and deviations from the intended interventions given the observational nature of the design[24]. Additionally, confounding, participant selection, and outcomes measurements were common reasons for a moderate risk of bias in the other studies[22,23].

DISCUSSION

This systematic review of the literature summarized the use of enteral clonidine for weaning of parental dexmedetomidine in the critically ill, dosing and titration schema of enteral clonidine and



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Figure 2 Risk of bias assessment.

dexmedetomidine, prevalence of adverse events associated with clonidine use, re-initiation of dexmedetomidine, duration of mechanical ventilation and ICU LOS. Meta-analysis was not feasible due to differences in methodology, patients, and procedures that led to variation in the reported results between studies.

Weaning off dexmedetomidine with enteral clonidine has gained much attention for the potential benefits of reduced ICU LOS and costs. Clonidine has shown promise in minimizing the withdrawal symptoms associated with cessation of prolonged dexmedetomidine[25]. Clonidine, like dexmedetomidine, is a centrally acting alpha 2 agonist and has a longer half-life (8-12 h *vs* 2 h); however, dexmedetomidine has an eight-fold higher affinity for central alpha receptors than clonidine[8]. Clonidine is thought to reduce central nervous system hyperactivity after dexmedetomidine withdrawal due to its alpha 2 agonist actions and decreased affinity for the alpha 2 receptors. Our review focusing on enteral clonidine for dexmedetomidine weaning in adults resulted in three studies, two prospective and one retrospective. Importantly, no randomized controlled trials were identified.

The results of this systematic review leave many unanswered questions regarding the optimal utility of enteral clonidine in the setting of dexmedetomidine weaning. It is difficult to draw comparisons among the available data from the three studies due to the heterogeneity of the groups studied. There seems to be a common dosing scheme for enteral clonidine in the setting of weaning from dexmedetomidine based on Gagnon *et al*[23] and their institutional experience with the medication. However, the process of determining who received enteral clonidine in the reviewed studies was largely left to clinician discretion, limiting the ability to draw conclusions about the impact of clonidine. For example, although Bhatt *et al*[22] demonstrated a higher incidence of agitation and rescue antipsychotic dosing in the patient group receiving enteral clonidine, potential confounders include unknown patient factors that led to higher dexmedetomidine dosing and the clinician's need to provide clonidine as a treatment rather than to evaluate its comparative effect vs. dexmedetomidine taper alone.

Dexmedetomidine is typically restricted to use in areas with critical care personnel and monitoring available such as the ICU and the perioperative care area. While it is valuable to have a study design with an inclusive patient population, the inclusion of both medical and postoperative patients in the studies reviewed pose challenges to the generalizability of the findings. For example, the sedation needs for a cardiac surgery patient in a rapid recovery protocol and the rapidity of sedation and mechanical ventilation liberation is often quite different than the medical patient requiring both treatment and stability after an acute cardiorespiratory insult requiring escalation to critical care needs. Terry *et al*[24] was highly skewed toward a post cardiac surgery population, whereas Gagnon *et al*[23] and Bhatt *et al*[22] included more mixed medical-surgical patients. The numerically lower total duration of dexmedetomidine in Terry *et al*[24] may have allowed for a lower general dose of enteral clonidine (*i.e.* 0.1 mg per dose) compared to the standard 0.2-0.3 mg clonidine doses used in the other two studies. However, given the lack of detail regarding exact dosing plan and the liberty clinicians were allotted regarding dosing selection, it is difficult to draw specific conclusions beyond the generalities offered in the study methods.

Adverse events from dexmedetomidine withdrawal included anxiety, agitation, decreased sleep, loose stools, emesis, tremors, and increased secretions[26]. Similarly, well-described phenomenon attributed to cessation of adrenal catecholamine secretion blockade and a subsequent surge in their circulating levels is associated with clonidine withdrawal resulting in rise in blood pressure, agitation, insomnia, and palpitations[27]. Risk factors for withdrawal are not known and were not identified in the studies reviewed. Further understanding of the risk factors for withdrawal and targeting appropriate patients for weaning could help minimize harm and improve quality of care. Patients on the enteral clonidine taper appeared to have more withdrawal symptoms than patients on dexmedetomidine taper. Re-initiation of dexmedetomidine was not explicitly addressed in any of the studies for withdrawal and should be an area of further investigation.

Although cost-effectiveness data is limited, the anticipated cost savings from drug acquisition ranged from $819 to $2338 per patient in two of the studies that reported data[22,23]. This price solely includes the drug acquisition cost and excludes the additional costs associated with dexmedetomidine, such as a dedicated ICU service line, monitoring, and titration. As a result, the shorter time on dexmedetomidine infusion following clonidine commencement may be greatly understated by these values.

Notably, in the two studies that reported information on enteral clonidine continuation at discharge from the hospital, approximately 25% of patients were still taking the medication[23,24]. Terry *et al*[24] also reported over half of patients were still taking enteral clonidine upon transfer from the intensive care unit. Several medications started in the ICU to expedite discharge, including antipsychotics and midodrine, are frequently prolonged without proper indication during transfer and upon discharge[28,29]. An order set and medication reconciliation during transitions of care may be helpful techniques for preventing the unintentional continuation of clonidine.

Strengths of this systematic review include the identification of a feasible enteral clonidine dosing strategy protocolized by Gagnon *et al*[23] that has been applied to other institutions as evidenced by Bhatt *et al*[22] and the elucidation of areas that could be optimized when utilizing enteral clonidine for dexmedetomidine weaning such as appropriate discontinuation prior to hospital discharge and the potential association of increased hypersympathetic withdrawal symptoms with its use. This systematic review has several limitations. All three studies have insufficient sample sizes, preventing the detection of withdrawal symptoms. Only one study had a matched control group, despite selection bias based on withdrawal risk assessment, which was not reported in any of the studies. Indications for weaning protocol varied according to the patient group and ICU site. There was heterogeneity of the research and data regarding the start date of clonidine weaning. The broad use of clinician discretion in the determination of enteral clonidine use and dosing limits the ability to systematically evaluate the available literature. Lastly, due to the heterogeneity in the reporting of the outcomes, quantitative meta-analysis was not possible.

CONCLUSION

Enteral clonidine has been utilized as a strategy to wean patients from parenteral dexmedetomidine due to similar mechanisms of action and potential for reduced costs and shorter ICU requirements. However, guidance on an appropriate taper strategy and resultant outcomes is limited. This systematic review investigated the literature related to weaning dexmedetomidine with and without an enteral clonidine taper. While there are some patterns in dosing schedules among the studies included, there is no consensus regarding an ideal taper strategy and the decision to utilize an enteral clonidine taper is left to clinical judgment. There may be an association of increased withdrawal symptoms and agitation with the use of an enteral clonidine taper, however we did not observe any appreciable difference in ICU LOS with or without a clonidine taper. Further research into risk factors for withdrawal, dose, and duration of dexmedetomidine use followed with appropriate clonidine dose and taper is needed.

ARTICLE HIGHLIGHTS

Research background

Clonidine, an enterally available alpha-2A adrenergic agonist, may be a suitable agent to taper off parenteral dexmedetomidine (centrally acting alpha-2A adrenergic agonist) and reduce withdrawal syndromes. This could lead to reduced intensive care unit (ICU) length of stay (LOS), among other outcomes. However, limited data exist on this topic.

Research motivation

To determine if oral clonidine is useful to wean off parenteral dexmedetomine and reduce ICU LOS.

Research objectives

To systematically review the practice, dosing schema, and outcomes of enteral clonidine use during dexmedetomidine weaning in critically ill adults.

Research methods

This was a systematic review of randomized controlled trials, prospective and retrospective cohorts, on the use of enteral clonidine during dexmedetomidine weaning in critically ill adults (≥ 18 years). The primary outcomes of interest were dosing and titration schema of enteral clonidine and dexmedetomidine and risk factors for dexmedetomidine withdrawal.

Research results

Three observational studies were included (two prospective and one retrospective). Weaning time ranged from 13 to 167 h on average. The adverse events associated with enteral clonidine use were higher than patients on dexmedetomidine taper alone with increased agitation. The re-initiation of dexmedetomidine was not documented in any study. Only 17 (37%) patients were mechanically ventilated with median duration of 3.5 d for 13 patients in one of the 2 studies. ICU lengths of stay were similar.

Research conclusions

Enteral clonidine is a strategy to wean critically ill patients from parenteral dexmedetomidine. However, there is an association of increased withdrawal symptoms and agitation with the use of a clonidine taper.

Research perspectives

It is unclear if oral clonidine is useful in weaning from dexmedetomidine. More data are needed in terms of both dosing schedule and outcomes.

FOOTNOTES

Author contributions: Rajendraprasad S, Wieruszewski P, and Smischney N designed the research; Rajendraprasad S, Wheeler M, and Wieruszewski E performed the research; Gottwald J and Wallace L analyzed the data; Rajendraprasad S, Wheeler M, Gottwald J, Wallace L, Wieruszewski P, and Smischney N drafted the paper; All authors reviewed and edited the manuscript and approved the final version.

Conflict-of-interest statement: All authors declare no conflicts of interest.

PRISMA 2009 Checklist statement: The study followed the PRISMA guidelines. The protocol was *a priori* registered in the PROSPERO database (No. CRD42022330666).

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S-Editor: Zhang H
L-Editor: A
P-Editor: Zhang H

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World Journal of Critical Care Medicine

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World J Crit Care Med 2023 January 9; 12(1): 29-34

DOI: 10.5492/wjccm.v12.i1.29

ISSN 2220-3141 (online)

CASE REPORT

Severe hypernatremia in hyperglycemic conditions; managing it effectively: A case report

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Specialty type: Critical care medicine

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Papadopoulos VP, Greece; Yahaya TO, Nigeria

Received: September 18, 2022
Peer-review started: September 18, 2022
First decision: September 27, 2022
Revised: October 7, 2022
Accepted: November 29, 2022
Article in press: November 29, 2022
Published online: January 9, 2023

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Abstract

BACKGROUND

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are common acute complications of diabetes mellitus with a high risk of mortality. When combined with hypernatremia, the complications can be even worse. Hypernatremia is a rarely associated with DKA and HHS as both are usually accompanied by normal sodium or hyponatremia. As a result, a structured and systematic treatment approach is critical. We discuss the therapeutic approach and implications of this uncommon presentation.

CASE SUMMARY

A 62-year-old man with no known past medical history presented to emergency department with altered mental status. Initial work up in emergency room showed severe hyperglycemia with a glucose level of 1093 mg/dL and severe hypernatremia with a serum sodium level of 169 mEq/L. He was admitted to the intensive care unit (ICU) and was started on insulin drip as *per* DKA protocol. Within 12 h of ICU admission, blood sugar was 300 mg/dL. But his mental status didn't show much improvement. He was dehydrated and had a corrected serum sodium level of > 190 mEq/L. As a result, dextrose 5% in water and ringer's lactate were started. He was also given free water *via* an nasogastric (NG) tube and IV Desmopressin to improve his free water deficit, which improved his serum sodium to 140 mEq/L.

CONCLUSION

The combination of DKA, HHS and hypernatremia is rare and extremely challenging to manage, but the most challenging part of this condition is selecting the

correct type of fluids to treat these conditions. Our case illustrates that desmopressin and free water administration *via* the NG route can be helpful in this situation.

Key Words: Diabetic ketoacidosis; Hyperglycemic hyperosmolar state; Hypernatremia; Hyperglycemia; Desmopressin; Case repot

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Core Tip: Hyperglycemia is usually associated with hyperkalemia, but it is rare to see hypernatremia with hyperglycemia as hyperglycemia is usually seen with pseudohyponatremia. Correcting hypernatremia with hyperglycemia is challenging because of the complex fluid requirements in this situation. We are describing a case here with severe hyperglycemia and severe hypernatremia. In our case, we have used free water flushes *via* nasogastric access and desmopressin to correct the free water deficit, which hasn't been described previously in the literature. This makes our case unique.

Citation: Lathiya MK, Errabelli P, Cullinan SM, Amadi EJ. Severe hypernatremia in hyperglycemic conditions; managing it effectively: A case report. *World J Crit Care Med* 2023; 12(1): 29-34
URL: https://www.wjgnet.com/2220-3141/full/v12/i1/29.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i1.29

INTRODUCTION

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are common acute complications of diabetes mellitus (DM) with a high risk of mortality. DKA is more common in patients with type 1 diabetes (T1DM), whereas HHS is more common in patients with type 2 diabetes. However, symptoms of DKA and HHS can sometimes overlap and result in a combined laboratory presentation of both conditions[1]. When it comes to managing this overlap presentation, glucose levels, electrolyte levels, and the patient's hemodynamics are all closely monitored because DKA and HHS can cause serious complications like brain edema, rhabdomyolysis, thrombosis[1]. When combined with hypernatremia, the complications can be even worse[2]. Hypernatremia is a rare condition associated with DKA and HHS as both can be accompanied by normal sodium or hyponatremia. As a result, a structured and systematic treatment approach is critical.

CASE PRESENTATION

Chief complaints

We present a case of successfully treated severe hypernatremia in an adult with DKA-HHS.

History of present illness

A 62-year-old male, who has not seen a physician for more than a decade presented to a local Emergency Department (ED) as a tele-stroke activation following a fall at home. A few days prior to the event he started having excessive thirst, dry mouth, and urinary frequency. He consumed large volumes of water, and when that did not quench his thirst, he started drinking V8 vegetable juice and Kool-Aid powdered drink mix. He was consuming approximately 16 to 18 cans of V8 (11.5 ounces each) and several Kool-Aid packets daily. Each 11.5-ounce V8 can contains 960 mg of sodium and each Kool-Aid packet contains 25 mg of sodium. His symptoms worsened, becoming increasingly fatigued, with multiple falls. Though, He did not suffer significant injury from the fall, however due to slurring of speech and altered mental status he was brought to the ED for evaluation.

History of past illness

He has no known prior medical history.

Personal and family history

Not a known alcoholic or a smoker. No history of illicit substance use. No family history of any chronic medical conditions.

Physical examination

He was evaluated in the ED and workup was negative for neurologic findings.

Laboratory examinations

His initial workup revealed sodium 169 mEq/L (Corrected sodium for hyperglycemia is 193 mEq/L), chloride 124 mEq/L, blood glucose 1093 mg/dL, bicarbonate 16 mEq/L, anion gap of 29, serum creatinine 2.27 mg/dL (baseline creatinine was 0.7), and potassium 4.6 mEq/L. Urine osmolality was 751 mOsm/kg, while serum osmolarity was 438 mOsm/kg (Figure 1). In the emergency department, HbA1c was > 18%, Serum lactate was 4.6 and the pH of venous blood gas was 7.33. During hospitalization, his serum bicarbonate, serum lactate, and anion gap were also elevated (Table 1). His arterial blood gas levels were determined during his hospitalization (Table 2). In addition, we have added his fluid balance and diuresis in the period of the first 5 d (Table 3).

FINAL DIAGNOSIS

DKA and Hyperosmolar hyperglycemic syndrome with hyperglycemia-induced hypernatremia were the definitive diagnoses in the case described.

TREATMENT

He was started on an insulin drip *per* DKA protocol and was admitted to the intensive care unit (ICU). On initial evaluation, his calculated serum sodium at this point was > 170 mEq/L and his free water deficit was close to 29 L. After 12 h of admission, the blood sugar was corrected to 300 mg/dL, but serum sodium remained elevated at > 170 mEq/L. Urine output remained suboptimal at 1.09 mL/kg/hr. He was hyperventilating and blood gas showed a PH 7.51, and a PCO_2 of 26. Creatine phosphokinase was 6300 U/L. He became increasingly confused and obtunded. He had multiple temperature spikes. Blood cultures were drawn, and empirical antibiotics were initiated. Given worsening mental status in the setting of acute kidney injury and severe hypernatremia, aggressive fluid resuscitation by increasing 5% dextrose solution (D5W) to 200 mL *per* hour and Ringer's lactate to 250 cc/h was undertaken. With nephrology consultation, dialysis was considered but withheld as it would correct his sodium too rapidly and might have adverse consequences. In addition to aggressive IV fluid resuscitation, a nasogastric tube (NG tube) was placed, and he was started on free water administration at 250 cc every 4 h. He was also started on desmopressin 0.2 g twice daily. Serum sodium was monitored every 4 h (Figure 1B).

Twenty-four hours after above interventions, serum sodium slowly dropped to 167 mEq/L (Figure 1B), creatinine improved to 1.9 mg/dL (from 2.27 mg/dL) and urine output improved. Desmopressin was continued until serum sodium corrected to 140 mEq/L. At this point his mental status had returned to baseline and NG tube free water replacement was discontinued. Patient eventually recovered with normalization of electrolytes and renal function at the time of discharge. He was discharged on insulin for newly diagnosed DM and atorvastatin for newly diagnosed hyperlipidemia with dietary recommendations.

OUTCOME AND FOLLOW-UP

After 24 h, we were able to achieve the desired decline in sodium level, improvement in both serum creatinine and urine output, improvement in urine and serum osmolarity (Figure 1A) and improvement in the mental status of the patient, suggesting that the altered mental status was driven by his severe hypernatremia.

DISCUSSION

Complications associated with undiagnosed and untreated DM can be disastrous, especially over an extended duration. The onset and development of this complex disease in our patient is particularly difficult to track due to a prolonged period of health care avoidance. However, the critical state of the patient upon presenting to the ED highlights the severity of several consequences, namely hypernatremia.

Hypernatremia, an elevated level of serum sodium, can be attributed to multiple processes, including hypertonic fluid gain, hypotonic fluid loss, or general water depletion. No matter the origin, the increased extracellular osmolality drives water outward from cells, resulting in cell shrinking. Although

Table 1 Initial work up at presentation (day 1) in the Emergency Department and subsequent hospitalization

Indicator	Normal value	In the Emergency Department day 1	Hospital day 2	Hospital day 3	Hospital day 4	Hospital day 5
Serum sodium (Na)	135-145 mmol/L	169				
Serum chloride (Cl)	98-107 mmol/L	124				
HCO3-	22-29 mmol/L	16	24	26	24	21
Glucose	70-140 mg/dL	1093				
Serum creatinine (Cr)	0.74-1.35 mg/dL	2.27				
Serum potassium (K)	3.6-5.2 mmol/L	4.6				
Serum lactate	5.2-2.2 mmol/L	4.1	4.6	3.9	1.6	
Serum osmolarity	276-306 mOsm/kg	438				
Urine osmolarity	150-1150 mOsm/kg	751				
HbA1c	5.7%-6.4%	> 18%				
pH venous blood Gas	7.32-7.43	7.33				
Anion gap	7-15	29	24	16	10	12
Fio2/Spo2	96%-99%/95%-100%	None/92%	2 Liter (nasal cannula)/92%-98%	Room Air/94%-100%		

Table 2 Blood gas studies during intensive care unit stay after initial resuscitation

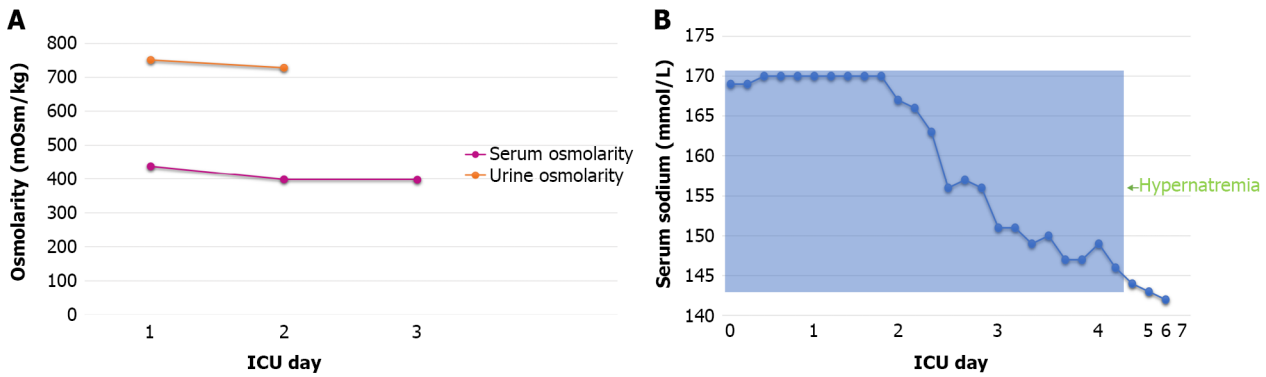
Arterial blood gas	Normal range	Hospital day 1	Hospital day 2
PH	7.35-7.45 pH	7.43; 7.45; 7.48	7.51
PCO_2	35-48 mmHg	30; 28; 25	26
PO_2	28-108 mmHg	78; 73; 72	78

Table 3 His fluid intake and output during hospital period (fluid balance and diuresis during hospital period)

Day (Hospital period)	Fluid intake (mL)	Fluid output (mL)
1	5381	950
2	6200	2935
3	2650	1900
4	1900	1205
5	3987	1925

an ionic osmolytic response serves to counter these dangerous effects, long-term damage is nearly inevitable. Such impairments manifest in various organ systems leading to short-term mortality rates between 50% and 60%[3]. Our patient's initial measured sodium level of > 170 mEq/L that later progressed to > 200 mEq/L indicated a precarious and time-sensitive situation requiring urgent intervention.

The development of hypernatremia in this patient should be considered in both DKA and HHS, in addition to the combination of these conditions. The appearance of hypernatremia in DKA can be attributed to a fluid imbalance. As significant volumes of free fluid are lost (most commonly by polyuria), electrolyte loss (through vomiting and diarrhea) may lag behind, leading to a very unusual occurrence of hypernatremia with osmolytic imbalance[4]. Although such cases of DKA-induced hypernatremia are infrequent, a 2019 paper reviews the cases of two female patients found to be



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Figure 1 Critical care admission. A: Urine and serum osmolarity throughout critical care admission; B: Serum sodium throughout critical care admission. ICU: Intensive care unit.

suffering from hypernatremia secondary to DKA after complaints of altered mental status and other symptoms[5]. Additionally, a 2020 study describes an altered male T1DM patient with a largely unknown medical history suffering from DKA and severe hypernatremia; aggressive treatment of DKA and fluid management yielded a positive outcome. While DKA and HHS diverge in incidence, mechanism, and prognosis, the rare occurrence of hypernatremia in HHS arises for similar reasons: A free water deficit develops through osmotic diuresis. A 2020 case report discusses a female patient with no known history of DM that presented to the ED for confusion amongst many other progressive symptoms. Investigations revealed extremely elevated blood glucose and sodium levels, which led to a diagnosis of HHS[6]. Our case differs from previous literature in that the patient was diagnosed with DKA, HHS, and acute hypernatremia. While a combination of these three constituents is detailed in a 2020 paper referencing two pediatric patients, this combination, to our knowledge, has not been identified in an adult patient[1].

The precise origin of hypernatremia in this patient is complicated by the patient's past medical history. For one, the incompleteness of his record, due to a ten-plus year hiatus from receiving even primary care, abridges available information to a matter of days before admission. Also, the polydipsia described by the patient himself led to the unintentional ingestion of excessive amounts of sodium, primarily through his beverages of choice. Nevertheless, the patient's hyperglycemia, hypernatremia, and free water deficit necessitated careful manipulation as a 2022 case series study describes the cases of DKA-HHS induced severe hypernatremia in three adolescents due to high soft drink consumption where one patient died due to development of severe hypovolemia[7]. As increased consumption of carbohydrate-rich beverages exacerbated glucose induced osmotic diuresis and resulted in worsening severe intravascular dehydration. To restore the water deficit, a large amount of fluid is needed. It is also important to choose right fluid to correct plasma sodium level with the aim of avoiding treatment-related dysnatremia. As an improper management of plasma sodium concentration and plasma osmolality during treatment has been associated with two rare potentially life-threatening complications such as hypovolemic shock, cerebral edema and osmotic demyelination syndrome. Previous literature suggests that the correction of hypernatremia is best achieved through the intravenous administration of a hypotonic solution such as D5W and safest as long as the etiology of hypernatremia is hypertonic sodium gain and treatment can be initiated at ≤ 12 h from the onset of the cause[8]. Since this patient's free water deficit was 29 L, effective fluid resuscitation required D5W, Ringer's lactate, and enteral free water for prompt change. The rate of sodium correction should be based on the type of fluid used. Although the blood glucose level was unusually high (300 mg/dL) to initiate D5W, we planned to perform fluid resuscitation with Ringer's lactate and D5W, which resulted in a slower decrease in serum sodium when compared to other isotonic or hypotonic fluids alone. In addition, we started giving free fluid *via* NG tube. According to de Vos and van der Voort[9], treating patients with ICU-induced hypernatremia with enteral free water did not result in a clinically significant decrease in serum sodium levels[9]. However, we noticed improving sodium as we combined desmopressin to conserve free water by its antidiuretic effects. After 24 h, we were able to achieve the desired decline in sodium level, improvement in both serum creatinine and urine output, improvement in urine and serum osmolarity (Figure 1A), and improvement in the mental status of the patient, suggesting the altered mental status was driven primarily by the hypernatremia.

CONCLUSION

This case report highlights three vital considerations when treating patients with hypernatremia in the DKA-HHS overlap disease state. First, the decision to treat hyperglycemia more aggressively than hypernatremia due to the intrinsic life-threatening risks. Second, at the initial stage, choosing a combination of hypotonic and isotonic fluid that contains sodium close to the lower limit of normal serum sodium allows glucose to decrease first, at the same time maintaining serum sodium at steady-state and not increasing. Third, giving water *via* oral, NG, or orogastric tube in combination with desmopressin to improve free water deficit and to prevent excessive hypotonic and/or isotonic fluid induced complications such as peripheral edema and pulmonary edema. This case report highlights the importance of understanding the management approach required for hypernatremia in DKA-HHS to prevent complications associated with these two conditions.

FOOTNOTES

Author contributions: Lathiya MK and Errabelli P contributed to the conceptualization, writing, original draft preparation, graphics, reviewing; Cullinan SM contributed to original draft preparation, reviewing and editing; Amadi EJ contributed to reviewing and editing.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Wei ZH
L-Editor: A
P-Editor: Wei ZH

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 January 9; 12(1): 35-40

DOI: 10.5492/wjccm.v12.i1.35

ISSN 2220-3141 (online)

CASE REPORT

Vasopressin-induced hyponatremia in an adult normotensive trauma patient: A case report

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Specialty type: Critical care medicine

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Esposito P, Italy; Fayed A, Egypt

Received: September 24, 2022
Peer-review started: September 24, 2022
First decision: October 21, 2022
Revised: November 3, 2022
Accepted: November 23, 2022
Article in press: November 23, 2022
Published online: January 9, 2023

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Abstract

BACKGROUND

Arginine vasopressin is a neuropeptide produced in the hypothalamus and released by the posterior pituitary gland. In addition to maintaining plasma osmolarity, under hypovolemic or hypotensive conditions, it helps maintain plasma volume through renal water reabsorption and increases systemic vascular tone. Its synthetic analogues are widely used in the intensive care unit as a continuous infusion, in addition to hospital floors as an intravenous or intranasal dose. A limited number of cases of hyponatremia in patients with septic or hemorrhagic shock have been reported previously with vasopressin. We report for the first time a normotensive patient who developed vasopressin-induced hyponatremia.

CASE SUMMARY

A 39-year-old man fell off a forklift and sustained an axial load injury to his cranium. He had no history of previous trauma. Examination was normal except for motor and sensory deficits. The Imagine test showed endplate fracture at C7 and acute traumatic disc at C7 with cortical degeneration. He underwent cervical discectomy and fusion, laminectomy, and posterior instrumented fusion. After intensive care unit admission post-surgery, he developed hyponatremia of 121-124 mEq/L post phenylephrine and vasopressin infusion to maintain blood pressure maintenance. He was evaluated for syndrome of inappropriate secretion of antidiuretic hormone, hypothyroid, adrenal-induced, or diuretic-induced hyponatremia. At the end of extensive evaluation for the underlying cause of hyponatremia, vasopressin was discontinued. He was also put on fluid restriction, given exogenous desmopressin, and a dextrose 5% in water infusion to prevent osmotic demyelination syndrome caused by sodium overcorrection which im-

proved his sodium level to 135 mmol/L.

CONCLUSION
The presentation of vasopressin-induced hyponatremia is uncommon in normotensive patients, and the most difficult aspect of this condition is determining the underlying cause of hyponatremia. Our case illustrates that, considering the vast differential diagnosis of hyponatremia in hospitalized patients, both hospitalists and intensivists should be aware of this serious complication of vasopressin therapy.

Key Words: Hyponatremia; Vasopressin; Normotensive; Therapy; Case report

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Core Tip: While hyponatremia can have many causes, vasopressin-induced hyponatremia in normotensive patients is unusual. Since the coronavirus disease 2019 pandemic, vasopressin use has increased in intensive care units across the country, and vasopressin-induced hyponatremia is likely underrated. We have intervened by discontinuing vasopressin, which led to rapid overcorrection of the sodium, and thus required temporary exogenous desmopressin and a dextrose 5% in water infusion. Through his care, the patient's serum sodium returned to normal and he made a full recovery. This makes our case unique.

Citation: Lathiya MK, Pepperl E, Schaefer D, Al-Sharif H, Zurob A, Cullinan SM, Charokopos A. Vasopressin-induced hyponatremia in an adult normotensive trauma patient: A case report. *World J Crit Care Med* 2023; 12(1): 35-40
URL: https://www.wjgnet.com/2220-3141/full/v12/i1/35.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i1.35

INTRODUCTION

Under normal conditions, the major physiological role of vasopressin (also known as antidiuretic hormone) is the maintenance of serum osmolarity *via* the regulation of water balance, through the activation of aquaporin channels in the renal collecting duct. Vasopressin is also an important endogenously released stress hormone, particularly during shock; it exerts vasoconstrictive properties *via* arginine vasopressin receptor 1A receptors. Consequently, this hormone has been used clinically as a vasoconstrictive, norepinephrine-sparing agent in the treatment of septic shock and other forms of hypotension[1]. Furthermore, it is utilized in the treatment central diabetes insipidus, von Willebrand disease, Hemophilia A, and nocturnal enuresis. However, vasopressin therapy carries a number of serious potential side effects, including cardiac and gastrointestinal complications, anaphylaxis, cutaneous gangrene, and venous thrombosis[2]. Vasopressin-induced hyponatremia is a rare adverse effect that has only recently been identified in patients suffering from vasodilatory shock[3]. Hyponatremia is mechanistically justified based on vasopressin's mechanism of action. In this article, we will discuss a case of clinically significant vasopressin-induced hyponatremia in a normotensive patient in the Mayo Clinic Health System Intensive Care Unit (ICU).

CASE PRESENTATION

Chief complaints

We present a case of successfully treated vasopressin induced hyponatremia in normotensive patient.

History of present illness

A 39-year-old previously healthy male presented as a high acuity trauma after falling off a forklift, sustaining an axial load injury on his cranium. He was evaluated in the emergency department and workup was negative for neurologic findings. His initial vital signs in the emergency department were normal and the patient had a Glasgow Coma Scale of 15. He was protecting his airway and had bilaterally clear lung sounds without chest wall trauma. He was noted to have a scalp laceration with no active bleeding.

History of past illness

He has no known prior history of trauma and illness.

Personal and family history

He has no known prior personal and family history.

Physical examination

The patient had a loss of sensation below the level of the nipples, loss of motor function of his lower extremities, and no rectal tone. In terms of upper extremity motor function, he had good power and grip strength in right hand but decreased on the left hand. No thoracic or lumbar spine step-off nor back trauma stigmata were noted.

Laboratory examinations

To rule out hyperglycemia-induced hyponatremia, we measured serum glucose and calculated corrected sodium. In order to rule out pseudohyponatremia, we measured serum protein and lipid profiles. We also performed a complete blood count and measured urinary osmolarity, plasma osmolarity, random urine sodium level, serum cortisol level, serum adrenocorticotropic hormone level, and serum thyroid-stimulating hormone level to rule out differential diagnosis of hypoosmotic hyponatremia.

Imaging examinations

On imaging in the emergency department, a focused assessment with sonography in trauma exam was done and was negative. A computerized tomography (CT) scan of the head was negative for acute intracranial processes, as well as negative CT scans of the thoracic and lumbar spines. CT scan of the cervical spine revealed a superior endplate fracture at C7, and an magnetic resonance imaging revealed what appeared to be an acute traumatic disc at the C7 Level with cortical degeneration. Subsequent CT angiogram of the neck revealed no acute vascular injuries.

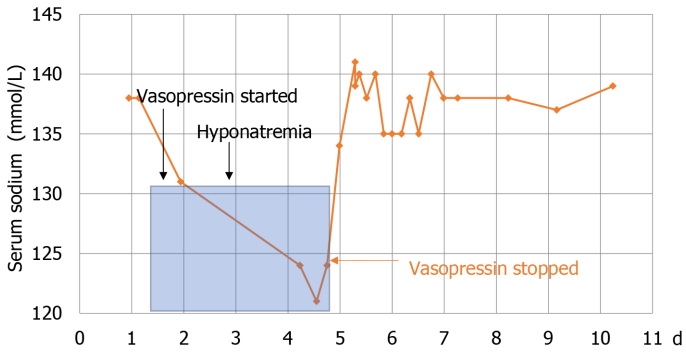
FINAL DIAGNOSIS

The definitive diagnosis in the case described is vasopressin-induced hyponatremia in a normotensive state.

TREATMENT

The patient was taken to the odd ratio where he underwent C6-C7anterior cervical discectomy and fusion, C6-C7 Laminectomy, and C4-T2 posterior instrumented fusion, as well as closure of the patient's scalp laceration.

He admitted to the critical care unit on phenylephrine postoperatively for maintenance of a mean arterial pressure (MAP) greater than 85mmHg. On day 2 and day 3 of ICU care, infusion of vasopressin was initiated with the addition of phenylephrine intermittently to maintain MAP goals of 80-85 mmHg to augment cord perfusion for 7 d from the time of his injury. His sodium level on ICU day 3 was 131 mmol/L. On day 4, he had an episode of hypoxemia and cough with a chest x-ray that revealed perihilar infiltrates concerning for possible volume overload. Furosemide was given and arterial blood gas showed minimal hypoxemia with normal pCO_2 and was managed on a high-flow nasal cannula. However, we encountered new onset hyponatremia with sodium levels 121-124 mmol/L and noted high urine osmolarity and high urine sodium. He was evaluated for syndrome of inappropriate secretion of antidiuretic hormone (SIADH), hypothyroid, adrenal-induced, or diuretic-induced hyponatremia. He was placed on fluid restriction without much improvement, so subsequently the vasopressin infusion was discontinued. After discontinuation of vasopressin, over ICU days 4 and 5, subsequent sodium levels at 6 h, 12 h, and 18 h were 124, 134, and 141 mmol/L respectively (Figure 1). Additionally, on day 5, Nephrology was consulted to manage the over-correction of hyponatremia to reduce the risk of osmotic demyelination syndrome, and he was started on exogenous desmopressin (DDAVP) and dextrose 5% in water (D5W) instead of hypertonic solution, as hypertonic solution is only used in cases of seizure or acute neurological signs and symptoms. Phenylephrine was continued to maintain MAP. On ICU day 6, the patient's sodium stabilized at 135 mmol/L overnight with DDAVP and free water was discontinued. On day 7, overnight sodium level was noted to stabilize between 135-138 mmol/L. A tertiary survey was performed and no occult injuries were identified. The patient was started on aggressive physical therapy and occupational therapy, and attempts were made to wean off phenylephrine as per Neurosurgery for spinal cord perfusion purposes. He was able to wean off vasopressors but due to orthostatic hypotension symptoms, the patient was started on a low dose of midodrine with subsequent improvement. On day 8, the patient was transferred for inpatient spinal



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Figure 1 Changes of serum sodium level before and after vasopressin withdrawal. After discontinuation of vasopressin, over intensive care unit days 4 and 5, subsequent sodium levels at 6 h, 12 h, and 18 h were 124, 134, and 141 mmol/L respectively.

cord rehabilitation, where he continued to demonstrate strength, functional improvement, and coordination of left upper extremity, as well as static and dynamic sitting balance and sensation to light touch and pressure in the lower extremity.

OUTCOME AND FOLLOW-UP

On 3 mo postop follow up, he showed improvement as he was upgraded from American Spinal injury Association Impairment Scale Score (ASIA) B to an ASIA C.

DISCUSSION

Vasopressin is critical for maintaining normal body osmolality and plasma volume in response to several pathways of stimuli, including osmotic and nonosmotic triggers[4-6]. Its mechanism of action begins with a cyclic adenosine monophosphate signaling cascade in the renal system and culminates with the insertion of aquaporin 2 channels into the apical membrane of the renal collecting duct. The resulting accumulation of these water channels leads to the reabsorption of water into the bloodstream [7-10]. This hormone also serves numerous related functions both when delivered endogenously and exogenously. For instance, in clinical settings, the vasoconstrictive effects of vasopressin correct depleted blood volume in patients facing vasodilatory shock[11]. In the case of this patient, the use of general anesthesia during and following a surgery to address an acute spinal cord injury required external maintenance of MAP for a stated period of seven days. Initially, phenylephrine, an α1-adrenergic receptor, was infused at a maximum dose for these purposes; vasopressin administration began concurrently with phenylephrine to continually reach goal MAPs of > 85 mmHg. Prior to the initiation of vasopressin, basic metabolic panels revealed that sodium levels were within normal limits, defined in this report as 135-145 mmol/L. After vasopressin support, the significant drop in the patient's sodium level down to 121 mmol/L indicated a state of hyponatremia, and lead to a significant risk for neurologic complications (Figure 1).

While hyponatremia is a relatively common affliction of hospitalized patients, the ramifications of unrecognized or untreated cases can be devastating for patient outcomes. With a decrease in serum sodium, the corresponding increase in intracellular osmolality can result in excess entrance of water into the cells[12,13]. This swelling of cells may engender several effects specifically secondary to brain edema, ranging from those as mild as headaches, lethargy, and nausea to ones as extreme as comas, seizures, and even eventual death[14]. Fortunately, hyponatremia can be carefully corrected *via* multiple treatments that encourage slow re-establishment of the standard osmotic gradient. Rapid overcorrection can become quickly dangerous to the patient, as brain cell dehydration leads to osmotic demyelination and numerous neurological defects[13,15]. The preferred intervention in correcting hyponatremia depends largely on the cause of this electrolyte imbalance, namely whether it can be described as isotonic, hypertonic, or hypotonic[13].

The investigation of the etiology of hyponatremia in this patient required a systematic approach to eliminating all possible causes of hyponatremia in a stable, normotensive, post-surgical trauma patient. First, it should be noted that blood glucose was within the normal range, noted as 110 mg/dL during the onset of hyponatremia, which concluded that hyperglycemia was not present. Neither hyperlipidemia nor hyperproteinemia were suspected as the serum was not lipemic, the patient did not exhibit jaundice, or have a history of plasma cell dyscrasia. These inquiries, along with a measured serum osmolality of 268 mOsm/kg, outside of defined normal limits of 276-306 mOsm/kg, suggested

hypotonic hyponatremia. His euvolemic status and elevated urine sodium level, on the other hand, made hypovolemic hyponatremia less likely, and there was no other obvious cause of SIADH. However, while encephalic trauma can cause transient changes in water-electrolyte balance, this patient's initial serum electrolytes levels, including sodium, potassium, bicarbonate, and chloride, were normal, and his urine output was also normal[16]. His urine output and lack of primary central nervous injury made cerebral salt wasting less likely. We became concerned for hyponatremia secondary to the recent vasopressin infusion[13]. In a combined diagnostic and therapeutic approach, cessation of vasopressin led to prompt improvements in serum sodium. The hyponatremia corrected too rapidly, reaching a high sodium level of 141 mmol/L. After DDAVP and D5W, this overcorrection was reversed and stabilization of sodium levels within the normal range ensued. These observed changes in sodium levels, both upon beginning and stopping vasopressin, heightened suspicions of vasopressin-induced hyponatremia.

Both in the intensive care setting and otherwise, the finding of vasopressin-induced hyponatremia, is still emerging and rare. A few previous studies have detailed cases of hyponatremia secondary to vasopressin administration in the treatment of specific conditions. For example, a 2015 study reviews the cases of two young adult ICU patients treated with vasopressin for septic shock; both patients developed hyponatremia following initiation of the medication, but quickly rebounded from hyponatremia following discontinuation of vasopressin. The aforementioned study also mentions the role of catecholamines, corticosteroids, and endotoxins in counteracting the potentially detrimental effects of vasopressin in shock patients[3]. Another study in 1984 compared the utility of intravenous somatostatin and vasopressin in cirrhotic patients with variceal bleeding; researchers discovered that a complication common only to the vasopressin group was hyponatremia[17]. Similarly, a 1995 case report follows a post-caesarean section patient that received intravenous vasopressin to control esophageal and gastric varices. This serum sodium of this patient dropped significantly following vasopressin infusion but rebounded quickly following discontinuation of the medication[18].

Following his axial loading injury, this trauma patient exhibited periods of hyponatremia while recovering in critical care. While the etiology of this deficiency was initially unknown, the vasopressin infusion’s mechanism of action was thought-provoking. Similar inductions of hyponatremia by vasopressors have been documented in patients suffering from septic shock, as well as in patients undergoing treatment for variceal hemorrhage; however, these consequences have not been examined in a stable, normotensive, adult patient[3,17,18]. Our study diverges from past literature through the patient presentation and the indication for vasopressin treatment and the lack of shock. A stable, normotensive, adult trauma patient received vasopressin post-operation to maintain MAP. The result in this case report illustrates the shared result of hyponatremia remedied through the cessation of vasopressin. As far as we are aware, potential hyponatremia complications include cerebral edema, non-cardiogenic pulmonary edema, permanent neurological damage, and death. Finding the underlying cause of hyponatremia is always necessary in order to prevent life-threatening complications. Although the majority of hyponatremia's underlying causes are treatable and reversible, rare causes such as vasopressin-induced hyponatremia should be considered. Due to the widespread use of this medication in hospitals, both critical care physicians and hospitalists should be aware of this vasopressin side effect. Ultimately, the potential for hyponatremia per vasopressin commands further study across all demographics, indications, and settings. An improved understanding of the risks and mechanisms of vasopressin-induced hyponatremia would better inform clinical decision-making and possible prophylactic salt restriction for these patients.

CONCLUSION

Vasopressin-induced hyponatremia is an overall rare occurrence, but this potential consequence should still be suspected under certain conditions to both prevent and mitigate harmful effects. While several previous studies have detailed the development of vasopressin-induced hyponatremia in pediatric, hemorrhage, and shock patients, our case study demonstrates this form of hyponatremia in an adult, normotensive trauma patient recovering in the critical care setting. In brief, our patient’s serum sodium dropped to hyponatremic levels concurrently with the administration of vasopressin and recovered promptly with the cessation of this medication. However, more research is needed to various factors that may be responsible for additive effects, such as additional comorbidities, duration of vasopressin use, dosage, and interaction with other medications.

FOOTNOTES

Author contributions: Lathiya MK, Schaefer D, Cullinan SM and Charokopos A designed and conceptualized the research; Lathiya MK and Pepperl E performed the research; Lathiya MK, Al-Sharif H, Zurob A, Cullinan SM and Charokopos A wrote the paper and assisted with graphics; Lathiya MK and Charokopos A revised the paper.

Informed consent statement: Informed written consent was obtained from the patient.

Conflict-of-interest statement: All authors report no relevant conflict of interest for this article.

CARE Checklist (2016) statement: All authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

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ISSN 2220-3141 (online)

World Journal of

Critical Care Medicine

World J Crit Care Med 2023 March 9; 12(2): 41-91



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WJCCM

World Journal of Critical Care Medicine

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World Journal of Critical Care Medicine

Bimonthly Volume 12 Number 2 March 9, 2023

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INDEXING/ABSTRACTING

The *WJCCM* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Li-Li Wang*.

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Hua-Dong Wang

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

PUBLICATION DATE
March 9, 2023

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World J Crit Care Med 2023 March 9; 12(2): 41-52

DOI: 10.5492/wjccm.v12.i2.41

ISSN 2220-3141 (online)

MINIREVIEWS

Enhancing the awakening to family engagement bundle with music therapy

Ariel M Modrykamien

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Hu B, China; Papamichalis P, Greece; Shelat VG, Singapore

Received: October 27, 2022
Peer-review started: October 27, 2022
First decision: December 19, 2022
Revised: December 19, 2022
Accepted: February 2, 2023
Article in press: February 2, 2023
Published online: March 9, 2023

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Abstract

Survivors of prolonged intensive care unit (ICU) admissions may present undesirable long-term outcomes. In particular, physical impairment and cognitive dysfunction have both been described in patients surviving episodes requiring mechanical ventilation and sedation. One of the strategies to prevent the aforementioned outcomes involves the implementation of a bundle composed by: (1) Spontaneous awakening trial; (2) Spontaneous breathing trial; (3) Choosing proper sedation strategies; (4) Delirium detection and management; (5) Early ICU mobility; and (6) Family engagement (ABCDEF bundle). The components of this bundle contribute in shortening length of stay on mechanical ventilation and reducing incidence of delirium. Since the first description of the ABCDEF bundle, other relevant therapeutic factors have been proposed, such as introducing music therapy. This mini-review describes the current evidence supporting the use of the ABCDEF bundle, as well as current knowledge on the implementation of music therapy.

Key Words: Bundle; Delirium; Mechanical ventilation; Mobility; Music therapy

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Core Tip: Data support the implementation of the (1) Spontaneous awakening trial; (2) Spontaneous breathing trial; (3) Choosing proper sedation strategies; (4) Delirium detection and management; (5) Early ICU mobility; and (6) Family engagement bundle for mechanically ventilated patients. The role of music therapy is evolving.

Citation: Modrykamien AM. Enhancing the awakening to family engagement bundle with music therapy. *World J Crit Care Med* 2023; 12(2): 41-52
URL: https://www.wjgnet.com/2220-3141/full/v12/i2/41.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i2.41

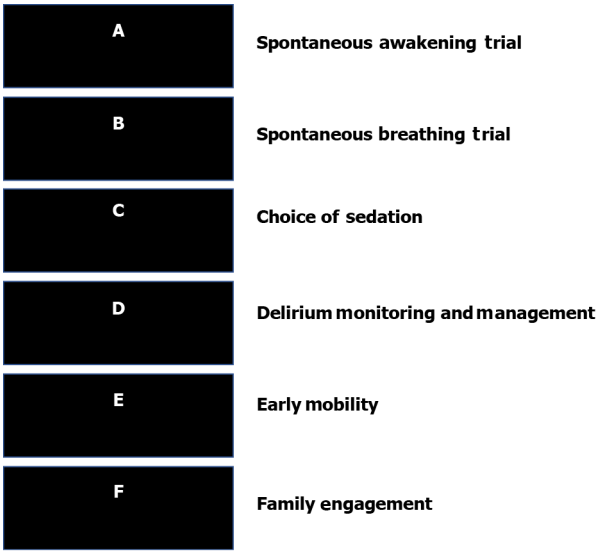
INTRODUCTION

Innovation of clinical practices and introduction of new technologies have improved survival of critically ill patients[1]. Furthermore, the implementation of specific strategies for mechanical ventilation [2], pharmacotherapy[3], fluid therapy[4] and bundles of care[5] brought about improvement in other relevant outcomes, such as shorter mechanical ventilation or intensive care unit (ICU) lengths of stay (LOS). Despite those aforementioned achievements, a variety of other long-term outcomes directly affected by ICU admissions still remain problematic for patients, families, and the entire society. Over the last two decades, multiple publications have described significant long-term post-ICU impairments. In particular, the presence of muscle waist with its consequent alteration of physical function, and high rates of cognitive dysfunction have been repeatedly reported. A landmark article, which described 1-year outcomes in 109 survivors of acute respiratory distress syndrome (ARDS) revealed that those patients had persistent functional disability[6]. The physical role domain score in the Medical Outcomes Study 36-item Short-Form (SF-36) questionnaire was only 25 points, while the score in normal population was 84. Strikingly, at 12 months from hospital discharge, only 49% of those individuals had returned to work. Among those, only 78% had returned to their original job. Reported reasons for not returning to work included chronic fatigue and weakness, stressing the relevance of general muscular debility as a cause of their inactivity. A follow-up study published by the same group, which addressed functional disability 5 years post-ICU discharge, showed that the mean score of the physical component of the SF-36 remained approximately 1 standard deviation below the mean score of an age and gender-matched control population[7]. Also, the distance walked in 6 min was significantly correlated with the physical-component score of this survey. Interestingly, the mental component domains of the SF-36 questionnaire remained within normal limits over the 5 years of follow up. These long-term quality of life alterations were not only limited to patients with ARDS. A study that followed a large cohort of patients for more than 6 years after admission to surgical ICUs (SICUs) showed significant impact in their response to the EuroQol-6D tool (another quality-of-life questionnaire)[8]. Specifically, 52% of patients reported impairment in mobility, 29% had anxiety and/or depression, and 43% disclosed cognitive impairment. Alterations in physiology during ICU admissions have been linked with the development of neurocognitive impairments[9]. A prospective cohort study that included 126 mechanically ventilated patients admitted in ICU, mostly due to sepsis and/or ARDS, showed that at 12 months post-discharge, 71% presented cognitive impairment[10]. Interestingly, increasing delirium duration was deemed as an independent predictor of poor cognitive performance among this population. Based on the aforementioned data, individual strategies have been studied in order to avoid the previously described outcomes. Specifically, reduction and/or possible avoidance in the use of sedatives, protocolized liberation from mechanical ventilation, selection of drugs with lower deliriogenic effect, detection and management of delirium, early mobilization, and family participation in care have all been investigated. The positive outcomes brought about by these individual strategies concluded with the development of a bundle of care, known as the ABCDEF bundle (Figure 1). Each element of the bundle corresponded to a demonstrated beneficial intervention, such as: (1) Awakening trial (SAT) ; (2) Spontaneous breathing trial (SBT) and mechanical ventilation liberation; (3) Selective choice of drugs, particularly sedatives; (4) Detection, management, and prevention of delirium; (5) Early patient mobilization; and (6) Family and/or caregiver involvement in care. While the ABCDEF bundle has been widely accepted and implemented, other interventions have been found potentially beneficial, and could enhance the bundle. Particularly, the utilization of music therapy may have promising outcomes. The next sections of the manuscript will describe: (1) Evidence supporting individual components of the ABCDEF bundle; (2) Evidence supporting the ABCDEF bundle implementation; and (3) Supporting data for the use of music therapy.

EVIDENCE SUPPORTING INDIVIDUAL COMPONENTS OF THE ABCDEF BUNDLE

Spontaneous awakening trials

Over the last few decades, the strategies for providing sedation to critically ill mechanically ventilated patients have followed a pendular fashion. In a thoughtful editorial written by Dr. Thomas L. Petty in 1998, he stated: "When we first started our unit in 1964, patients who required mechanical ventilation were awake and alert and often sitting in a chair by being awake and alert, these individuals could interact with their family, friends, and the environment". In another paragraph, referring to practices



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Figure 1 Bundle components.

held in 1998, he mentioned: "What I see these days are paralyzed, sedated patients, lying without motion, appearing to be dead, except for the monitors that tell me otherwise"[11]. Evidence published by the end of the '90s and during the 2000s has caused a movement back towards patient awakening. A prospective observational cohort study that followed 93 mechanically ventilated patients receiving intravenous (IV) continuous sedations *vs* 149 patients receiving sedation boluses or no-sedation showed significant longer duration on mechanical ventilation within the group receiving continuous IV sedation (185+/-190 h *vs* 56+/-75.6 h; $P < 0.001$)[12]. Furthermore, the ICU and hospital LOS were also longer within the continuous IV sedation group (13.5+/-34 d *vs* 4.8+/-4; and 21 +/-25 d *vs* 13+/-14, $P < 0.001$, respectively). A year later, a randomized, control trial studied whether a nurse-implemented protocol-directed sedation strategy *vs*. no protocol resulted in improved outcomes in mechanically ventilated patients[13]. Notably, duration of mechanical ventilation was shorter in the protocol-directed group (89 h ± 134 h *vs* 124 h ± 154, $P = 0.003$). ICU and hospital stays were also shorter within this group (5.7 d ± 6 *vs* 7.5 d ± 7, $P = 0.013$; and 14 d ± 17 *vs* 20 d ± 24, $P < 0.001$, respectively). Based on the aforementioned data, it became apparent that intermittent (rather than continuous) and protocol-directed sedation strategies were beneficial compared with prior usual practices. A landmark randomized control study (RCT), which included 128 mechanically ventilated patients sedated by a continuous IV strategy, allocated patients to an intervention of daily sedation vacation to awakening trials *vs* sedation management at the discretion of clinicians[14]. This study confirmed the previously described findings. In more detail, patients assigned to the intervention group had a ventilator duration of 4.9 d, compared with 7.3 d in the control group ($P = 0.004$). The median LOS in the ICU was 6.4 d *vs* 9.9 d, respectively ($P = 0.02$). Contrary to the sufficient evidence that exists regarding daily awakening trials and using protocol-directed strategies, the depth of initial sedation implemented immediately after intubation has been an area of uncertainty. However, a multicenter, longitudinal cohort study evaluated whether initial sedation depth (assessed by Richmond Agitation-Sedation Scale – RASS) within 24-48 h post-intubation was associated with time-to-extubation and/or survival[15]. Notably, initial depth of sedation resulted an independent predictor of time to ventilator liberation [hazard ratio (HR): 0.90; $P < 0.01$], hospital mortality (HR: 1.1; $P = 0.01$), and 180-d mortality (HR: 1.08; $P = 0.02$). Based on these findings, a strategy of 'light' initial sedation upon institution of mechanical ventilation became justified. Finally, a randomized study evaluated 140 critically ill, mechanically ventilated patients to a strategy of no-sedation *vs* a control group, which involved initial sedation with propofol and subsequent midazolam [16]. This group underwent daily awakening trials. Of note, patients receiving no sedation had significantly more ventilator-free d (13.8 d *vs* 9.6 d; $P = 0.0191$) than those receiving interrupted sedation. No sedation was also associated with a shorter ICU LOS. As a summary, based on the previously described data, current sedation standard of care involves light or no sedation over deep sedation, daily awakening trials over continued sedation, and protocol-directed strategy over individual clinician decisions. Despite evidence supporting light sedation strategies, certain areas of concern still remained, regarding whether these strategies would affect patient mental health by causing post-traumatic stress disorder (PTSD), anxiety or depression post-hospital discharge. In order to answer that question, a randomized, open-label, control study included 137 patients who had undergone light *vs* deep sedation. Patients self-reported measures correlated with PTSD, anxiety or depression upon hospital discharge and 4 weeks later. Interestingly, at the 4 week follow-up, patients in the deep sedation arm had a tendency toward more PTSD symptoms ($P = 0.07$), more difficulty remembering the

ICU event (37% *vs* 14%; *P* = 0.02) and more disturbing recollection of the ICU (18% *vs* 4%; *P* = 0.05)[17]. These findings may be explained by prior evidence, which suggested that memory recall (more commonly seen after light sedation) could have a protective effect against subsequent mental health disorders post-discharge. Conversely, the presence of delusional memories after deep sedation could have an association with development of PTSD.

Spontaneous breathing trials

Observational studies attempting to identify the best methods for discontinuing mechanical ventilation have been reported for many decades[18]. However, a landmark study published in 1996 provided the framework that would be accepted as current standard of care in ICU. In this study, 149 patients were enrolled to a strategy involving 3 phases: (1) Daily screening of respiratory function; (2) A trial of spontaneous breathing; and (3) Notifying the physician of successful results. 150 other patients were the control group, with physician guided weaning. The results of this study revealed that the median duration of mechanical ventilation was 4.5 d in the intervention group and 6 d in the control group (*P* = 0.003)[19]. Furthermore, the weaning time was shortened by 2 d by using the intervention strategy (*P* < 0.001). This study incorporated the notion of protocol-directed weaning. It also confirmed the benefits of SBTs, rather than the gradual reduction of ventilator support. Years later, building on the prior knowledge regarding the benefits of awakening trials, an RCT including 336 mechanically ventilated patients was published. The study allocated half of these patients to an intervention strategy involving the performance of SAT followed by an SBT. The control group involved sedation *per* usual care plus SBT, without coordination[20]. The study showed that patients in the intervention group spent more days breathing without assistance during the 28-day trial period than those in the control arm (14.7 d *vs* 11.6 d; *P* = 0.02). They were also discharged earlier from the ICU (median time in intensive care 9 d *vs* 13 d; *P* = 0.01). Strikingly, at any point during the 12-month follow up, patients included in the intervention arm had less chances to expire compared with subjects in the control one (HR 0.68; *P* = 0.01). The positive outcomes of this study enhanced the rational of linking SAT with subsequent SBT in clinical practice. In fact, a multicenter quality improvement (QI) collaborative, coordinated by the Center for Disease Control and Prevention Wake Up and Breath, studied whether the implementation of the SAT/SBT bundle was associated with a reduction of ventilator-associated events (VAEs)[21]. The QI showed that the VAE rate went from around 10 events *per* 100 episodes of mechanical ventilation in 2011 to 5 events *per* 100 episodes in 2013 [adjusted odds ratio (OR): 0.63; 95% confidence interval (CI): 0.42 to 0.97]. Furthermore, the mean duration of mechanical ventilation decreased by 2.4 d (95%CI: 1.7 to 3.1), and the ICU LOS by 3.0 d (95%CI: 1.6 to 4.3) after implementing the SAT/SBT bundle.

Choice of sedatives

As described above, a strategy of daily awakening trials on sedated mechanically ventilated patients has shown reduction on ventilation duration and ICU stay. In addition, several studies revealed that certain sedatives may be associated with intrinsic complications. A Canadian multicenter randomized open label study allocated patients to be sedated with midazolam *vs* propofol[22]. Patients were subsequently divided for analysis accordingly to length of sedation in: (1) Short time, < 24 h on sedation; (2) Intermediate time, 24 h - 72 h on sedation; and (3) Long time, > 72 h on sedation. Overall, pooled results demonstrated that patients treated with propofol were extubated earlier than those treated with midazolam (6.7 h *vs* 24.7 h, respectively; *P* < 0.05) following discontinuation of sedation. A meta-analysis of 16 studies compared outcomes of midazolam *vs* propofol within groups of post-acute surgery and critically ill patients. The analysis showed that propofol was generally associated with reduced ventilation time of 4.46 h (*P* = 0.004, 6 studies). In critically-ill patients, sedation with propofol was associated with reduced extubation time of 32.68 h (*P* = 0.0001, 9 studies). For post-surgical patients, propofol was associated with a reduction of ICU LOS of 5.07 h (*P* = 0.006, 5 studies), ventilator time of 4.28 h (*P* < 0.0001, 3 studies), and extubation time of 1.92 h (*P* = 0.00001, 9 studies)[23]. Recently, the introduction of dexmedetomidine in clinical practice brought about new data. A prospective, double-blind, randomized trial conducted in 5 countries compared dexmedetomidine *vs* midazolam in their ability to maintain patients within a predefined level of sedation (RASS range). Secondary outcomes included prevalence of delirium, duration of mechanical ventilation, and ICU LOS. Even though there was no difference between groups in percentage of time within sedation range, there were significant differences in secondary outcomes. In particular, the prevalence of delirium was 54% in the dexmedetomidine-treated patients *vs* 76.6% in the midazolam group (*P* < 0.001). Median time to extubation was about 2 d shorter in the dexmedetomidine group (*P* = 0.01). The ICU LOS was similar in both groups (5.9 d *vs* 7.6 d; *P* = 0.24)[24]. Another double-blind RCT, which included 106 mechanically ventilated in medical and surgical ICU at 2 tertiary care centers, compared dexmedetomidine *vs* lorazepam for the outcome of days alive without delirium or coma. The study also aimed at comparing both drugs in terms of the percentage of days spent within 1 RASS point of an established goal. The trial showed that patients sedated with dexmedetomidine had more days alive without delirium or coma (median days, 7.0 *vs* 3.0; *P*= 0.01). Patients assigned to this group also spent more time within 1 RASS point of their sedation goal compared with patients sedated with lorazepam (median percentage of days, 80% *vs* 67%; *P* = 0.04)[25]. Finally, two RCTs, which were published simultaneously, compared dexmedetomidine *vs* midazolam and dexmedetomidine *vs* propofol, respectively. In both studies,

outcomes included non-inferiority of dexmedetomidine (compared with control groups) in regards to proportion of time at target sedation level, and its superiority (compared with controls) in regard to mechanical ventilation duration. The secondary outcome included subjects' capability to disclose pain [by utilizing the visual analogue scale (VAS)]. Both studies reveal that dexmedetomidine was not inferior compared with midazolam or propofol in maintaining light to moderate sedation ranges. Nevertheless, median duration of mechanical ventilation was shorter with dexmedetomidine (123 h) *vs* midazolam (164 h; $P = 0.03$). There were no differences on ventilation duration between dexmedetomidine *vs* propofol. Patients' interaction (measured using VAS) was superior with dexmedetomidine compared to both midazolam and propofol ($P < 0.001$, for both studies)[26]. In summary, based on the higher deliriogenic effect and prolonged stay on mechanical ventilation, benzodiazepines should not be selected as medications of choice for mechanically ventilated patients. Dexmedetomidine or propofol are currently deemed as preferred medications, the choice between them depending on other anticipated side-effects (*i.e.*, bradycardia, hypotension, *etc.*).

Delirium detection, management and prevention

The presence of delirium in mechanically ventilated patients is common, with some studies describing a prevalence up to 48%[27]. Due to difficulties in assessing this complication in non-communicative patients, a number of tools have been developed to allow its detection. In more detail, the original description of the Confusion Assessment Method for the ICU (CAM-ICU) tool reported sensitivities of 100% and 93% and specificities of 98% and 100% (when performed by two different nurses). The interrater reliability was very high, as well (kappa = 0.96; 95%CI: 0.92 to 0.99)[28]. Another tool, the Intensive Care Delirium Screening Checklist (ICDSC) was also proved to be very accurate. Its ability to predict delirium was assessed by a receiving operating characteristic (ROC) curve, which showed an area under the curve (AUC) of 0.9. Sensitivity and specificity, when using 4 points as a cut-off, were 99% and 64%, respectively[29]. A comparison between the two was performed by a meta-analysis that included 13 studies. Its results showed that the pooled sensitivity of the CAM-ICU was 80.0% (95%CI: 77.1 to 82.6), and the pooled specificity was 95.9% (95%CI: 94.8 to 96.8). The pooled sensitivity of the ICDSC was 74% (95%CI: 65.3 to 81.5), and the pooled specificity was 81.9% (95%CI: 76.7 to 86.4). The AUCs in the CAM-ICU and ICDSC ROCs for their ability in diagnosing delirium were 0.97 and 0.89, respectively[30]. These data revealed that CAM-ICU may have higher accuracy for the detection of delirium in mechanically ventilated patients. Over the years, focus has been placed on describing delirium severity. A recent instrument, the CAM-ICU-7 delirium severity scale has been introduced. In more detail, a 7-point scale (0-7) was derived from responses to the CAM-ICU and Richmond Agitation-Sedation Scale items. The CAM-ICU-7 scores showed correlation with higher odds of in-hospital mortality (OR = 1.47; 95%CI = 1.30 to 1.66) and lower odds of being discharged home (OR = 0.8; 95%CI: 0.72 to 0.9) after adjusting for age, race, gender, severity of illness, and chronic comorbidities. Furthermore, higher CAM-ICU-7 scores were also associated with increased ICU stay ($P = 0.001$)[31]. Pharmacologic management of delirium has been studied over many years. Nevertheless, up to this day, no medication has shown clear benefits for its management in mechanically ventilated patients. A randomized, double-blind, placebo-controlled trial allocated 101 mechanically ventilated patients to receive haloperidol or ziprasidone or placebo every 6 h for up to 14 d. During the 21-d study period, patients in the haloperidol group had similar number of days alive without delirium or coma, as did patients in the ziprasidone and placebo groups (14 d *vs* 15 d *vs* 12.5 d, respectively; $P = 0.66$). There were no differences in other outcomes, such as hospital LOS, ventilator-free days, and mortality[32]. A subsequent RTC allocated ventilated and/or patients with shock to receive intravenous boluses of haloperidol, ziprasidone, or placebo. In this trial, dose of drug or placebo were halved or doubled every 12 h intervals, based on the presence or absence of delirium. This study confirmed prior data. In more detail, the median number of days alive without delirium or coma (primary outcome) were 7.9 d, 8.7 d, and 8.5 d for the haloperidol, ziprasidone, and placebo groups, respectively ($P = 0.26$)[27]. Another double-blind, placebo-controlled, parallel-group RCT included 74 mechanically ventilated patients with delirium and agitation. Patients were allocated to dexmedetomidine at a rate of 0.5 μg/kg/h (or placebo) and increased up to 1.5 μg/kg/h to reach provider-directed sedation goals. The trial showed an increase in ventilator-free hours within 7 d post-randomization in the dexmedetomidine group (144.8 h) *vs* placebo (127.5 h), ($P = 0.01$)[33]. Finally, a recently published multicenter, blinded, placebo-controlled trial randomized 1000 ICU patients with delirium to receive intravenous haloperidol (2.5 mg 3 times daily plus 2.5 mg as needed up to a maximum daily dose of 20 mg) *vs* placebo[34]. The medications were administered for as long as delirium continued. At 90 d, the mean number of days alive and out of the hospital (primary outcome) was 35.8 (95%CI: 33 to 39) in the haloperidol group and 32.9% (95%CI: 30 to 36) in the placebo group ($P = 0.22$). This study re-affirmed the lack of effective pharmacological treatment for delirium management. Of note, some publications reported possible effectiveness of non-pharmacological interventions for the reduction of incidence and duration of delirium. Nevertheless, these multi-component strategies are still under investigation[35]. The recognition of cognitive impairment after development of delirium motivated several researchers at investigating its prevention. An RCT included 142 mechanically ventilated patients within 72 h post-admission. The study allocated patients to receive haloperidol 2.5 mg or 0.9% saline placebo intravenously every 8 h, irrespective of coma or delirium status. As a result, patients in the haloperidol

arm spent about the same number of days alive, without delirium, and without coma as did patients in the placebo one (median 5 d *vs* 6 d; $P = 0.53$)[36]. A subsequent study performed at 21 ICUs included 1,789 critically ill patients to receive either haloperidol at 1 mg or 2 mg, or placebo. Haloperidol doses (or placebo) were ad-ministered 3 times *per* day intravenously. Whereas the 1-mg haloperidol group was prematurely stopped because of futility, the haloperidol 2 mg and placebo groups showed no difference in 28-d survival ($P = 0.93$)[37]. Finally, a two-center, double-blind, placebo-controlled trial randomized 100 delirium-free critically ill adults, already receiving sedatives, to receive nocturnal (9:30 pm to 6:15 am) intravenous dexmedetomidine or placebo. The result of the study revealed that nocturnal dexmedetomidine was associated with a greater proportion of patients remaining delirium-free (80%) *vs* placebo (54%) ($P = 0.006$)[38]. In summary, despite high accuracy for delirium detection in ICU patients by using the CAM-ICU and ICDSC tools, the ability to provide pharmacologic management or prevention remains disputable. In addition, underutilization of those tools may result in low delirium detection, as well[39]. Studies using dexmedetomidine showed promising results. However, further investigations are needed to extrapolate these findings in to clinical practice.

Early mobility

The recognition of physical impairment as one of the most important factors affecting Quality of Life post-ICU admission has triggered a number of investigations to explore the benefits of early mobilization in the ICU setting. In 2007, a pilot study aimed at showing the feasibility and safety of patient mobilization in the ICU[40]. The study reported a total of 1,449 activity events in 103 ventilated patients. The activities involved sitting on the bed, sitting in a chair, and ambulation. Of note, there were less than 1% activity-related adverse effects, as pre-specified by the investigators. Since this experience, other investigators have explored early mobility in ICU, reaching positive results. A prospective cohort study in a university medical ICU included 230 ventilated patients to receive early mobility within 72-hours of intubation *vs* usual care. Patients in the intervention group had at least one physical therapy session compared with those included in the usual care group (80% *vs* 47%, $P < 0.001$). Furthermore, patients in the early mobility group were out of bed earlier (5 d *vs* 11 d, $P < 0.001$). Notably, patients in the intervention group had shorter ICU (5.5 d *vs* 6.9 d; $P = 0.025$) and hospital LOS (11.2 d *vs* 14.5 d; $P = 0.006$)[41]. Two years later, a seven-month prospective before-and-after quality improvement project involving the implementation of full-time physical and occupational therapists who followed specific ICU guidelines, showed an increase in the number of rehabilitation events *per* subject (1 pre- *vs* 7 post-implementation, $P < 0.001$), and a higher level of functional mobility (56% *vs* 78%, $P = 0.03$). Furthermore, there was a reduction of ICU and hospital LOS post-implementation (7 d *vs* 4.9 d, $P = 0.020$; and 17.2 d *vs* 14.1 d, $P = 0.030$, respectively)[42]. In addition to the aforementioned data, the highest level of evidence was presented by an RCT. This study allocated 104 patients to early exercise and mobilization (physical and occupational therapy) during periods of daily interruption of sedation *vs* daily sedation vacation episodes with therapy as ordered by the primary care team. The primary outcome was defined as the percentage of individuals able to regain functional independence at hospital dismissal. Functional independence entailed the capability to perform 6 activities of daily living, and walk with independence. The primary outcome was seen in twenty-nine (59%) subjects in the intervention arm, whereas it was achieved in nineteen (35%) subjects in the control one ($P = 0.02$). Furthermore, patients in the intervention arm had shorter duration of delirium (median 2.0 d *vs* 4.0 d, $P = 0.02$), and more ventilator-free days (23.5 d *vs* 21.1 d; $P = 0.05$) during the 28-d follow-up period[43]. This study provided the framework for the implementation of early mobility in ICU as standard practice. Further publications with mixed results have been published ever since. A multicenter, international, parallel-group, assessor-blinded RCT in SICUs was published in 2016[44]. Two hundred mechanically ventilated patients were allocated to receive early mobility *vs* usual care. Three outcomes were assessed: The mean SICU optimal mobilization score (SOMS) level; length of stay in SICU; and functional independence, measured by the mini-modified functional independence measure score (mmFIM) at hospital discharge. The study showed a mean SOMS of 2.2 in intervention group *vs* 1.5 in control group ($P < 0.0001$). There was a decrease in the SICU length of stay of 3 d, favoring the intervention group ($P = 0.0054$). Lastly, functional independence measured by mmFIM score was also improved ($P = 0.0002$). Few years later, a systematic reviewed and meta-analysis, which included twenty-three RCTs comprising 2308 critically ill patients, assessed the impact of early mobility[45]. The results showed that early mobilization decreased the incidence of ICU-acquired weakness at hospital discharge [three studies, relative risk (RR): 0.60; 95%CI: 0.40 to 0.90; $P = 0.013$], increased the number of ventilator-free days [six studies, standardized mean difference (SMD): 0.17; 95%CI: 0.02 to 0.31; $P = 0.023$], and increased the discharged-to-home rate (seven studies, RR: 1.16, 95%CI: 1.00 to 1.34; $P = 0.046$). Despite the aforementioned positive studies, a number of articles showing lack of impact with the implementation of an early mobility program were also published. Particularly, a meta-analysis that included fourteen studies with a total of 1753 patients showed that early mobilization had no significant impact on short- or long-term mortality, quality of life, or mechanical ventilation duration ($P > 0.05$) [46]. Nevertheless, the program led to greater muscle strength as measured by the Medical Research Council Sum Score, and greater probability of walking without assistance. Both outcomes were measured at hospital discharge. An RCT that included mechanically ventilated patients to receive an intervention of intensive physical therapy *vs* usual care showed that the intensive physical therapy

program did not improve long-term physical performance at 1, 3- or 6-months post-discharge[47]. In this study, physical performance was assessed by a Continuous Scale Physical Functional Performance Test short form. A randomized, parallel-group, assessor-blinded, controlled trial allocated patients who had received a minimum of 48 hours of invasive or non-invasive ventilation to an intervention of 90-min of physical rehabilitation *per* day *vs* a control group, which received 30-min *per* day[48]. At 6 months, there was no difference in the Physical Component Summary of the SF-36 (primary outcome). Another single-center RCT allocated mechanically ventilated patients to an intervention consisting of passive range of motion, physical therapy, and progressive resistance exercises on a daily basis (intervention group) *vs* weekday physical therapy when ordered by the clinical team (control group)[49]. Within tree-hundred randomized subjects, the median hospital stay was 10 d [interquartile range (IQR), 6 to 17] in the intervention arm *vs* 10 d (IQR, 7 to 16) in the control one (median difference, 0; 95%CI: -1.5 to 3; P = 0.41). No differences were seen in ICU or ventilation LOS. Furthermore, no effects were seen at six months in handgrip (P = 0.23), SF-36 physical health score (P = 0.05), or SF-36 mental health score (P = 0.19). Lastly, a recently published RCT that assigned 750 mechanically ventilated patients to receive early mobilization *vs* usual care showed that the median number of days that patients were alive and out of the hospital (primary outcome) was 143 d (IQR 21 to 161) in the intervention group *vs* 145 d (IQR 51 to 164) in the usual care one (P = 0.62)[50]. Of note, the difference of mobilization time between groups was only 12.0 min *per* day (95%CI: 10.4 to 13.6). Despite the previously described data, which showed mixed findings, early mobilization remains a broadly accepted treatment by bedside clinicians and patients. Furthermore, the appropriate 'physical therapy-dose', which may have explained differences in outcomes, remains unknown.

Family involvement

In recent years, a growing number of reports supported the benefits of family member or caregiver involvement in the medical care of critically ill patients. A recent before-and-after study showed that a change in the visiting hour policy from 6-hour to 24-hours resulted in a reduction in the incidence of delirium from 12.1% to 6.7% (P = 0.03)[51]. Furthermore, another study that randomized ICU patients to receiving recorded messages in a family member's voice *vs* same messages in a non-family voice *vs* no messages, resulted in an increase in delirium-free days in the group allocated to receiving familiar voice messages (P = 0.044)[52]. A recently published retrospective cohort study, which compared the effect of physical presence of family *vs* telephone phone calls *vs* no presence, showed no significant association between those events and the prevalence of delirium. However, physical presence of family and telephone encounters were both associated with a reduction on delirium duration compared with no presence (-1.87 d and -1.41 d, respectively; P < 0.001)[53]. These studies underscore the importance of family presence and interaction during critical illness. Nevertheless, research regarding this area is still in its infancy.

EVIDENCE SUPPORTING THE ABCDEF BUNDLE IMPLEMENTATION

In the section above, evidence supporting individual elements of the ABCDEF bundle was described. In this section, the focus is placed on evidence supporting the implementation of the bundle as a whole. Despite its acceptance and broad implementation, evidence supporting the ABCDEF bundle is based on quality improvement projects or observational trials. A prospective cohort quality improvement study, which involved 7 community hospitals within the state of California, assessed hospital survival and delirium- and coma-free days according to the rate of compliance (total *vs* partial) with the ABCDE bundle. Interestingly, among the 6064 patients assessed for survival, for each 10% increment in compliance with the complete bundle, subjects presented 7% higher chances of hospitalization survival (OR, 1.07; 95%CI: 1.04 to 1.11; P < 0.001). Similarly, for each 10% increment in compliance with partial components of the bundle, patients presented 15% higher chances of hospitalization survival (OR, 1.15; 95%CI: 1.09 to 1.22; P < 0.001). Among the 5581 subjects evaluated for delirium and coma-free days, they experienced more days alive and free of delirium and coma with both total and partial bundle compliance [incident rate ratio (IRR) 1.02; 95%CI: 1.01 to 1.04; P = 0.004; and IRR 1.15; 95%CI: 1.09 to 1.22; P < 0.001, respectively][54]. This study demonstrated the value of implementing bundle elements, even when compliance with the entire bundle was not feasible. A subsequent prospective, multicenter, cohort study from a national quality improvement collaborative, which included 15226 critically ill patients demonstrated the benefit of complete bundle compliance and a 'dose-effect' response. In more detail, full bundle compliance resulted in lower likelihood of hospital death within 7 d (adjusted hazard ratio: 0.32; 95%CI: 0.17 to 0.62), delirium (adjusted OR: 0.60; 95%CI: 0.49 to 0.72), coma (adjusted OR: 0.35; 95%CI: 0.22 to 0.56), ICU readmission (adjusted OR: 0.54; 95%CI: 0.37 to 0.79), physical restraint use (adjusted OR: 0.37; 95%CI: 0.30 to 0.46), and dismissal to a facility (adjusted OR: 0.64; 95%CI: 0.51 to 0.80)[55]. Furthermore, a higher proportion of bundle elements utilized in patient care was associated with a lower likelihood of those outcomes. This study demonstrated that full compliance with the bundle was better than partial. Also, within the group of patients who received partial bundle compliance, the higher the number of elements achieved resulted in better outcomes. Finally, a

prospective cohort study assessed the impact of a stepwise implementation of the complete *vs* partial ABCDE bundle on mechanical ventilation duration, ICU and hospital LOS, and costs[56]. At baseline, the ICUs were already compliant with element 'B' of the bundle. In the first phase, elements 'A' and 'D' were implemented in both groups. In the last stage, element 'C' and 'E' were implemented in the group allocated to the fully compliant bundle, whereas no further elements were incorporated in the ICUs allocated to partially compliant. The implementation of the complete (B-AD-EC) *vs* partial (B-AD) bundle was associated with a reduction of ICU LOS (-10.3%; $P = 0.028$), hospital LOS (-7.8%; $P = 0.006$), and mechanical ventilation duration (-22.3%; $P < 0.001$). This study also demonstrated the value of implementing the full ABCDE bundle, rather than partial elements. Further studies assessed the value of the ABCDE bundle in a pre- *vs* post-implementation fashion. An eighteen-month, before-and-after study, which included five ICUs, one step-down unit, and one oncology care unit, showed that patients in the post-implementation period spent three more days breathing without mechanical assistance than those in the pre-implementation group (median, 24 *vs* 21; $P = 0.04$). After adjusting for multiple covariates, patients managed with the bundle had near half odds of presenting delirium (odds ratio, 0.55; 95%CI: 0.3 to 0.9; $P = 0.03$)[57]. Another implementation study, which evaluated the effect of the ABCDE bundle in the prevalence and duration of delirium (measured by the ICDSC tool), showed that after instituting the ABCDE bundle, the prevalence of delirium was reduced (from 38% to 23%, $P = 0.01$) and the mean number of days with delirium also decreased (from 3.8 to 1.72 d, $P < 0.001$)[58]. Lastly, a recently published meta-analysis that included 20 studies assessed the effect of implementing the ABCDE bundle in ICUs. The results revealed a lower incidence of delirium, shorter time on mechanical ventilation and ICU LOS, increased early mobility, and decreased ICU and hospital mortality after bundle implementation[59]. In addition, the study identified frequent barriers for bundle implementation, which included communication and planning challenges, excessive documentation, and fear of risks to the patient. It is important to note that previously described studies addressed the implementation of an ABCDE bundle, rather than an ABCDEF one. The evidence supporting the importance of family involvement (letter F) in ICU care was recently studied. Therefore, at the time the previously described studies were published, data on the relevance of family support were lacking.

MUSIC THERAPY IN THE ICU

Over the last few years, evidence has emerged regarding the impact of music listening in the critical care setting. An RCT performed in an academic medical-surgical ICU randomized mechanically ventilated patients to receive personalized music *vs* slow-tempo music *vs* an audiobook. Each session lasted about 1-hour and they were conducted twice a day for 7 consecutive days. The study revealed equivalent delirium-free days in all 3 groups, but provided feasibility of the aforementioned interventions[60]. A systematic review that included eighteen RCTs with a total of 1173 participant showed that music interventions of 20 to 30 min each were efficacious to reduce pain in adult ICU patients, who were able to self-report[61]. Importantly, 'music listening' should be differentiated from the concept of 'music therapy'. While music listening refers to the passive act of listening to pre-recorded music administered by registered nurses or caregivers, music therapy requires specific training and expertise for its delivery. The American Music Therapy Association defines music therapy as "the clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship by a credentialed professional who has completed an approved music therapy program." Beyond a Bachelor's degree in music therapy, a minimum of 1200 h of clinical training, in addition to credentialing by the Music Therapy-Certification Board are required to provide this therapy[62]. A recent RCT that included 373 mechanically ventilated patients from 12 ICUs at 5 hospitals in Minnesota allocated subjects to self-initiated patient-directed music (PDM) tailored by a music therapist *vs* patient-initiated noise canceling headphones *vs* usual care. The main endpoints were daily evaluations of anxiety (by a 100-mm VAS), and measures of sedative frequency and intensity. Patients included in the music therapy arm listened to music for a mean of 79.8 min/day. The study showed that the PDM group had an anxiety score that was 19.5 points lower than patients in the usual group ($P = 0.003$). There were no differences compared with the noise canceling group. In terms of sedative intensity and frequency, PDM showed lower points on both aspects of sedation (intensity and frequency) compared with noise canceling ($P = 0.01$) and usual care groups ($P = 0.04$)[63]. A subsequent study published by the same group, reported the cost-effectiveness analysis of such music therapy implementation. Direct costs were calculated on US$ based on 2015 standards. Overall, the total mean cost of the PDM was $329.14. The mean anxiety scores -VAS were 33 for PDM and 52 for usual care. The cost savings of PDM over usual care included $2460 in ICU costs, $170 in physician costs, and $22 in sedative medication costs, totaling $2652 (a value eight times the costs of implementing PMD). Notably, the major contributing factor to the cost savings were the estimated 1.4 fewer days of mechanical ventilatory support of patients randomized to PDM[64]. Finally, a recent publication proposed an interesting algorithm for the delivery of music therapy in ICU, incorporating familiar auditory sensory training, in addition to patient-specific music listening. The aforementioned integration resulted in the positive stimulation for medically sedated protocol. Of note, the implementation of this protocol required a previous training in the use of the Music Therapy

Assessment Tool for Awareness in Disorders of Consciousness or its adaptation[65]. In summary, the implementation of music therapy as an enhancement for the ABCDEF bundle is still in its infancy. More studies are needed to assess the effect of such intervention. Nevertheless, current information (although scarce) supports its use in this patient population.

CONCLUSION

Over the last two decades, strong evidence emerged supporting each element of the ABCDEF bundle. Consequently, observational trials and quality improvement projects reported positive outcomes resulting from full bundle implementation. In the author's opinion, recently described interventions may enhance the ABCDEF bundle. The introduction of music therapy protocols in ICU demonstrated reduction in patients' anxiety and direct costs. This intervention seems to be cost-effective, balancing cost-saving *vs* cost of implementing and could be considered as a possible addition to the ABCDEF bundle.

FOOTNOTES

Author contributions: Modrykamien AM Planned and wrote manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Liu GL
L-Editor: A
P-Editor: Liu GL

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 March 9; 12(2): 53-62

DOI: 10.5492/wjccm.v12.i2.53

ISSN 2220-3141 (online)

MINIREVIEWS

Point-of-care ultrasound in diagnosis and management of congestive nephropathy

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Chan AHY, Canada; Hatamnejad MR, Iran

Received: December 23, 2022
Peer-review started: December 23, 2022
First decision: January 5, 2023
Revised: January 8, 2023
Accepted: February 17, 2023
Article in press: February 17, 2023
Published online: March 9, 2023

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Abstract

Congestive nephropathy is kidney dysfunction caused by the impact of elevated venous pressures on renal hemodynamics. As a part of cardiorenal syndrome, the diagnosis is usually made based on history and physical examination, with findings such as jugular venous distension, a third heart sound, and vital signs as supporting findings. More recently, however, these once though objective measures have come under scrutiny for their accuracy. At the same time, bedside ultrasound has increased in popularity and is routinely being used by clinicians to take some of the guess work out of making the diagnosis of volume overload and venous congestion. In this mini-review, we will discuss some of the traditional methods used to measure venous congestion, describe the role of point-of-care ultrasound and how it can ameliorate a clinician's evaluation, and offer a description of venous excess ultrasound score, a relatively novel scoring technique used to objectively quantify congestion. While there is a paucity of published large scale clinical trials evaluating the potential benefit of ultrasonography in venous congestion compared to gold standard invasive measurements, more study is underway to solidify the role of this objective measure in daily clinical practice.

Key Words: Ultrasound; Point-of-care ultrasonography; Doppler; Venous excess ultrasound score; Congestion; Hemodynamics; Heart failure; Nephrology

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Core Tip: Congestive nephropathy denotes kidney dysfunction in fluid overload states as a result of venous congestion. Conventional methods to assess congestion at the bedside lack sensitivity and diagnostic accuracy. Point-of-care ultrasound is emerging as an enhancement to physical examination for objective assessment of congestion and guide therapy. Future research should focus on its impact on practical outcomes such as freedom from congestive symptoms, quality of life, and recurrent hospitalizations.

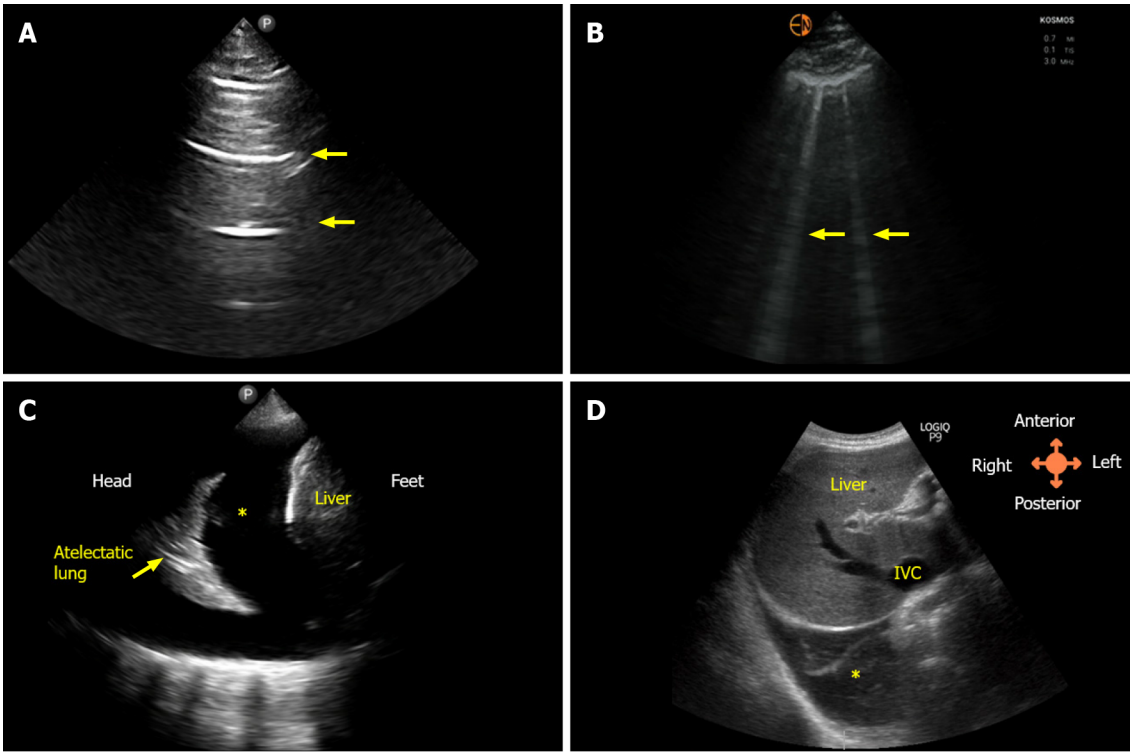
Citation: Turk M, Robertson T, Koratala A. Point-of-care ultrasound in diagnosis and management of congestive nephropathy. *World J Crit Care Med* 2023; 12(2): 53-62
URL: https://www.wjgnet.com/2220-3141/full/v12/i2/53.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i2.53

INTRODUCTION

It is well known that unresolved congestion is associated with adverse outcomes in patients with heart failure, increasing the risk of re-hospitalization and death[1,2]. In 2017 alone, heart failure admissions occurred at a rate of approximately 5 per 1000 United States adults with about a quarter of those patients experiencing readmissions, which highlights the magnitude of this problem[3]. The deleterious effects of fluid overload are now being recognized outside of heart failure, with multiple studies showing a positive fluid balance being associated with increased mortality[4,5]. Though seemingly straightforward, evaluation and management of congestion require a thorough understanding of the pathophysiology and hemodynamic principles. Multiple bedside diagnostic methods and tools exist for clinicians to assess congestion including signs and symptoms, physical examination, laboratory data, and radiography, but these all have limitations. On the other hand, timely diagnosis is vital as faster rates of decongestion are associated with a reduced risk of mortality and hospitalization[6]. In addition, end-organ effects of fluid overload are being increasingly recognized, which brings us to the topic of congestive nephropathy. Congestive nephropathy is defined as renal dysfunction that occurs due to venous congestion leading to impaired organ perfusion[7]. While this term was recently coined[8], several studies have previously shown that elevated central venous pressure (CVP) is associated with worsening renal function despite preserved cardiac index[9]. This does have pathophysiologic basis as the renal perfusion pressure is the difference between mean arterial pressure and CVP; if the CVP is elevated, the perfusion pressure drops, impairing renal blood flow. In addition, activation of the renin angiotensin-aldosterone system and consequent sodium and water retention, interstitial edema, endothelial dysfunction, and increased intra-abdominal pressure all contribute to increased pressure within the encapsulated kidney (*renal tamponade*), ultimately leading to organ dysfunction. Further, renal dysfunction can exacerbate the existing fluid overload, resulting in a vicious cycle. In this article, we will provide a kidney-centric overview of the bedside tools available to assess congestion, focusing on advances in point-of-care ultrasonography (POCUS).

CONVENTIONAL METHODS TO ASSESS CONGESTION

The bedside assessment of a patient's intravascular volume is challenging. Traditionally, this assessment involves taking a thorough history and performing cardiopulmonary physical examination. A patient's given history can often be misleading or not reflective of their hemodynamic physiology. Physical examination, including assessment of jugular venous pressure, lower extremity edema, presence of an 'S3', and auscultation of the lungs for evidence of pulmonary edema, has traditionally been a common way for clinicians to assess intravascular volume status at the bedside. This is wrought with subjectivity and inaccuracies, and has almost no correlation with right heart catheterization, which is the invasive gold-standard assessment[10,11]. Similarly, chest X-ray remains a common modality to diagnose pulmonary congestion resulting from heart failure or other etiologies, despite having considerable diagnostic limitations including high false negative rate[12]. The degree of venous congestion beyond that of the jugular vein, specifically the alteration of blood flow in the hepatic, portal, and renal veins leading to congestive organ injury, cannot be assessed by physical examination or an X-ray. All these traditional approaches have significant limitations and cannot reliably detect hemodynamic congestion. Diagnosis of congestive nephropathy is challenging as no gold standard exists. Traditionally, the diagnosis of congestive nephropathy has been based on clinician gestalt after a trial-and-error period without any objective way to evaluate renal hemodynamics. POCUS using vascular Doppler analysis is emerging as a promising modality to assess for venous congestion along the continuum from the heart to the kidneys.



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Figure 1 Lung ultrasound images. A: Normal lung showing horizontal artifacts, *i.e.*, A-lines (arrows); B: Vertical artifacts (arrows) known as B-lines indicating interlobular septal thickening, typically seen in congestion; C: Pleural effusion (asterisk) as seen on lateral scan; D: Right pleural effusion (asterisk) as seen from subxiphoid scanning window. IVC: Inferior vena cava.

POINT-OF-CARE ULTRASOUND

POCUS is a limited ultrasound examination performed at the bedside and interpreted by the treating physician. It is used to answer focused clinical questions, and is integrated with the patient's history, physical examination, and other available data to narrow the differential diagnosis and inform management. POCUS is becoming more accessible to clinicians owing to the recent advances in ultrasound technology and availability of the low-cost, highly portable equipment. Compared to conventional examination, POCUS offers substantially higher diagnostic accuracy[13]. In the context of heart failure and congestion, POCUS not only aids in the diagnosis, but also guides decongestive therapy with potential implications for patient outcomes. In this section, we will outline the various components of sonographic evaluation of a patient with suspected fluid overload/venous congestion.

Lung ultrasound

Lung ultrasound (LUS) has shown superiority over chest X-ray for nearly all clinical indications[14] and can detect extravascular edema prior to the onset of clinical symptoms. From diagnosing pneumonia[15] to identifying pulmonary edema[16], LUS has proven to be more accurate, and in some settings, more accessible. In a meta-analysis of six studies and more than 1800 patients, LUS had better sensitivity (88% *vs* 73%) when compared to chest X-ray for the diagnosis of cardiogenic pulmonary edema[17]. LUS findings are shown to have prognostic significance in various clinical scenarios including heart failure and end-stage renal disease[18,19]. With respect to guiding therapy, in the recent LUST trial[20], LUS-guided ultrafiltration strategy was associated with a reduction in the recurrence of decompensated heart failure and other cardiovascular events in hemodialysis patients. Similarly, in heart failure patients, LUS-guided management has shown to reduce acute decompensation events and urgent care visits[21, 22]. LUS is an important diagnostic, prognostic, and management tool in the assessment of clinical or subclinical fluid overload. While it does not directly diagnose congestive nephropathy, it influences the treatment by establishing fluid tolerance *vs* intolerance. For example, in a patient with acute kidney injury, presence of extravascular lung water on LUS would sway away the clinician from administering empiric intravenous fluids, thus avoiding iatrogenic fluid overload. Figure 1 illustrates normal and abnormal LUS findings seen in fluid overload.

Focused cardiac ultrasound

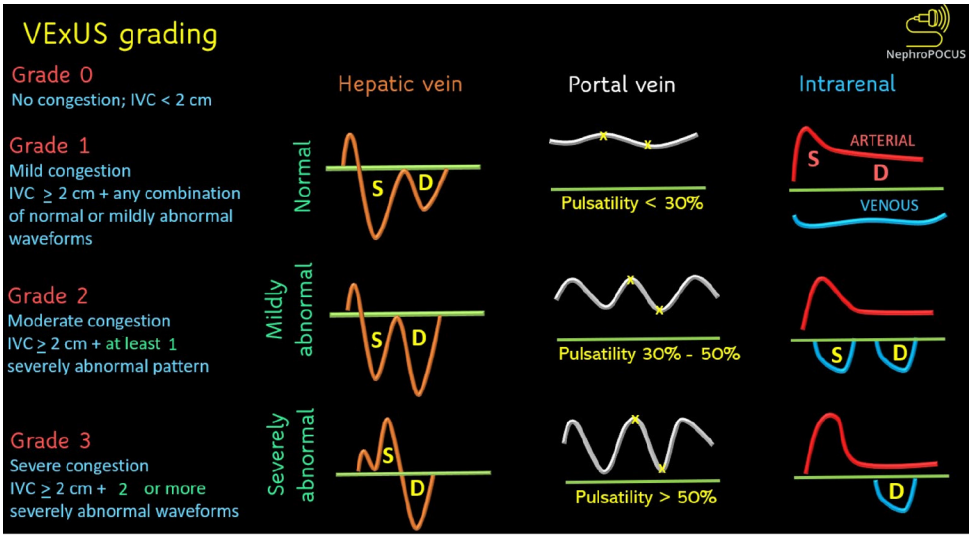
Focused cardiac ultrasound (FoCUS) is a POCUS examination of the heart and inferior vena cava (IVC). Essentially, it is a limited and problem-focused evaluation performed by any clinician trained in POCUS

analogous to auscultation and not restricted to cardiologists. On the contrary, consultative echocardiography involves a comprehensive evaluation documenting a predefined set of parameters and measurements. FoCUS has a much higher diagnostic accuracy than conventional physical examination [23] and quickly provides vital information related to cardiac structure and function. Pathologies requiring immediate attention such as pericardial effusion, impaired contractility, gross chamber enlargement, and valvular anomalies can be diagnosed at the bedside and promptly addressed. In addition, IVC ultrasound allows non-invasive estimation of the CVP/right atrial pressure (RAP). As mentioned, elevated CVP is the starting point of venous congestion and is associated with impaired renal function as well as mortality[24]. In spontaneously breathing patients, current guidelines recommend stratifying RAP as follows. RAP is estimated to be 3 mmHg (0-5 mmHg) if the maximal anteroposterior diameter of the IVC is < 2.1 cm with > 50% collapse during a sniff. If the IVC is > 2.1 cm and collapses < 50%, RAP is documented as 15 mmHg (10-20 mmHg). An intermediate value of 8 mmHg (5-10 mmHg) is assigned where IVC parameters do not fit this paradigm. Elevated RAP estimated by IVC ultrasound is associated with hospital readmissions and mortality[25,26]. Despite its simplicity and apparent clinical utility, isolated IVC ultrasound has several pitfalls. First, estimation of RAP by IVC ultrasound is not accurate in mechanically ventilated patients. Even in those who are spontaneously breathing, strength of 'sniff' considerably varies among patients, leading to false impressions. Moreover, trained athletes and active young adults can have a chronically dilated IVC without elevated RAP whereas patients with elevated intra-abdominal pressure may have a collapsed IVC despite high RAP. In addition, IVC POCUS in long axis is subject to cylinder effect, which means when the ultrasound beam bisects the three-dimensional vessel (presumably a cylinder) in the periphery rather than the center, a falsely low diameter will be recorded. This leads to incorrect interpretation during follow-up studies, particularly when different operators are performing the study. Therefore, the IVC must be examined in both long and short axis views, where feasible[27,28]. Also, in conditions such as cirrhosis, IVC size/shape may be altered by the local structural changes, making it unreliable to predict RAP. Furthermore, it must be noted that isolated IVC POCUS does not provide real-time information on end-organ congestion, which in turn depends on both RAP and venous compliance. In other words, a plethoric IVC increases the probability of congestive organ injury but cannot objectively demonstrate it.

Venous excess ultrasound score: Venous excess ultrasound score (VExUS) stands for venous excess Doppler ultrasound. It involves Doppler evaluation of the abdominal veins (hepatic, portal, and intrarenal) to assess the flow pattern and thereby detect venous congestion that effects organ perfusion. While the Doppler patterns in these individual veins have been studied long before[29-32], the concept of VExUS is fairly new and first documented by Beaubien-Souligny *et al*[33] in 2020. In their study including 145 cardiac surgery patients, the investigators found that severe flow abnormalities in at least two of the three above-mentioned veins together with a dilated IVC (≥ 2 cm) predicts the risk of acute kidney injury (*i.e.*, congestive nephropathy) with a hazard ratio of 3.69, outperforming isolated CVP measurement. Therefore, adding VExUS to IVC ultrasound improves the risk prediction of organ dysfunction. Based on the degree of flow alteration in individual veins, a scoring system was proposed to quantify systemic venous congestion, which is illustrated in Figure 2. In addition to diagnosing congestion, VExUS allows objective monitoring of congestion while the patient is receiving decongestive therapy as these waveforms are dynamic[34]. For example, Argaiz *et al*[35] have demonstrated that improvement in portal vein pulsatility coincides with improvement in renal function in patients with heart failure receiving diuretic therapy. In addition, several case reports exist demonstrating this phenomenon in multiple veins[36-41]. While there have not been published randomized clinical trials to date, outcome data for VExUS is emerging in the literature. For example, a high VExUS score, indicating severe hemodynamic congestion, has been shown to be associated with development of acute kidney injury in various clinical settings[34,42]. Specifically in heart failure patients, altered renal vein flow has been shown to confer worse outcomes[32,43,44]. In isolation, all these waveforms have limitations, which we have discussed in detail previously and is beyond the scope of this manuscript[45,46]. Of particular note, VExUS cannot distinguish between volume and pressure overload. For instance, a patient with precapillary pulmonary hypertension can have the same Doppler stigmata of congestion as a patient with iatrogenic fluid overload. It is up to the clinician to interpret the findings in the appropriate clinical context and in conjunction with other sonographic parameters (*e.g.*, Doppler echocardiography). Having said that, congestion from any cause (pressure or volume) still leads to congestive nephropathy. In a large cohort of patients with pulmonary hypertension, Husain-Syed *et al* [47] showed that intrarenal venous congestion correlates with renal dysfunction as well as mortality/morbidity end point, which exemplifies this concept.

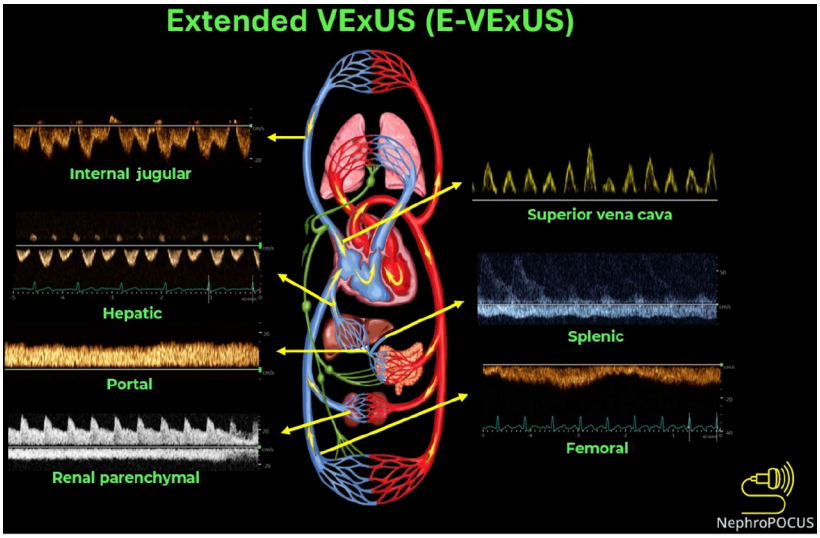
Extended VExUS

The term extended venous excess ultrasound score (E-VExUS) or extended VExUS has been proposed to include Doppler interrogation of additional veins such as the internal jugular, superior vena cava, splenic, and femoral veins in situations where the primary veins (*e.g.*, hepatic, portal in cirrhosis, and intrarenal in advanced kidney disease) suffer from limitations[28,48]. This also includes estimation of RAP by greyscale POCUS of the internal jugular vein where IVC is not accessible or unreliable. Doppler



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Figure 2 Venous excess ultrasound grading. When the diameter of the inferior vena cava is > 2 cm, three grades of congestion are defined based on the severity of abnormalities on hepatic, portal, and renal parenchymal venous Doppler. Hepatic vein Doppler is considered mildly abnormal when the systolic (S) wave is smaller than the diastolic (D) wave, but still below the baseline; it is considered severely abnormal when the S-wave is reversed. Portal vein Doppler is considered mildly abnormal when the pulsatility is 30% to 50%, and severely abnormal when it is ≥ 50%. Asterisks represent points of pulsatility measurement. Renal parenchymal vein Doppler is mildly abnormal when it is pulsatile with distinct S and D components, and severely abnormal when it is monophasic with D-only pattern. Figure adapted from NephroPOCUS.com with permission.



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Figure 3 Doppler components of extended venous excess ultrasound score examination. Figure adapted from NephroPOCUS.com with permission.

components of E-VExUS are illustrated in Figure 3. Similar to the components of original VExUS, these veins have also been studied individually and shown to be useful to gauge the effects of elevated RAP [49-53]. Of late, femoral vein Doppler is gaining attention due to relative ease of image acquisition. In a recent study including 57 patients undergoing right heart catheterization, femoral vein flow alteration graded by stasis index showed excellent diagnostic performance to detect elevated RAP (specificity: 92.3% [80.0-99.3]; diagnostic accuracy: 90.4 [77.4-97.3]; positive likelihood ratio: 12.5 [3.01-51.97])[54]. However, caution must be exercised in 'excluding' elevated RAP/venous congestion based on the femoral vein alone as earlier studies showed a relatively low sensitivity[55]. This VExUS expansion is still in its early stages of adoption, so there is need for more data to establish its clinical utility in routine practice. Figure 4 is the sonographic representation of chain of venous congestion from the right heart to femoral vein. Table 1 summarizes the key sonographic findings and limitations of each application in the context of congestive nephropathy.

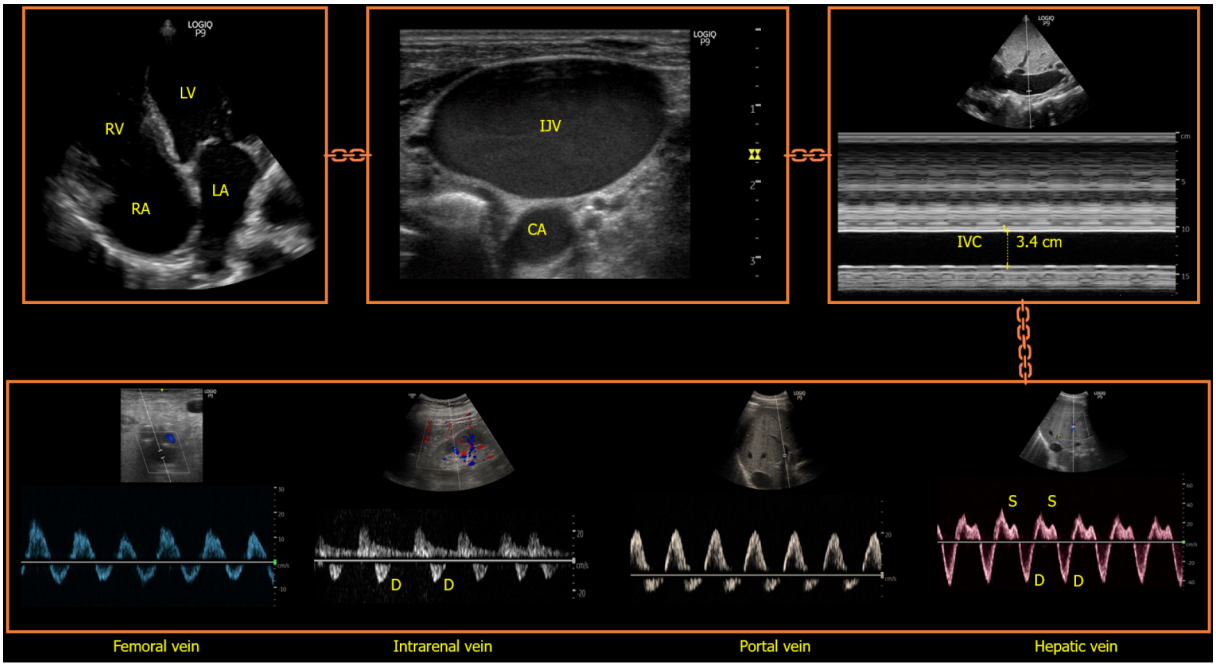
Table 1 Key sonographic findings and limitations of each application in the evaluation of congestive nephropathy

Sonographic application	Possible findings in the context of congestive nephropathy	Limitations
Lung ultrasound	Elevated extravascular lung water (B-lines) and pleural effusion	B-lines are non-specific and can be seen in non-cardiogenic pulmonary edema, lung fibrosis, contusion, and alveolar hemorrhage
Focused cardiac ultrasound (basic)	LV systolic dysfunction (qualitative and M-mode); RV systolic dysfunction (qualitative and M-mode); Pericardial effusion; Gross chamber enlargement (*e.g.*, RV dilation leading to interventricular septal flattening); Gross valvular dysfunction (*e.g.*, tricuspid regurgitation on color Doppler); Elevated right atrial pressure (plethoric IVC)	Lack of spectral Doppler provides limited information. Qualitative assessment relies on operator experience. IVC cannot reliably estimate RAP in mechanically ventilated patients. IVC can be small in intra-abdominal hypertension despite elevated RAP. IVC can be dilated without elevated RAP in trained athletes
Focused cardiac ultrasound (advanced)	Reduced stroke volume assessed by LV outflow tract velocity time integral. Elevated LV filling pressures assessed by mitral inflow Doppler and mitral annular tissue Doppler. Elevated pulmonary artery pressures/right ventricular systolic pressure assessed by continuous wave Doppler through the RV outflow tract and tricuspid valve. Elevated right atrial pressure assessed by tricuspid inflow and tissue Doppler	Requires higher operator skill level and training than basic cardiac ultrasound. Suboptimal views/Doppler angle limit the accuracy of measurements obtained. Some of the parameters lack validation in critical illness
Hepatic vein Doppler	Reduced amplitude or reversal of the systolic wave (Normally, systolic wave is larger than the diastolic wave)	Prone to erroneous interpretation without EKG. Cannot differentiate pressure and volume overload (applies to all components of VExUS and E-VExUS). Influenced by factors other than RAP (*e.g.*, atrial fibrillation, RV systolic excursion). Diminished pulsatility in cirrhosis; may not accurately reflect the degree of congestion
Portal vein Doppler	Increased pulsatility (normal waveform is near-continuous)	Pulsatile portal vein can be seen in cirrhosis and healthy, young individuals without an elevated RAP. Can appear falsely normal despite elevated RAP in patients with portal hypertension
Intra-renal venous Doppler	Increased pulsatility, systolic wave reversal (normal waveform is near-continuous)	Most technically challenging of the three components of VExUS. Sampling a larger vessel such as the main renal vein instead of interlobar vein leads to mistaken interpretation
E-VExUS	IJ vein: Reduced amplitude or reversal of the systolic wave (normally, systolic wave is larger than the diastolic wave); Splenic vein: Increased pulsatility (normal waveform is near-continuous); SVC: Reduced amplitude or reversal of the systolic wave (normally, systolic wave is larger than the diastolic wave); Femoral: Increased pulsatility and elevated velocity of the retrograde component (normal waveform is near-continuous)	Not validated as a combination score though individual components are studied. EKG is required when there is no simultaneous arterial trace to delineate cardiac cycles. IJ vein: Susceptible to probe pressure due to its relatively superficial location. Splenic vein: Similar limitations as portal vein. SVC: Technically challenging to access *via* transthoracic windows. Femoral: Relatively less sensitive to detect elevated RAP. Severe intra-abdominal hypertension may influence the waveform

LV: Left ventricle; RV: Right ventricle; M-mode: Motion mode; IVC: Inferior vena cava; EKG: Electrocardiogram; VExUS: Venous excess ultrasound; RAP: Right atrial pressure; RV: Right ventricle; E-VExUS: Extended venous excess ultrasound; IJ: Internal jugular; SVC: Superior vena cava.

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

While POCUS has gained a lot of traction over the last several years, it is sometimes met with a degree of skepticism. Detractors are quick to point out that a significant mortality benefit with use of POCUS has not been shown. For example, the SHoC-ED trial randomized almost 300 patients with undifferentiated shock into a POCUS plus standard of care *vs* standard of care without ultrasonography to help diagnose the etiology of shock and help manage the condition. This showed no mortality benefit, no decrease in length of stay, decrease in intravenous fluid use, or decrease in rates of computed tomography scanning[55]. Conversely, the supporters of POCUS are quick to point out that achieving a mortality benefit in an intervention that is not therapeutic is a mountain that may prove too high to climb; in essence, unfair to expect of a diagnostic modality. In most cases, POCUS and VExUS scoring help quantify congestion in an objective manner and allow clinicians to rely much less on other unreliably recorded measures such as daily weights and intake-output documentation. Several randomized controlled trials incorporating VExUS are currently underway to determine its efficacy not only in the diagnosis but also in guiding the management such as for dosing diuretics. The use of elements of the extended VExUS examination needs to be further validated in population wide studies before becoming mainstays of the evaluation. Due to the medical community's long-standing affinity for objective scoring systems, VExUS will without a doubt become more commonplace. However, there will continue to be significant demand from clinicians for a show of mortality reduction before the practice becomes widely adopted. In the meantime, it is important to give weight to other outcomes such as time to diagnosis, readmission rates, recovery of renal function, symptom burden from heart failure and congestion, and quality of life in the judgment of this emerging technique. On the other hand, we do acknowledge that POCUS training remains an unmet need currently. Applications such as Doppler echocardiography, VExUS, and E-VExUS require solid technical skills that can only be garnered by longitudinal training. Especially in nephrology, there are a very few fellowship programs that offer



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Figure 4 The chain of venous congestion: Apical view of the heart is shown in the upper left corner where bulging of the interatrial septum into the left atrium can be noted suggestive of high right atrial pressure. Next image shows significantly dilated internal jugular vein followed by a plethoric inferior vena cava. Lower panel represents the commonly assessed Doppler parameters to assess systemic venous congestion, all of which are severely abnormal. Please see Figure 3 for the normal appearance of these waveforms and Figure 2 for venous excess ultrasound score grading. RA: Right atrium; RV: Right ventricle; LA: Left atrium; LV: Left ventricle; CA: Carotid artery; S: Systolic wave; D: Diastolic wave.

training in comprehensive hemodynamic assessment at this time[56,57]. This is ironic given that most of the consults in a typical nephrology practice revolve around managing fluid disorders. While the situation is slightly better in critical care medicine, guideline-mandated training requirements remain vague. As such, professional organizations must step up and establish robust POCUS certification and competency assessment standards. Otherwise, performance of advanced sonographic applications by inadequately trained physicians may potentially result in patient harm.

CONCLUSION

It is well known that hemodynamic congestion has adverse effects on multi-organ function and is associated with adverse clinical outcomes. Ultrasonographic techniques have long been used to quantify venous congestion and have been validated extensively in the medical literature. The combination of Doppler findings from several organ systems into an objective evaluation is a process that has been undergoing significant study in recent years. While VExUS has its limitations, it has promise as a dependable tool in the management of congestive nephropathy and is superior to any other bedside noninvasive assessment. As with other diagnostic tools, it is critical that clinicians analyze their findings as just one part of the larger clinical puzzle in conjunction with other objective data points. In the correct clinical context, using VExUS findings to apply individualized changes to care plans may ultimately help deliver more accurate care to patients with suspected congestive nephropathy.

FOOTNOTES

Author contributions: Turk M and Roberson T drafted the manuscript; Koratala A designed and reviewed the manuscript, and revised it for critical intellectual content; all authors have read and approved the final version.

Conflict-of-interest statement: All the authors declare no potential conflicts of interest for this article.

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S-Editor: Liu JH
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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 March 9; 12(2): 63-70

DOI: 10.5492/wjccm.v12.i2.63

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Observational Study

Elevated soluble fas blood concentrations in patients dying from spontaneous intracerebral hemorrhage

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Exbrayat JM, France; Lei Y, China

Received: October 14, 2022
Peer-review started: October 14, 2022
First decision: November 22, 2022
Revised: December 9, 2022
Accepted: February 1, 2023
Article in press: February 1, 2023
Published online: March 9, 2023

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Abstract

BACKGROUND

Several studies of spontaneous intracerebral hemorrhage (SICH) patients have shown apoptotic changes in brain samples after hematoma evacuation. However, there have been no data on the association between blood concentrations of soluble fas (sFas) (the main surface death receptor of the extrinsic apoptosis pathway) and the prognosis of spontaneous intracranial hypotension (SIH) patients.

AIM

To determine whether there is an association between blood sFas concentrations

and SICH patient mortality.

METHODS
We included patients with severe and supratentorial SIH. Severe was defined as having Glasgow Coma Scale < 9. We determined serum sFas concentrations at the time of severe SICH diagnosis.

RESULTS
We found that non-surviving patients (n = 36) compared to surviving patients (n = 39) had higher ICH score (P = 0.001), higher midline shift (P = 0.004), higher serum sFas concentrations (P < 0.001), and lower rate of early hematoma evacuation (P = 0.04). Multiple logistic regression analysis showed an association between serum sFas concentrations and 30-d mortality (odds ratio = 1.070; 95% confidence interval = 1.014-1.129; P = 0.01) controlling for ICH score, midline shift, and early hematoma evacuation.

CONCLUSION
The association of blood sFas concentrations and SICH patient mortality is a novel finding in our study.

Key Words: Spontaneous intracerebral hemorrhage; Soluble fas; Apoptosis; Patients; Mortality

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Core Tip: Several studies of spontaneous intracerebral hemorrhage (SICH) patients have shown apoptotic changes in brain samples after hematoma evacuation. However, there are no data on the association of blood concentrations of soluble fas (sFas) (the main surface death receptor of the extrinsic apoptosis pathway) with SICH patient prognosis. The objective of our study was to determine whether there is an association between blood sFas concentrations and SICH patient mortality. The association of blood sFas concentrations with SICH patient mortality is a novel finding of this study.

Citation: Lorente L, Martín MM, Pérez-Cejas A, Ramos-Gómez L, Solé-Violan J, Cáceres JJ, Jiménez A, González-Rivero AF. Elevated soluble fas blood concentrations in patients dying from spontaneous intracerebral hemorrhage. *World J Crit Care Med* 2023; 12(2): 63-70
URL: https://www.wjgnet.com/2220-3141/full/v12/i2/63.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i2.63

INTRODUCTION

Spontaneous intracerebral hemorrhage (SICH) leads to many disabilities and deaths annually worldwide[1]. Several studies of SICH patients undergoing surgical hematoma evacuation have shown apoptotic changes in brain samples from areas of hematoma compared with areas of the healthy brain[2-8]. Apoptosis can be activated by the release of mitochondrial cytochrome c into the cytoplasm (named the mitochondrial or intrinsic apoptosis pathway) or by the binding of a surface death receptor to its ligand (named extrinsic apoptosis pathway). The main surface death receptor is Fas, and its ligand is the FasL[2-8]. When binding between Fas and FasL occurs, a death signal appears and the the extrinsic pathway is activated. This death signal is responsible for the activation of caspase-8 (initiator caspase in the extrinsic apoptosis pathway), which leads to the activation of caspase-3 (the main effector caspase in extrinsic and intrinsic apoptosis pathways). Finally, caspase-3 is responsible for cell death[2-8]. Lower plasma Fas concentrations have been found in SICH patients than in healthy controls[9]. However, there are no data on the association between blood Fas concentrations and SICH patient prognosis.

Thus, the objective of this study was to determine whether there is an association between blood Fas concentrations and SICH patient mortality.

MATERIALS AND METHODS

Design and subjects

The following five Spanish Intensive Care Units recruited patients from 2016 to 2017 in this observational and prospective study: H General de La Palma, H Insular de Las Palmas de Gran Canaria, H Universitario de Canarias (San Cristóbal de La Laguna), H Universitario Nuestra Señora de Candelaria

(Santa Cruz de Tenerife), and H Universitario Dr. Negrín (Las Palmas de Gran Canaria). The study was performed with approval of the research ethic committee of each hospital, and written informed consent was provided by a family member of each patient.

We recruited 75 patients (29 females and 46 males) with severe and supratentorial SICH. Severe was defined as Glasgow coma scale (GCS) < 9[10]. We excluded patients aged < 18 years, pregnancy, malignant disease, or limited interventions order at hospital admission. In addition, we excluded patients with traumatic hemorrhage, hemorrhagic transformation of brain infarction, infratentorial hemorrhage or primary intraventricular hemorrhage (IVH). We also excluded patients in whom SICH was due to aneurysm, arteriovenous malformation, anticoagulant treatment, or fibrinolytic treatment.

We considered that SICH was due to hypertension if the patient was hypertensive and had no other cause of SICH. We considered that SICH was due to amyloid angiopathy if the patient was not hypertensive and any other cause of SICH was recorded. We considered that SICH was due to arteriovenous malformation or aneurysm if some of those findings were shown in computed tomography angiography. We considered that SICH was due to anticoagulant treatment or fibrinolytic treatment if some of those drugs were administered to the patient.

We registered the following data: Age, sex, GCS, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, fibrinogen, international normalized ratio, platelets, activated partial thromboplastin time, lactic acid, glycemia and creatinine[11]. We also registered volume (calculated by the formula $AxBxCx0.5$); site and cause of SICH; ICH score; and the existence of transtentorial herniation, hydrocephalus, IVH, or midline shift. In addition, we registered the existence of early hematoma evacuation (within first 24 h of SICH diagnosis) and of mortality during the first 30 d[12,13].

Blood samples and determination of serum Fas concentrations

We collected serum samples at the time of severe SICH diagnosis and froze the samples at -80 °C. We determined all soluble fas (sFas) concentrations at the same time with a Human Fas enzyme-linked immunoassay (ELISA) Kit (Elabscience, Houston, TX, United States), which had 19 pg/mL as the detection limit and < 6% as the intra- and inter-assay variation coefficients. This kit uses sandwich ELISA as the method. The micro ELISA plate provided in this kit was pre-coated with an antibody specific to human Fas. The optical density (OD) was measured with spectrophotometry at a wavelength of 450 ± 2 nm. The OD value was proportional to the concentration of human Fas. The concentration of human Fas in samples was calculated by comparing the OD of the samples with the standard curve. Some of those patients were included in our previous publication determining serum sFasL concentrations, and serum sFas concentrations were determined in the current work[14].

Statistical analyses

We described continuous variables as medians (interquartile ranges) and categorical variables as frequencies (percentages). We compared continuous variables by the Wilcoxon-Mann-Whitney test and categorical variables by the chi-square test. The estimation of 30-d mortality prediction for serum sFas concentrations was performed using receiver operating characteristic analysis. We constructed Kaplan-Meier curves of 30-d mortality in patients with serum sFas concentrations higher and lower than 63 ng/mL (which was the Youden J index). We analyzed the possible association of serum Fas concentrations and SICH patient mortality controlling for ICH score, midline shift, and early hematoma evacuation. Statistical analyses were performed using LogXact 4.1 (Cytel Co., Cambridge, MA, United States) and SPSS 17.0 (SPSS Inc., Chicago, IL, United States), and $P < 0.05$ was considered statistically significant.

RESULTS

We found that non-surviving patients ($n = 36$) with respect to surviving patients ($n = 39$) had higher age ($P = 0.001$), APACHE-II score ($P < 0.001$), ICH score ($P = 0.001$), ICH volume ($P = 0.04$), midline shift ($P = 0.004$), and serum sFas concentrations ($P < 0.001$). In addition, non-surviving patients with respect to surviving patients had lower GCS ($P < 0.001$) and lower rate of early hematoma evacuation ($P = 0.04$) (Table 1).

We found that serum sFas concentrations had an area under the curve for mortality prediction of 83% (95% confidence interval [CI] = 72%-90%; $P < 0.001$) (Figure 1). The mortality prediction for serum sFas concentrations cutoff point of 63 ng/mL had sensitivity of 72% (55%-86%), specificity of 77% (61%-89%), negative likelihood ratio of 0.4 (0.2-0.6), positive likelihood ratio of 3.1 (1.7-5.7), negative predictive value of 75% (63%-84%), and positive predictive value of 74% (61%-84%). We found in the Kaplan-Meier analysis that patients with serum sFas concentrations > 63 ng/mL showed higher death risk (hazard ratio = 4.7; 95%CI = 2.3-97; $P < 0.001$) (Figure 2). Multiple logistic regression analysis showed an association between serum sFas concentrations and 30-d mortality (odds ratio = 1.070; 95%CI = 1.014-1.129; $P = 0.01$) controlling for ICH score, midline shift, and early hematoma evacuation (Table 2).

Table 1 Clinical and biochemical characteristics of 30 d surviving and non-surviving patients with spontaneous intracerebral hemorrhage

Variable	Surviving, *n* = 39	Non-surviving, *n* = 36	*P* value
Sex, *n* (%)			0.35
Female	13 (33.3)	16 (44.4)	
Male	26 (66.6)	20 (55.6)	
Age in yr, *n* (median *P* 25-75)	57 (51-63)	68 (57-75)	0.001
Cause of SIH, *n* (%)			0.99
Hypertension	35 (89.7)	33 (91.7)	
Amyloid angiopathy	4 (10.3)	3 (8.3)	
Volume of SIH in cc, *n* (median *P* 25-75)	41 (23-66)	72 (29-98)	0.04
Transtentorial herniation, *n* (%)	2 (5.1)	2 (5.6)	0.99
Hydrocephalus, *n* (%)	17 (43.6)	23 (63.9)	0.11
Intraventricular hemorrhage, *n* (%)	13 (33.3)	20 (56.6)	0.07
Site of SIH, *n* (%)			0.91
Lobar	24 (61.5)	23 (63.9)	
Basal ganglia	7 (17.9)	7 (19.4)	
Thalamus	8 (20.5)	6 (16.7)	
Midline shift in mm, *n* (median *P* 25-75)	5 (0-8)	10 (5-15)	0.004
GCS, *n* (median *P* 25-75)	8 (6-8)	4 (3-7)	< 0.001
APACHE-II score, *n* (median *P* 25-75)	19 (15-21)	25 (23-28)	< 0.001
ICH score, *n* (median *P* 25-75)	2 (1-3)	3 (2-4)	< 0.001
aPTT in s, *n* (median *P* 25-75)	29 (26-30)	29 (24-33)	0.28
Platelets as $\times 10^3/mm^3$, *n* (median *P* 25-75)	208 (161-262)	200 (143-259)	0.83
Fibrinogen in mg/dL, *n* (median *P* 25-75)	402 (311-626)	487 (366-542)	0.42
INR, *n* (median *P* 25-75)	1.07 (0.94-1.21)	1.09 (0.90-1.21)	0.76
Lactic acid in mmol/L, *n* (median *P* 25-75)	1.60 (0.90-2.10)	1.75 (1.20-2.70)	0.07
Glycemia in g/dL, *n* (median *P* 25-75)	140 (120-194)	166 (133-211)	0.06
Sodium in mEq/L, *n* (median *P* 25-75)	140 (137-143)	139 (136-145)	0.79
Creatinine in mg/dL, *n* (median *P* 25-75)	0.80 (0.60-0.91)	0.80 (0.60-1.10)	0.90
PaO_2/FIO_2 ratio, *n* (median *P* 25-75)	296 (194-375)	270 (214-387)	0.83
Early hematoma evacuation, *n* (%)	15 (38.5)	6 (16.7)	0.04
sFas in ng/mL, *n* (median *P* 25-75)	22 (17-63)	141 (49-286)	< 0.001

APACHE II: Acute Physiology and Chronic Health Evaluation; aPTT: Activated partial thromboplastin time; FIO_2: Fraction inspired of oxygen; GCS: Glasgow Coma Scale; ICH: Intracerebral hemorrhage; INR: International normalized ratio; PaO_2: Pressure arterial of oxygen; SICH: Spontaneous intracerebral hemorrhage; SIH: Spontaneous intracranial hypotension.

DISCUSSION

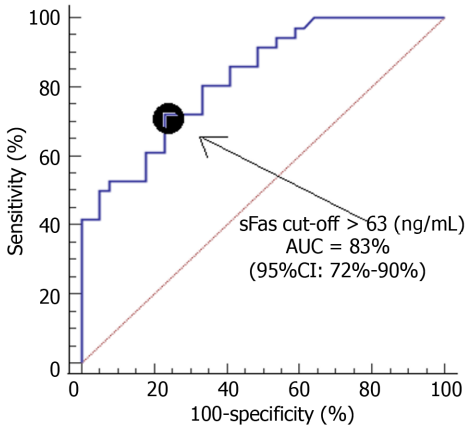
Several studies of SICH patients have shown apoptotic changes in brain samples after hematoma evacuation[2-8]. However, there are no data on the association of blood concentrations of sFas with SICH patient prognosis. Our study reports the novel findings of the existence of higher serum sFas concentrations in non-survivor than survivor SICH patients and the existence of an association between serum sFas concentrations and 30-d mortality controlling SICH severity and early hematoma evacuation.

Fas is the main surface death receptor of the apoptosis extrinsic pathway. After binding to its specific receptor (FasL), a death signal appears that is responsible for the activation of caspase-8 activation[2-8].

Table 2 Multiple logistic regression analysis to predict 30 d mortality

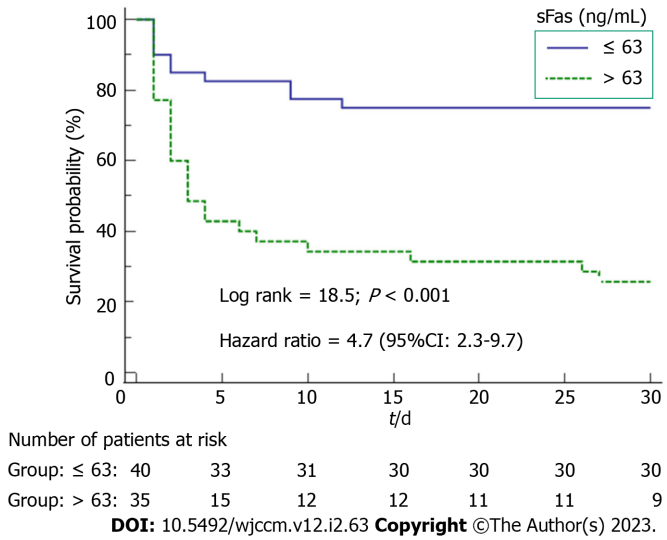
Variable	Odds ratio	95%CI	*P* value
Serum sFas in ng/mL	1.070	1.014-1.129	0.01
ICH score as points	47.71	2.24-1012.34	0.01
Midline shift in mm	1.758	1.133-2.727	0.01
Early hematoma evacuation as yes *vs* no	0.002	0.001-0.210	0.01

CI: Confidence interval; ICH: Intracerebral hemorrhage.



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Figure 1 Receiver operating characteristic analysis using serum soluble fas levels as a predictor of mortality at 30 d. AUC: Area under curve; CI: Confidence interval.



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Figure 2 Survival curves at 30 d using serum soluble fas levels of 63 ng/mL as the cutoff. CI: Confidence interval.

Afterwards, when this initiator caspase of the apoptosis extrinsic pathway (caspase-8) is activated, the activation of executor caspase (caspase-3) occurs. Finally, activation of this executor caspase is responsible for apoptotic cellular death[2-8]. Thus, it is possible that the findings of our study showing higher serum sFas concentrations in non-survivor with respect to survivor patients may reflect a lower apoptosis degree due to lower activation of the apoptosis extrinsic pathway in survivor patients. However, a limitation of our study was the fact that apoptotic brain damage was not assessed. In addition, the absence of serum sFas concentrations during patient evolution and in healthy subjects were other limitations. A promising finding is that the administration of Fas/FasL system inhibitors is associated with a reduction of neuronal cell death in rat models of brain ischemia[15-17]. Therefore, we

believe that the findings from our study showing higher serum sFas concentrations in non-survivor with respect to survivor SICH patients and those findings from brain ischemia animal models showing the reduction of neuronal cell death using Fas/FasL system inhibitors could motivate research on the Fas/FasL system and its modulation in SICH patients.

CONCLUSION

The association of blood sFas concentrations and SICH patient mortality is a novel finding in our study.

ARTICLE HIGHLIGHTS

Research background

Several studies of spontaneous intracerebral hemorrhage (SICH) patients have shown apoptotic changes in brain samples after hematoma evacuation.

Research motivation

There are no data on the association of blood concentrations of soluble fas (sFas) (the main surface death receptor of extrinsic apoptosis pathway) with SICH patient prognosis.

Research objectives

To determine whether there is an association between blood sFas concentrations and SICH patient mortality.

Research methods

We included patients with severe and supratentorial SICH. Severe was defined as having Glasgow coma scale < 9. We determined serum sFas concentrations at the time of severe SICH diagnosis.

Research results

We found that non-surviving patients (n = 36) compared to surviving patients (n = 39) had higher ICH score (P = 0.001), higher midline shift (P = 0.004), higher serum sFas concentrations (P < 0.001), and lower rate of early hematoma evacuation (P = 0.04). Multiple logistic regression analysis showed an association between serum sFas concentrations and 30-d mortality (odds ratio = 1.070; 95% confidence interval = 1.014-1.129; P = 0.01) controlling for ICH score, midline shift, and early hematoma evacuation.

Research conclusions

The association of blood sFas concentrations and SICH patient mortality is a novel finding in our study.

Research perspectives

The beneficial results of blockade of the Fas system in animal models could motivate its investigation in these patients.

FOOTNOTES

Author contributions: Lorente L conceived, designed and coordinated the study, made substantial contributions to the acquisition, analysis and interpretation of data, and drafted the manuscript; Martín MM, Ramos-Gómez L, Solé-Violan J, and Cáceres JJ made substantial contributions to the acquisition of data and provided useful suggestions; Pérez-Cejas A and González-Rivero AF determined the blood concentrations; Jiménez A made substantial contributions to the data analysis and interpretation.

Institutional review board statement: The Institutional Board of each hospital approved the study protocol: H. General de La Palma, H. Insular de Las Palmas de Gran Canaria, H. Universitario de Canarias (San Cristóbal de La Laguna), H. Universitario Nuestra Señora de Candelaria (Santa Cruz de Tenerife), and H. Universitario Dr. Negrín (Las Palmas de Gran Canaria).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors have no conflicts of interest to declare.

Data sharing statement: The datasets generated during the current study are available from the corresponding author

on reasonable request.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Wang LL
L-Editor: Filipodia
P-Editor: Wang LL

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World Journal of Critical Care Medicine

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World J Crit Care Med 2023 March 9; 12(2): 71-88

DOI: 10.5492/wjccm.v12.i2.71

ISSN 2220-3141 (online)

SYSTEMATIC REVIEWS

Extracorporeal blood purification strategies in sepsis and septic shock: An insight into recent advancements

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Specialty type: Critical care medicine

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Rodrigues AT, Brazil; Wang HD, China

Received: November 22, 2022
Peer-review started: November 22, 2022
First decision: December 26, 2022
Revised: January 5, 2023
Accepted: February 17, 2023
Article in press: February 17, 2023
Published online: March 9, 2023

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Abstract

BACKGROUND

Despite various therapies to treat sepsis, it is one of the leading causes of mortality in the intensive care unit patients globally. Knowledge about the pathophysiology of sepsis has sparked interest in extracorporeal therapies (ECT) which are intended to balance the dysregulation of the immune system by removing excessive levels of inflammatory mediators.

AIM

To review recent data on the use of ECT in sepsis and to assess their effects on various inflammatory and clinical outcomes.

METHODS

In this review, an extensive English literature search was conducted from the last two decades to identify the use of ECT in sepsis. A total of 68 articles from peer-reviewed and indexed journals were selected excluding publications with only abstracts.

RESULTS

Results showed that ECT techniques such as high-volume hemofiltration, coupled plasma adsorption/filtration, resin or polymer adsorbers, and CytoSorb® are emerging as adjunct therapies to improve hemodynamic stability in sepsis. CytoSorb® has the most published data in regard to the use in the field of septic shock with reports on improved survival rates and lowered sequential organ failure assessment scores, lactate levels, total leucocyte count, platelet count, interleukin- IL-6, IL-10, and TNF levels.

CONCLUSION

Clinical acceptance of ECT in sepsis and septic shock is currently still limited due to a lack of large random clinical trials. In addition to patient-tailored therapies, future research developments with therapies targeting the cellular level of the immune response are expected.

Key Words: CytoSorb®; Hemadsorbers; Inflammatory mediators; Extracorporeal therapies; Sepsis

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Core Tip: Sepsis is one of the leading causes of mortality in critically ill patients globally. Substantial progress is made in the field of extracorporeal therapies and sepsis. CytoSorb® is emerging as an adjunct therapy to improve hemodynamic stability. This device is an International Organization for Standardization certified, European Conformité Européenne mark-approved class IIb medical device that is designed to remove excess inflammatory cytokines from the blood. There are extensive published reports of its use in the field of septic shock with improved survival rates and other improved biochemical parameters. However, clinical acceptance is still limited due to a lack of large random clinical trials.

Citation: Mehta Y, Paul R, Ansari AS, Banerjee T, Gunaydin S, Nassiri AA, Pappalardo F, Premužić V, Sathe P, Singh V, Vela ER. Extracorporeal blood purification strategies in sepsis and septic shock: An insight into recent advancements. *World J Crit Care Med* 2023; 12(2): 71-88
URL: https://www.wjgnet.com/2220-3141/full/v12/i2/71.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i2.71

INTRODUCTION

Sepsis is a global major life-threatening syndrome causing multiple organ dysfunction syndrome (MODS)[1]. The World Health Organization described the global estimate of sepsis morbidity and mortality[2] in 2017, as 48.9 million cases with 11 million sepsis related deaths. This estimate accounts for 20% of deaths worldwide[3]. In the United States, the incidence of severe sepsis and septic shock is reported as 300 cases per 100000 individuals, costing more than 20 billion dollars per year[4]. In 2005, there were 430 cases of severe sepsis per 100000 people in Sweden. Furthermore, in clinical cohort studies involving 198 European intensive care unit (ICU), the incidence of sepsis is 11.8% in Australia and New Zealand, 14.6% in France, 27.1% in the United Kingdom, and 30% in the SOAP study. Sepsis has steadily increased in most developed countries over the last several decades[5,6].

The definition of sepsis has evolved over the years and is currently defined as a life- threatening organ dysfunction caused by a dysregulated immune response of the host to infection[1]. Over stimulation of the immune response leads to a cytokine storm, which may lead to septic shock, capillary leakage, and microcirculatory disturbances finally resulting in MODS. The dysregulated reaction,

however, may also lead to a protracted phase of immunoparalysis, contributing to the risk of secondary, hospital acquired infections[7].

Conventional therapies for sepsis mainly focus on fluid resuscitation, source control measures and antimicrobial administration within 1 h of recognition[8]. New therapeutic strategies aim to restore the immune balance by eliminating/ deactivating inflammatory mediators[7,9]. Extracorporeal therapies (ECT), otherwise known as blood purification therapies target attenuation of the immune response by reducing the circulating levels of cytokines and triggers that potentiate the response (endotoxins, pathogen associated molecular patterns – (PAMPs), damage associated molecular patterns (DAMPs), and leukocytes), thereby trying to achieve immune balance/homeostasis[7].

ECT is a blood purification technique in which blood and its components are removed from the body, circulated in the EC circuit and treated with various technologies before being readministered to the patient[10]. Different ECTs include; hemofiltration, hemoperfusion, intermittent or continuous high volume hemofiltration (HVHF), hemadsorption and plasmapheresis[11].

The concept of ECT is based on the objective of nonspecific clearance of inflammatory mediators and/or toxins, attenuating the overwhelming systemic expression of inflammatory mediators in the early phase of sepsis[12]. As per the '*cytokine peak concentration*' hypothesis, eliminating the peak cytokine concentration during the early stage of sepsis can halt the inflammatory cascade, thereby limiting the organ damage and decreasing the incidence of MODS[13,14].

MATERIALS AND METHODS

An extensive literature search was conducted for articles published in last two decades that provided information on the use of ECT in sepsis, using the key words "sepsis", "septic shock", "extracorporeal therapy", "blood purification", and "CytoSorb®", that were in PubMed, MEDLINE, Cochrane Library, or Science Direct databases and with the filters "humans", "English language", "full text articles" (review articles, case reports, randomized controlled trials (RCTs) applied. Only articles published in peer-reviewed and indexed journals from 2002-2021 were selected; abstracts were excluded. The PRISMA diagram for inclusion and exclusion of articles is presented in Figure 1.

RESULTS

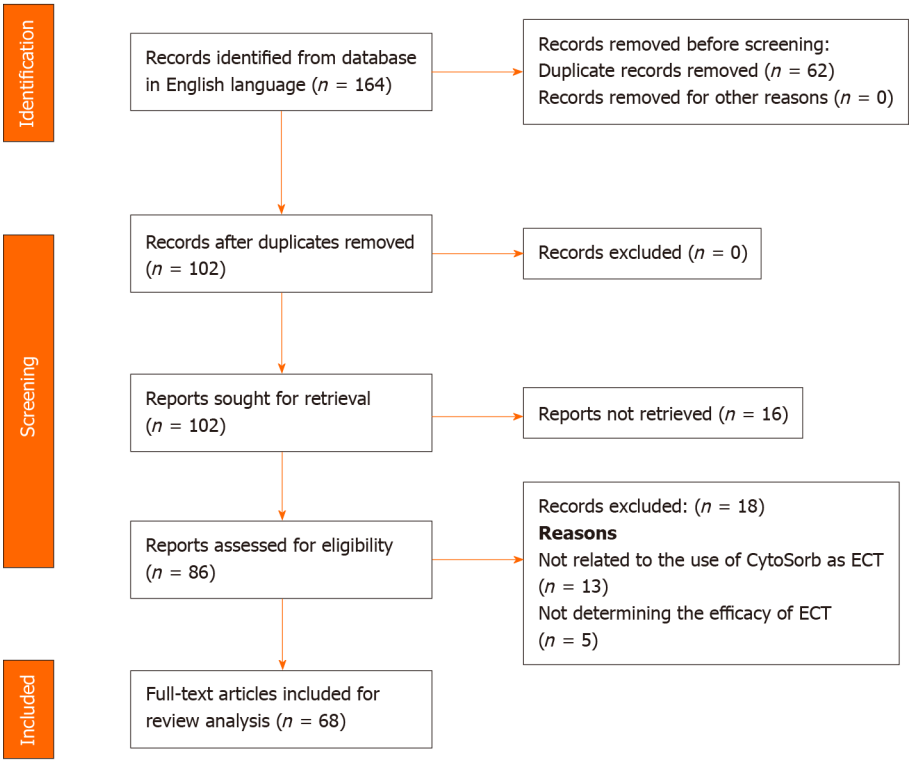
Pathophysiology of sepsis

Sepsis is a multi-layered disruption of the host immune balance. Its pathophysiology involves a complex interplay between the host and the infectious agent[15]. The first step in this process, is activation of the innate immune system (macrophages, monocytes, neutrophils and natural killer cells) which occur as a result of the binding of PAMPs and DAMPs such as adenosine triphosphate and mitochondrial DNA, to the specific pattern recognition receptors present on the immune cells, which include toll like receptors, C-type leptin receptors and nucleotide binding oligomerization domain like receptors[16]. This results in intracellular signal transduction and activation of pro-inflammatory cytokines, such as interleukin - IL1, IL6, IL12, IL18 and tumor necrosis factor alpha (TNF-α)[17]. Subsequently, cytokines cause activation of leukocytes, complement system, coagulation pathways, tissue factor production, chemokine expression and overexpression of endothelial adhesion molecules [15,16]. Following this negative feedback, a compensatory anti-inflammatory response syndrome (CARS) is initiated, which down regulates the components of the adaptive immune system[17]. Upregulation of both pro- and anti-inflammatory cytokines marks the early stage of sepsis[18]. A poorly regulated systemic inflammatory response syndrome (SIRS) and CARS can lead to a mixed antagonistic response syndrome leading to progressive tissue damage and potentially causing MODS[15,19].

Coagulopathy in sepsis occurs as a result of simultaneous activation of inflammatory and hemostatic pathways. It is thought to be driven by the release of tissue factor from damaged endothelial cells, leading to systemic activation of the coagulation cascade[20]. Activation of this cascade results in thrombin production, platelet activation and formation of fibrin clots leading to perfusion defects[16, 21]. In addition to this, procoagulant effects are further potentiated by suppression of natural anticoagulants such as protein C, anti-thrombin, and thrombomodulin along with tissue plasminogen activator, leading to microvascular coagulation and ultimately MODS[21,22]. Pathophysiology of sepsis is detailed[15,16,23] in Figure 2.

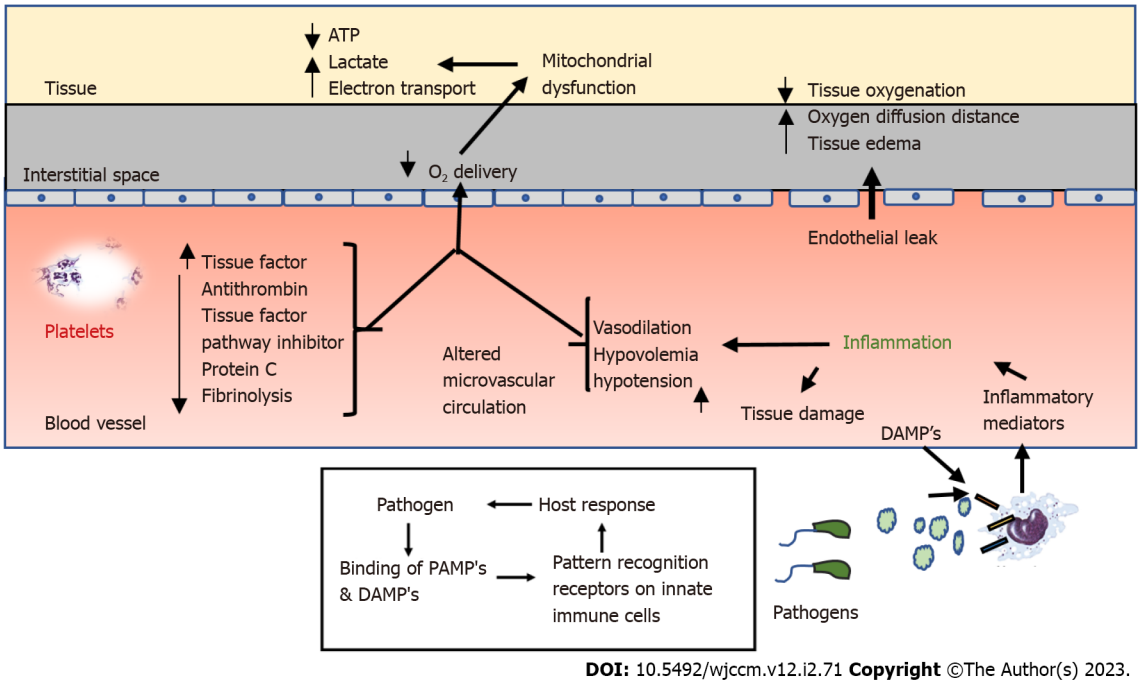
Management of sepsis

Sepsis is a medical emergency and measures taken in the initial hours after its recognition have a significant impact on the outcomes, including survival. In 2018, the Surviving Sepsis Campaign (SSC) guidelines introduced an "Hour-1-Bundle", replacing the previous recommendation of 3- and 6-hour bundles. The 'Hour-1 Bundle' consists of 5 clinical interventions, which prompt immediate initiation of sepsis management and fluid resuscitation measures[24]. Management of sepsis including screening



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Figure 1 PRISMA diagram. ECT: Extracorporeal therapies.

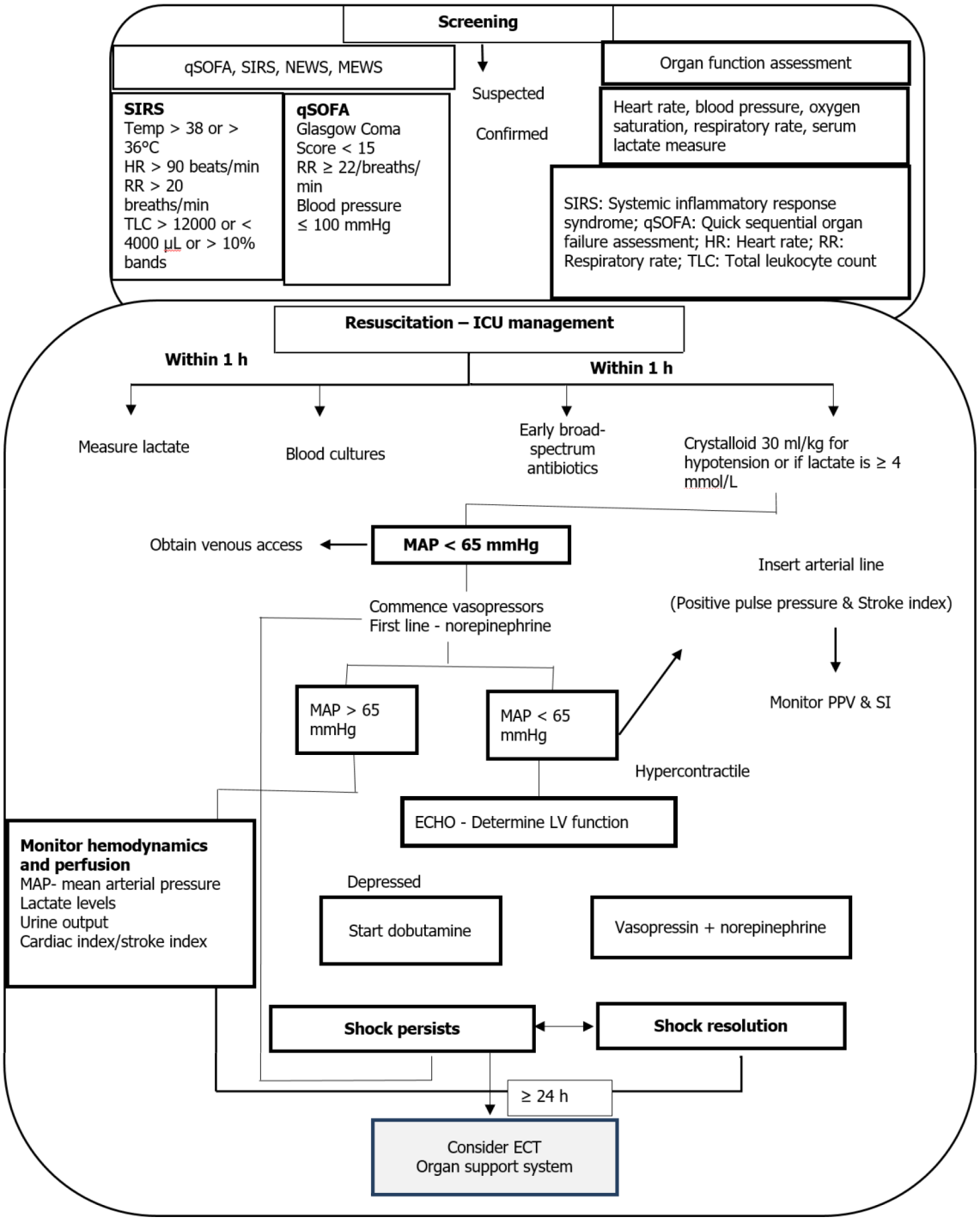


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Figure 2 Pathophysiology of sepsis. ATP: Adenosine triphosphate; DAMP: Damage associated molecular pattern.

and ICU standards of care is presented in Figure 3[7,16,25,26].

Blood purification therapies: MODS caused due to an excessive release of cytokines and inflammatory mediators is a major cause of ICU morbidity and mortality in sepsis[27]. Blood purification therapies (BPTs) are the strategies proposed to restore the immune balance by eliminating or deactivating the inflammatory mediators and originates as an off-shoot of renal replacement therapy (RRT). Various approaches have been identified to maximize the effect of RRT, which include HVHF, high cut-off membranes (HCO), hemadsorption techniques alone or in combination and coupled plasma filtration



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Figure 3 Treatment algorithm for sepsis-screening to intensive care unit management. SIRS: Systemic Inflammatory Response Syndrome; NEWS: National Early Warning Score; MEWS: Modified Early Warning Score; qSOFA: Quick Sequential Organ Failure Assessment; Temp: Temprature; HR: Heart rate, RR: Respiratory rate; TLC: Total leukocyte count; MAP: Mean arterial pressure; PPV: Pulse pressure variation; SI: Stroke index.

adsorption (CPFA)[9,15,27]. Studies determining the efficacy of different modalities in cytokine and endotoxin removal are presented in Table 1[28-33].

EXTRACORPOREAL THERAPY IN SEPSIS

History of ECT

Extracorporeal BPTs such as hemodialysis, have been used traditionally to replace renal functions in critically-ill patients. Knowledge of solute and water transport through physico-chemical mechanisms in

Table 1 Studies showing efficacy of different devices for cytokine and endotoxin removal

Ref.	Study type	Population	Modality	Intervention	Outcomes
Tapia *et al* [28], 2012	Prospective cohort study	31 severe septic shock patients	HVHF, Cytokine removal	HVHF – single short term – 6 h at 40 mL/kg/h	25/31 responded to HVHF. Decrease in NE dose and improvement in hemodynamic, metabolic and respiratory parameters were significantly improved by 4 h
Joannes-Boyau *et al* [29], 2013	Prospective, randomized, open multicentre trial	137 septic shock patients (AKI < 24 h)	HVHF, Cytokine removal	HVHF – 70 mL/kg/h *vs* standard volume hemofiltration at 35 mL/kg/h	No difference in hemodynamic stability, severity scores, 28-d mortality, length of stay and vasopressor free days
Livigni *et al* [30], 2014	Prospective, randomized, multicentre parallel group trial	192 septic shock patients	CPFA, Cytokine & endotoxin removal	Conventional therapy (n = 93) *vs* CPFA (n = 91)	Decreased mortality in patients receiving high dose of CPFA. No difference in length of ICU stay and new organ failures in 30 d
Atan *et al* [31], 2018	Randomized controlled trial	76 critically ill patients with AKI	CVVH - HCOCytokine removal	CVVH-HCO (n = 38) – cut off point 100 kDa *vs* CVVH -Std (n = 38) – cut off point 30 kDa	No difference was observed in mortality, duration of hemofiltration, norepinephrine dose, serum albumin levels and filter life
Dellinger *et al*[32], 2018	Randomized, multicentre trial	449 septic shock patients	Polymyxin B hemoperfusion; Endotoxin removal	Polymyxin B hemoperfusion + Standard therapy *vs* Sham hemoperfusion + Standard therapy	No significant difference in 28 d mortality in overall population or in patients with MODS score of > 9
Kaçar *et al* [33], 2020	Prospective observational study	23 septic shock patients with AKI	HA 330 Cytokine removal	HA 330 hemoperfusion + CVVH for 2 h once daily for 3 d	Increase in pH was observed after 1st application HA330 hemoperfusion; CRP and PCT levels decreased significantly after 2nd application

HVHF: High volume hemoperfusion; CPFA: Coupled plasma filtration adsorption; CVVH: Continuous veno-venous hemoperfusion; HCO: High cut off membrane; ICU: Intensive care unit; NE: Norepinephrine; AKI: Acute kidney injury; CRP: C-reactive protein; PCT: Procalcitonin.

dialysis forms the basis of extracorporeal (continuous) renal replacement techniques (CRRT) and ECT. Observations of recovering ICU septic patients treated with RRT sparked the idea of tilizing ECT in sepsis[34,35]. Different theories have been postulated to explain the effect of blood purification in restoring hemodynamic stability. *Peak concentration hypothesis* suggests that eliminating the peaks of cytokine blood concentrations during the early phase of sepsis could halt the inflammatory cascade, resulting in improved immune-dysregulation[14,36]. Variations in interstitial and tissue concentrations of inflammatory mediators cannot be explained by this theory. To combat the failure of *peak concentration theory*, a new dynamic hypothesis "*threshold immunomodulation*" was developed by Honore and Matson, which correlated the removal of inflammatory mediators from the blood compartment to changes in interstitial and tissue mediator levels. According to this new theory, inflammatory mediators are gradually taken from interstitium and tissues after removal from the blood compartment until a threshold is reached, at which the inflammatory cascade comes to a halt preventing further organ damage. However, it is difficult to correctly determine this threshold as changes in inflammatory mediators in the interstitium and tissues might not be reflected accurately by changes in the blood compartment in different BPT[37]. To find out how blood purification affects the passage of mediators and cytokines from the tissue and interstitium into the blood compartment, a new hypothesis *i.e.*, "*mediator delivery*" hypothesis was proposed by Di Carlo and Alexander. This hypothesis suggested that use of high replacement volumes, (around 20 to 40 -fold increase in lymphatic volumes) might displace the inflammatory mediators in the blood compartment from where these could be removed during the blood purification process. Thus, high replacement volumes enhance the lymphatic transport between the blood compartments and tissue/interstitium[38]. However, Honore *et al*[37] developed a fourth cytotoxic hypothesis to explain the relationship between different compartments. This theory explained that removal of inflammatory mediators from central circulatory system required assistance of active transportation along with passive one. Peng *et al*[39] proposed a *cytokinetic theory* which suggested that the BPT restores immune function by regulating monocytes, neutrophils and lymphocytes at the cellular level. Many studies have reported that polymyxin B hemoadsorption could increase the expression of leukocyte surface markers such as HLA-DR making hemoadsorption a 're-programming system' for the leukocytes. Another unique element proposed in this theory is that the concentration gradient from plasma to infected tissues can be restored by removing mediators from the plasma in systemic inflammation. This concentration gradient has notable effects on leukocyte trafficking and bacterial clearance [11,36,39].

Mechanics and factors affecting ECT

Mechanisms involved in extracorporeal blood purification are either diffusion, convection or adsorption. With the diffusion process, the solute is transported through a semi permeable membrane down/across its concentration gradient, whereas in convection, solute transport happens as part of solvent drag, and ultrafiltration is driven by a transmembrane pressure gradient. In hemadsorption, blood is passed through sorbents which attract the solutes to adhere to them (adsorb), through a series of hydrophobic and ionic interactions[27,40]. Solute clearance by diffusion depends on molecular weight (MW), membrane permeability, dialysate flow and surface area. Various EC blood purification techniques are described in Figure 3[15,40,41].

Cytokine removal in sepsis

It has been postulated that sepsis induced organ injury can be mitigated by curtailing the inflammatory cascade. This could be achieved by disrupting the peak of inflammatory mediators[13]. BPT used for cytokine removal are the convection therapies [CRRT, HVHF, HCO, adsorption therapies (Polymixin B, CytoSorb® (hemadsorption)] and combination therapies[7,15].

HVHF: HVHF is defined as continuous hemofiltration at a rate of 50-70 mL/kg/h for 24 h or 100-120 mL/kg/h intermittently for 4-8 h followed by conventional renal dose hemofiltration[42]. Circulating inflammatory mediators are water insoluble with a MW of < 60 kDa (kilodaltons), and can thus be effectively removed from the plasma *via* the convection method. Additionally, these membranes have adsorptive properties which further enhance molecular clearance[12]. Recent meta-analysis studies have observed improvements in hemodynamic variables and reduced mortality in critically ill patients with HVHF therapy[28,43]. However, HVHF has also shown contradictory results with no improvement in mortality or hemodynamic variables in randomized trials[29,44-46]. Potential drawbacks of HVHF are the loss of small molecules (vitamins, nutrients, antibiotics) and large volume replacement which may increase treatment costs and the risk of electrolyte imbalance[12,47]. In order to avoid the drawbacks of HVHF, the concept of cascade hemofiltration was introduced which allows selective removal of middle weight molecules. It includes two hemofilters with different cut off values incorporated into a single EC unit, through which only middle molecular weight molecules are filtered and the lower molecular weight molecules are reinfused into the blood circuit. However, in the study conducted by Quenot *et al* [48] cascade hemofiltration failed to provide any beneficial effects in comparison to standard care.

Coupled plasma filtration and adsorption: In this technology, plasma is separated from the blood with the help of a high cut off filter and then passed through a sorbent cartridge for adsorption of cytokines and endotoxins. The filtrate plasma is then redirected to the dialyzer to combine with blood and used in RRT[7,49]. Several studies evaluating CPFA in sepsis and septic shock patients resulted in hemodynamic improvement compared to Continuous Veno-Venous Haemofiltration (CVVH). However, the evidence was weak as the patient sample size was small[50,51]. Primary studies on efficacy of CPFA in a large multi-centric trial showed no improvement in mortality rate, however, secondary analysis showed encouraging results with lower mortality in comparison to controls[30].

CytoSorb® hemoadsorber: Hemoadsorption is a technique where the sorbents contained in cartridges are placed in direct contact with the blood *via* an EC circuit, removing toxins and inflammatory mediators[12,36]. The rationale of using adsorption therapy is to restore the (proinflammatory and anti-inflammatory) immune balance[52].

Features: CytoSorb®(CytoSorbent, New Jersey, United States) hemoadsorption device is an International Organization for Standardization certified, European CE mark approved class IIb medical device, made up of biocompatible as well as hemocomaptible polystyrene divinylbenzene copolymer beads, designed to remove excess inflammatory cytokines from the blood (IL-1B, IL-6,8,10, TNFα monomer, TNFα trimer, IFN γ)[15,53,54]. It has a surface area of > 45000 m^2, so in principle has a far greater capacity for adsorption than with dialyzers/hemofilters and provides size-selective removal of hydrophobic subtstances with a molecular cut-off size of 60kDa, thus resulting in adsorption of both pro and anti-inflammatory mediators, toxins and drugs. However, endotoxins are an exception, as their MW is 100kDa[7,11]. CytoSorb® is compatible with both citrate anticoagulation and systemic heparin, and the duration of therapy is up to 24 h/sessions/d for 2-7 consecutive days depending on the clinical situation with blood flow ranging between 150-700 mL/min[55]. CytoSorb® also eliminates proteins (myoglobin, free hemoglobin dimer, ferritin, free hemoglobin tetramer), metabolites (bilirubin and bile acids), PAMPs (aflatoxin, *Staph. aureus* hemolysin, *Staph. aureus* toxic shock toxin, *Strept. pyogenes* exotoxin, *Clostr. perfringens* toxin and Shiga-like toxin), DAMPs (C5A, S100 and HMGB-1), which may in part be responsible for the dysregulated inflammatory response[7,53,54]. Due to the size-selectivity substances such as immunoglobulins, albumin and coagulation factors are not adsorbed in a significant manner by CytoSorb® as shown in studies[56,57] CytoSorb® can be used as a standalone therapy on cardiopulmonary bypass (CPB), or with CRRT and ECMO. CytoSorb® is approved for hemoperfusion/hemadsorption and for intraoperative use in CPB surgery for removal of $P2Y_{12}$-Inhibitor like Ticagrelor and/or the factor Xa-Inhibitor, Rivaroxaban[7,53,54].

Clinical evidence: Various clinical publications support the use of CytoSorb® in septic shock patients and have shown promising results prompting the need for RCTs to conclude on the benefits of blood purification with CytoSorb® in critically ill patients[58]. Brouwer *et al*[59] observed in their retrospective analysis on patients in septic shock requiring CRRT a significantly improved 28-d mortality by adding CytoSorb® as an adjunctive therapy, when they applied the statistical Inverse Probability Treatment Weighting method to compensate for baseline differences. In a follow-up long-term analysis of the same patient cohort, the authors concluded that the addition of CytoSorb® to CRRT improved survival from 28 d to 1 year. Lactate level > 6.0 mmol/L at the initiation of CytoSorb® therapy had a 79% positive predi -ctive value for mortality, underlining the need for timely intervention[60]. Rugg *et al*[61] retrospectively analysed data of septic shock patients who received CytoSorb® +RRT in comparison to matched CRRT only controls. Despite matching, CytoSorb® group showed even higher sequential organ failure assessment (SOFA) scores (13 *vs* 12) and mean norepinephrine requirements (0.54 μg/kg/min *vs* 0.25 μg/kg/min) at baseline compared to the control group. Moreover, catecholamine requirements as well as hospital mortality was reduced within 24 h in the CytoSorb® group compared to the control patients.

An international (130 centres from 22 countries) registry established in 2015 evaluated the use of CytoSorb® in critically-ill patients in the 'real world'. The interim analysis reported an observed mortality of 65% in comparison to acute physiology and chronic health evaluation II (APACHE II) predicted mortality of 78%. No significant reduction was observed in SOFA. Moreover, a marked reduction in IL-6 levels was observed[52].

In a prospective single center study including 20 patients with refractory septic shock, CytoSorb® therapy led to significant reductions in norepinephrine requirements improvements in lactate clearance and resolution of shock in 65% of patients[62].

Studies conducted in India by Mehta *et al*[53] also reported a favourable outcome in sepsis or septic shock patients with the use of CytoSorb® therapy. A retrospective observational study showed a decrease in total leucocyte count, reduction in biomarkers such as procalcitonin (PCT) (65%), C-reactive protein (CRP) (27%), serum lactate (27%), bilirubin (43%), IL-6 (87%), IL-10 (92%) and TNF (24%) levels and decrease in SOFA scores by 16.2% post therapy. Mehta *et al*[53] developed a CytoSorb® Scoring (CS) system that categorized patients in < 8, 8-13 or > 13, where 8-13 scores based on 5 parameters repres-enting 5 organ systems to determine the number of devices required for therapy. The score of 8-13 was observed as the most appropriate for initiating CytoSorb® therapy. Study results revealed that survivors had a mean score of 12, whereas non-survivors a mean score of 14.

Kogelmann *et al*[63] reported that the effects of hemadsorption therapy (hemodynamic stabilization and survival) using CytoSorb® was more pronounced in patients in whom therapy was started in < 24 h of sepsis onset, whereas a poor response was associated with a delay in therapy, in terms of vasopressor demand and survival. Further research is required to establish its use in treatment of sepsis[64]. CytoSorb® has shown promising results in sepsis both individually as well as an adjunct therapy by reducing SOFA scores, lactate levels, total leucocyte count, platelet count, IL-6, IL-10, TNF levels and improving survival[65-68] as presented in Tables 2[52,53,59,60-63,68,69] and 3[64,70-73].

However, other retrospective analysis did not support the above findings. Wendel Garcia *et al*[74] did not see differences in IL-6 or vasopressor needs in their analysis on the use of CytoSorb® in septic shock patients compared to historical control patients and even discussed an increased hazard of death associated with hemoadsorption. Similar Scharf *et al*[75] showed no difference in IL-6 reduction and hemodynamic stabilization, or mortality in patients with CytoSorb® treatment compared to a matched patient population.

De Wolf *et al*[76] in a recent meta-analysis suggested that the evidence with a low degree of certainty signified that administering CytoSorb® to critically ill patients with inflammatory conditions could even increase mortality. Adverse events were common, but they were not routinely evaluated and were also underreported. A need for high-quality RCTs to clarify mortality and adverse events related to CytoSorb® is suggested by the findings with significant uncertainty, which prevents drawing firm conclusions.

Regardless of the fact that all the included studies were not powered for mortality as an endpoint, it can also be discussed whether mortality is a reasonable endpoint for a single intervention in critically-ill patients with numerous potential causes for death.

However, considering the aspect that patient selection, timing and dosing was not always applied to the best possible manner or the current understanding respectively, might explain at least partly the contradictory results of the studies presented above. CytoSorb® should primarily be used in refractory cases where standard measures of care are not sufficient to stabilize the patient rapidly and start of the therapy should ideally be within the first 6-24 h after diagnosis of septic or vasoplegic shock. The therapy should be continued until sufficient stabilization. For this the adsorber should be replaced every 12-24 h depending on the degree of hemodynamic stabilization being observed. With regard to adequate timing, Kogelmann *et al*[77] evaluated a dynamic scoring system intended to support initiation of CytoSorb® in septic shock patients. The study reported that earlier treatment was associated with a better outcome. Additionally, outcomes improved if CytoSorb® was applied within 12 h after diagnosis in patients with the highest CS score > 8.

Table 2 Multiple logistic regression analysis to predict 30 d mortality

Ref.	Study design	Population	Intervention	Outcomes
Friesecke *et al*[62], 2017	Prospective, single center study	20 septic shock patients	CytoSorb hemoperfusion	Norepinephrinedose reduced after 6 and 12 h; Improved lactate clearance; SOFA scores unchanged; Shock reversal achieved in 65% of patients; 28-d survival – 45%
Kogelmann *et al*[63], 2017	Case series	26 septic shock patients	CytoSorb+CVVHD	Rapid hemodynamic stabilization; Reduction in Vasopressor dose by 67%; Decrease in blood lactate by 26.4%; Shock reversal in 38.5% patients; Decreased mortality than predicted by APACHE II; No adverse events reported
Friesecke *et al*[52], 2017	International registry	135 septic shock patients	CytoSorb hemoperfusion	Reduced observed mortality of 65% than predicted by APACHE II of 78%; Marked reduction in IL6 levels; No significant reduction in SOFA scores; Safe and well tolerated without any adverse events
Brouwer *et al* [59], 2019	Retrospective, investigator-initiated study	116 septic shock patients	CytoSorb +CRRT CRRT alone	In CytoSorb group, the mean predicted mortality rate was 74.5%, while 28 d mortality rate was 47.8%; In CRRT group, the mean predicted mortality rate was 67.9%, while 28-d mortality was 51.0%; CytoSorb group was associated with a reduced 28-d mortality in comparison to CRRT (53% *vs* 72.3%)
Brouwer *et al* [60], 2021	Long term follows up Retrospective cohort study	116 septic shock patients	CytoSorb +CRRT CRRT alone	CytoSorb was significantly associated with long term outcome compared to CRRT
Mehta *et al* [53], 2020	Retrospective, observational study	40 septic shock patients	CytoSorb hemoperfusion (Survivor group *vs* non survivor group)	Improvement in MAP (62.82 ± 9.73mmHg); Reduction in vasopressor dose; Reduction IL-6 levels (87%) and TNF levels (24%); Decrease in SOFA scores by 16.2%
Paul *et al* [68], 2021	Prospective, real time, observational multicentre study	45 septic shock patients	CytoSorb+ Standard therapy (Survivor *vs* non survivor group)	26 patients survived post therapy; Reduction in vasopressor dose (NE- 51.4%, Epinephrine – 69.4% and Vasopressin -13.9%); 52.3% reduction in IL-6 levels; Reduction in APACHE II and SOFA scores, 20.1 ± 2.47 and 9.04 ± 3.00 respectively
Akil *et al* [69], 2020		20 patients with pneumogenic sepsis and ARDS	CytoSorb + Combined high flow veno-venous ECMO (CytoSorb group); ECMO therapy alone (Control group)	The 30-d mortality rate was 0% in CytoSorb group, whereas 57% was observed in control group; Significant reduction in procalcitonin and C-reactive levels were observed in CytoSorb group in comparison to control group
Rugg *et al* [61], 2020	Retrospective single center study	42 septic shock patients compared to 42 matched controls	Cytosorb +RRT	Catecholamines requirements decreased to 0.26 μg/kg/min within 24 h of therapy with CytoSorb; In hospital mortality was significantly lower in CytoSorb group as compared to controls (35.7% *vs* 61.9%); Risk factors in CytoSorb group were high lactate levels and low thrombocyte counts proior to therapy. Lactate value of 7.5 mmol/L, predicted mortality with high specificicty (88.9%)

CVVHD: Continuous veno-venous hemodilation; NE: Norepinephrine; MAP: Mean arterial pressure; SOFA: Sequential organ failure assessment; APACHE: Acute physiology and chronic health evaluation; IL: Interleukin; TNF: Tumor necrosis factor; ARDS: Acute respiratory distress syndrome; CRRT: Continuous renal replacement therapy; RRT: Renal replacement therapy.

The CS still requires prospective validation and adapatibility. Nevertheless, more robust evidence is needed to better understand ideal patient selection, timing and dosing.

Novel use of CytoSorb®: CytoSorb® also has CE approval for the reduction of bilirubin and myoglobin in liver failure and severe trauma/rhabdomyolysis. It can also be used in severe acute pancreatitis and severe cardiogenic shock. Patients undergoing major aortic surgery with CytoSorb® incorporated in the CPB circuit demonstrated a promising therapeutic option for critically ill patients with multiorgan failure after cardiac surgery and may help in cytokine reduction with improved organ function[78]. In 2020, CytoSorb® was also approved for the removal for two antithrombotic drugs – ticagrelor and rivaroxaban in emergent and urgent cardiothoracic surgery, in order to reduce the risk of intra- and post-operative bleeding.

Jafron HA-330 and HA-380 adsorber: (Jafron Biomedical Co., Ltd.No.98, Technology Sixth Road, High-tech Zone, Zhuhai City, 519085, Guangdong, China).

The HA-330 (HA-380 is 15% bigger than HA-330) is a disposable hemoperfusion cartridge with an adsorbent material made up of *neutral microporous resin* and collodion coating. It is indicated for the removal of middle to large pathogenic substances from the blood (endogenous or exogenous), such as residual drugs, toxins and metabolic substances. It is used either as a stand alone or in combination with hemodialysis and hemoperfusion circuits. However, it is not clear if integration with ECMO is recommended or not.

Table 3 Studies determining efficacy of CytoSorb in coronavirus disease 2019 infection

Ref.	Study type	Population	Intervention	Outcomes
Alharthy *et al*[70], 2020	Retrospective case series	50 COVID-19 patients with AKI, ARDS, Sepsis and hyperinflammation	CytoSorb + CRRT [Survivors (n = 35) *vs* non survivors (n = 15)]	Decreased SOFA score, lactate levels, ferritin, D-dimers, CRP and IL-6 levels in th survivor group after 2 ± 1 sessions of CRRT + CytoSorb
Mehta *et al* [64], 2021	Case series	3 critically ill COVID-19 patients	CytoSorb hemoperfusion other prescribed medications (tocilizumab, antivirals, hydroxy-chloroquine, azithromycin)	Significant improvement in biochemical parameters and clinical outcomes post CytoSorb therapy; Reduction in CRP levels by 91.5%, 97.4% and 55.75%, respectively; Improvement in MAP by 18%, 23% and 17% by 7th day post therapy
Nassiri *et al*[71], 2021	Retrospective case series	26 COVID-19 patients with ARDS	CytoSorb hemadsorption therapy	21 patients survived; Significant decrease in NE requirement; PCT, CRP and ferritin reduced post therapy; Significant improvement in SOFA scores; Therapy was well tolerated
Paisey *et al* [72], 2021	Retrospective case series	15 severely ill COVID-19 patients	CytoSorb hemadsorption therapy	Adjunctive treatment with CytoSorb lead to reduction in ferritin, CRP, PCT and lactate levels
Song *et al* [73], 2021	Multicenter observational study	52 ICU COVID -19 patients on ECMO	ECMO + CytoSorb hemadsorption therapy	ICU mortality was 17.3% on day 30, 26.9% on day 90, and 30.8% at final follow up of 143 d; Lower baseline D-Dimer levels were observed among survivors (2.3 ± 2.5 *vs* 19.8 ± 32.2 μg/mL) compared to non survivors; Borderline association observed between baseline D-Dimer levels and mortality with a 32% increase in risk of death per 1 μg/mL increase

COVID-19: Coronavirus disease 2019; CRRT: Continuous renal replacement therapy; SOFA: Sequential organ failure assessment; CRP: C-reactive protein; IL: Interleukin; AKI: Acute kidney injury; ARDS: Acute respiratory distress syndrome; MAP: Mean arterial pressure; NE: Norepinephrine; ECMO: Extracorporeal membrane oxygenation.

HA-330 (and HA-380) have limited options for circuit configurations and a shorter treatment time up to 4 h when used in conjunction with a dialyser. Moreover, HA-330 (and HA380) have a maximum blood flow and operating time depending on the mode of operation.

Both HA-330 and HA-380 adsorbers have a storage fluid considered to be extremely acidic, with a pH of 1.8, which, even after a careful and 45-min-long rinsing procedure, remains as low as pH 3.3. A case series conducted in septic pediatric patients with cancer and other hematological disorders has confirmed the efficacy of HA-330 and HA-380. However, detailed studies in a larger population was recommended by the authors[79]. Treatment with CytoSorb®, resulted in significant removal of IL-6 in a severely ill patient population with septic shock, ARDS, and multi-organ failure in a multicenter randomised study. This, however, had no effect on normalised IL-6-plasma levels[80,81]. A comparative in-vitro study was conducted on both the CytoSorbents and Jafron hemoadsorption technologies and showed that both systems can remove cytokines from whole blood, but the CytoSorb® 300 device appears to be more effective and dynamic in this regard. Therefore, in severe septic state where quick cytokine clearance is desired, it might be the preferred device[82]. HA-330 and HA-380 have very limited published articles (far less than 50) to support its therapeutic benefits and clinical experience.

Biosky MG 350 adsorber: (Biosun Medical Technology Co. Ltd, China). The Biosky MG350 adsorber is another disposable hemoperfusion cartridge made up of *microporous adsorptive resin*, recommended for application in sepsis and hyperinflammation. Published literature in the English language is extremely scarce, and currently limited to one case report. Sequential use of CytoSorb® and the MG350 filter was carried out in a coronavirus disease 2019 (COVID-19) patient with severe ARDS. After initial successful CytoSorb® use, an MG350filter was used in parallel to an ECMO circuit. The combination of an antibiotic regimen and Biosky filter resulted in decreased inflammatory markers (CRP, PCT, IL-6 and IL-2). However, the patient suffered with severe respiratory failure and later died[83]. Biosky MG350 has a blood flow of 400 mL/min with an operating time of 2 h depending on the mode of operation. Compared to other adsorbers, Biosky MG350 requires a long rinsing procedure (Table 4[84-88]).

Miscellaneous: Several other cartridges available for adsorption include Hemofeel (Toray, Tokyo, Japan), a polymethyl methacrylate hemofilter, and Theranova 400/500 dialysers developed by Baxter. Multiple other cartridges that have an affinity to bind to bacteria and viruses are also under investigation. The Seraph 100 Microbind Affinity blood filter (ExThera, California, United States) is an adsorbing technology which consists of non-porous heparin coated beads designed to reduce blood-borne pathogens during bloodstream infections. Hemopurifier (Aethlon Medical, California, United States) and FcMBL (Opsonix Inc, United States) is also other make that is also available[7].

Table 4 Multiple logistic regression analysis to predict 30 d mortality

Feature	CytoSorb 300[84,85,86]	Jafron HA-series (80, 130, 180, 230, 280, 330, 380) [87]	Biosky MG-Series[88]
Manufacturer	CytoSorbents™ Inc, United States	Jafron Biomedical Co., Ltd. No. 98, Technology Sixth Road, High-tech Zone, Zhuhai City, 519085, Guangdong, China	Biosun Medical Technology Co. Ltd, China
IFU version	October 1, 2021[87]	11-Sep-19	1-Aug-18
Adsorbent	Crosslinked Divinylbenzene	Neutral Macroporous Resin	Medical Neutral Macroporous Synthetic Resin
Coating	Polyvinylpyrollidone	Collodion	No data
Adsorbent Surface	> 45000 m^2	100000m^2	No data
Storage fluid	Isotonic saline	Water for injection	Sterile water
Use time/cartridge	24 h, Can be administered up to 7 consecutive days	Depending on mode of operation: Hemoperfusion 100-250 mL/ min; Dialysis < 320 ml/ min with use upto 4 h; CRRT 150-250 mL/min with use upto 12 h; CPB up to 700 mL/ min with use upto 2.5 h	120-180 min, Not suggested to use more than 3 times within 24 h
Blood flow	100-700 mL/min, Recommended > 150 mL/min	100-700 mL/min	100-400 mL/min; Highest rate is 250 mL/min
Pmax	760 mmHg	750 mmHg	750 mmHg
Mode of operation covered	Hemoperfusion, Intermittent hemodialysis, CRRT, Cardiopulmonary bypass (CPB) ECMO	Hemoperfusion; Hemodialysis; CRRT; CPB	Hemoperfusion; Hemodialysis; CRRT; CPB only as comment in anticoagulation, not in setup
Shelf life	3 yr	2 yr	2 yr
Safety report status	As of 2021: > 162000 treatments distributed without confirmed serious device related events	No data	No data

IFU: Instructions for use; CRRT: Continuous renal replacement therapy; CPB: Cardiopulmonary bypass; ECMO: Extracorporeal membrane oxygenation.

Endotoxin removal in sepsis

Lipopolysaccharide (LPS) an endotoxin, is a component of gram-negative bacteria that induces an inflammatory response. A dysregulated host response to LPS might lead to multiple organ failure or fatal septic shock if unchecked. Endotoxin activity (EA) levels are measured on a scale of 0 to 1: low (< 0.4 units), intermediate (0.4-0.6 units), high (> 0.6 units). More than 80% of septic shock patients have intermediate or high EA levels indicating the function of endotoxin as a critical activator of the sepsis cascade. Clinical evidence for LPS is obtained from case series in critically ill patients reporting a reduction in endotoxin levels and improvement in hemodynamics with no significant adverse effects [89-91].

Polymyxin B: A polymyxin B-(PMX) immobilised fiber column (Toraymyxin: Toray, Tokyo, Japan) has been extensively used for endotoxin removal. The findings of a subsequent RCT in Europe, the EUPHAS study, which was carried out in Italy, were published in 2009, demonstrating that PMX has a significant effect on sepsis-related mortality[92]. The EUPHRATES RCT trial compared Polymyxin B hemoperfusion to a combination of sham hemoperfusion and standard therapy (n = 226) showing no significant difference in 28 d mortality among the overall population[32]. Subsequently, a post hoc analysis of the EUPHRATES trial demonstrated a significant reduction in 28 d mortality and improvement in MAP and ventilator free days in patients with an endotoxin assay of 0.6–0.9[93]. The ABDOMIX trial had inconclusive results on efficacy of the polymyxin B-immobilised fiber column for removing endotoxins and improving mortality rates in patients with septic shock[94].

Alteco LPS adsorber: The Alteco LPS adsorber (Alteco Medical; Sweden) is an endotoxin adsorber cartridge, consisting of polyethylene plates with peptides which have a high affinity to adsorb LPS. A multicentre feasibility trial of the Alteco LPS adsorber –the ASSET trial was terminated early due to patient recruitment difficulties[95].

Combined endotoxin and cytokine removal

oXiris membrane: The oXiris filter is a modified AN69ST membrane which has an affinity to adsorb both endotoxins and cytokines. Initially, it was approved in 2009 in Europe, and in 2017 the indication was extended for patients requiring blood purification, CRRT and in conditions with excessive levels of inflammatory mediators and endotoxins[96]. It was also authorised by the FDA for emergency use for

COVID-19 treatment[97]. However, its use is only indicated with the Prismaflex unit. Evidence supporting the use of oXiris comes largely from case series. In the study conducted by Shum *et al*[98], 6 patients with septic AKI received oXiris-CVVH and were compared to historical controls with a similar disease severity (n = 24). Results showed a significant reduction in SOFA scores by 37% after the use of oXiris-CVVH for 48 h whereas there was a 3% increase in the control group. However, there was no significant difference observed in length of ICU stay and hospital mortality. A single centred prospective study by Premužić *et al*[84] showed the efficacy of oXiris filters in reducing IL-6 and SOFA score severity in ICU patients. Improvement in respiratory status, chest X-ray severity score and other clinical symptoms were also reported in this study. Russell *et al*[85] used a hybrid purification system in fifteen critically ill sepsis patients. Treatment involved RRT with the oXiris filter and a CytoSorb® adsorbent cartridge also included in RRT system. Procalcitonin, IL6, cardiorespiratory function and endotoxins were monitored at baseline and at the completion of treatment. It was concluded that RRT with the oXiris filter and CytoSorb® cartridge were associated with improved hemodynamic stability, inflammatory response and renal function.

In an *in-vitro* comparison of three different blood purification devices – oXiris, polymyxin B, and CytoSorb®, oXiris showed a similar reduction in endotoxins and cytokines in comparison to polymyxin B and CytoSorb®, respectively[86]. Feri *et al*[99] pointed out the flaws in this *in-vitro* investigation, including the fact that the *in-vitro* comparison was carried out for two hours using 500 mL plasma solutions, pre-incubated with pathological quantities of inflammatory mediators. As stated by Feri *et al*[99], all the three devices (oXiris, polymyxin B, and CytoSorb®) work with whole blood and not just plasma, and the volume utilised by Malard *et al*[86] was very limited (500 mL), in humans the devices work with blood volume of 5 L. Furthermore, the concentration of inflammatory mediators was low, as was the duration of the experiment.

Feri *et al*[99] further stated that the actual application time of CytoSorb® and oXiris is 24 h and 72 h, respectively. Potential advantages and comparable results in endotoxin and cytokine clearance is limited to case series/reports, and no large, randomized trials exist thus far[96]. However, several ongoing trials have recently been completed and it is expected that oXiris may provide some new insights in the management of sepsis and septic shock. Studies showing the efficacy of oXiris in endotoxin and cytokine removal are presented in Table 5[49,96,98,100].

Novel therapeutic advances

Renal assisting device (RAD) is a cell-based therapy containing human proximal tubular cells. It was developed based on the concept that the kidney also have metabolic, immune and endocrine functions during sepsis[51]. RAD was found to be beneficial in replacing solute and water clearance along with active reabsorptive transport and metabolic functions[101]. However, its development was discontinued due to manufacturing and distribution issues. A selective cytopheretic device (SCD) is another therapeutic strategy targeting activated leucocytes. With a CRRT circuit, it results in sequestration of activated leucocytes. Evaluation of SCD was carried out in a randomized trial of 134 AKI patients. No significant differences in mortality were found between the treated (SCD) and control populations (CRRT)[102]. Molecular adsorbent recirculating system (MARS™) is another extracorporeal system which supports the liver by removing albumin-bound toxins from the blood. Short-term benefits of MARS have been evaluated in 3 prospective randomized studies showing improvement in survival rates of patients with hepato-renal syndrome and hepatic encephalopathy[103].

DISCUSSION

Based on SSC guidelines, evidence of ECT efficacy is evolving and has a sound rationale based on our current understanding of sepsis pathophysiology. Overall, however, hard evidence based on prospective RCTs is still scarce. As with every therapy proper patient selection, timing and dosing is crucial for therapeutic success. ECT has to be seen as an adjunctive therapy aiming at restoring homeostasis in hyperinflammatory conditions. In the light of the critically-ill patients with numerous co-morbidities usually treated with ECT in multi-nodal approach, one should not target mortality as the primary endpoint of such trials, but rather consider the improvements in organ dysfunction. Additionally, the challenge of patient heterogeneity usually mentioned in many of these trials and coming from the fact that sepsis is a syndrome rather than a specific disease, has to be taken into consideration for trial planning, too.

Challenges and limitations of ECT

In clinical practice, timing of ECT is still often delayed as doctors see it too much as a final rescue therapy. So better guidance in regard to patient selection, timing and dosing has to compiled and provided to the user at the bedside. Importantly and with regard to the different ECT systems available in the market, it has to be stated that clinical results, but particularly safety relevant aspects, are not transferable between various hemoadsorption products due to technical differences[104].

Table 5 Studies determing oxiris efficacy for removal of endotoxins and cytokines

Ref.	Study type	Population	Intervention	Outcomes
Shum *et al* [98], 2013	Prospective case series with historical controls	6 patients with septic AKI	oXiris + CVVH	Significant reduction in SOFA scores by 37% after 48 h of therapy
Ugurov *et al* [96], 2020	Single centre case series	15 COVID -19 patients	oXiris hemofilter	Early initiation of oXiris was associated with stable or reducing levels of IL-6,8,10 and TNFα
Zhang *et al* [49], 2021	Case series	5 COVID-19 patients	CRRT followed by oXiris hemofilter therapy	Reduced levels of cytokines, haemodynamic stabilization and improvement of organ function was observed with oXiris.
Rosalia *et al* [100], 2020	Prospective cohort study	44 COVID 19 cases	CVVH + oXiris	Reduction in CRP, ferritin, fibrinogen and other inflammatory mediators were observed

COVID-19: Coronavirus disease 2019; CRRT: Continuous renal replacement therapy; SOFA: Sequential organ failure assessment; CRP: C-reactive protein; IL: Interleukin; CVVH: Continuous veno venous hemofiltration; TNFα: Tumornecrosis factor alpha.

Future directions

Hemodynamic improvements, length of ICU stay and decreasing mortality were among the frequently studied end-points in most of the studies that have evaluated different ECT modalities. Further sepsis trials should target patient populations as homogeneous as possible and therefore focus on patient pheno- and endotypes including biomarker-based approaches to try to obtain more consistent outcomes of the therapy, thereby increasing the understanding of optimal therapy management and reducing the possibility of conflicting results.

CONCLUSION

Substantial progress has been made in the field of ECT therapies and sepsis. Among the presented technologies in this review, CytoSorb® seems to currently represent the most investigated and clinically established procedure. However, more robust evidence is still needed. Additionally, the achievement of beneficial clinical effects of these adjunct modalities in routine use requires identification of the right patient, right timing and right dose. Therefore, high quality RCTs are needed to provide definitive answers for these questions and also to facilitate individualised ECT treatments of critically ill patients.

ARTICLE HIGHLIGHTS

Research background

Sepsis is one of the main causes of mortality in patients in critical care units worldwide, despite the fact that it can be treated with a variety of medications. Extracorporeal treatments (ECT), which aim to balance the dysregulation of the immune system by eliminating high quantities of inflammatory mediators, have drawn attention as a result of knowledge about the biology of sepsis.

Research motivation

The biology of sepsis has brought attention to extracorporeal therapies (ECT), which try to regulate immune system dysregulation by removing large amounts of inflammatory mediators.

Research objectives

To analyze new research on ECT use in sepsis and evaluate its impact on key inflammatory and clinical outcomes.

Research methods

To find the usage of ECT in sepsis, a thorough search of the English literature from the previous two decades was done for this review. The selection process excluded publications that had only abstracts and resulted in a total of 68 articles from peer-reviewed and indexed journals.

Research results

The findings demonstrated the emergence of ECT approaches such as high-volume hemofiltration, coupled plasma adsorption/filtration, resin or polymer adsorbers, and CytoSorb® as adjuvant therapy to enhance hemodynamic stability in sepsis. With findings on increased survival rates and decreased

sequential organ failure assessment scores, lactate levels, total leucocyte count, platelet count, interleukin-IL-6, IL-10, and TNF levels, CytoSorb® has the most published evidence in relation to its usage in the field of septic shock.

Research conclusions

The absence of significant random clinical trials currently limits the clinical adoption of ECT in sepsis and septic shock. Future research breakthroughs with treatments aiming at the cellular level of the immune response are anticipated, in addition to patient-tailored medicines.

Research perspectives

To achieve more consistent treatment outcomes, future clinical trials involving patients with sepsis should be as homogeneous as feasible and focus on patient phenotypes and endotypes, including biomarker-based techniques. This will not only increase our grasp of how to handle proper therapy, but it will also lessen the possibility of inconsistency.

FOOTNOTES

Author contributions: The above all authors have equally contributed towards ideation, data analysis and manuscript review.

Conflict-of-interest statement: All the authors declare no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 March 9; 12(2): 89-91

DOI: 10.5492/wjccm.v12.i2.89

ISSN 2220-3141 (online)

LETTER TO THE EDITOR

The artificial intelligence evidence-based medicine pyramid

Valentina Bellini, Federico Coccolini, Francesco Forfori, Elena Bignami

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Hanada E, Japan; Morya AK, India

Received: October 14, 2022
Peer-review started: October 14, 2022
First decision: November 14, 2022
Revised: November 21, 2022
Accepted: February 1, 2023
Article in press: February 1, 2023
Published online: March 9, 2023

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Abstract

Several studies exist in the literature regarding the exploitation of artificial intelligence in intensive care. However, an important gap between clinical research and daily clinical practice still exists that can only be bridged by robust validation studies carried out by multidisciplinary teams.

Key Words: Artificial intelligence; Intensive care; Intensive care unit; Evidence-based medicine; Clinical research

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Core Tip: Artificial intelligence (AI) use in intensive care is now a reality. However, there is still an important discrepancy between the results found in the scientific literature and the day-to-day clinical implementation of this technology. One reason for this is that the AI evidence pyramid in intensive care has only just begun to emerge. We need to focus on the next steps in AI pyramid evidence, amplifying the external validation of models and increasing the number of randomized clinical trials. Only robust validation studies carried out by multidisciplinary teams will help bridge this existing gap between clinical research and clinical practice.

Citation: Bellini V, Coccolini F, Forfori F, Bignami E. The artificial intelligence evidence-based medicine pyramid. *World J Crit Care Med* 2023; 12(2): 89-91
URL: https://www.wjgnet.com/2220-3141/full/v12/i2/89.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i2.89

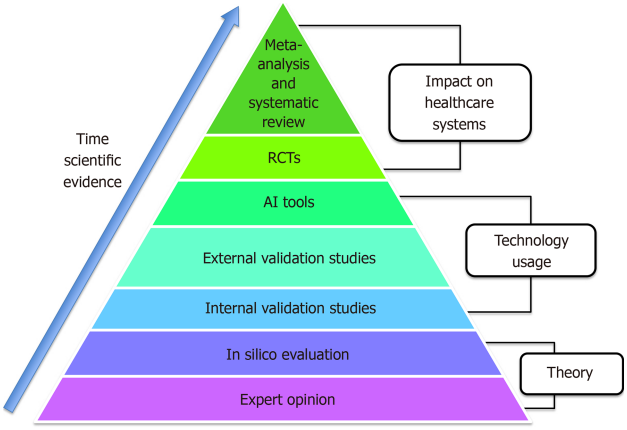
TO THE EDITOR

We read with great interest the editorial by Luo *et al*[1] where the authors cogently present the main results regarding the use of artificial intelligence (AI) in the intensive care unit (ICU) for decision making and resource allocation. They simultaneously exposed the current limitations of the large-scale use of AI clinical tools in this setting. We share many of the reflections set out by Luo *et al*[1]. The presence of AI in medicine science and clinical practice has become a reality. Knowing how this new technology can assist the medical profession and how clinicians might take advantage of it are characteristics that are now required and are likely to be of assistance as far as personal career development is concerned[2]. However, the gap between the excellent results derived from biomedical research and the rare use in clinical practice is clear to everyone[3]. While this is probably the biggest deterrent to AI application on a daily professional basis, we must not stop considering it as a valuable ally. On the contrary, we need to ask clinical researchers to find answers for how these models can help intensivists carry out day-to-day activities.

Without external validation, the positive performance of these models in observational studies is no longer sufficient. This, however, should not lead to the erroneous conviction that AI implementation in the ICU should remain purely a scientific speculation, as its application outside the clinical reality regularly disproves this hypothesis. Intelligent vocal assistants and accurate search engines are just two examples of the efficient support offered to us by well-devised AI. The first results from clinical trials point in the same direction, with an example being the hypotension prediction index[4]. This is an algorithm implemented to predict hypotension, even before adverse events occur. Since its marketing, a number of clinical trials have tried to interpret its possible usefulness in clinical practice with most results showing a lower incidence of hypotensive events when compared with standard care[5-7].

We should bear in mind that anything stemming from evidence-based medicine (EBM) has a history based on the progressive collection of increasingly solid results, and the application of AI in the ICU follows the same path (Figure 1). We began with the intuition that AI might be useful in critical patients. Subsequently, stronger results, initially from retrospective followed by prospective observational studies, appeared. In the literature, a few clinical trials as well as sporadic systematic reviews and meta-analyses are available[8,9]. Presently, we are only halfway up the pyramid of the AI scientific evidence we initially imagined, and it is therefore logical that the use of AI tools is not widespread. This phenomenon is consistent with the concept of EBM. At this point, we need to focus on the second part of the pyramid, increasing the external validation of models and multiplying the number of randomized clinical trials.

Furthermore, we must not underestimate the fact that this gap can only be bridged by the intervention of multidisciplinary teams. As with the creation of the AI surgical department in anesthesiology[10], similar systems need to be considered for the ICU. Engineers, data scientists and intensivists must create units capable of managing each phase of the AI application in the ICU, from the design and then to the creation and exploitation of AI clinical instruments. This cooperation should also take place in the post-marketing phase, with constant verification of the quality and safety of AI tools together with continuous systems updates. In conclusion, it is not surprising that AI is not yet widely used in daily ICU activities. We are still at the very beginning of the EBM pyramid, and the gap between bytes and the bedside will only be bridged by robust validation studies carried out by multidisciplinary teams.



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Figure 1 A pyramid for artificial intelligence scientific evidence is proposed. Starting from the bottom and moving to the top, emerging results are becoming increasingly solid and strong. The two lowest rungs are the theory followed by the third, fourth and fifth steps that represent studies analyzing the use of artificial intelligence (AI) in clinical practice. From creation of the model with internal validation, we move towards external validation studies and the creation of usable

real instruments (AI tools). The penultimate step [randomized controlled trials (RCTs)] and the tip of the pyramid (meta-analysis and systematic reviews) represent the strongest methodological analysis to reach conclusions on the real impact of this technology on healthcare systems. If we then imagine the support base of the pyramid we have the necessary tools for each step of clinical research in AI applied to the intensive care unit: Electronic health record, solid big data systems, internet of things technologies and models of eXplainable AI.

FOOTNOTES

Author contributions: Bellini V, Coccolini F, Forfori F and Bignami E made substantial contributions to the conception and design of the study as well as the acquisition and interpretation of data; Bellini V and Bignami E drafted the article; Coccolini F and Forfori F made critical revisions related to important intellectual content within the manuscript; Bellini V, Coccolini F, Forfori F and Bignami E approved the final draft of the article.

Conflict-of-interest statement: All the authors report having no relevant conflicts of interest for this article.

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S-Editor: Xing YX
L-Editor: Filipodia
P-Editor: Xing YX

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ISSN 2220-3141 (online)

World Journal of

Critical Care Medicine

World J Crit Care Med 2023 June 9; 12(3): 92-187



Published by Baishideng Publishing Group Inc

WJCCM World Journal of Critical Care Medicine

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World Journal of Critical Care Medicine

Quarterly Volume 12 Number 3 June 9, 2023

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INDEXING/ABSTRACTING

The *WJCCM* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Li-Li Wang*.

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Quarterly

EDITORS-IN-CHIEF
Hua-Dong Wang

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

PUBLICATION DATE
June 9, 2023

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ONLINE SUBMISSION
https://www.f6publishing.com

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World Journal of Critical Care Medicine

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World J Crit Care Med 2023 June 9; 12(3): 92-115

DOI: 10.5492/wjccm.v12.i3.92

ISSN 2220-3141 (online)

REVIEW

Sleep during and following critical illness: A narrative review

Laurie Showler, Yasmine Ali Abdelhamid, Jeremy Goldin, Adam M Deane

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Arunachala Murthy T, Australia; Jha P, United States; Sánchez JIA, Colombia

Received: December 28, 2022
Peer-review started: December 28, 2022
First decision: January 31, 2023
Revised: February 13, 2023
Accepted: March 22, 2023
Article in press: March 22, 2023
Published online: June 9, 2023

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Abstract

Sleep is a complex process influenced by biological and environmental factors. Disturbances of sleep quantity and quality occur frequently in the critically ill and remain prevalent in survivors for at least 12 mo. Sleep disturbances are associated with adverse outcomes across multiple organ systems but are most strongly linked to delirium and cognitive impairment. This review will outline the predisposing and precipitating factors for sleep disturbance, categorised into patient, environmental and treatment-related factors. The objective and subjective methodologies used to quantify sleep during critical illness will be reviewed. While polysomnography remains the gold-standard, its use in the critical care setting still presents many barriers. Other methodologies are needed to better understand the pathophysiology, epidemiology and treatment of sleep disturbance in this population. Subjective outcome measures, including the Richards-Campbell Sleep Questionnaire, are still required for trials involving a greater number of patients and provide valuable insight into patients' experiences of disturbed sleep. Finally, sleep optimisation strategies are reviewed, including intervention bundles, ambient noise and light reduction, quiet time, and the use of ear plugs and eye masks. While drugs to improve sleep are frequently prescribed to patients in the ICU, evidence supporting their effectiveness is lacking.

Key Words: Critical illness; Critical care; Sleep; Sleep deprivation; Polysomnography; Melatonin

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Core Tip: Disturbed sleep is common among the critically ill and contributes to adverse physiological and psychological outcomes. Multiple contributory factors have been identified, including environmental, care-related and patient elements. Assessing sleep in the ICU is challenging, and objective and subjective methods are required to evaluate the disruption to sleep architecture and the patient's experience of this. Both pharmacological and non-pharmacological interventions to improve sleep quality and quantity have been studied with mixed results, however, a multimodal approach to sleep optimisation is likely necessary to improve outcomes.

Citation: Showler L, Ali Abdelhamid Y, Goldin J, Deane AM. Sleep during and following critical illness: A narrative review. *World J Crit Care Med* 2023; 12(3): 92-115
URL: https://www.wjgnet.com/2220-3141/full/v12/i3/92.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i3.92

INTRODUCTION

Sleep is an essential biological process that is frequently disturbed in patients with critical illness[1,2]. Sleep deprivation in healthy adults is associated with adverse effects on neuropsychiatric, cognitive, cardiovascular, respiratory and endocrine systems and with acute and long-term detrimental effects[3].

There are concerns that an inadequate quantity and quality of sleep during critical illness contributes to increased delirium, depression, and a lesser quality of life in survivors and, potentially, increased mortality, with the detrimental effects of sleep deprivation compounded among those with prolonged admission to the intensive care unit (ICU)[4]. In addition, sleep disturbance is frequently reported as a source of patient distress and has been proposed to have financial implications related to longer ICU admission and increased risk of delirium[5].

Sleep disturbance in the ICU is multifactorial, with pre-morbid diagnoses, acute pathology, treatment and environment all contributing[6,7]. Given the complex pathophysiology, it should be expected that the studied interventions, including pharmacological and non-pharmacological strategies, have had mixed results on sleep[7,8].

This review aims to describe the current understanding of sleep disruption during and after critical illness, current strategies to measure sleep in the ICU, and provide an overview of interventions to improve the quality and quantity of sleep in this population.

LITERATURE SEARCH

A narrative review of the literature was performed. Relevant articles were identified by searching Medline, Embase and the Cochrane database. Search terms included "intensive care unit", "high dependency unit", "critical illness", "sleep", "sleep disturbance", "sleep deprivation", "sleep-wake disorder", and "sleep fragmentation". Searches were limited to human adult subjects and English language articles. No restrictions on the date of publication were imposed. Abstracts were reviewed for relevance, and the reference list of these articles was searched for related articles. The full text of relevant articles was reviewed for inclusion.

OVERVIEW OF NORMAL SLEEP

Sleep is a complex and active process, recognized by reversible perceptual disengagement from, and unresponsiveness to, the environment[9]. The initiation and maintenance of the sleep state are controlled by the coordinated interplay of circadian and homeostatic mechanisms[10-13]. On the basis of polygraphic recordings of brain, muscle and eye activity, normal sleep can be divided into distinct periods, which are recognized as non-rapid eye movement (NREM) and rapid eye movement (REM) sleep[11]. Characteristic features of each sleep stage are described in Table 1[14,15]. NREM sleep is further subdivided into three stages, N1, N2 and N3, reflecting an increasing depth of sleep[16,17]. The N2 phase has characteristic K-complexes and sleep spindles, electrical features which are believed to represent important functions, including the promotion of deeper sleep and memory consolidation[11,18,19]. The N3 phase is synonymous with slow wave sleep, during which many of the physiologically restorative processes of sleep occur[11,20]. REM sleep is when dreaming occurs and is important for memory consolidation and learning[11,21,22]. The brain normally cycles through each phase of sleep over 90-120 min, with 4-5 cycles occurring over the course of the night[11,23]. While the total amount of time spent asleep varies significantly, observational studies indicate that adverse outcomes are

Table 1 Simplified polysomnographic features of the American Academy of Sleep Medicine's phases of sleep

Sleep stage	Electroencephalogram	Electrooculogram	Chin electromyogram
Wake	Alpha activity (sinusoidal 8-13 Hz)	Rapid eye movements; Reading eye movements; Slow eye movements; Blinks	Normal or high tone
N1	< 50% alpha activity; > 50% low amplitude mixed frequency activity (4-7 Hz)	Slow eye movements	Variable, usually lower than wake
N2	Sleep spindles; K-complexes	None	Variable tone
N3	Slow (delta) wave (0.5-2 Hz) ≥ 20%; Sleep spindles may occur	None	Variable tone
REM	Low amplitude mixed frequency activity; No sleep spindles or K-complexes	Rapid eye movements	Low tone

REM: Rapid eye movement.

associated with sleeping less than seven hours or greater than nine hours per day over the long term[24-26]. In summary, both the architecture, or quality, and duration of sleep are important to mediate its beneficial effects.

EPIDEMIOLOGY OF SLEEP DISTURBANCE DURING AND AFTER CRITICAL ILLNESS

Disturbed sleep in the ICU is a near-universal phenomenon. Subjective perception of poor sleep determined using a variety of questionnaires has been reported by 47%-59% of patients[27-30]. Studies using objective measures, including polysomnography and actigraphy, estimate that 67%-100% of patients experience abnormal sleep quality[29,31,32].

Following discharge from the ICU, sleep disturbances persist in 10%-61%[33]. Both objective and subjective measures indicate that sleep disruption improves over time but is still present in up to 61% of ICU survivors 6-12 mo after discharge[34]. In a single-centre, prospective cohort study of 347 patients, Combes *et al*[35] identified sleep disturbance as far as three years after ICU discharge. Women appear to be more affected by persistent sleep disturbances than men[36]. Sleep disruption was associated with other adverse features, including persistent post-traumatic stress disorder, depression, weakness, fatigue, pain and reduced quality of life, although these associations are likely bidirectional[37-42].

Studies that assess sleep using objective methodologies report improvements in sleep architecture between one week and six months post-discharge. Sleep fragmentation, with a high number of arousals, was prominent up to three months, and sleep efficiency remained impaired out to six months[39,43,44]. Objective sleep disturbances correlated with subjectively measured patient perception.

There is a high prevalence of sleep disturbances among ICU patients and survivors that persists for at least 12 mo following discharge and appear to be associated with other long-term, adverse patient outcomes and reduced quality of life.

CAUSES OF SLEEP DISTURBANCE IN THE CRITICALLY ILL

The cause of sleep disruption in the critically ill is multi-factorial and can be divided into environmental, therapy-related and patient factors.

Patient factors

Patient factors, including increasing age, male sex, and poor sleep quality at home, have been associated with worse ICU sleep parameters[36,45]. The relationship between acute illness severity and sleep disruption is biologically plausible but has been inconsistently demonstrated. Two small studies, including a total of 35 patients, found a correlation between greater illness severity, determined by Acute Physiology and Chronic Health Evaluation (APACHE III) score and Simplified Acute Physiology Score (SAPS II) respectively, and greater sleep disruption[46,47]. In contrast, illness severity, as measured by the patient's Acute Physiology and Chronic Health Evaluation (APACHE III) score, was not found to be correlated with total sleep time, sleep fragmentation or subjective perception of sleep quality from four studies involving 264 patients[31,36,45,48].

Patients report that distress, anxiety, and pain are factors that impair their ability to sleep[49-53]. Sleep deprivation has, in turn, been identified as a stressor contributing to patient anxiety and distress and creating a positive feedback loop[51,54-56].

Environmental factors

Loss of diurnal variation and circadian entrainment: Critically ill patients have been shown to have temporally recognized circadian rhythmicity, likely due to the absence or disruption of normal external entraining cues, such as light exposure, changes in ambient temperature and eating patterns[13,42,57,58]. In health, circadian rhythms are crucial for sleep regulation, and disrupted sleep during critical illness is likely to be part of the circadian dysfunction that occurs in these patients[13,58,59].

Ambient light: Diurnal variation in light is an important entrainer of the circadian rhythm. Light intensity, wavelength and spectral distribution all affect the physiological response to light exposure [60]. ICU patients rate ambient light as a common contributing factor to poor sleep[30,61-63]. Both low levels of daytime light and peak light levels in the early evening have been reported, which pose a risk to circadian rhythms and maintenance of normal sleep-wake patterns[6]. Prolonged light exposures have been documented to occur frequently during the nocturnal sleep period[64].

Noise: Patients perceive noise as a significant factor leading to poor sleep in the ICU, with talking, equipment alarms, the television, and use of the bedside phone by staff being common causes[36,46,65]. The World Health Organisation recommends that noise levels within hospital environments should not exceed 35 decibels (dB) during the day and 30 dB at night[66]. Multiple studies report noise levels are frequently greater than this, with equivalent continuous sound levels of 50-75 dB and peaks up to 96 dB [67-69]. This noise level is associated with sleep disruption[45,70]. Polysomnography detected sleep disturbances were observed when sound thresholds exceeded 63 and 59 dB during daytime and nighttime, respectively. Estimates of noise-related sleep disturbance in the ICU vary from 11% to 58% [31,46,62,63,71-74].

Patient-care related

Critically ill patients require intensive monitoring and care 24 h a day. Nursing and medical interventions, including mouth and eye care, decubitus ulcer care, change of dressings, medication administration, blood sampling, endotracheal tube suctioning, clinical examination, and procedures may interfere with patient sleep[46,75]. Patients perceive these care activities as a substantial contributor to sleep disruption[30,62,74]. It has been reported that over the course of a night, patients were subjected to an average of 42.6 to 51 care interactions, with approximately 20% of these resulting in a clinically evident sleep disruption[46,75,76]. One study even identified increased care activities occurring between 02:00 and 05:00[75].

A proportion of nocturnal care activities are essential in the ICU. Whether the frequency and intrusiveness of nocturnal care activities are excessive and lead to harm due to sleep fragmentation and sleep deprivation, such as neurological observations performed and recorded at one-hourly intervals, remains uncertain[77,78].

Treatment-related

Mode of mechanical ventilation: Critically ill patients frequently require respiratory support, and mechanical ventilation contributes to sleep disruption. Patient-ventilator dyssynchrony, abnormal gas exchange, and mechanical ventilation-related central apnoeas are all considered contributory[6,79,80]. Mechanically ventilated patients experience disturbed sleep architecture with frequent arousals and decreased amounts of slow wave and REM sleep[48,57,81]. The effect of the mode of ventilation on sleep has been studied, but due to the limited number of patients observed and methodological limitations, the impact of ventilator mode remains to be determined.

Studies comparing pressure support ventilation (PSV) to assist-control ventilation report point estimates suggesting assist-control decreases fragmentation, increases total sleep time, slow wave sleep and REM sleep, and reduces central apneas, but the wide confidence intervals are indicative of considerable uncertainty about this effect[79,81,82].

A single study comparing pressure control ventilation to pressure support ventilation reported statistically significant improvements in sleep efficiency and proportion of time in N2, N3 and REM sleep with a pressure control mode[83]. Notably, all 26 patients included in the study had chronic respiratory disease, which limits the application of these findings to a broader patient population, and whether nocturnal pressure control ventilation delays liberation from ventilation is also unknown.

Several proportional assist ventilatory modes have been compared to pressure support ventilation with mixed results[84-86]. Details of these studies have been recognized in Table 2.

The association between non-invasive ventilation use and sleep quality has also been evaluated. Using an ICU ventilator, rather than a dedicated non-invasive ventilator, to provide non-invasive respiratory support is associated with reduced patient-ventilator dyssynchrony and number of arousals [87]. In addition, detection of early abnormal sleep architecture in patients with hypercapnoeic respiratory failure was associated with late NIV failure[88].

In the immediate period following discharge from ICU and at both 6 and 12 mo following discharge, exposure to mechanical ventilation during a patient's ICU stay does not seem to be associated with subsequent sleep disturbance[34,47].

Table 2 Comparison of studies assessing the effects of ventilator mode on sleep quantity and quality

Ref.	Study Design	*n*	Treatment arms		Sedation	Outcomes	
Studies comparing pressure support ventilation against assist control ventilation							
Parthasarathy *et al*[79], 2002	Single centre, randomised, cross over study	11	2 h each of: **PSV**; PS to achieve Vt 8 ml/kg	**ACV**; Vt: 8 mL/kg; f: Set as patient RR minus 4/min	Yes	Sleep efficiency: Arousal index, *mean (SD)*	Not reported; ACV 39 (6); PSV 35 (7); No statistically significant difference between ventilation modes
Toublanc *et al* [81], 2007	Single centre, randomised, cross over study	20	4 h each of: **PSV**; PS = 6 cmH2O; Trigger sens = 0.5 cmH2O	**ACV**; Vt: 10 ml/kg; f: 12/min; Increased until no spontaneous inspiratory effort	Free from sedation for 48 h	Sleep efficiency: Arousal index, *mean (SD)*	No difference, values not reported; ACV 7 (SD 5); PSV 7 (SD 5); No statistically significant difference between ventilation modes
Cabello *et al* [82], 2008	Single centre, randomised, cross over study	15	6 h each of: **cPSV**; PS to achieve Vt 6-8 ml/kg (PBW); RR < 35/min; **aPSV**	**ACV**; Vt: 8 mL/kg; f: 10/min (back up)	Free from sedation for 24 h	Sleep efficiency, *median [IQR]*: Arousal index, *median [IQR]*	ACV 58 [48-82], cPSV 44 [29-30], aPSV 63 [29-80]; ACV 30 [17-41], PSV 28 [17-53], aPSV 23 [21-45]; No statistically significant difference between ventilation modes
Studies comparing pressure support ventilation against pressure control ventilation							
Andréjak *et al* [83], 2013	Single centre, randomised,cross over study	26	4 h each of: **PSV**; PS = 6 cmH2O; Trigger sens = 0.5 cmH2O	**PCV**; PS = 20 cmH2O; f: Greater than patient RR I/E ratio: 1/1.2 to 1/1.5	Not reported	Sleep efficiency, *median [IQR]*: Arousal index	PCV 63 [9-100]; PSV 37 [0-96] Not reported; Significantly improved sleep efficiency with PCV
Studies comparing pressure support ventilation against proportional assist ventilation							
Bosma *et al* [84], 2007	Single centre, randomised, cross over study	13	1 night each of: **PSV**	**PAV**	Propofol, midazolam or lorazepam	Sleep efficiency, *mean (SD)*: Arousal index, *median [IQR]:* Patient-ventilator asynchrony per hour, *mean (SD)*	PSV 58% (25); PAV 60 (23); PSV 16 (2-74); PAV 9 (1-41); PSV 53 (59); PAV 24 (15); PAV associated with statistically significantly fewer arousals and episodes of asynchrony
Alexopoulou *et al*[85], 2007	Single centre, randomised, cross over study	17	1 night each of: **PSV_{base}**; PS as before study; **PS_{high}**; Pressure assist increased by 40%-50% from PSVbase or until Paw = 30 cmH2O	**$PAV+_{base}$**; Set to achieve mean inspiratory pressure similar to PSV_{base}; **$PAV+_{high}$**; Percentage of unloading increased by 40%-50% from PSVbase or until it reached 85%	Group A; *n* = 11; Propofol; Group B; *n* = 9; Non-sedated	Group A; Sleep efficiency, *mean (SD)*: Arousal index, *mean (SD)*: Group B; Sleep efficiency, *mean (SD)*: Arousal index, *mean (SD)*	$PAV+_{base}$ 99 (2); PAV_{high} 98 (5); PSV_{base} 93 (11); PSV_{high} 88 (16) (P < 0.05); $PAV+_{base}$ 4.6 (4.9); PAV_{high} 7.4 (11); PSV_{base} 5.4 (3.6); PSV_{high} 6.5 (6.7); $PAV+_{base}$ 76 (11); PAV_{high} 71 (21); PSV_{base} 68 (19); PSV_{high} 72 (15); $PAV+_{base}$ 12 (8.0); PAV_{high} 11 (7.6); PSV_{base} 8.4 (4.8); PSV_{high} 10.5 (9.9); In sedated patients (Group A), PAV+ is associated with a modest, albeit statistically significant at the 0.05 level, improvement in sleep efficiency; No statistically significant differences found between ventilation modes in non-sedated group
Alexopoulou *et al*[86], 2013	Single centre, randomised,cross over study	14	Alternating 4-h blocks over 24 h of: **PSV**; PS maintained at pre-study level	**PAV+**; % of unloading set to achieve a mean inspiratory pressure similar to PSV	Free from sedation and opioids for 24 h	Sleep efficiency, *median [IQR]*: Arousal index, *median [IQR]*	PAV+ 51 [13-66]; PSV 27 [6-22]; PAV+ 11 [4-25]; PSV 12 [3-16]; No statistically significant improvement found with PAV+
Studies comparing pressure support ventilation against neurally adjusted ventilatory assist							
Delisle *et al* [236], 2011	Single centre, randomised, cross over study	14	2 non-consecutive 4-h blocks (d/night) of: **PSV**; PS to achieve Vt 8 mL/kg; RR < 35/min	**NAVA**	Free from sedation and opioids for 24 h	Sleep efficiency, *median [IQR]*: Fragmentation index, *median [IQR]*	NAVA 74 [52-77]; PSV 44 [29-74]; NAVA 18 [8-22]; PSV 34 [25-54]; NAVA statistically significant improvement in the efficiency and reduced fragmentation of sleep

PSV: Pressure support ventilation; cPSV: Clinician adjusted PSV; aPSV: Automatically adjusted PSV; PCV: Pressure control ventilation; PAV: Proportional assist ventilation; PAV+: Proportional assist ventilation with load adjustable factors; NAVA: Neurally adjusted ventilatory assist; IQR: Interquartile range; SD: Standard deviation; *n*: Number of patients. P=NS: Not statistically significant result; Vt: Tidal volume; RR: Spontaneous respiratory rate; f: Mechanical

ventilatory cycle frequency; PS: Pressure support; I/E ratio: Inspiratory-expiratory ratio.

In summary, there appears to be some effect of ventilatory mode on sleep quality and quantity, however, a consistent physiological rationale remains elusive. In addition, the included studies are hindered by small sample sizes, and further larger-scale studies are required to elaborate on the relationship between ventilation mode and sleep.

Feeding and nutrition: Nutritional support is an essential ICU treatment and would commonly be administered as a continuous infusion over 24 h in those that cannot eat[89]. The timing of meals and the associated release of nutritional hormones is an important entraining cue for circadian rhythms. Continuous delivery of nutrition may contribute to circadian rhythm and sleep disruption, and intermittent feeding may reduce this effect[90]. However, intermittent feeding regimens have not been shown to improve patient outcomes, possibly because of delayed gastric emptying[91,92]. Hitherto, there have been no trials evaluating intermittent enteral nutrition on circadian rhythm and sleep parameters, but a randomised clinical trial will soon be completed (ClinicalTrials.gov Identifier: NCT04737200).

Pharmacological: Critically ill patients are exposed to multiple drug classes that may affect sleep quantity and quality. However, very little published research directly quantifies this, and much of the information below is extrapolated from drug effects in other patient populations.

Sedatives and analgesics

Several studies have demonstrated that mechanically ventilated patients receiving sedation have longer total sleep time and higher sleep efficiency but more atypical sleep than patients who are not intubated and sedated[57,93,94]. Propofol is one of the most frequently used sedative agents in the ICU, but there is conflicting evidence of its effect on sleep. Propofol is reported to disrupt REM sleep and delay sleep onset latency, however, in animal models there is evidence that propofol-induced sedation may confer some of sleep's restorative effects[95,96]. A single-centre, prospective cohort study of 50 intubated patients found that sedation with propofol as a single agent was associated with increased sleep duration and decreased fragmentation when compared to fentanyl, propofol and fentanyl, or no sedation[97]. In contrast, a small crossover study of 12 mechanically ventilated patients reported that propofol, compared to no sedation, did not significantly affect total sleep duration or fragmentation, but adversely impacted the duration of REM sleep[98].

Benzodiazepine use is associated with increased total sleep time, resulting from decreased sleep latency and prolongation of the N2 sleep phase, at the cost of reduced slow wave and REM sleep[99]. Opioids, even as a single dose, have been shown to reduce the duration of slow wave and REM sleep [100-102]. The central alpha-2 adrenoreceptor agonist, dexmedetomidine, is associated with increased sleep efficiency and proportions of N3 sleep but decreased REM sleep[96,103,104].

Cardiovascular medications

Adrenergic catecholamines can cause suppression of REM and slow wave sleep[105,106]. Both amiodarone and lipid soluble beta-blockers may theoretically have adverse effects on sleep that include decreased REM sleep and nightmares[99]; however, whether these drugs have any effect during critical illness has not been evaluated.

Antidepressants and antipsychotics

In other patient groups, sedating tricyclic antidepressants such as amitriptyline decrease sleep latency, increase the proportion of slow wave sleep and decrease the proportion of REM[99,107]. Venlafaxine is recognised to suppress REM sleep and cause nightmares, while selective serotonin inhibitors can cause increased wakefulness, reduced total sleep time and decreased REM sleep[99,107,108]. Antipsychotic medications are of particular interest due to their use in the management of delirium and have been observed to have variable effects on sleep architecture. Haloperidol has been shown to increase sleep efficiency, whereas the atypical agents, olanzapine and risperidone, have the additional effect of promoting slow wave sleep[99,109-111].

Miscellaneous

Corticosteroid use is associated with multiple neurocognitive, behavioural and circadian changes that may contribute to poor sleep[99,112]. Exogenous steroid use may cause misalignment of the hypopituitary adrenal axis with adverse effects on the circadian rhythm, which may be further exacerbated by steroid-induced suppression of melatonin secretion[112].

Multiple pharmacological agents may diminish sleep in the ICU. Sedation is frequently necessary to facilitate treatment and reduce patient distress. The true impact of current sedative regimes on sleep quantity and quality remains incompletely defined. Multiple pharmacological agents suppress slow wave and REM sleep, which may contribute to sleep deficit-related morbidity.

SLEEP DISTURBANCE IN THE CRITICALLY ILL

Sleep disturbance may be characterised by abnormalities, including difficulties falling asleep (sleep initiation), staying asleep (sleep maintenance), frequent awakenings or arousals (fragmentation), and atypical sleep architecture. Patients with critical illness largely preserve their total time asleep, or total sleep time, however, this sleep is highly fragmented and spread over 24-h[63,113-118]. Instead of being consolidated in a single nocturnal sleep period, approximately 50% of sleep in critically ill patients occurs during daytime hours[63,114,115].

Sleep architecture during critical illness is frequently abnormal[31,32]. Polysomnographic studies demonstrate a lack of variability in the electroencephalogram (EEG), with a predominance of the 'lighter' N1 and N2 phases, paucity or absence of N3 and REM sleep, and frequent arousals[119,120]. Additional features of atypical sleep include the relative absence of K-complexes and sleep spindles, as well as dissociation of the EEG from behavioural findings. Such dissociations manifest as either pathologic wakefulness, characterised by an EEG frequency consistent with sleep in awake patients or unresponsive patients with EEG frequencies associated with being awake[119]. These EEG abnormalities mean that 16-85% of polysomnographic data in observational studies were not able to be qualified using standard scoring systems[113-115,117,121]. Amended criteria have been proposed that recognise this atypical sleep pattern[113,115]. Watson *et al*[115] proposed an additional seven criteria for sleep scoring in the critically ill with robust reported interrater reliability (weighted kappa 0.80; bootstrapped 95% confidence interval 0.48, 0.89) but this has not been externally validated. Notably, the development of an atypical sleep pattern was strongly associated with the subsequent development of delirium, a longer ICU length of stay, and higher odds of death[116].

In summary, critically ill patients display multiple and severe perturbations in their sleep that are not well described by current sleep scoring classifications. Several of these abnormalities are associated with a worse prognosis, yet it remains unclear if these are modifiable endpoints or markers of disease severity.

MEASURING SLEEP IN THE CRITICALLY ILL

Measuring sleep in the critically ill poses many challenges and is frequently confounded by sedation, encephalopathy, primary neurological insults, and prioritisation of more imminently life-threatening issues[6]. Both objective and subjective measurement tools have been used independently or in combination[59].

OBJECTIVE MEASUREMENT OF SLEEP IN THE CRITICALLY ILL

Polysomnography

Polysomnography uses polygraphic recording of electroencephalographic, electromyographic, and electro-oculographic data to measure sleep and is considered the gold-standard technique. There are two predominant systems for scoring polysomnographic sleep data. The Rechtschaffen and Kales (R&K) criteria, first published in 1968, describe five phases of sleep in healthy individuals but were superseded in 2007 by the American Academy of Sleep Medicine's (AASM) sleep scoring rules[16]. The AASM and R&K scoring rules share many similarities (Table 3) but show relatively low concordance when scoring NREM phases[15-17,122,123]. Moreover, both lack accuracy in quantifying the atypical sleep seen in the critically ill[124]. Logistical, technical, and financial barriers to the use of polysomnography in ICU have been described, including access to specialist equipment and the support of a sleep service for set-up and analysis[119,125,126]. The device itself is reported to interfere with the delivery of patient care, is tolerated poorly by up to 25% of patients, and patient discomfort from the device may worsen sleep[119, 127]. Accordingly, while polysomnography remains the gold-standard technique for ambulant patients, there is a need for other methodologies to quantify sleep during critical illness.

EEG spectral analysis

The electroencephalogram used in polysomnography provides invaluable information about sleep stages. Multiple attempts to simplify this element of sleep analysis have been described, using a reduced number of EEG leads, spectral analysis of the EEG frequencies, and automated scoring algorithms. Several studies have attempted to analyse limited EEG leads using different techniques. Bispectral Index (BIS) was developed as a depth of anaesthesia monitor for use in the operating theatre. A limited channel EEG signal is acquired using a single strip of electrodes applied to the forehead. Bispectral and power spectral analysis of the EEG is used to generate a numerical score to indicate depth of sedation [128]. While BIS has been used to investigate sleep in the critically ill, studies of BIS for sleep monitoring in both healthy volunteers and critically ill adults have reported that BIS is inaccurate for the detection of various sleep stages, particularly in differentiating REM from N1/N2 sleep phases, and correlates

Table 3 Comparison of American Academy of Sleep Medicine's and Rechtschaffen and Kales criteria sleep stage nomenclature

	AASM	R&K
Wake	Stage W	Stage W
NREM sleep	Stage N1	Stage 1
	Stage N2	Stage 2
	Stage N3	Stage 3
		Stage 4
REM sleep	Stage R	Stage REM

AASM: American Academy of Sleep Medicine; R&K: Rechtschaffen and Kales criteria; REM: Rapid eye movement.

weakly with multiple domains on the Richards-Campbell Sleep Questionnaire[129,130].

Alternative attempts to use spectral EEG analysis to monitor sleep in the critically ill, including the odds-ratio product index and ICU depth of sleep index, offer potentially useful alternatives[131]. Spectral EEG analysis using fast Fourier transformation showed perfect inter-observer and intra-observer agreement, however, the sample size of only 14 patients limits the generalizability of this finding[124]. These techniques do not rely on traditional scoring parameters, such as the presence of sleep spindles, and consequently are not affected by the absence or atypia of these features as reported by other authors[113]. The use of spectral analysis has the potential to simplify sleep assessment in the ICU, however, correlation with standard polysomnography parameters, as well as standardization and external validation, will be necessary before it can be more widely applied.

Limited lead EEG

To reduce the complexity associated with the use of polysomnography, several 'simplified' proprietary devices have been trialled. The Sedline™ is a portable monitor that is able to acquire limited lead EEG using bifrontal electrodes to derive a Patient State Index, which represents varying levels of consciousness. Vacas *et al*[132] assessed the feasibility of using the Sedline to monitor sleep in three volunteers and 23 ICU patients and reported that the device was well tolerated but had poor agreement with polysomnography for stages N1 and N3. The Sleep Profiler™ is a wireless device that is applied to the forehead to acquire frontopolar EEG and uses auto-staging software to interpret the data. The Sleep Profiler™ has been evaluated by Jean *et al*[97] and Romagnoli *et al*[133] to assess the effects of sedation on sleep architecture in ICU patients. While reported accuracy is comparable to polysomnography in healthy volunteers, this comparison has not been reported in the ICU population[93].

Actigraphy

Actigraphy devices, commonly worn on the wrist or ankle, use omnidirectional accelerometers to detect limb movement; these limb movements are interpreted using automated algorithms to estimate sleep-wake state[125,134]. These devices are minimally invasive, relatively straightforward to use, and have been used to assess sleep in outpatient settings[135]. Given the frequency and magnitude of critical illness weakness, studies of actigraphy in the critical care setting have identified poor overall accuracy, with over-estimation of total sleep time and sleep efficiency, when compared to polysomnography, nurse observation, or BIS[136]. Actigraphy has been used to evaluate sleep-promoting interventions in ICU, however, the poor correlation with other validated measures of sleep limits inferences from these studies[136,137].

Novel devices: The Nemuri SCAN™, an under-bed mattress sensor, has been evaluated to measure sleep in a total of 29 ICU patients in two prospective observational studies[138,139]. When compared to polysomnography, moderate agreement but poor specificity was reported. In addition, there was no correlation with subjective sleep, quantified using the Richards-Campbell Sleep Questionnaire.

The most frequently used research methods to objectively measure sleep in the critically ill have been summarised in Table 4. There is no methodology available that provides clinicians with real-time objective information each morning regarding the quantity and quality of a patient's sleep the night before. Such information has the capacity to transform clinical care.

SUBJECTIVE MEASUREMENT OF SLEEP IN THE CRITICALLY ILL

Understanding the subjective quality of patients' sleep is an important component of a holistic assessment. Direct patient self-report is of greatest interest, however, due to factors such as delirium and

Table 4 Summary of objective methods of sleep measurement in the critically ill

Method	Benefits	Limitations
Full polysomnography (PSG)	Gold standard technique; Provides polygraphic data on EEG, eye movements and chin tone; Established guidelines for interpreting data for normal sleep	Complex set up; Relatively expensive; Poorly tolerated in 25% of patients; Interferes with nursing care; May interfere with patient sleep; Interpretation requires sleep specialist; No validated criteria for atypical EEG found commonly in critically ill
Bispectral index (BIS) monitor	Small anatomic footprint; Simplified set up compared to PSG; Does not require sleep specialist for interpretation; Less affected by atypical EEG common in critically ill	Inaccurate differentiation of REM from N1/N2 sleep; Correlates weakly with RCSQ; No validated criteria for interpretation of results; Primarily designed to monitor depth of sedation
Limited lead EEG	Small anatomic footprint; Simplified set up compared to PSG; May not require sleep specialist for interpretation	Accuracy dependent on device and auto-staging software; Interpretation dependent on sleep specialist if not using auto-staging
Actigraphy	Minimally invasive; Simple set up; Easy to perform serial measures; Established use in outpatient setting	Poor accuracy compared to PSG and nurse observation, including overestimation of total sleep time and sleep efficiency; Confounded by immobility, weakness, sedation, and neurological injury
Under mattress sensor	Non-invasive modality; Simple set up	Moderate agreement, but poor specificity compared to PSG; No correlation with RCSQ

EEG: Electroencephalogram; N1: Non-REM sleep stage 1; N2: Non-REM sleep stage 2; PSG: Polysomnography; REM: Rapid eye movement sleep; RCSQ: Richards-Campbell Sleep Questionnaire.

administration of sedation and analgesic drugs, it is estimated that only around 50% of the ICU population can participate in such efforts[73].

Thirteen different questionnaires have been used to quantify sleep in the ICU, of which 10 were reported by patients and three reported by ICU nurses[119,140]. Several tools allow for either the patient or nurse to complete them, although accuracy is inconsistent[140].

Of the 13 sleep questionnaires used, the most rigorously studied is the Richards-Campbell Sleep Questionnaire (RCSQ). The RCSQ was specifically designed for use in the ICU population and uses five visual analogue scales to assess the domains of sleep latency, sleep efficiency, sleep depth, number of awakenings and overall sleep quality (Figure 1)[141]. Individual domain scores can be interpreted respectively or combined into a global score, with a score of ≥ 63 out of 100 reported as the optimal cut-off for self-reported 'good sleep'[142]. Both content and criterion validity have been established against polysomnography[143]. While the RCSQ was designed as a patient self-assessment tool, it may also be completed by clinical staff. The accuracy of clinician-completed RCSQ remains unclear with a reported strength of agreement including slight to moderate, moderate, and strong[73,144]. The use of the RCSQ in the outpatient setting has also been established, allowing serial assessments to be continued following ICU discharge[145]. The RCSQ has been translated and validated in multiple languages[146].

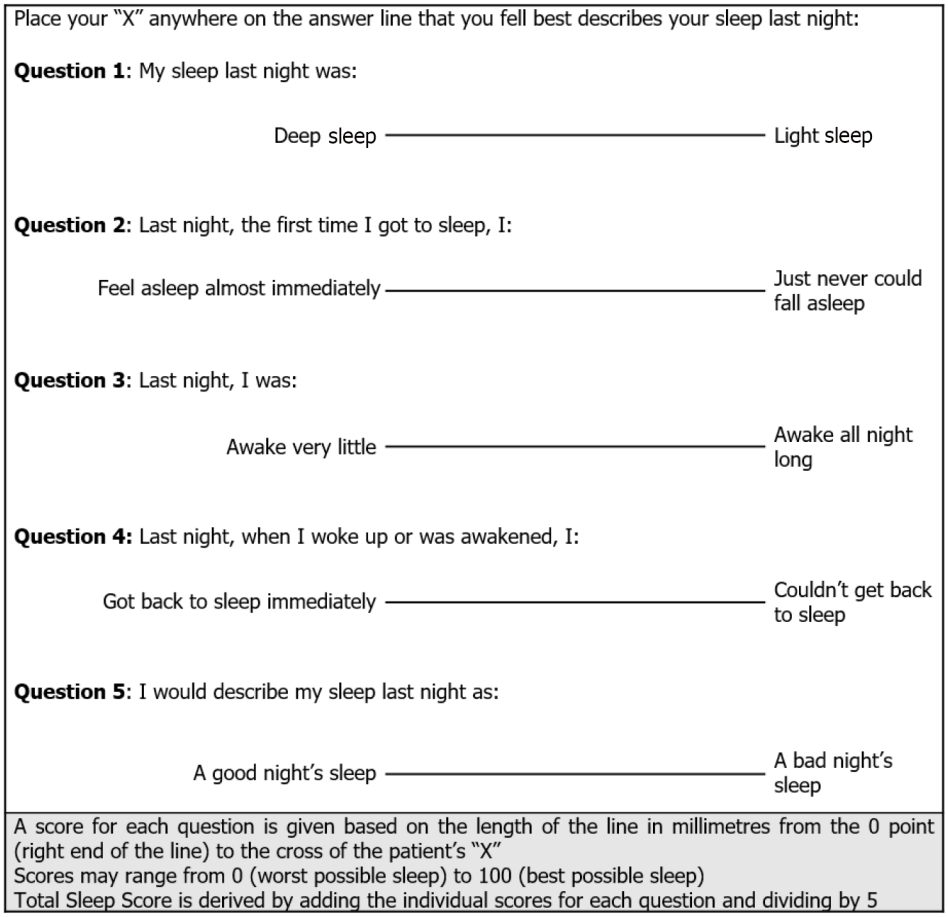
The Verran Snyder-Halpern (VSH) sleep scale is an 8-15 visual analogue scale, self-reported sleep questionnaire that assesses similar domains to the RCSQ but, due to its higher number of questions, is considered more labour intensive[125]. The VSH sleep scale was designed to assess sleep in hospitalised patients without known sleep disorder[125,147,148]. The VSH has been validated for use in the ICU in several studies, but the association between patient and clinician-reported sleep was low[120,149-152].

The Pittsburgh sleep quality index (PSQI) is a nine-item, self-reported sleep questionnaire initially developed for use in the psychiatric population[153]. However, the use of the PSQI in critical care has mainly been to assess sleep following ICU discharge and has no association with objective sleep parameters[154].

Integrating sleep assessment into a daily patient assessment is hindered by the complexity of current tools. The Numeric Rating Scale for sleep (NRS-Sleep) is a single-item assessment tool that requires patients to rank their sleep on a scale of 0 to 10. It was developed in a prospective, multicentre study of 456 ICU patients and using receiver operator curves, a score greater than five was determined as the threshold for good sleep. The NRS-sleep is significantly correlated with mean RCSQ score (Pearson's correlation coefficient 0.88, $P < 0.01$)[155].

The sleep observation tool (SOT) requires an observer to assess and document the patient's sleep or wake status every 15 min and has been found to correctly identify sleep 81.9% of the time compared to polysomnography. It has been used in its standard format to assess the effect of therapeutic interventions and in an amended format that uses 30-min intervals[156-158].

The use of subjective measurement tools alongside objective measures is vital to ensure that future research maintains a patient-focused outcome. The RCSQ is promising as a tool for the measurement of sleep both during and after ICU admission. It may be beneficial for researchers to use a core subjective methodology to facilitate comparisons between studies.



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Figure 1 Patient completed Richards-Campbell sleep questionnaire.

EFFECTS OF SLEEP DISTURBANCE DURING CRITICAL ILLNESS

The effects of disrupted sleep in the critically ill remain poorly understood. In healthy adults, short-term sleep deprivation is associated with multi-system physiologic disturbances, and longer term is associated with increased risks of obesity, type 2 diabetes, malignancy and death[3].

Neurological

Delirium occurs in up to 80% of mechanically ventilated patients and is independently associated with increased mortality[159]. There are suggestions of a bidirectional relationship with sleep deprivation contributing to the development of delirium, and delirium worsening sleep disturbances[160]. A causal link between sleep deprivation and delirium has not been established, but several studies support an association. The detection of atypical sleep on EEG, commonly seen in critically ill patients, was associated with a significantly increased risk of developing delirium in the following 48 h[113]. A prospective observational before and after study of the introduction of a quality improvement intervention to promote sleep in 300 ICU patients reported a marked reduction in the incidence of delirium (odds ratio 0.46; 95% confidence intervals, 0.23-0.89), however, improvements in RCSQ measured sleep did not reach statistical significance[161]. A similar study on the introduction of a multicomponent, multidisciplinary bundle of interventions in 338 ICU patients reported improved sleep efficiency, decreased daytime sleepiness, and reduced incidence and duration of delirium[162]. The results of a meta-regression conducted by Kakar *et al*[94] reported a somewhat unexpected relationship between total sleep time and delirium, where each hour increase in total sleep time per night was associated with a 5.8% increase in the risk of delirium. This counterintuitive result may be due to confounders, such as duration of mechanical ventilation, depth of sedation or disease severity.

Seizures are exacerbated by sleep deprivation and in focal epilepsy, the risk of seizure has been shown to correlate with day-to-day variations in daily sleep[163,164]. In animal models, REM sleep seems to play an important role in enhancing the seizure threshold[165]. However, the impact of sleep deprivation on seizures during critical illness is yet to be described or quantified.

Sleep deprivation in healthy adults is associated with cognitive dysfunction, including impaired attention, memory and situational awareness[166]. Critical illness survivors frequently report

troublesome short- and long-term impairments of cognitive function[167]. For example, a multicentre observational study of 102 ICU survivors reported that sleep fragmentation was associated with cognitive impairment at seven days post discharge from ICU in patients who had been mechanically ventilated[168]. No measured sleep parameters were associated with cognitive outcomes at 6 or 12 mo.

Endocrine function

Sleep and circadian disruption during critical illness have been proposed to result in endocrine abnormalities, including decreased secretion of anabolic hormones, including testosterone, growth hormone and insulin-like growth factor, as well as increased secretion of catabolic hormones that results in reduced protein synthesis and increased protein breakdown[169]. This net loss of protein contributes to muscle atrophy and critical illness weakness, which may be more marked in older populations and contribute to adverse outcomes, including increased frailty and functional decline in ICU survivors[169, 170].

A single night of sleep deprivation in healthy adults causes impaired glucagon secretion, elevated evening cortisol, and insulin resistance[171,172]. In the critically ill, these endocrine disturbances may conceivably contribute to the development of impaired glucose tolerance and hyperglycaemia[173].

Melatonin is a circadian regulating hormone produced by the pineal gland[174]. Critically ill patients may experience reduced plasma melatonin concentrations due to loss of light-related physiological regulation of melatonin secretion and lack of normal diurnal variation[175-177]. These abnormalities likely contribute to sleep disturbances in the ICU population and have been associated with increased morbidity and mortality in animal models[178].

Immune function

Immune upregulation, including immune cell proliferation and production of pro-inflammatory cytokines, is typical during the early phases of sleep[179]. Natural killer cell activity is reduced by 28% after one night of sleep deprivation, and a significant increase in total white blood cell count is seen after 3-5 d of sleep restriction[180,181]. A reduced response to influenza and hepatitis A vaccination is seen with sleep deprivation, which does not improve with catch-up sleep[182,183]. A retrospective cohort study of 135 patients with coronavirus disease 2019 (COVID-19) reported that poor sleep was linked to more severe lymphopaenia and a more frequent need for ICU admission[184].

Respiratory function

Sleep deprivation is associated with an impaired ventilatory response to hypercapnia and hypoxaemia, reduced cortical respiratory motor output, and decreased inspiratory muscle endurance[185]. In addition, sleep fragmentation, but not sleep deprivation, has been found to increase the risk of upper airway collapsibility, which may predispose to extubation failure[186].

A prospective observational study of 45 patients evaluating sleep alterations and duration of mechanical ventilation, reported that the detection of atypical sleep on polysomnography was associated with a longer period of invasive respiratory support[187]. This relationship remained after multivariate logistic regression. Furthermore, a separate study reported that each percentage increase in slow wave sleep was associated with 0.58 d increase in the duration of mechanical ventilation[94]. Slow wave sleep is usually considered a deeper, restorative sleep phase and is typically reduced or absent during critical illness. Consequently, confounding variables, such as sedation, are influencing these associations.

Psychological

The relationship between sleep deprivation and psychiatric disorders may be bidirectional[188]. Total sleep deprivation in healthy adults disrupts affective functioning[189]. In contrast, one night of total sleep deprivation has been shown to improve depressive symptoms in up to 60% of depressed patients. However, this improvement is not evident in the majority after recovery sleep[190]. Anxiety and depression frequently occur in ICU survivors, occurring in up to 43% and 48% respectively[191]. ICU survivors with depressive symptoms three months after discharge were observed to have a higher likelihood of sleep disturbance, yet the direction of causality is unclear[161].

SLEEP OPTIMISATION STRATEGIES

Given the prevalence, persistence and impact of sleep disturbance during critical illness, there is considerable interest in improving patients' sleep duration and quality. In 2018, the Society of Critical Care Medicine published its clinical practice guidelines for the prevention and management of pain, agitation, delirium, immobility and sleep disruption to summarise the contemporary evidence on this subject[192]. Sleep optimisation strategies can be categorised into non-pharmacological and pharmacological interventions.

NON-PHARMACOLOGICAL MANAGEMENT OF SLEEP DISTURBANCES

Intervention bundles

Several authors have reported on implementing nurse-led or multi-disciplinary, multi-component, intervention bundles to improve patient sleep. Eight domains that could be included in an intervention bundle were described by Beck Edvardsen *et al*[193] including noise reduction; use of earplugs and eye masks; use of music; promotion of natural circadian rhythms; managing pain; use of "quiet time"; clustering of nursing activities, and optimising mechanical ventilation. However, evidence regarding such sleep-promoting intervention bundles is mixed. Improved objective and subjective measures of sleep have been reported in two studies[162,194]. Bundles from each study were implemented by a multi-disciplinary team and contained over 10 interventions, including the offer of eye masks and ear plugs. In contrast, no significant benefit of a sleep promotion bundle was reported in two further studies that had fewer interventions and did not include the provision of ear plugs and eye masks[195,196]. Studies of bundled care assess the net effect of multiple interventions, obscuring the magnitude and direction of effect from the individual components. Consequently, it is unclear which interventions contained in the reported studies are mediating the benefit[197].

Noise reduction

Several strategies have been described to reduce the effect of noise disturbance on sleep. For example, Walder *et al*[198] reported the implementation of five policy steps, including the closure of doors, reducing monitor alarm volumes and, between 23:00 and 05:00, limiting nursing care, conversational noise and direct light in patients' rooms. These interventions successfully reduced nocturnal noise and light. The implementation of a behavioural modification program for nursing staff reported similar results that such measures could reduce ambient noise and light in the ICU to provide a better sleeping environment[199]. However, neither study measured patients' sleep, making it impossible to assess the impact of these environmental interventions on sleep outcomes.

Quiet time

'Quiet time' protocols designate a 1–2-h period during the day during which ambient noise and light are reduced to facilitate patient sleep. Three prospective studies of quiet time, involving 361 patients and using once or twice daily two hour sessions, report that patients are more likely to be reported as asleep during quiet time than during the control period[156,157,200]. Sleep was determined using a novel subjective nurse assessment or the Sleep Observation Tool[201]. Given the short available sleep period, the highly subjective nature of the assessments, and the inability to interpret reported sleep in the context of total sleep time, the inferences are limited. A quasi-experimental, non-randomised, post-test-only study of a once-daily session of quiet time in 129 patients did not detect a significant improvement in sleep measured by RCSQ with increasing numbers of quiet time sessions[202].

While quiet time is a simple, safe and low-cost intervention, methodological issues in the few available studies mean the impact of quiet time on sleep in the ICU remains uncertain.

Ear plugs and eye masks

Earplugs and eye masks offer an inexpensive and potentially low-risk intervention to reduce or diminish the impact of nocturnal ambient noise and light. Despite the intuitive appeal, the available literature reports mixed results (Supplementary Table 1).

Studies evaluating earplugs as a single intervention include a total of 276 patients but are methodologically heterogeneous with respect to duration of the intervention, inclusion of intubated patients, use of sedation, and choice of sleep measurement tool[152,203,204]. One study reported a statistically significant improvement in sleep satisfaction with earplugs but had a 12% dropout rate[152]. Van Rompaey *et al*[204] reported that earplugs were associated with improved sleep on the first study night, but this improvement lessened on the second night and reported sleep was worse than the intervention group by the third night. Litton *et al*[203] proved that using earplugs for noise abatement in the ICU setting was feasible but did not demonstrate a statistically significant benefit to sleep quality.

The combination of ear plugs and eye masks has been assessed together. Several single-centre studies report an improved subjective perception of sleep compared to usual care[195,205-214]. Earplugs and eye masks have also been reported to significantly improve sleep compared to relaxing ocean sounds played for 30 min around the onset of the sleep period[215].

Within the methodological limitations (single centre and lack of blinding), there is increasing evidence that combined eye masks and ear plugs improve self-reported sleep. In contrast, the available literature does not support using earplugs alone.

Music

The use of non-commercial music as a sleep-promoting therapy has been evaluated. In a prospective, quasi-experimental, randomised study, 96 patients who were post-op following coronary artery bypass grafting were exposed to either a daily 30 minute session of music or a rest period[216]. Patients receiving the music intervention were reported to have significantly improved sleep, as measured by

RCSQ, on postoperative day three. Further studies on music to improve sleep in the ICU were unable to identify clear evidence of benefit. A small, randomised, controlled trial of 28 ICU patients receiving either 45 min of music prior to sleep or usual care did not identify a difference in total sleep time or subjective sleep assessment[120]. An increased duration of N3 sleep was reported in the first two hours, however, the polysomnogram was not assessed beyond this window and the significance of this finding is obscured by this methodological choice. A cross-over, randomised, experimental study evaluated the effect of 20 min of music therapy against uninterrupted rest on the BIS[217]. The bispectral index was reduced during the music session; however, no assessment of nocturnal sleep quantity or quality was made, obfuscating any association with improved sleep.

The use of music therapy to improve sleep is not well supported by the published literature. Factors including the type, volume, duration and timing of the intervention are likely all important but have not been well explored to date.

Massage

Studies of massage or therapeutic touch to aid sleep in the ICU have conflicting results. A case series of 53 patients receiving therapeutic touch from a trained nurse could not identify any statistically significant change in physiologic variables[218]. Patients were reported to fall asleep frequently during treatments, but no effect on nocturnal sleep was reported. A quasi-experimental study in 60 patients compared the efficacy of a 10-minute back massage on three consecutive days against usual care and reported improvements in self-reported sleep and actigraphy-determined total sleep on the second and third days of the intervention.

Acupressure

A randomised controlled trial of acupressure for three hours on two consecutive nights was compared to usual care and reported a statistically significant difference in actigraphy-derived total sleep time and sleep quality, as per the Stanford Sleepiness Scale[137]. However, the use of actigraphy, which overestimates total sleep time and is not accurate in the ICU setting, and the Stanford Sleepiness Scale, which has not been validated for use in the ICU, raises questions about the internal validity of this result.

PHARMACOLOGICAL MANAGEMENT OF SLEEP DISTURBANCES

About half of the ICU survivors asked about their sleep believe a sleeping pill would have improved their sleep, but there is scant evidence to support the use of pharmacological sleep aids in this setting [30]. Cohort studies indicate that pharmacological sleep aids are frequently administered to ICU patients[219,220].

Melatonin

Because of the disturbed secretion of melatonin (described above), there is a biologically plausible rationale to support the use of exogenous melatonin. However, a meta-analysis of four studies reported that melatonin, at doses of between 3 and 10 mg per day, had uncertain effects on objective and subjective measures of sleep quantity and quality (Table 5)[136,158,221-223].

More recently, a blinded, parallel-group, placebo-controlled, randomised clinical trial compared 10 mg melatonin to placebo in 203 ICU patients reported a statistically significant improvement in sleep with melatonin represented by an increase in RCSQ by nine points, but no difference in nurse-observed total sleep time[224]. Finally, the Pro-MEDIC study was a multicenter, parallel-group, placebo-controlled randomised clinical trial that included 841 patients and assessed a 4 mg dose of melatonin [225]. While the primary outcome was the incidence of delirium, sleep was recorded using RSCQ. The investigators identified no effect of melatonin on sleep and, as the largest trial to date, provides the greatest certainty as to the effect of melatonin on sleep in the ICU.

Accordingly, while there is a physiological rationale that melatonin should be an effective pharmacological sleep aid in the critically ill, there is a lack of clinical trial data to support its use.

Melatonin receptor agonists

The melatonin receptor agonist, Ramelteon, has been assessed in a single centre, blinded, randomised, placebo-controlled trial using 8 mg ramelteon per day in 88 ICU patients[226]. While the primary outcome was delirium, the use of ramelteon was associated with fewer awakenings and a higher proportion of nights without awakenings but no difference in mean hours of sleep. Determination of sleep status was performed by non-validated, retrospective means, creating uncertainty regarding this tertiary outcome.

Temazepam

There is no clinical trial data to guide the use of temazepam in the critically ill. A single-centre, placebo-controlled, blinded, randomised trial evaluating temazepam is currently recruiting (ANZCTR

Table 5 Summary of randomised clinical trials assessing nocturnal melatonin as a pharmacological sleep aid

Ref.	Design	Patients	Intervention & control	Sedation	Outcome
Ibrahim *et al* [158], 2006	Single centre, double-blind, randomised trial	32 pts	I: Melatonin 4 mg; C: placebo; For ≥ 48 h	Infusions ceased for ≥ 12 h	No significant difference in total sleep time by modified SOT
Bourne *et al* [136], 2008	Single centre, double-blind, randomised trial	24 pts	I: Melatonin 10 mg; C: Placebo; For 4 nights	Ceased for ≥ 30 h	No significant difference in total RCSQ or sleep efficiency by BIS
Foreman *et al* [222], 2015	Single centre, pilot, randomised trial	12 pts	I: Melatonin 3 mg plus eye masks and headphonesC: Standard care; For 1-7 d	Propofol allowed. Opiates ceased > 24 h	Primary outcome not determined in 65% due to uninterpretable PSG
Mistraletti *et al*[221], 2015	Single centre, double-blind, randomised trial	82 pts	I: Melatonin 3+3 mg; C: Placebo; From day 3 of ICU until ICU discharge	Enteral hydroxyzine and lorazepam allowed	No significant difference in total sleep time by nurse observation
Gandolfi *et al* [224], 2020	Double centre, double-blind, randomised trial	203 pts	I: Melatonin 10 mg; C: Placebo For 7 d or until hospital discharge	As per treating clinician	Statistically improved total RCSQ, *mean (SD):* I: 61 (26) C: 70 (21) (P = 0.03); No significant difference in total sleep time by nurse observation
Wibrow *et al* [225], 2021	Multicentre (12), double blind, randomised, trial	841 pts	I: Melatonin 4 mg; C: Placebo; For 14 d or until ICU discharge	As per treating clinician	No significant difference in total RCSQ

BIS: Bispectral index; ICU: Intensive care unit; PSG: Polysomnography; RCSQ: Richards-Campbell Sleep Questionnaire; SOT: Sleep observation tool.

registration number: ACTRN12621000742875).

Nocturnal propofol

Propofol is an intravenous anaesthetic agent that enhances GABA-ergic inhibition in the brain and is frequently administered in the ICU for patient sedation[227]. Engelmann *et al*[228] conducted a single-centre, blinded trial comparing an intravenous infusion of 2 mg/kg/h propofol against a single bolus of intravenous 0.015 mg/kg flunitrazepam for a single night. Sleep quantity was measured using BIS, and the investigators reported a statistically significant improvement in the propofol group. However, the comparison of a continuously infused agent against a single bolus, and the use of BIS to monitor sleep undermine the validity of this result. A randomised cross-over trial of nocturnal propofol infusion in 12 mechanically ventilated ICU patients reported no difference in total sleep time or NREM sleep distribution using polysomnography[98]. A prospective clinical study of 30 mechanically ventilated patients sedated with propofol and morphine evaluated additional doses of propofol to achieve a diurnal sedation pattern[229]. The authors report that 60% of patients receiving additional nocturnal propofol developed a diurnal rhythmicity, which they attributed to natural sleep, rather than deeper anaesthesia, despite using increased sedation in this group. An open-label, randomised, comparative study of 0.3-3 mg/h propofol infusion compared to 0.03-0.2 mg/hr midazolam infusion was performed in 40 conscious ICU patients overnight to assess sleep quality, anxiety and depression[230]. Using the Hospital Anxiety and Depression Scale, no significant difference in sleep quality could be detected. Notably, the Hospital Anxiety and Depression scale is not validated for sleep assessment and is likely to be insufficiently sensitive or specific to measure this outcome accurately.

Overall, there is no convincing published evidence that propofol is able to improve sleep quality or quantity in critically ill patients.

Dexmedetomidine

Two, small pilot experimental studies have assessed the effect of dexmedetomidine on sleep quality and polysomnographic appearances in critically ill patients[85,231]. Subsequent randomised trials have shown that when compared to placebo, dexmedetomidine increases sleep efficiency, total sleep time and percentage of N2 sleep phase in intubated and non-intubated patients[103,133,232]. Subjective measures of sleep have infrequently been assessed but have not reached statistical significance when reported[103]. A single, non-randomised clinical trial of non-intubated, post-abdominal surgery ICU patients compared dexmedetomidine and sufentanil infusion against sufentanil infusion alone[104]. BIS monitoring showed increased total sleep time in the dexmedetomidine group. Although this result is consistent with prior data, the outcome must be interpreted in the context of the significant limitations created by non-random allocation, small sample size and use of BIS monitoring. A blinded, parallel-group, placebo-controlled clinical trial evaluated the effect of nocturnal dexmedetomidine in 100 delirium-free, critically ill patients[233]. The secondary outcome of sleep quality, measured by the Leeds Sleep Evaluation Questionnaire, reported no significant difference in sleep quality with dexmedetomidine.

Studies of dexmedetomidine report objective improvements in sleep duration and architecture. However, many of the studies of dexmedetomidine do not have sleep as a primary outcome; therefore, interpreting these findings should be undertaken with cautious curiosity.

Orexin receptor antagonists

Suvorexant is an orexin receptor antagonist used as a novel hypnotic agent[234]. A single randomised, placebo-controlled trial of 15 mg/d of suvorexant for the prevention of delirium reported a significantly decreased incidence of delirium in the suvorexant group[235]. No other measured parameters, including time to sleep onset, number of awakenings, subjective quality of sleep, or total sleep time, were statistically different.

There are no currently available pharmacological sleep aids that have a robust evidence base to support their use in the ICU population.

CONCLUSION

Sleep is an important issue for the critically ill. Observational studies report that sleep disturbance is common during critical illness, and a growing body of evidence reports that this is subjectively distressing for the patient, causes physiological derangements and is associated with adverse outcomes. The causes for disrupted sleep in this population are multifactorial and, while not unique to the ICU, may be exacerbated by the treatment modalities, the intensity of care delivery, and the severity of illness that is synonymous with the management of critical illness in this setting.

Measuring sleep in the ICU for clinical and research purposes poses many issues. Polysomnography remains the gold-standard technique but is hindered by logistical issues and the frequent occurrence of atypical electroencephalographic findings. Other objective modalities, including actigraphy and BIS, have not proven sufficiently accurate and do not have a clear role in the ICU setting. Validated, subjective measures of sleep provide an important, patient-centred perspective. However, future research may benefit from adopting a core subjective methodology that would facilitate comparisons between studies.

Many interventions have been assessed to improve sleep during critical illness. When used together, earplugs and eye masks seem to improve sleep. However, a clear and reproducible benefit from other non-pharmacologic strategies has been hard to demonstrate. The use of pharmacological sleep aids to improve sleep is common, yet the currently available evidence does not demonstrate consistent, patient-oriented benefits from any agent. Sleep is a complex physiological process, and successful management of sleep disturbance will likely require a multimodal approach to benefit this vulnerable patient group.

ACKNOWLEDGEMENTS

The primary author, Laurie Showler, was supported through an Australian Government Research Training Program Scholarship.

FOOTNOTES

Author contributions: All authors contribute equally to the design and structure of this review; Showler L was the primary reviewer of the included literature and wrote the manuscript; Deane AM was the second reviewer of the included articles and edited the manuscript; Ali Abdelhamid Y and Goldin J wrote and edited the manuscript.

Conflict-of-interest statement: There are no conflicts of interest to disclose.

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 June 9; 12(3): 116-129

DOI: 10.5492/wjccm.v12.i3.116

ISSN 2220-3141 (online)

MINIREVIEWS

Approaches to neuroprotection in pediatric neurocritical care

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Aydin S, Turkey; Govindarajan KK, India

Received: December 28, 2022
Peer-review started: December 28, 2022
First decision: March 1, 2023
Revised: March 30, 2023
Accepted: April 12, 2023
Article in press: April 12, 2023
Published online: June 9, 2023

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Abstract

Acute neurologic injuries represent a common cause of morbidity and mortality in children presenting to the pediatric intensive care unit. After primary neurologic insults, there may be cerebral brain tissue that remains at risk of secondary insults, which can lead to worsening neurologic injury and unfavorable outcomes. A fundamental goal of pediatric neurocritical care is to mitigate the impact of secondary neurologic injury and improve neurologic outcomes for critically ill children. This review describes the physiologic framework by which strategies in pediatric neurocritical care are designed to reduce the impact of secondary brain injury and improve functional outcomes. Here, we present current and emerging strategies for optimizing neuroprotective strategies in critically ill children.

Key Words: Neuroprotection; Pediatric neurocritical care; Cerebral perfusion; Cerebrovascular pressure reactivity

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Core Tip: Acute neurologic injuries are a common cause of morbidity and mortality in critically ill children. A fundamental goal of pediatric neurocritical care is to mitigate the impact of secondary neurologic injury in critically ill children. Here, we discuss strategies for optimizing neuroprotective strategies in critically ill children.

Citation: Kochar A, Hildebrandt K, Silverstein R, Appavu B. Approaches to neuroprotection in pediatric neurocritical care. *World J Crit Care Med* 2023; 12(3): 116-129
URL: https://www.wjgnet.com/2220-3141/full/v12/i3/116.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i3.116

INTRODUCTION

Neurologic injuries represent a substantial component of pediatric intensive care unit (PICU) utilization in the United States. Analyses of admissions to a large tertiary PICU have demonstrated that neurologic diagnoses are present in approximately one quarter of PICU admissions (25.4%)[1] and acute brain injury is the most common proximate cause of death in children admitted to a PICU accounting for up to 65% of PICU mortality[2]. Additionally, children admitted to the PICU are estimated to acquire new long-term functional disability at a rate of 4.8%[3] by hospital discharge with evidence of further decline in functional status after discharge[4]. The significant contribution of neurologic injury to PICU morbidity and mortality has resulted in an increasing emphasis to develop evidence-based practices to prevent acute brain injury in systemically ill patients and to mitigate the impact of such injuries once they occur. Here, we review current approaches to neuroprotective care in commonly seen pediatric critical care conditions as well as ongoing and future research targets that promise individualized, precision-based care.

MECHANISMS OF SECONDARY NEUROLOGIC INJURY

The evolution of neurologic dysfunction after an acute insult is multiphasic. The primary neurologic injury represents an initial inciting event which results in neuronal cell death, for example acute energy failure in the setting of arterial ischemic stroke or direct mechanical shearing of axons in traumatic brain injury (TBI). Some of the damage caused by the primary injury is typically complete at the time of recognition or presentation to care. However, in many situations there remains at-risk brain tissue that can be acutely rescued if brain homeostasis is optimized with appropriate cerebral blood flow (CBF) to meet metabolic demand. A classic example of such an intervention in adult neurocritical care is thrombolytic and other reperfusion therapy that salvages the ischemic penumbra after acute arterial ischemic stroke. Minimizing ongoing or recurrent mismatch between cerebral perfusion and brain metabolic demand during critical care management represents one of the primary goals of neurocritical care.

Following the primary injury, multiple parallel physiologic pathways emerge that result in further cellular injury if not prevented (Figure 1). A fundamental goal in pediatric neurocritical care is to limit secondary brain injury by optimizing cerebral oxygen delivery and its use[5]. Secondary brain injury is the additive cerebral injury which is created by an imbalance of supply and demand in cerebral metabolism.

TARGETS FOR NEUROPROTECTION IN THE PICU

Neuroprotection generally refers to the preservation of cerebral function by mitigating the above sources of secondary injury[6]. In the PICU, this approach can be broken down into a variety of directives including optimization of cerebral perfusion, limitation of cerebral metabolic demand, and mitigation against cerebral edema.

Optimize cerebral perfusion

The process of optimizing cerebral perfusion for a given patient or pathology requires attention to several physiologic and hemodynamic targets for neuroprotection with consideration of both CBF as well as blood content.

CBF is primarily determined by cerebral perfusion pressure (CPP) and cerebral vascular resistance. CPP is calculated as the difference between mean arterial pressure (MAP) and intracranial pressure (ICP). Importantly, however, measurements of MAP vary significantly by site and methodology[7]. Additionally, adult data has demonstrated that invasive arterial blood pressure measurements levelled at the heart underestimates the MAP at the level of the circle of Willis by approximately 15% when a patients head of bed is elevated to 30° or 45° suggesting head of bed positioning is an important consideration in critically ill patients[8]. Hypotension in pediatric ICU patients has been associated with increased mortality after cardiac arrest and worse outcomes after stroke and TBI[9-13]. Consensus-based pediatric guidelines have focused on maintaining MAPs above minimum thresholds and CPP thresholds when invasive ICP monitoring is available (Table 1)[14-16]. While specific thresholds have been proposed for both MAPs and ICPs, some evidence suggests optimal values varies by age and are on average higher than current guidelines-based recommendations[17]. Further research is needed to identify appropriate minimum thresholds in pediatric neurocritical care populations.

Cerebral vascular resistance is the other major determinant of CBF. Arterial carbon dioxide tension ($PaCO_2$) is the primary modifiable physiologic parameter that impacts cerebral vascular resistance in patients with intact cerebrovascular reactivity, though significant hypoxemia can also play a role in cerebrovascular vasodilation[18]. Increased $PaCO_2$ results in cerebrovascular vasodilation which is often

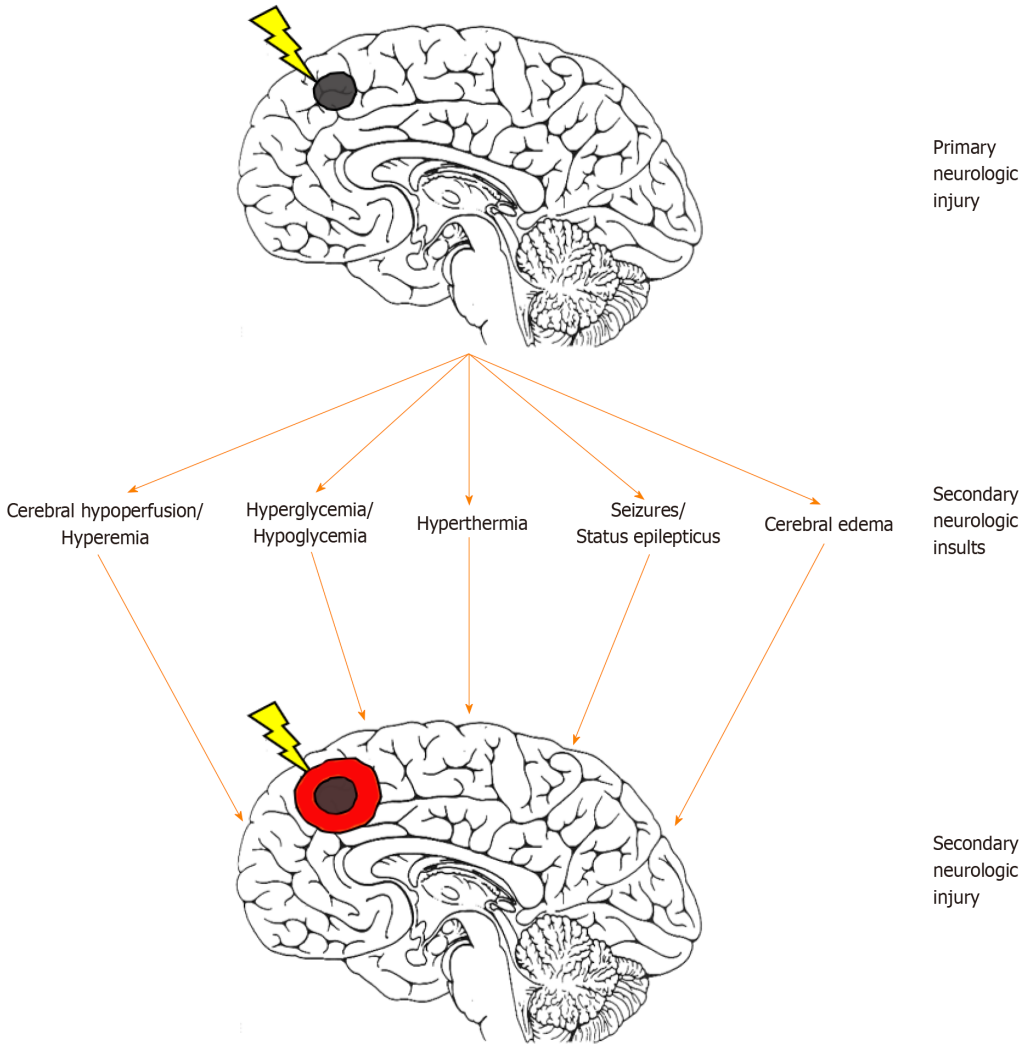
Table 1 Summary of consensus-based guideline recommendations for pediatric neuroprotection

Pathology	Optimize cerebral perfusion	Limit cerebral metabolic demand	Mitigate cerebral edema
Severe traumatic brain injury[15]	Maintain age appropriate CPP (Minimum ≥ 40 mmHg)	Targeted normothermias: 35 °C−38 °C	Maintain sodium: ≥ 140 mEq/L
	If PbtO2 available: ≥ 10 mmHg	Maintain adequate sedation and analgesia	Maintain HOB = 30 °C
	Maintain ICP < 20 mmHg	Benzodiazepine + Opiate as initial therapy	Second tier therapies
	Targeted normoxemia: SpO2 92%−99%	Consider continuous EEG	Surgical intervention
	Maintain PaCo2: 35-40 mmHg	Phenytoin or levetiracetam for seizures	Barbiturate infusion
	Target euglycemia: 100–180 mg/dL		Moderate hypothermia (32 °C−34 °C)
	Target euvolemia: CVP 4−10 mmHg		Hyperventilation (PaCO2 28-34 mmHg)
	Maintain hemoglobin: > 7 g/dL		Increased hyperosmolar therapy
Post-Cardiac arrest[14]	Maintain MAP ≥ 5th percentile for age	Targeted normothermia: 36 °C−37.5 °C	
	Targeted normoxemia: SpO2 94%−99%	Consider 48 h of T 32 °C− 34 °C for OHCA	
	Maintain PaCo2: 35-45 mmHg	Maintain adequate sedation and analgesia	
	Target euglycemia: 80−180 mg/dL	Continuous EEG	
		Treat seizures if identified	
Acute arterial ischemic stroke[80]	Treat hypertension with caution in patients with intracranial vascular stenosis	Maintain temperature < 38 °C	Consider decompressive surgery for malignant edema
	Aggressively treat hypotension		For large volume infarcts (> 1/2 MCA territory)
	Treat hyperglycemia to target 140-180 mg/dL		Consider early decompressive hemicraniectomy (< 24 h)
	Treat hypoglycemia: < 60 mg/dL		Serial imaging and frequent assessments for 72 h

CPP: Cerebral perfusion pressure; PbtO2: Partial pressure of brain tissue oxygenation; ICP: Intracranial Pressure; SpO2: Peripheral oxygen saturation; PaCo2: Arterial carbon dioxide tension; CVP: Central venous pressure; EEG: Electroencephalography; HOB: Head of bed; MAP: Mean arterial pressure; OHCA: Out-of-hospital cardiac arrest; MCA: Middle cerebral artery.

desirable when hypoperfusion is the primary insult as seen with permissive hypercapnia in acute stroke care, though is less desirable in cases where cerebral edema and intracranial hypertension are predominant as it results in a net increase in the intracranial blood volume compartment further contributing to increased ICP. Current pediatric literature supports maintaining normocapnia in most pathologies. Impaired carbon dioxide reactivity to brain tissue oxygenation ($PbtO_2$) can be observed after injuries such as TBI, and recognition of such situations may influence targeting of $PaCO_2$ levels.

Partial pressure of blood oxygenation (PaO_2), glucose and hemoglobin content are also important in ensuring adequate cerebral perfusion after acute brain injury. Both hyperoxia and hypoxia are common in pediatric patients after cardiac arrest and TBI, however the impact of oxygen exposure on outcomes remains unclear[19-21]. Arterial hypoxemia in the injured brain results in reduced cerebral oxygen delivery, potentiating injury in ischemic tissue and further contributing to neuronal excitotoxicity. Conversely, hyperoxia is thought to increase oxidative stress through increased production of free radical species and has been associated with increased mortality after cardiac arrest in adult populations [22]. Available data from pediatric investigations has been equivocal on the effect of arterial hypoxia or hyperoxia on morbidity or mortality after cardiac arrest or TBI. One large retrospective review demonstrated increased mortality in pediatric post arrest patients with a $PaO_2 \geq 300$ mmHg or $PaO_2 \leq 60$ mmHg on the first arterial blood gas after PICU admission[23]. Other retrospective cohort studies as well as one prospective multicenter observational study of pediatric post-arrest patients have not redemonstrated this association[19,21,24]. Retrospective analysis of pediatric TBI patients has not demonstrated an association between hypoxia and outcome, though extrapolation of this data is limited as hypoxia is often identified and treated rapidly during resuscitation[20,25,26]. A recently published



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Figure 1 Development of secondary neurologic injury after pediatric acute brain injury. After primary brain injury (black circle), a host of secondary neurologic insults can contribute to worsening of the initial injury, resulting in secondary neurologic injury (red circle). Neuromonitoring for secondary brain insults and optimization of neuroprotection may help mitigate against secondary neurologic injury in children with acute brain injuries.

systematic review and meta-analysis did demonstrate an association between arterial hyperoxia (as defined by PaO_2 > 250 mmHg) and increased mortality pediatric study populations that included post-cardiac arrest, TBI, extracorporeal membrane oxygenation and general pediatric critical care[27]. Neuroprotective strategies in pediatric critical care generally support maintaining normoxemia while avoiding hyperoxia, though specific thresholds vary. Emerging data in pediatric TBI patients where invasive $PbtO_2$ monitoring is available suggests that episodes of cerebral hypoxia (as measured by $PbtO_2$ < 10 mmHg or 15 mmHg) is associated with unfavorable clinical outcomes as well as reduced performance on neuropsychiatric testing > 1 year post injury[28-30].

Hyperglycemia (serum glucose > 200 mg/dL) on admission after pediatric TBI has been demonstrated to be a predictor of mortality and ICU length of stay suggesting high serum glucose may be a marker of brain injury severity[31-34]. Similarly, persistent hyperglycemia 12-72 h after admission has also been independently associated with mortality and poor clinical outcomes, though prospective data assessing the impact of narrow glycemic control on outcomes is limited[35-37].

Retrospective evaluations of anemia in pediatric TBI patients have not demonstrated a significant association between anemia or need for packed red blood cell transfusion with outcomes to support transfusion thresholds that differ from standard pediatric ICU practices[38,39].

Limit cerebral metabolic demand

Decreasing the mismatch between cerebral perfusion and metabolic demand is a critical component to neuroprotection after acute brain injury by reducing the amount of tissue experiencing relative ischemia. Mechanisms that limit cerebral metabolism may also slow the pathological processes that contribute to secondary injury such as the enzymatic pathways that result in cell death and the neuro-inflammatory cascade that potentiates vasogenic edema. Physiologically, there are three primary targets

for intervention that affect cerebral metabolic activity: Temperature, sedation, and antiseizure medications to combat acute symptomatic seizures.

Optimal temperature management for patients with acute brain injuries has been the subject of extensive research in both adult and pediatric populations. Early animal data demonstrated a linear relationship between temperature and CBF and oxygen consumption suggesting a 6% decrease in cerebral metabolic demand for each decrease of 1 °C compared to normothermia[40]. Conversely, animal studies conducted in the 1980-1990s concluded that mild hypothermia of up 2 °C conferred significant neuroprotective benefits in rat models of focal and global cerebral ischemia[41-43]. Conversely, even brief periods of hyperthermia of 3 h in similar models were associated with increased infarct volume[44-46]. The deleterious effect of fever in neurological injuries has since been redemonstrated in both adult and pediatric populations across multiple neurologic pathologies including stroke, TBI and post cardiac arrest[46-48]. In light of this data, targeted temperature management with the goal of aggressive avoidance of fever has been adopted as standard of care in patients with acute brain injury.

Of greater debate is whether the practice of induced hypothermia (typically within the range of 32-35 °C) improves neurologic outcomes in selected pediatric populations. A recent meta-analysis of eight randomized controlled trials assessing therapeutic hypothermia in pediatric severe TBI found a non-statistically significant trend towards increased mortality in patients who were treated with therapeutic hypothermia compared to normothermic controls[49]. In post-arrest care, two large, multicenter, randomized controlled trials have been conducted to assess the benefit of therapeutic hypothermia after cardiac arrest in children separately evaluating comatose children after in-hospital (THAPCA-IH) and out-of-hospital (THAPCA-OH) arrests. These trials investigated the impact of 48 h of targeted hypothermia (target 33 °C) followed by gradual rewarming and continued targeted temperature management (target 36.8 °C) for a total of 120 h after protocol initiation compared with 120 h of targeted normothermia (target 36.8 °C) on 1-year survival with a good functional outcome (defined as an age corrected standard score of 70 or higher on the Vineland Adaptive Behavior Scales, second edition). The THAPCA-IH trial was terminated during interim analysis for futility as the primary outcome did not differ between groups, though notably the safety analysis did not demonstrate any significant differences in adverse events or 28-d mortality across groups[50]. THAPCA-OH found slightly higher rates of 1-year survival with good functional outcomes in the hypothermia group compared to (20% *vs* 12%) though this difference was not statistically significant. Secondary analysis found significantly increased survival time in the therapeutic hypothermia group when compared to normothermia (149 d *vs* 119 d)[51]. Given these findings, investigation into the potential benefit of therapeutic hypothermia in pediatric out-of-hospital cardiac arrest remains ongoing and there remains provider and center dependent variability in practice. The Pediatric Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients trial (NCT05376267) aims to assess the efficacy of cooling and optimal duration of hypothermia in pediatric survivors of out-of-hospital cardiac arrests and is currently enrolling with estimated completion in 2028.

Effective sedation and analgesia play an important role in limiting cerebral metabolic demand and have also been shown to have independent agent-specific effects on CBF, autoregulation and vasomotor reactivity[52]. As such, the optimal selection of anesthetic agents for pathology dependent neuroprotection is a target for ongoing research. In general, for critically ill children in the ICU the most frequently reported anesthetic agents used are benzodiazepines and opiates with frequently used secondary agents including dexmedetomidine, propofol, barbiturates, ketamine and clonidine[53]. Of these, benzodiazepines, dexmedetomidine, propofol and barbiturates have the effect of decreasing both cerebral oxygen consumption and CBF and are often used in patients where there is concern for increased ICP or significant risk for cerebral edema. Ketamine has historically been avoided in patients with acute brain injury as early data suggested its use resulted in direct cerebrovascular vasodilation leading to increased CBF and potentially increased ICP[54]. A more recent prospective pediatric trial suggested that ketamine administration in ventilated patients with intracranial hypertension refractory to initial therapies may in fact reduce ICP by an average of 30% while increasing CPPs and may therefore be safe and effective in patients with acute brain injury[55]. Neuromuscular blockade has also been shown to decrease global oxygen consumption and energy expenditure in mechanically ventilated children. This is an important consideration in children who are shivering when undergoing targeted temperature management and is used extensively in patients with refractory elevations in ICP[56,57]. The use of barbiturate coma to treat acute, refractory intracranial hypertension for pediatric TBI has been shown to be effective in decreasing ICP and is included as a consideration for second-tier therapies in the most recent consensus-based Brain Trauma Foundation guidelines[15,16,58].

The emergence of continuous electroencephalography (cEEG) has allowed for a greater understanding that seizures and ictal-interictal continuum (IIC) patterns are common after acute brain injury and are associated with physiologic changes that suggest an increase in metabolic demand[59,60]. The IIC represents a pattern on EEG that does not qualify as an electrographic seizure but has a reasonable chance to be contributing toward neuronal injury or pathologic clinical symptoms[61]. Periodic discharges, an IIC pattern, has been observed to be associated with elevated lactate-pyruvate ratios in adult TBI patients undergoing cerebral microdialysis monitoring, indicating metabolic crisis[62]. Higher frequency periodic discharges have been observed to be associated with increases in regional CBF and

CPP, and when reaching frequencies of ≥ 2.0 Hz, are associated with reductions in brain tissue hypoxia [63]. These findings indicate that periodic discharges are associated with increases at metabolic demand which are partially compensated at lower frequencies but are insufficiently compensated at ≥ 2.0 Hz. In a cohort of adult patients with aneurysmal subarachnoid hemorrhage, seizures themselves were associated with tachycardia, tachypnea, hypertension, as well as rise in delayed CBF[64]. Among pediatric TBI patients, specific quantitative electroencephalographic components of seizure activity have been linked to changes in cerebral and systemic physiology, with ictal spectral edge frequency being negatively associated with ICP and peak value frequency being positively associated with heart rate [65]. Seizures and IIC patterns can often be treated effectively with antiseizure medications, indicating that their use may be important as a neuroprotective strategy to mitigate against metabolic crises.

Mitigate against cerebral edema

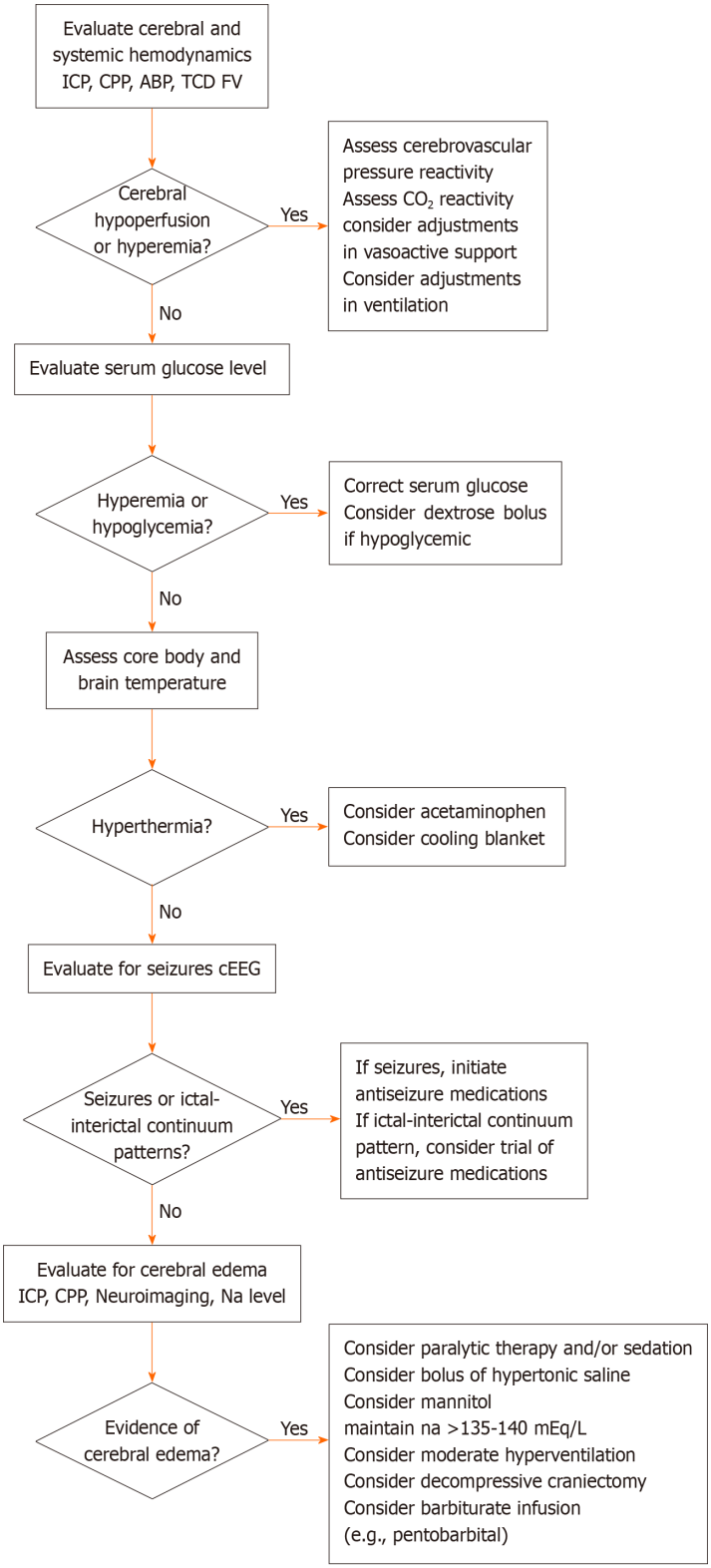
Cerebral edema represents an increase in brain volume that is contained within cerebral interstitial tissue, and can manifest as vasogenic, cytotoxic, hydrostatic, or osmotic edema[66,67]. Vasogenic edema manifests with blood brain barrier breakdown and increased water permeability within brain interstitia. Cytotoxic edema results due to metabolic crisis, cell death, and an influx of water and ions into intracellular space. Hydrostatic edema can occur in the setting of obstructive hydrocephalus and is the result of a net influx of spinal fluid from the ventricular space into brain parenchyma. Osmotic edema is a very particular form of cerebral edema in which there is a specific isolated osmotic gradient between brain parenchyma and the cerebrovascular system. Optimizing temperature management, ventilation, and sedative therapy, as described above, remain important elements in mitigating secondary brain insults arising from cerebral edema. Hyperosmolar therapy exists to aid in mitigation of cerebral edema, with common utilization of hypertonic saline and mannitol. A recent comparative effectiveness study of pediatric TBI patients demonstrated bolus dosing of hypertonic saline to be superior to mannitol in reduction of intracranial hypertension[68]. Some evidence suggests that hyperosmolar therapy is more likely to be effective in reducing intracranial hypertension when there is evidence of efficient cerebrovascular pressure reactivity (CVPR)[69-71]. Emerging research has demonstrated several biomarkers that target the blood-brain barrier or receptors of aquaporin-4 or vasopressin V1a to mitigate cerebral edema, although these are not yet standard treatment targets in clinical care[72]. When medical efforts to mitigate against malignant cerebral edema have failed in the setting of refractory intracranial hypertension, therapeutic decompressive craniectomy can be considered[15].

STANDARDIZED AND INDIVIDUALIZED APPROACHES TO NEUROPROTECTION

The emergence of neurocritical care as a subspecialty has been strengthened by increasing evidence that clinical care implemented with specialized expertise is associated with improved outcomes for critically ill patients with neurologic injuries. A recent large meta-analysis suggested that adult patients who underwent interventions arising from neurocritical care units, neurointensivists or neurocritical care consulting services had improved survival and functional outcomes as compared to adults with similar conditions who experienced general care in intensive care units[73]. A cohort study of pediatric TBI patients demonstrated that implementation of a pediatric neurocritical care program with a standardized evidence-based approach to neurologic monitoring and clinical care was associated with improved outcomes[74]. Such findings have helped the maturation of several specialized pediatric neurocritical care services across the United States and North America, with an array of diverse models including multidisciplinary consultation services as well as dedicated pediatric neurocritical care units that include involvement from neurologists, pediatric intensivists and neurosurgeons[75-79]. These services work toward providing institutional standardized care pathways for common neurocritical care conditions founded upon the latest evidence-based guidelines, often providing standardized or age-based thresholds for intervention (Figure 2).

Whereas the implementation of standardized institutional pathways for neurocritical care carries an association with improved outcomes at an epidemiological level, there is a severe lack of high-level evidence to demonstrate that specific clinical interventions improve outcomes for commonly seen conditions such as TBI, cardiac arrest, and arterial ischemic and hemorrhagic stroke[14-16,80]. Given the lack of high-level evidence, clinical decisions are often made in context of moderate or low-level evidence alongside fundamental and conceptual knowledge regarding pathophysiological mechanisms of critical care diseases. To this end, there are opportunities to evaluate, at the patient-level, whether individualized targeting of care may aid in optimizing neuroprotection.

Critically ill patients in the ICU often have an abundance of continuous physiologic data collected *via* various monitoring techniques including heart rate, invasive arterial blood pressure, end-tidal CO2 and respiratory rate or ventilator settings. Patients with acute brain injuries typically warrant additional neurophysiologic monitoring. This includes ICP monitoring using an external ventricular drain or intraparenchymal monitor, intraparenchymal brain tissue oxygenation, regional oxygen saturation *via* near infrared spectroscopy, cEEG, pupillometry, or information on CBF provided by various imaging techniques including transcranial doppler and thermal diffusion flowmetry[81,82]. Until recently, this



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Figure 2 Stepwise algorithm for neuroprotection in pediatric neurocritical care. ICP: Intracranial pressure; CPP: Cerebral perfusion pressure; ABP: Arterial blood pressure; TCD: Transcranial Doppler ultrasound; FV: Flow velocities; CO_2: Carbon reactivity; cEEG: Continuous electroencephalography; NA: Sodium; mEq/L: Milliequivalents per liter.

information was typically evaluated in isolation or in small subsets. Recent advances in technology have facilitated the development of integrated platforms that aggregate and time-synchronize this information, allowing for easier visualization by the clinician. This approach, known as multimodality neurologic monitoring, has also allowed for investigation of how changes in one physiologic parameter potentially affect others. This allows for a greater understanding of real-time, patient-specific physiology to inform clinical decision making[83].

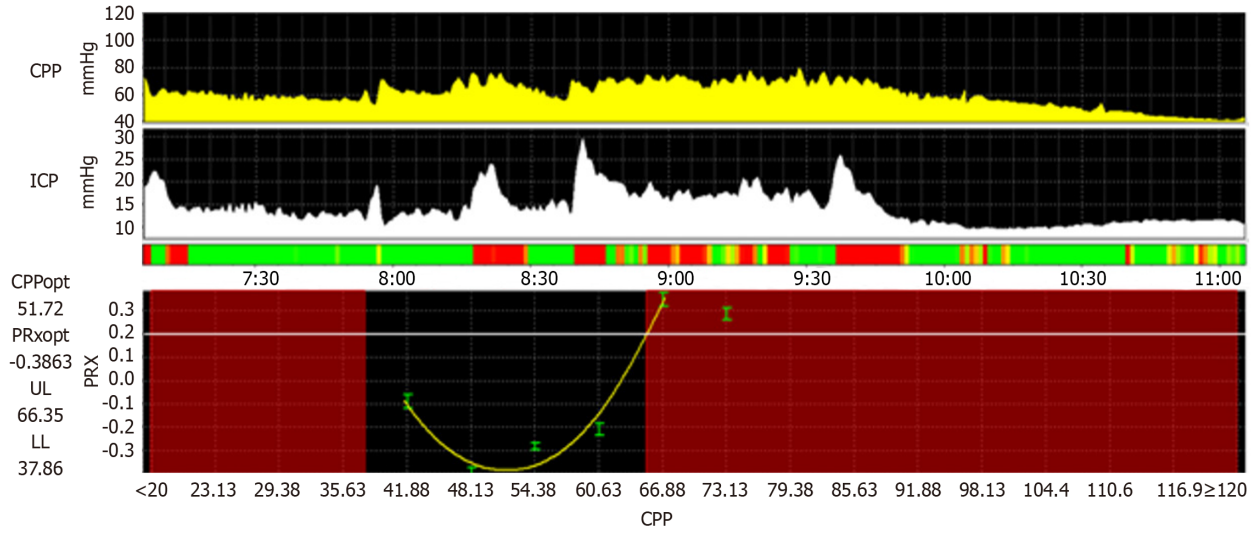
The utilization of neurologic monitoring is aimed towards recognition of biosignatures of secondary brain injury and initiation of treatment based upon such features. The most common and non-invasive form of this is the recognition and treatment of seizures and IIC patterns based on cEEG. Invasive methods allow for detection of intracranial hypertension and brain tissue hypoxia, with a variety of neuroprotective strategies available to use depending on the underlying source of such insults. A recent survey of pediatric neurocritical care centers in 2020 demonstrated that 20 hospitals use transcranial Doppler ultrasound as part of clinical care for management of pediatric intracranial hemorrhage, arterial ischemic stroke, or TBI, with utilization aimed toward determining when to obtain neuroimaging, how to manipulate CPP, and whether to perform surgical interventions[84]. A single-center cohort of TBI patients undergoing standardized multimodality neurologic monitoring reporting demonstrated that such reporting influenced timing of neuroimaging, ICP monitoring discontinuation, use of paralytic, hyperosmolar and pentobarbital therapies, neurosurgical interventions, use of provocative cerebral autoregulation testing, ventilator and CPP adjustments and neurologic prognostication discussions[85]. Future multicenter work describing use of integrated multimodality neurologic monitoring as a means for detecting biosignatures of secondary brain injury may aid in better understanding benign and malignant neurophysiologic patterns, methods of determining therapeutic efficacy of specific interventions, and comparative effectiveness strategies to determine whether such interventions may improve functional outcomes.

The integration of multiple streams of time-synchronized physiologic data has allowed for the development of real-time biomarkers of key neurophysiologic processes. CVPR can be assessed when integrating arterial blood pressure with neuromonitoring features that may act as surrogates of CBF [83]. Using transcranial Doppler ultrasound, the mean velocity index or systolic velocity index describes CVPR utilizing transcranial doppler ultrasound flow velocity characteristics with arterial blood pressure [86,87]. With patients undergoing continuous ICP monitoring, the pressure reactivity index (PRx) and other similar indices can be utilized with an assumption that slow wave fluctuations in ICP are directly related to changes in cerebral arterial blood volume[83]. The PRx, as an example, represents a moving Pearson correlation coefficient relating slow wave fluctuations in arterial blood pressure with ICP. Elevated PRx values (approaching +1) are postulated to represent inefficient CVPR, whereas lower values (approaching -1) are postulated to represent efficient CVPR[88].

When PRx is plotted with error bars across a range of CPP, parabolic curves can often be extrapolated, with the lowest PRx value, or nadir of the parabolic curve, representing the 'optimal CPP' at which CVPR is most efficient. From this, theoretical lower and upper limits of CVPR can be estimated based upon specific thresholds of elevated PRx values[89] (Figure 3). Multiple pediatric TBI studies have linked higher PRx values to worsened outcomes, and there is also evidence that increased time below the lower limit of CVPR is associated with unfavorable outcomes[90-93]. A recent feasibility randomized control trial of adult TBI patients evaluated patients who were treated with CPP targets based upon existing Brain Trauma Foundation guidelines and compared them to patients who were individualized to optimal CPP targets based upon PRx. This trial of 60 patients demonstrated that there were no significant differences in safety endpoints between the two groups, supporting the notion that prospective trials powered for clinical outcomes may be safe and feasible[94]. Other model-based indices of CVPR exist using brain tissue oxygenation, cerebral regional oximetry or other neuromonitoring techniques, with evidence from cardiac arrest, extracorporeal membrane oxygenation and other conditions that suggest that inefficient CVPR or deviations from optimal values of CVPR may be associated with unfavorable outcomes[95-98]. Future prospective work with such techniques may help in determining the efficacy for which they can be used to optimize neuroprotection across a wide range of critical care conditions.

EXISTING KNOWLEDGE GAPS AND FUTURE DIRECTIONS

While emerging evidence demonstrates that specific physiologic biomarkers are linked to functional outcomes after pediatric acute brain injuries, there is a severe lack of evidence toward specific neurotherapeutic strategies that improve functional outcomes. Knowledge gaps remain regarding whether biomarkers can be used to better understand whether specific neuroprotective treatments confer potential to benefit for patients stratified toward specific underlying physiologic profiles. Neuroprotective measures optimal toward care in TBI using invasive neuromonitoring may not necessarily translate to other non-traumatic conditions in which invasive monitoring may not be used. It also remains unclear whether implementation of specific strategies, such as vasoactive support for CPP-guided management, may be appropriate for neonates and very young infants where CBF differs from older children[99]. Future comparative effectiveness studies and clinical trials involving different pediatric acute brain injury conditions will be needed to further address these knowledge gaps.



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Figure 3 Example of identification of optimal cerebral perfusion in a 2-year-old male with severe traumatic brain injury. Here, the PRx is plotted across a range of CPP values over a four-hour window, demonstrating a parabolic curve which suggests that the lowest point of the curve (51.72 mmHg; CPPopt) represents the CPP at which cerebrovascular pressure reactivity is most efficient. By using cutoffs of greater than 0.2, the lower limit of cerebrovascular pressure reactivity is estimated at 37.86 mmHg and the upper limit of cerebrovascular pressure reactivity is estimated at 66.35 mmHg. PRx: Pressure reactivity index; CPP: Cerebral perfusion pressure; CPPOpt: Optimal cerebral perfusion pressure; ICP: Intracranial pressure; PRXopt: Optimal pressure reactivity index; UL: Upper limit of cerebrovascular pressure reactivity; LL: Lower limit of cerebrovascular pressure reactivity.

CONCLUSION

Neuroprotection is a foundational component of pediatric neurocritical care. Standardized clinical approaches that integrate evidence-based guidelines with fundamental and conceptual neurophysiologic knowledge have been associated improved outcomes for patients with acute neurologic injuries. Substantial knowledge gaps remain regarding key clinical interventions that may improve patient outcomes. Multimodality neurologic monitoring demonstrates strong promise toward augmenting a patient-centered approach for optimized neuroprotection.

FOOTNOTES

Author contributions: Kochar A, Hildebrandt K, Silverstein R and Appavu B contributed to the conception of this review, analysis of the data, and writing of the manuscript, and all authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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L-Editor: A
P-Editor: Xu ZH

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 June 9; 12(3): 130-138

DOI: 10.5492/wjccm.v12.i3.130

ISSN 2220-3141 (online)

MINIREVIEWS

Upper extremity deep vein thrombosis: An intensivist's perspective

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bloomfield DA, United States; Navarrete Arellano M, Mexico

Received: December 29, 2022
Peer-review started: December 29, 2022
First decision: March 15, 2023
Revised: March 16, 2023
Accepted: April 20, 2023
Article in press: April 20, 2023
Published online: June 9, 2023

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Abstract

Upper extremity deep vein thrombosis (UEDVT) is less common than lower extremity DVT but is a cause of significant morbidity and mortality in intensive care unit patients. Increasing cancer incidence, prolonged life expectancy and increasing use of intravascular catheters and devices has led to an increased incidence of UEDVT. It is also associated with high rates of complications like pulmonary embolism, post-thrombotic syndrome and recurrent thrombosis. Clinical prediction scores and D-dimer may not be as useful in identifying UEDVT; hence, a high suspicion index is required for diagnosis. Doppler ultrasound is commonly employed for diagnosis, but other tests like computed tomography and magnetic resonance imaging venography may also be required in some patients. Contrast venography is rarely used in patients with clinical and ultrasound findings discrepancies. Anticoagulant therapy alone is sufficient in most patients, and thrombolysis and surgical decompression is seldom indicated. The outcome depends on the cause and underlying comorbidities.

Key Words: Catheter associated deep vein thrombosis; Pacemaker associated deep vein thrombosis; Paget-von Schröetter syndrome; Thoracic outlet syndrome; Upper extremity deep vein thrombosis

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Core Tip: Upper extremity deep vein thrombosis (UEDVT), is largely under-recognised and an often missed diagnosis. Even though it is less common than the lower extremity DVT, it is increasingly being diagnosed, especially in intensive care unit patients because of presence of venous catheters and devices in these patients. Traditionally used clinical probability scores and tests like D-dimer may not be as effective in diagnosing UEDVT. Bedside Doppler ultrasound is the most commonly employed diagnostic tool which may aid in clinching the diagnosis. Contrast venography remains the gold standard, but is rarely required. Pulmonary embolism is the most dreaded complication but the rates of other complications including post thrombotic syndrome and recurrent DVT also remain significant. Anticoagulant therapy alone is sufficient in most patients. However, UEDVT may be associated with high mortality rates unless early diagnostic and therapeutic measures are initiated.

Citation: Singh O, Juneja D. Upper extremity deep vein thrombosis: An intensivist's perspective. *World J Crit Care Med* 2023; 12(3): 130-138
URL: https://www.wjgnet.com/2220-3141/full/v12/i3/130.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i3.130

INTRODUCTION

Lower extremity deep vein thrombosis (LEDVT) is a well-recognized and dreaded complication among critically ill patients. All efforts regarding its early recognition and prompt treatment are incorporated into the teachings of critical care physicians and nurses. However, upper extremity DVT (UEDVT) is largely under-recognized and an often missed diagnosis. Even though it is less common than the LEDVT, it is increasingly being diagnosed, especially in intensive care unit (ICU) patients, because of certain inherent risk factors present in these patients. It may lead to several complications causing significant morbidity and mortality. Simple tests like bedside doppler ultrasound may enable us to make an early diagnosis and initiate prompt therapeutic measures with anticoagulants to improve clinical outcomes. Hence, critical care physicians must be aware of this dreadful condition and keep a high index of suspicion to diagnose it.

EPIDEMIOLOGY

UEDVT refers to the formation of fibrin clots within the deep veins of the upper extremities. Superficial veins, like the basilic and cephalic, which have anastomoses with the deep veins, can also be affected with superficial thrombophlebitis, which may progress to cause DVT. As the UEDVT involving the distal veins (radial, ulna and interosseous veins) is generally asymptomatic and does not require any clinical intervention, clinically relevant UEDVT generally denotes thrombosis of subclavian, axillary, and brachial veins. Subclavian veins (SCVs) are most commonly implicated in 76% of cases, followed by axillary (47%) and brachial veins (36%). Multiple veins are usually involved; a single vein is involved in only 38% of cases. Other deep veins, like the internal jugular and brachiocephalic, may also be involved in up to 50% of cases[1,2].

LEDVT is a much more commonly recognized and reported complication, with UEDVT constituting only 10% of all cases of DVT[3,4]. However, the risk and incidence of UEDVT would depend on the population studied, with certain patient populations having a much higher incidence. Nonetheless, the incidence of UEDVT is increasing, especially in ICU patients with several risk factors for developing UEDVT[5,6]. In an observational study conducted in a surgical ICU, out of 862 patients, 15% developed UEDVT despite standardized heparin thromboprophylaxis[7]. Some reports even suggest that the UEDVT may be as common in hospitalized medical patients as the LEDVT[8].

RISK FACTORS

UEDVT may be classified as primary or spontaneous, without any apparent risk factors and secondary, due to identifiable risk factors.

Primary UEDVT

Primary UEDVT may be further categorized due to "effort thrombosis", Paget-Schroetter syndrome (PSS), and idiopathic thrombosis. Primary causes account for up to 33% of cases of UEDVT, among which PSS is reported to be more common[9-11]. PSS generally affects young, otherwise healthy, adult males. The underlying anatomical abnormalities at the thoracic outlet, like the cervical rib, congenital

bands, scalenus tendons hypertrophy, and abnormal insertion of the costoclavicular ligament, cause compression of the SCV and stasis to the flow of blood. The repetitive movements of the dominant arm, as in athletes, cause repetitive trauma to the endothelium of the SCV, leading to intimal hyperplasia, inflammation, and fibrosis, which may worsen venous stasis and lead to the formation and progression of thrombus. People involved in occupations requiring excessive upper extremity motion, such as painting, hairdressing or sports like golf, tennis, weightlifting, baseball or gymnastics, are more commonly affected. The onset of symptoms is generally acute or subacute, precipitated by repeated arm movement, but rarely patients may present with chronic symptoms[12,13]. A subset of patients in whom no cause can be identified are labelled as having idiopathic thrombosis. Underlying occult malignancies have been reported in up to 25% of such patients[14]. These patients are older and have a higher prevalence of underlying coagulation abnormalities[10,15]. Their prognosis is also worse than those with PSS[5].

Secondary UEDVT

Secondary UEDVT is much more common and is responsible for up to 80% of cases[10]. The risk factors for UEDVT differ from the traditionally recognised factors for LEDVT (Table 1). These risk factors are particularly important in critically ill patients admitted to ICUs. Central venous catheters (CVCs) have been recognized as the single most important factor associated with the development of UEDVT and are responsible for up to 50% of cases[5,6]. The use of CVC has been shown to increase the risk of developing UEDVT by up to 14 times[16]. The use of peripherally inserted central catheters is associated with an even higher risk of developing UEDVT[8]. Even among those with CVCs, patients with technically difficult insertions, those with left-sided catheters, misplaced catheter tips, previous catheter placements, and large or multiple lumen catheters have a higher risk of developing UEDVT[17]. Underlying malignancies, especially ovarian cancers and lung adenocarcinomas, have been associated with a higher risk of UEDVT[3]. The risk of developing UEDVT may be compounded if multiple risk factors exist. The reported risk as high as 66%, has been reported in cancer patients having CVCs[18]. Patients who develop non-CVC-associated UEDVT are more likely to be younger, thinner (body mass index of < 25 kg/m^2) and smokers[16].

PATHOPHYSIOLOGY

The presence of the contributing factors from Virchow's Triad (venous stasis, vascular injury, and hypercoagulability) is implicated in thrombus formation in patients with UEDVT. In patients with PSS, thoracic outlet obstruction leads to venous stasis, and repeated movement of the arm causes trauma and endothelium injury leading to thrombosis. CVC or venous devices also cause venous stasis, platelet adherence, and endothelial trauma, increasing the risk of thrombus formation. Patients with malignancies have underlying hypercoagulable states, and excessive cancer cells may lead to vascular damage and venous stasis, making these patients prone to develop thrombosis.

CLINICAL FEATURES

Patients with UEDVT generally present with unilateral upper limb erythema, oedema, reduced mobility, pain, discomfort and low-grade fever. Urschel's sign, dilated and visible veins over the affected shoulders and upper arms, may be seen, especially in patients with long-standing thrombosis [13]. If CVC is present, it may be blocked. Cyanosis and pain while movement or exercise may be reported by patients with PSS. Clinical features related to complications may also be present. Patients with pulmonary embolism (PE) may develop breathlessness, chest pain and haemoptysis. In patients with central vein obstruction or occlusion, superior vena cava (SVC) syndrome features may be present. Brachial plexus compression may present with paraesthesia and arm pain, worsening with hyperabduction of the shoulder. However, in up to 19% of patients, UEDVT may be asymptomatic[5].

DIAGNOSIS

The clinical prediction scores used for LEDVT have been shown to have poor sensitivity and specificity, 78% and 64%, respectively, for diagnosing UEDVT. Hence, specific scores like the Constans clinical decision score have been developed for predicting UEDVT. It uses four variables to risk stratify patients with suspected UEDVT (Table 2)[19]. Only a few studies have evaluated its efficacy in diagnosing UEDVT and have reported sensitivity and specificity of up to 86% and 93%, with an area under the curve ranging from 0.70-0.81[20]. Hence, because of its comparatively low diagnostic accuracy and lack of clinical evidence, it is not recommended to use this clinical probability score as a standalone tool to diagnose UEDVT. However, it may aid physicians in recognizing high-risk patients and undertaking

Table 1 Risk factors for developing upper extremity deep vein thrombosis

Risk factors
Central venous catheters/dialysis catheters
Implantable cardiac rhythm devices
Personal or family history of thrombosis and thrombophilia
Surgery or trauma of the arm
Immobilization of the arm
Pregnancy
Use of oral contraceptive
Malignancy
Post-operative *e.g.*, esophagectomy, retrosternal reconstruction

Table 2 Constans clinical decision score

Patient characteristic	Score	
Venous material present (CVC/pacemaker)	Yes	1 point
	No	0 point
Localised pain	Yes	1 point
	No	0 point
Unilateral oedema	Yes	1 point
	No	0 point
Other diagnosis at least as plausible	Yes	-1 point
	No	0 point
Risk for UEDVT		
Low: 12% probability of UEDVT	-1 to 0 points[1]	
Intermediate: 20% probability of UEDVT	1 point[1]	
High: 70% probability of UEDVT	2-3 points[1]	

[1]Total score.
CVC: Central venous catheter; UEDVT: Upper extremity deep vein thrombosis.

further diagnostic testing. Variations of this score, like the extended Constans score, have also been tried, but they require further testing and validation[20].

Even D-dimer has not been extensively evaluated in diagnosing UEDVT and has shown low specificity of only 14%[21]. Hence, it should be used cautiously to rule out UEDVT. Combination of D-dimer and Constans score has been shown to increase their accuracy in predicting UEDVT[20]. Duplex ultrasonography (US) is commonly employed as the initial diagnostic procedure. It has several advantages: Easy availability, non-invasive nature, easy portability, inexpensive and no radiation exposure (Table 3)[22]. It has high sensitivity and specificity of 97% and 96%, respectively[23]. The presence of echogenicity's in the vascular lumen can suggest a thrombus. Further, a normal vein easily compresses on pressure, but when a thrombus is present, the vein becomes incompressible. However, as the pressure cannot be applied to central veins like SVC, a compression test cannot be used for such veins. Blood flow dynamics can further be evaluated using pulsed wave and colour flow Doppler, which may show an absence of flow or change of normal biphasic flow into a non-pulsatile flow pattern suggestive of obstruction[10,24]. As per a systematic review by Di Nisio *et al*[23], compression US (97% and 96%), Doppler US (84% and 94%) and Doppler US with compression (91% and 93%) all showed high sensitivity and specificity.

Contrast venography is considered the gold standard for diagnosing UEDVT with good sensitivity and specificity and can even visualize areas not accessible to ultrasound. However, because of inherent disadvantages, it is not routinely performed but may be done when there are contradictory clinical and US findings[24]. Contrast venography may also be required before performing catheter-directed

Table 3 Advantages and disadvantages of various diagnostic tests for upper extremity deep vein thrombosis

Diagnostic tests	Advantages	Disadvantages
D-dimer	High sensitivity. Readily available	Poor specificity. Not extensively evaluated for UEDVT
Ultrasound	Non-invasive. Readily available. Bedside. Less expensive. Good sensitivity and specificity	Not appropriate for evaluating central veins. Operator dependant
Doppler ultrasound	Non-invasive. Readily available. Bedside. Less expensive. Good sensitivity and specificity	Operator dependant
Computed tomography venography	Can help in diagnosing other underlying pathologies or rule out other diagnosis	Radiation exposure. Logistical issues. Moderate sensitivity and specificity
Magnetic resonance venography	Can help in diagnosing other underlying pathologies or rule out other diagnosis	Not widely available. Expensive. Logistical issues. Not suitable for patients with surgical implants and pacemakers. Moderate sensitivity and specificity
Contrast venography	Gold standard. High sensitivity and specificity. Can visualize the entire deep venous system. Can define complex and difficult anatomy	Invasive. Radiation exposure. Allergic reactions

UEDVT: Upper extremity deep vein thrombosis.

thrombolysis or surgery for thoracic outlet decompression as a part of a comprehensive workup[13].

Computed tomography (CT) and magnetic resonance imaging (MRI) venography can also be performed for diagnosing UEDVT. However, they have not been extensively evaluated, have moderate sensitivity and specificity, and are less accurate than contrast venography[25,26]. Routine screening for the underlying hypercoagulable state should also be conducted. Homocysteinemia should also be ruled out in such patients. Patients with primary UEDVT have a higher incidence of antiphospholipid antibodies, factor V Leiden, and prothrombin gene mutations[27].

TREATMENT

The treatment of UEDVT is primarily based on the data extrapolated from the studies on LEDVT. Hence, the management principles remain the same. However, in contrast with LEDVT, there is a lack of evidence regarding the effectiveness of compression devices in patients with UEDVT; hence, they are not recommended[28]. In most patients, only anticoagulant therapy is required, along with supportive management[29]. Use of low molecular weight heparin (LMWH), unfractionated heparin, or fondaparinux is generally recommended in the acute phase, followed by vitamin K antagonists (VKA) for 3 mo in patients with idiopathic thrombosis. Prolonged VKA therapy beyond three months is generally not advocated after the first episode of idiopathic UEDVT[28]. However, in patients with underlying malignancy, prolonged LMWH monotherapy extended for up to 6 mo or till cancer remains active, is recommended in non-CVC associated UEDVT[28]. In CVC-associated UEDVT, anticoagulant therapy is recommended for 3 mo if the CVC has been removed. However, if the CVC remains in situ, anticoagulation should be continued until the CVC is present[28]. The routine removal of the catheter is not advocated, even in patients with CVC-associated UEDVT, as long as the catheter is required and is functional[28].

The role of direct oral anticoagulants has not been extensively evaluated in the management of UEDVT. Even though early data from small studies suggest that they may be effective in preventing complications and the need for catheter removal, larger studies are required before they are routinely prescribed for managing UEDVT[30]. However, they may provide an excellent therapeutic alternative to LMWHs in cancer patients in whom VKA may not be as effective[29,31]. Patients on anticoagulants for UEDVT have significant bleeding risks; up to 5% have been reported to develop major bleeding[32]. The risk of bleeding may be higher in patients with underlying malignancies; hence, they must be monitored accordingly[32].

Additional therapeutic measures are rarely required to manage UEDVT[29]. Evidence regarding the efficacy of thrombolysis in UEDVT is lacking. Even though it may improve the patency of the vein, it is associated with a high risk of bleeding[28]. Hence, the American College of Chest Physician guidelines suggests using anticoagulation alone over thrombolysis[28]. Thrombolysis should be considered only in patients with severe symptoms, in patients with extensive involvement of SCV or axillary vein, acute symptoms of less than 14 d duration, good functional status and low risk for bleeding complications [28]. Anticoagulation should be initiated after thrombolysis and continued for at least three months to prevent a recurrence. SVC filters may be considered in patients with PE, and in those with contraindications to anticoagulants[28].

Physical therapy and lifestyle modification may be helpful in patients with UEDVT secondary to PSS. However, if symptoms persist and there is persistent SCV stenosis, as evidenced by positional venography, surgical decompression may be indicated to open the thoracic outlet[13]. Some authors have reported better symptom relief with thrombolysis followed by early surgical decompression by removing the first rib and the costoclavicular ligament, restoring normal blood flow in the SCV[33].

COMPLICATIONS

Common complications associated with UEDVT include recurrent DVT, post-thrombotic syndrome (PTS), PE, SVC syndrome and compression of the brachial plexus[13]. Even though the incidence of PE is lesser than that in LEDVT, it is the most dreaded complication associated with UEDVT[34]. The reported incidence ranges from 2.6% to 17%, with higher incidence reported in secondary UEDVT, especially in CVC-associated cases[7,35]. PE following non-CVC-associated UEDVT is rare, with a reported incidence of less than 1%[36]. Studies evaluating long-term outcomes of patients with UEDVT have reported an incidence of PE of up to 36% over a 2 years follow-up[37]. A review of data from the RIETE registry reported that the incidence of recurrent PE was similar in patients with UEDVT and LEDVT[38].

Recurrent DVT is another significant complication after UEDVT, with some data suggesting that incidence is even higher than that after LEDVT[38]. The data from a recent systematic review suggests that the rate of recurrent UEDVT in patients with idiopathic thrombosis ranges from 0%-23%[39]. Another meta-analysis has reported a pooled incidence of 7.5% for the development of recurrent thrombosis after UEDVT[40]. The reported rate of recurrent UEDVT is significantly higher in secondary DVT, more so in patients with CVC-related UEDVT[40]. Cancer patients have also been reported to have a 2-3 times higher risk of recurrent thrombosis[41].

Persistent obstruction and valvular insufficiency in patients with UEDVT may lead to PTS in around 4% to 32% of cases[28,29]. The incidence of PTS is significantly lower than that in patients with LEDVT, in whom it may develop in up to 50% of cases[34]. PTS has been reported to be more common in primary UEDVT than secondary[40]. It is characterized by persistent pain, oedema, and functional limitation of the affected arm. However, compression therapy, as used in managing LEDVT, is not recommended for PTS of the arm because of lack of evidence of efficacy given the different underlying pathophysiology. Hence, management is mainly supportive[28].

PROGNOSIS

The reported long-term mortality, two and 12 mo, after diagnosis of UEDVT is 30 and 40%, respectively [42,43]. However, these studies included patients with significant comorbidities, and mortality attributable to UEDVT could not be determined. The prognosis depends on the cause of UEDVT and underlying comorbidities. A systematic review of 45 studies with 4580 patients compared clinical courses and outcomes of UEDVT in patients with and without cancer. Overall, the one-year mortality rate in prospective trials was 24%, whereas, in retrospective studies, it was 35%. However, patients with cancer had an 8-fold higher risk of death than non-cancer patients. Patients with PSS are generally younger and have good functional status without many comorbidities. Hence, they have good overall outcomes and longer life expectancies.

CONCLUSION

UEDVT is an under-recognized and under-diagnosed complication in critically ill patients. Its incidence may be attributable to the increasing incidence of cancer, improving life expectancy, and increasing use of intravenous devices and catheters in hospitalized patients. Any unilateral oedema or erythema in an ICU patient with underlying risk factors should raise a concern, and further workup should be initiated. Bedside ultrasound with Doppler may help make a rapid diagnosis and contrast venography or CT/MRI venography is rarely indicated. Most patients can be managed with anticoagulant therapy, which is safe and effective. However, many patients may develop complications like bleeding, PTS and PE, so they should be monitored closely. The long-term outcome of these patients may depend on the cause of UEDVT and the underlying comorbidities. Early recognition and prompt therapy may help achieve favorable outcomes and prevent complications.

FOOTNOTES

Author contributions: Singh O and Juneja D performed all the writing, researched the project, prepared the tables, performed data accusation, and reviewed the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Xu ZH

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 June 9; 12(3): 139-152

DOI: 10.5492/wjccm.v12.i3.139

ISSN 2220-3141 (online)

MINIREVIEWS

Sepsis-induced mitochondrial dysfunction: A narrative review

Wagner Nedel, Caroline Deutschendorf, Luis Valmor Cruz Portela

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Liu LP, China; Zhong GQ, China

Received: January 20, 2023
Peer-review started: January 20, 2023
First decision: February 20, 2023
Revised: March 8, 2023
Accepted: April 14, 2023
Article in press: April 14, 2023
Published online: June 9, 2023

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Abstract

Sepsis represents a deranged and exaggerated systemic inflammatory response to infection and is associated with vascular and metabolic abnormalities that trigger systemic organic dysfunction. Mitochondrial function has been shown to be severely impaired during the early phase of critical illness, with a reduction in biogenesis, increased generation of reactive oxygen species and a decrease in adenosine triphosphate synthesis of up to 50%. Mitochondrial dysfunction can be assessed using mitochondrial DNA concentration and respirometry assays, particularly in peripheral mononuclear cells. Isolation of monocytes and lymphocytes seems to be the most promising strategy for measuring mitochondrial activity in clinical settings because of the ease of collection, sample processing, and clinical relevance of the association between metabolic alterations and deficient immune responses in mononuclear cells. Studies have reported alterations in these variables in patients with sepsis compared with healthy controls and non-septic patients. However, few studies have explored the association between mitochondrial dysfunction in immune mononuclear cells and unfavorable clinical outcomes. An improvement in mitochondrial parameters in sepsis could theoretically serve as a biomarker of clinical recovery and response to oxygen and vasopressor therapies as well as reveal unexplored pathophysiological mechanistic targets. These features highlight the need for further studies on mitochondrial metabolism in immune cells as a feasible tool to evaluate patients in intensive care settings. The evaluation of mitochondrial metabolism is a promising tool for the evaluation and management of critically ill patients, especially those with sepsis. In this article, we explore the pathophysiological

aspects, main methods of measurement, and the main studies in this field.

Key Words: Sepsis; Mitochondria; Mitochondrial dysfunction; Oxidative phosphorylation; Inflammation; Respirometry

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Core Tip: The evaluation of mitochondrial metabolism is a promising tool for the evaluation and management of critically ill patients, particularly those with sepsis. In this article, we explore the pathophysiological aspects, main methods of measurement, and main studies in this field.

Citation: Nedel W, Deutschendorf C, Portela LVC. Sepsis-induced mitochondrial dysfunction: A narrative review. *World J Crit Care Med* 2023; 12(3): 139-152
URL: https://www.wjgnet.com/2220-3141/full/v12/i3/139.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i3.139

INTRODUCTION

Sepsis is a major health problem worldwide and can be characterized by a dysregulated host response to infection[1-3]. Particularly, an imbalanced systemic inflammatory response to infection contribute to the clinical progress to multi-organ dysfunction[2,4]. There is a great effort in the recognition and prompt treatment of sepsis, especially with regard to early antibiotic administration, hemodynamic resuscitation, and evacuation of septic foci[1]. The ultimate cause of death in patients with sepsis, however, remains unclear. Infections usually are eradicated through an intense, but localized, inflammatory response. Nonetheless, fatal infections are characterized by an inability to resolve the inflammatory response because cytokines released into the systemic circulation, activates inflammatory cells in remote locations[5]. This response leads to organ injury and dysfunction, which cannot be completely explained by a decrease in tissue oxygenation due to an impairment of blood flow[2,4,5] but likely to problems in oxygen utilization.

Mitochondria is a highly specialized organelle that is considered the power plant of cells thus supporting energy in the form of adenosine triphosphate (ATP) according to functional demands[6]. In the blood, except for erythrocytes, all cell types possess mitochondria which imply they are dependent on oxidative metabolism. Remarkably, mitochondria tightly connect ATP biosynthesis with oxygen consumption, and even minor changes in mitochondrial functional integrity affect many aspects of cellular homeostasis. Although, the main proposed function of mitochondria is to generate ATP *via* oxidative phosphorylation (OXPHOS) of adenosine diphosphate (ADP), additional functions include generation and detoxification of reactive oxygen species (ROS), calcium homeostasis, involvement in apoptosis, synthesis and catabolism of metabolites, and transport of organelles within the cell[6,7]. Any alteration in one of these processes can be defined as mitochondrial dysfunction[8]. Actually, we know that impaired mitochondrial metabolism is an important mechanism that leads to organ dysfunction[2,5]. In acute diseases, such as sepsis, the measurement of mitochondrial metabolism, through cellular respiration, has the potential to identify those patients at risk of progressing in their organ failures. In addition, it can potentially help in monitoring the therapeutic response of these patients[6,9].

Considering that mitochondria interact with various other pathways involved in inflammation, Ca^{2+} balance, redox signaling, and apoptosis, it can be assumed that mitochondria are fundamental in cell survival and death[10]. Mitochondrial metabolism has been shown to be severely impaired during the early phase of an acute disease, with a reduction in biogenesis, increased generation of ROS, and a decrease in ATP synthesis[11,12]. The presence of an impaired mitochondrial metabolism is associated with the presence of a multiple organ failure syndrome, highlighting mitochondrial components as potential targets for therapeutic strategies[4,11,13]. There has been an increased interest in this field, with new studies exploring mitochondrial impairment and organ dysfunction and their relationship with prognosis in sepsis[14-17].

The main objective of this review is analyze the current state of the art in this field, explore potential methods for assessing mitochondrial metabolism in intensive care settings, and explore future perspectives on mitochondrial metabolism as a biomarker of clinical outcomes in sepsis.

PHYSIOPATHOLOGY

ATP is produced by mitochondria through OXPHOS by F1Fo-ATP synthase. ATP is generated to a greater extent by the oxidation of metabolic substrates in the tricarboxylic acid cycle leading to reduction of the electron acceptors NAD^+ and FAD to nicotinamide adenine dinucleotide (NADH) and 1,5-dihydroflavin adenine dinucleotide (FADH2)[18]. Both NADH and FADH2 are subsequently oxidized in the electron transport system of mitochondria. The electron transport chain is composed by enzyme complexes I to IV and the transporters ubiquinone and cytochrome c. With the electrons movement across the respiratory chain, protons are pumped across the inner mitochondrial membrane, generating an electrical potential. This proton-motive force provides the energy for F1Fo-ATP synthase, as known as Complex V, to phosphorylate ADP to ATP (Figure 1). This mechanism is favored by the electrochemical gradient produced by the proton motive force. Oxygen is the terminal electron acceptor of the chain in Complex IV and is reduced to water[19]. An incomplete reduction of oxygen increases superoxide radical production in Complex III and at Complex I. As part of this process, ROS are generated as by-products of the incomplete four-electron reduction of molecular oxygen to water[20,21].

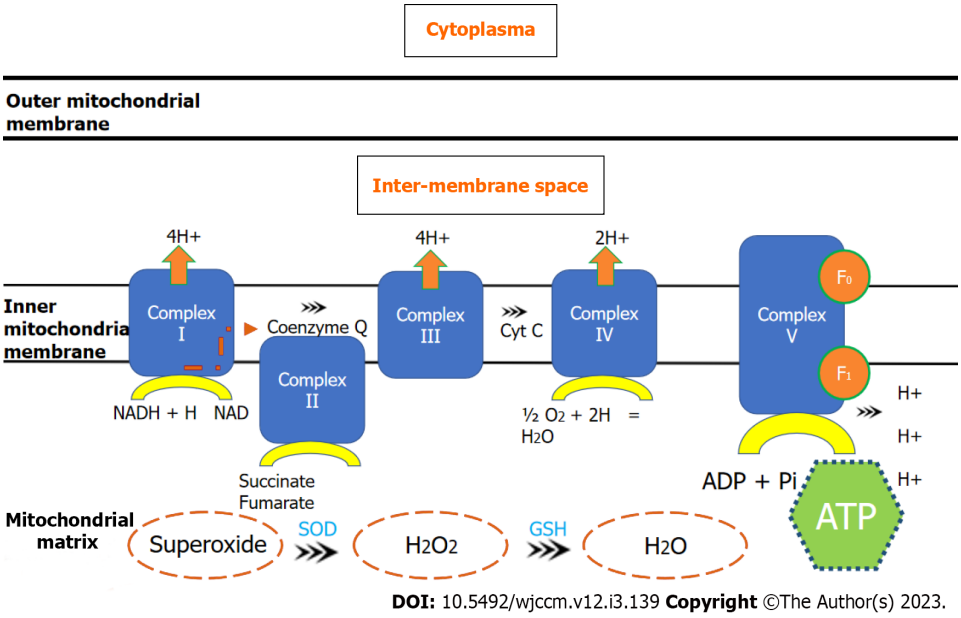
Under physiological conditions, mitochondria consume approximately 90% of the cellular O_2; however, 1%-4% of the respiratory chain reactions lead to a leak of electrons that directly react with O_2 to form O_2(*-), which can oxidize lipids, DNA, or proteins[22]. To avoid self-damage, mitochondria have intrinsic defense mechanisms that protect against ROS-induced damage through a large array of antioxidants[12]. In sepsis, not only ROS are generated, but also reactive nitrogen species (RNS), nitric oxide, and peroxynitrite[7,20,21]. Enzymatic defenses, such as the superoxide dismutase 2 (SOD2), convert O_2(*-) into hydrogen peroxide (H_2O_2), which can then be detoxified to water by catalase or selenium-containing glutathione peroxidase[23,24]. SOD2 expression is higher in survivors of critical illness[22]. Glutathione and Coenzyme Q10 (CoQ10) also have an important mitochondrial antioxidant function. CoQ10 Levels are lower in sepsis, suggesting a potential role in mitochondrial dysfunction[25].

Mitochondria are also essential for other cellular functions, such as calcium homeostasis, apoptosis, autophagy, and cellular signaling[6,9,12]. Mitochondrial DNA (mtDNA) is susceptible to mutations and deletions due to ROS increased levels and requires a set of self-regulated repair mechanisms[6]. mtDNA damage resulting from this phenomenon is associated with reduced mitochondrial respiratory capacity, which are potentially irreversible, depending on the intensity of oxidant "attack"[23]. Mitochondrial function is maintained by an equilibrium between fission, fusion, biogenesis, and autophagy[26]. In the case of an impairment in mitochondrial metabolism, various signaling routes allow an interaction between the mitochondria and nucleus, triggering mitochondrial biogenesis[10]. Defective mitochondria can become toxic by excessive ROS production, that can lead to apoptosis. Autophagy compensates for nutrient depletion or copes with cellular stress by recycling cellular components, to produce amino acids and fatty acids that can be metabolized and used in OXPHOS[27]. Despite being important for critical illness recovery, excessive induction of autophagy can trigger apoptosis[28]. ROS is one of some signaling pathways that regulate autophagy, and, since mitochondria are the primary source of ROS, mitochondria themselves play a key role in regulating autophagy[10]. Disturbances in mitochondrial function leading to impaired ATP biosynthesis, increased ROS production, and oxidative stress are associated with skeletal muscle damage, which correlates with septic shock severity and is associated with impaired clinical outcomes[18].

Many inflammatory mediators are linked to the altered mitochondrial metabolism. Tumoral necrosis factor-alpha (TNF-α) is a major interleukin that participates in the host response to sepsis and is capable of causing mitochondrial impairment[29]. TNF-α binds to several TNF receptors, ultimately promoting the intracellular release of ceramides and production of ROS, which may lead to mitochondrial dysfunction. TNF receptor activation promotes pro-inflammatory responses in polymorphonuclear leukocytes and monocytes, that induce ROS formation, leading to mtDNA damage and inhibition of mitochondrial metabolism in these cells[30]. Inhibition of mitochondrial complexes causes deviation of electrons, also producing even more ROS. These phenomena can lead to an imbalance between ROS production and mitochondrial antioxidant capacity, through manganese superoxide dismutase and glutathione reductase. This imbalance can trigger mitochondrial uncoupling related to the opening of mitochondrial permeability transition pores (PTP)[31]. The resulting mitochondrial permeability transition leads to dissolution of the electrochemical gradient required to form ATP, and these dysfunctional mitochondria are targeted for removal *via* autophagy. The induction of mitochondrial PTP win this context can promote apoptosis. Therefore, the pro-inflammatory activity in sepsis, especially in its initial phase, can lead to both a reduction in mitochondrial mass and a decrease in its function.

MECHANISMS OF MITOCHONDRIAL DYSFUNCTION

Hypoxia has been assumed to be the main causative agent of mitochondrial dysfunction[32]. However, it was later shown that tissue oxygen levels are normal or even elevated in sepsis[33]. Instead of a lower availability of oxygen, there is a lower use of it in septic patients[24]. Thus, OXPHOS dysfunction explain the inability to maintain ATP levels in this context, leading to increased glycolysis and increased



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Figure 1 Electron transport chain through mitocondrial complexes and oxidative phosphorylation. ADP: Adenosine diphosphtate; ATP: Adenosine triphosphate; Cyt c: Cytochrome c; GSH: Gluthatione synthetase; NAD: Nicotinamide adenine dinucleotide; NADH: Nicotinamide adenine dinucleotide (reduced); SOD: Superoxide dismuthase.

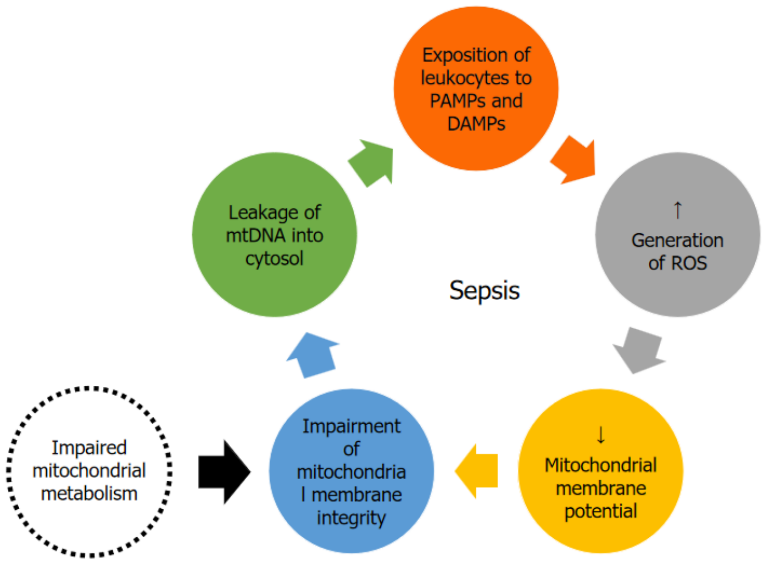
lactate levels[6]. This imbalance between ROS production and antioxidant capacity leads to an oxidative stress that damage the electron transport chain and mtDNA, creating a vicious circle of mitochondrial damage and ROS production[20]. ROS and calcium overload cause an increased membrane permeability, and mitochondrial products such as mtDNA leak into the circulation, acting as danger-associated molecular patterns and contributing to multiorganic failure[13] in a vicious cycle (Figure 2). This cascade can trigger cell apoptosis[7], a component of tissue damage and organ failure.

Changes in mitochondrial form and function in critical illnesses suggest that mitochondria try to rescue mechanisms and adapt to harmful environments. Mitochondrial fission and fusion are upregulated during critical illness, although it appears to be insufficient for restoring mitochondrial function[34]. Mitochondrial biogenesis was observed in skeletal muscle taken on days 1 to 2 in intensive care unit (ICU) survivors, but not in non-survivors[35]. During extreme conditions, such as refractory shock, mitochondrial damage is disseminated, causing the induction of mitochondrial PTP in many mitochondria and a great decrease in ATP production[36]. In contrast, a reduction in mitochondrial density was observed after the onset of sepsis, suggesting that although upregulated, biogenesis may be insufficient to maintain homeostasis[10].

Mitochondrial metabolism and inflammatory activity in sepsis-what is the relationship?

The hallmark of sepsis inflammatory response is an imbalance between a systemic inflammatory response and compensatory anti-inflammatory response[37,38]. The imbalance of pro- and anti-inflammatory responses often results in immunoparalysis among critically ill patients, making them more vulnerable to additional infections, and is linked to higher mortality rates[39]. Actually, the cause of immune dysfunction is matter of debate[38], and immune response is dependent of metabolic pathways [40], that is known as "immunometabolism". Mitochondria are a hub of the immune system, playing a crucial role in regulating the function of immune cells and shaping and modulating the response of the immune system to infection[7]. Evidence suggests that leukocytes from critically ill patients display mitochondrial dysfunction, which is thought to be the root cause of immunoparalysis and could be responsible for the onset of organ dysfunction[41,42]. Moreover, the recovery of mitochondrial function is associated with improved recovery in critically ill patients[14]. These changes are mostly detected in lymphocytes, monocytes, and macrophages[43].

Lymphocytes respond to cytokine stimuli induced by monocyte-macrophages, dendritic cells, and neutrophils, which are responsible for the innate immune response. Activated phagocytic cells, such as monocytes and macrophages, release the proinflammatory cytokines interleukin-1 (IL-1) and IL-6[44]. This phenomenon has been associated with energy deprivation[45]. Lymphocytes also attenuate the potentially harmful effects of the proinflammatory response, and this modulation of the immune response has a major impact on prognosis in septic patients[46]. On the other hand, IL-10 plays a major role in modulating the immune system by inhibiting monocyte-macrophage activation and suppressing the production of TNF-α, IL-1, and interferon-gamma (IFN-γ) from lymphocytes acting at the level of accessory cells[47]. In addition to cytokines, Krebs cycle intermediates, such as citrate, succinate, and itaconate, can activate pro-inflammatory gene expression[48]. Metabolites from the Krebs cycle impact



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Figure 2 Mitochondrial DNA damage as a potential trigger for the inflammatory response. DAMP: Damage associated molecular patterns; mtDNA: Mitochondrial deoxyribonucleic acid; PAMP: Pathogen associated molecular patterns; ROS: Reactive oxygen species.

the reprogramming of macrophages from the M1 phenotype (pro-inflammatory) to the M2 phenotype (anti-inflammatory). M1 macrophages have impaired OXPHOS, and M2 macrophages have an intact Krebs cycle, with OXPHOS as the main source of ATP generation[43].

Two major pathways are implicated in this interaction between mitochondrial function and inflammatory responses. The mammalian target of rapamycin (mTOR) pathway plays a pivotal role in metabolic regulation by modulating glycolysis. Furthermore, metabolic reprogramming and a transition to glycolysis for energy production in $CD4^+$ and $CD8^+$ T cells are also induced by the activation of mTOR and OXPHOS[30]. The nuclear factor kappabeta (NF-κβ) is a stress-induced pathway (*i.e.*, tissue damage, cytokine, and PAMPs release) that promotes the expression of target genes involved in the immune response. Upon activation of the NF-κβ pathway and subsequent induction of cytokine expression, macrophages undergo differentiation into either M1 or M2 subtypes, contingent on the local cytokine milieu present at the site of infection. IFN-γ typically drives the differentiation of M1 macrophages, which in turn produce pro-inflammatory cytokines. Conversely, M2 cells refer to macrophages exposed to immune complexes, IL-4, IL-13, and IL-10[30].

MEASUREMENT OF MITOCHONDRIAL DYSFUNCTION

Regrettably, it is currently impractical to perform a thorough and accurate real-time analysis of the modified cells and tissues within malfunctioning organs of living human patients in a hospital setting. Therefore, mechanisms must be inferred from tissue specimens obtained from nonvital organs (*e.g.*, blood, skeletal muscle) or from postmortem examinations. In postmortem studies, septic patients exhibit mild to moderate mitochondrial swelling and autophagocytosis, with minimal cell death or indications of permanent damage, such as tissue fibrosis[49].

Mitochondrial biogenesis

The process of mitochondrial biogenesis encompasses the synthesis of mitochondrial proteins encoded by nuclear DNA, which are subsequently imported and integrated into the mitochondria. Additionally, biogenesis can also occur through mitochondrial DNA, which encodes 13 proteins primarily located within the OXPHOS pathway. In this way, biogenesis serves to replace damaged proteins and enhances the ability to generate energy if energy demand increases over time[4]. Increased mitochondrial biogenesis is detected in postmortem studies in critically ill patients, with increased expression of transcription factors[34]. A decrease in mitochondrial content has also been reported in the muscles of critically ill patients with sepsis-induced multiple organ failure[50]. Taken together, these data suggest that biogenesis activation may have a role in the recovery phase of critical illness[22], time when there was also an increase in RNA expression, participating in the restorative process[16]. These data point to compromised mitochondrial biogenesis in critically ill patients; and an activation of the biogenesis pathway may represent a key prognostic factor in critically ill patients, associated with recovering of the initial injury[22].

From this point of view, it seems reasonable to imagine that the dynamic processes of mitochondrial fusion and fission must change during acute inflammatory injury observed in sepsis. This activity can be measured by assessing the concentrations of mitochondrial fusion proteins (mitofusins 1 and 2, optic atrophy 1 protein) and mitochondrial fission proteins (dynamin-related protein 1 and fission 1 protein) [22]. Currently, adequate characterization in relation to the pro-fusion or mitochondrial fission profile in sepsis is merely speculative, lacking clinical studies that may show some signs regarding its *in vivo* effects.

Mitochondrial DNA

Mitochondria experience various morphological changes during fusion and fission events, which help to sustain a healthy mitochondrial population by facilitating mitochondrial DNA exchange, preserving mitochondrial DNA integrity, and regulating the size, quantity, distribution, and upkeep of OXPHOS capacity[22]. These morphological changes also play a crucial role in cell division and proliferation, as well as in the selective elimination of damaged or excess mitochondria through a process referred to as mitophagy[4]. Proteins that facilitate fusion events (such as mitofusin-2) and fission events (such as dynamin related protein-1) have been linked to changes in mitochondrial membrane potentials and diminished oxygen consumption[51]. Fission and fusion processes become more prevalent under stressful conditions and play a crucial role in eliminating damaged mitochondria and enhancing repair mechanisms. Currently, there is insufficient data regarding these mitochondrial dynamics in septic patients, and the data may vary based on the tissue type. From a hypothetical perspective, the balance of mitochondrial dynamics in septic patients may shift in favor of mitochondrial fusion, which could represent a cellular response aimed at improving mitochondrial function and decreasing oxidative stress[52].

However, mitochondrial DNA levels in the serum should be interpreted as a potential damage-associated molecular pattern, propagating an inflammatory response through interactions with the immune system[12,53]. Thus, mtDNA damage can lead to a pathological cycle, resulting in metabolic dysfunction, especially in white blood cells[54]. A reduction in mtDNA content in the peripheral blood, observed in the acute phase of sepsis, could be due to an increased concentration of neutrophils in the peripheral blood[55]. Therefore, it remains uncertain whether there is an interaction between DNA concentration and changes in mitochondrial function, especially in immune cells. Mitochondria contain their own DNA, and the depletion of mtDNA in an injury process may theoretically cause a respiratory chain defect and compromise ATP synthesis[23,55].

Qualitative measurements of mitochondrial metabolism

In addition to changes in mitochondrial mass, the quality of mitochondrial function and a shift towards glycolytic pathways are regulated by several hormones, enzymes, and regulatory pathways within cells. Reactive derivatives of nitric oxide and superoxide anion (such as peroxynitrite), which cause oxidative stress, promote glycolysis by activating the rate-limiting step of the pentose pathway, glucose-6-phosphate dehydrogenase. The pentose pathway results in the formation of NADPH relative to NADH. While NADH is the substrate for mitochondrial OXPHOS of high-energy phosphates, NADPH is crucial for the formation and repair of proteins, DNA, and lipids. Thus, by diverting glycolytic intermediates from the Krebs cycle to suppress aerobic mitochondrial respiration, cells and tissues transition to a state of decreased oxygen consumption and ATP production. This phenomenon is commonly referred to as the "Warburg effect", particularly in the context of cancer[41]. In this context, cells are less dependent on oxidative metabolism, thus reducing oxidative stress and promoting the formation of reducing equivalents (*e.g.*, lactic acid and NADPH) that induce cell repair[56]. The Warburg effect and related mediators, such as HIF-1α, are induced under conditions that model sepsis, confer cytoprotection to vital organs, and inhibit inflammation under conditions of acute cell stress[57]. However, the HIF-1α activation in immune cells could perpetuate the activation of the pro-inflammatory pathway[58].

The proton pumps of the electron transport chain, in conjunction with F1Fo-ATP synthase, establish a proton gradient across the inner membrane, generating both an electrochemical potential (proton motive force, pmf, in mV) and a flux of protons (proton current in nmol of protons/min). The mitochondrial membrane potential is a critical component of healthy mitochondrial metabolism and contributes to determining the pmf[8].

Reductions in both the expression and activity of complexes I, II, III, and IV have been reported in critically ill patients[14,22]. However, it is still doubtful whether these alterations are determinants of the patient's prognosis, or if they are just epiphenomena in the acute context of critical illness. However, they are useful and commonly used measurements to assess mitochondrial activity[35,59-61], especially when normalized by enzymatic activity, protein, or DNA concentration.

Respirometry

Measurement of mitochondrial respiration is a cost-effective and time-efficient method compared to traditional methods of assessing mitochondrial function in biopsies, making it readily available for use. Advanced instruments equipped with highly sensitive micro-cathode oxygen electrodes enable high-resolution measurements of mitochondrial respiration and can be utilized in acute care settings.

Mitochondrial respiration can be quantified by performing substrate-uncoupler-inhibitor titrations, commonly known as the SUIT protocol. This protocol involves titration with various combinations of substrates, uncouplers, and inhibitors to assess mitochondrial respiratory function[9]. This protocol allows the study of complex interactions of coupling and substrate control in a single assay, measuring multiple aspects of mitochondrial physiology[62].

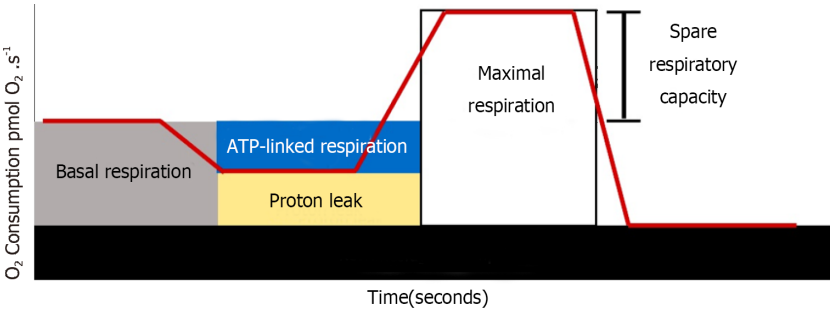
Respirometry enables the real-time measurement of mitochondrial respiration, with key parameters obtainable through the use of established inhibitors and uncouplers that act as sensitive indicators of response to mitochondrial stress. Figure 3 depicts the mitochondrial respiration trace derived from the SUIT protocol, which was employed in the following procedures[9,62]: (1) Routine respiration: Routine respiration also known as basal respiration, measures the oxygen consumption resulting from ATP production and proton leak. This represents energy demand under steady-state conditions. Changes in routine respiration in patients with disease compared to controls may indicate altered mitochondrial function and should be interpreted in the context of the following mitochondrial parameters; (2) proton leak: After measuring routine respiration, cells are exposed to oligomycin, an inhibitor of complex V. The remaining mitochondrial respiration after the addition of oligomycin is attributable to proton leak. While some proton leaks are expected under physiological conditions, significant proton leak may indicate damage to the mitochondrial membrane and/or complex damage. The use of oligomycin also allows for the estimation of oxygen consumption secondary to ATP production, often referred to as ATP-linked respiration; (3) maximal respiration: The addition of a mitochondrial uncoupler, such as dinitrophenol or carbonyl cyanide-4-(trifluoromethoxy) phenylhydrazone, stimulates maximal respiration by mimicking the physiological energy demand, leading to an increase in oxygen consumption. The difference between maximal respiration and routine respiration represents the spare respiratory capacity (SRC) of the cell. SRC indicates the ability of the cell to respond to energetic stress and is a measure of a cell's fitness. A decrease in SRC may limit the cell's ability to handle stressors, resulting in mitochondrial dysfunction; and (4) residual oxygen consumption: The addition of mitochondrial inhibitors, such as the combination of rotenone (complex I) and antimycin (complex III), completely inhibits electron transport system. The remaining oxygen is consumed by non-mitochondrial respiration in the form of oxidases and other cellular enzymes that use oxygen. Residual oxygen consumption may increase in the presence of a stress response.

Under normal conditions with excess ADP and oxygen, mitochondrial respiration occurs rapidly, known as state 3 respiration. Conversely, when ADP is fully consumed, state 4 respiration occurs, which is significantly slower. This state 4 respiration can be induced by "uncoupling" oxygen consumption from OXPHOS, leading to proton leakage back into the mitochondrial matrix without the production of cellular energy. One of the most promising indicators of mitochondrial function is the biochemical coupling efficiency (BCE), which is calculated as the quotient between OXPHOS and proton leak. BCE reflects the true effectiveness of mitochondria in utilizing oxygen for ATP production[62]. It is a useful way to gain more insight into the site of the dysfunction, namely, respiratory control decreases because of dysfunction in localized sites of substrate oxidation, ATP synthesis, proton conductance, or F1Fo-ATP synthase[8].

Although we understand that small clinical centers may have limited access to equipment for measuring real-time mitochondrial respiratory rates, this limitation could be easily overcome using simpler biochemical colorimetric methods that still maintain a reasonable level of sensitivity, the time to assay is usually short, and easy to implement in the laboratory hospital routine. For instance, the measurements of enzymatic activity of succinate dehydrogenase: Complex II (succinate: DCIP-oxidoreductase), complex, and complex V are routinely performed in research laboratories, and at the current state require standardization as a step forward to reach clinical settings[63,64]. However, the aforementioned colorimetric methods restrict the evaluation of metabolic activity to one complex each time, whereas in mitochondrial respirometry assays the metabolic activity of complexes can be assayed both, individually or more than one at the same time.

Which cells are ideal for measuring the mitochondrial activity? And what is the most suitable method?

Although it is logical that dysfunction in mitochondrial metabolism leads to a certain degree of organ failure, its measurement is often not feasible, because the ethical questions, costs, and viability of obtaining adequate mitochondrial samples from vital organs in critically ill patients[61]. Therefore, it is feasible to assess mitochondrial dysfunction in cells that are easy to collect, especially those that may reflect the "systemic" effect of sepsis on the body. Peripheral blood cells have been used to access bioenergetic functions in translational research. Peripheral blood mononuclear cells (PBMCs) are mitochondria-rich with high rates of respiration[16]; therefore, they are prime candidates in circulating blood to provide reliable estimation of global oxidative metabolism, particularly the metabolism linked to immune response. Lymphocytes comprise the majority of PBMCs and are traditionally used to measure defects in mitochondrial OXPHOS[30]. Exhaustion of lymphocytes, especially T cells, leads to an increased risk of secondary infections, which is correlated with mortality[65]. Circulating immune cells play an important role in the pathophysiology of sepsis because their activation may remotely induce inflammation in non-infected organs[66]. The measurement of mitochondrial respiration in



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Figure 3 Example of a respirometry assay. ATP: Adenosine triphosphate.

PBMCs of septic patients has the potential to identify those at risk of negative outcomes, and also can monitor the clinical course and response to treatment, making it a useful marker for acute care settings [9]. Thus, it is a candidate biomarker in sepsis.

In addition, this approach allows us to unravel mechanist readouts associated with impaired metabolism that follow this syndrome and also challenges how or whether this could be improved by therapeutic intervention. These primary observations collected from the literature are encouraging, and more clinical studies will help to advance methodological issues, clinical validation, and the level of reproducibility and sensitivity (Table 1).

SEPSIS AND MULTI-ORGANIC FAILURE

Various systemic inflammatory processes can exert different effects on mitochondria. In the early stages of sepsis, reduced perfusion resulting from intrinsic and extrinsic fluid losses, decreased intake, myocardial depression, microcirculatory redistribution of blood flow, and loss of vascular tone, can lead to tissue hypoxia. This condition, characterized by insufficient oxygen levels at the mitochondrial level, impedes the ability of mitochondria to carry out OXPHOS, leading to a deficit in ATP production[12]. Although Complex IV exhibits distinctive enzyme properties that facilitate its functionality under hypoxic conditions, severely diminished oxygen concentrations may compromise ATP generation and activate cell death pathways, thereby adversely impacting cellular homeostasis[12,67,68]. Hormonal alterations in sepsis also affect mitochondrial function and efficiency. For example, thyroid hormones are believed to work predominantly through the modulation of mitochondrial activity[4,33]. Thirdly, genes that transcribe mitochondrial proteins are downregulated early in the inflammatory response. This was first recognized in human volunteers receiving endotoxins[69] and subsequently described in critically ill patients[35].

Impairment of mitochondrial metabolism in sepsis

Different studies, in different contexts, have evaluated mitochondrial activity in septic compared to nonseptic or control patients. Muscular cells are prone to impaired mitochondrial metabolism during critical illness[70] and are an important research field. Carré *et al*[35] used muscle tissue biopsies from critically ill patients, comparing them to those of controls subjected to hip surgery. They found a decrease in mitochondrial density in critically ill patients, without a decrease in Complex I and Complex IV activity. In a study evaluating patients with ICU-acquired weakness, comparing ATP synthesis in this population with metabolically healthy controls, ICU patients had an approximately 50% reduction in the ability of skeletal muscle to synthesize ATP in mitochondria, with a depletion of complex III and IV concentrations[71]. A similar loss of mitochondrial activity was detected in a previous study in a population with sepsis and multiorgan failure[72]. Complex I and complex IV activity was reduced in the intercostal and leg muscles, respectively, compared to controls.

Belikova demonstrated a higher baseline PBMC oxygen consumption and attenuated response to ADP stimulation in patients with sepsis than in healthy volunteers[66]. In blood mononuclear cells, Kraft *et al*[16] demonstrated an early sepsis-mediated disruption of mitochondrial quality control in septic patients, with a later activation of mitochondrial biogenesis in this population. These patients also showed increased mitochondrial damage (measured by mtDNA levels) during the early phase of sepsis management. In a cohort of septic and non-septic ICU patients with measurement of mitochondrial function in isolated lymphocytes, critically ill patients had increased mitochondrial oxygen consumption but no significant difference in mitochondrial membrane potential[17]. Jang *et al*[15] also found a lower routine, uncoupled Complex I, and maximal respiration in septic patients, when compared to controls in the early sepsis management. A respirometric study in PBMC developed by Japiassú *et al*[73] reported reduced F1Fo-ATP synthase activity, thereby reducing ATP production. This

Table 1 Different methods of mensuration of mitochondrial damage and recovery

Item	Description
Mitochondrial biogenesis	PPAR-γ coactivator 1-α, nuclear respiratory factor 1, mitochondrial transcription factor A. Material obtained from tissue biopsy or from peripheral PBMC
Mitochondrial content	Mitochondrial mass, concentration and area
Mitochondrial DNA content	PGC-1α, NRF-1, absolute DNA number of copies
Mitochondrial fusion	Mitofusins 1 and 2, optic atrophy 1 protein
Mitochondrial fission	Dynamin-related protein 1 and fission 1 protein

PPAR-γ: Peroxisome proliferator-activated receptor gamma; PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator-1 alpha; NRF-1: Nuclear respiratory factor-1; PBMC: Peripheral blood mononuclear cells.

may contribute to the energetic failure reported in these cells during the course of septic insult. In addition, septic shock PBMC have reduced O_2 consumption, ADP-induced state 3 respiration, and respiratory control ratio compared to control PBMC. Inhibition of complexes I, III, and IV in PBMCs from septic patients compared with controls was also detected in another study[74]. In a pediatric population, Weiss *et al*[75] detected a decrease in spare respiratory capacity on days 1-2 of sepsis compared with controls. Spare respiratory capacity normalized on days 5-7. Patients with sepsis also had a higher ratio of leak to maximal respiration than controls, with normalization in the later phase of sepsis. Patients with sepsis did not show differences in basal or ATP-linked oxygen consumption or membrane potential.

In patients admitted to the emergency department with and without sepsis, Puskarich[76] did not find differences in plasma levels of cytochrome B, NADH, and Cox-III mtDNA between groups. Pyle *et al*[55], in a protocol that evaluated mononuclear cell mtDNA content, found that these levels were lower in patients with sepsis, with depletion of monocyte and lymphocyte mtDNA. Platelet studies have also evaluated mitochondrial metabolism in patients with sepsis. Sjövall *et al*[61] found an increase in state 3 and a decrease in RCR in patients with sepsis compared to controls during sequential evaluations in the first week of sepsis diagnosis. Additionally, patients with sepsis had increased rates of complex I and complex II respiration compared to controls. However, the mtDNA concentration did not differ between the platelets of patients with sepsis and controls.

Are mitochondrial metabolisms associated with mortality?

A criticism can be made of the differences in mitochondrial measurements between survivors and non-survivors observed in studies. Whether they are pathological or just another measure of disease severity requires further investigation[77]. In human subjects, a significant constraint of this research approach is the uncertainty surrounding whether mitochondria sourced from PBMCs, platelets, or muscle cells can accurately serve as proxies for the mitochondria present in essential organs like the liver, kidneys, and heart[77]. The establishment of a workable, all-encompassing strategy to investigate the complete energy production pathway in human beings would signify a more significant achievement, as it would facilitate a deeper comprehension of the origin of lactate in distinct patients and across time, thereby enabling more targeted clinical trials for novel treatments for bioenergetic dysfunction.

Defects in leukocyte energy metabolism[78], particularly in T lymphocyte cells[79], are intrinsically associated with the state of immunoparalysis in sepsis. Metabolic events in the mitochondria of macrophages, dendritic cells, and T-lymphocytes have profound effects on immunity. When exposed to infectious injury, OXPHOS levels decrease, with a concomitant increase in glycolysis. An outcome of the reduced ATP production *via* OXPHOS is the redirection of mitochondria towards generating mitochondrial ROS, which function as signaling molecules essential for eliciting an appropriate immune response[54]. Therefore, mitochondrial respiration is essential for the functioning of these cells.

Despite the fact that the current knowledge suggests a potential role of mitochondrial metabolism impairment in septic patients (when compared with controls) with a potential impact on prognosis, the literature is quite heterogeneous with regard to the findings of mitochondrial dysfunction (Table 2). It is still necessary to define the most practical way of measuring, with the greatest clinical applicability, the greatest prognostic impact, and, above all, the most accurate in predicting the clinical course of the disease.

Are mitochondrial metabolisms associated with recovery?

Therefore, mitochondrial biogenesis is critical for recovery, and the recovery from organ dysfunction is preceded by an increased mitochondrial biogenesis[33]. In our study of patients with multi-organ failure in intensive care, we found that those who ultimately survived had higher levels of PGC-1α and better-preserved levels of Complex protein, along with a more robust antioxidant response (specifically, manganese superoxide) in the early stages of their disease progression[35]. The ability to clear damaged

Table 2 Studies that explored association of mitochondrial dysfunction and prognosis in sepsis

Ref.	*n* of critically ill septic patients	Mitochondrial measurement	Main findings (survivors *vs* nonsurvivors)
Belikova *et al*[66], 2007			
Brealey *et al* [18], 2003	28	ATP concentration, Complex I, II, and IV activities in biopsied muscle cells	Sepsis survivors had an increased level of ATP and Complex I and IV activity
Carré *et al* [35], 2010	16	Mitochondrial morphology (surface density and volume), RT-PCR of mitochondrial biogenesis factors and concentration of Complex I and Complex IV mitochondrial proteins and OXPHOS transcripts in muscle biopsy specimens	Nonsurvivors had an increased decline in mitochondrial surface density, with a similar mitochondrial volume in these groups; OXPHOS transcripts were more abundant in survivors; increased ATP content in survivors; no difference between groups in Complex I and Complex IV activity
Kraft *et al* [16], 2019	37	qRT-PCR for genes that regulate mitochondrial biogenesis in PBMCs	Increased genetic activation of mitochondrial biogenesis in day 3 compared with day 1; decrease in mtDNA in septic patients compared with controls, with a recovery on day 5; early activation of mitochondrial biogenesis by day 1 associated with ICU discharge; increased mRNA levels in survivors
Japiassú *et al*[73], 2011	20	Respirometry of PBMC evaluating state 3, 4 and respiratory control ratio	No difference in ADP-stimulated respiration in nonsurvivors, when compared with survivors
Nedel *et al* [14], 2021	90 patients	Respirometry of permeabilized lymphocytes	Improvement in Complex I, Complex II, basal and in BCE in day 3, compared with day 1, were associated with lower mortality. In multivariate analysis, BCE improvement was associated with lower 6-mo mortality
Puskarich *et al*[77], 2015	28 patients	Respirometry of platelets	Routine and state 3 respiration were significantly higher in non-survivors compared to survivors; state 4 respiration had a non-significant increase in non-survivors
Pyle *et al* [55], 2010	Not reported (147 patients, including septic)	mtDNA content from mononuclear cells	No relationship between mtDNA content and survival outcome at 180 d
Sjövall *et al* [61], 2010	18 patients	Respirometry of isolated platelets evaluating Complex I, state 3, 4 and respiratory control ratio	Non-survivors had an increased Complex I, Complex II, state 3 respiration and an increased respiratory control ratio at day 6-7 of sepsis when compared with survivors
Sjövall *et al* [82], 2013	20 patients	Respirometry of permeabilized peripheral blood immune cells	Survivors and non-survivors at 90 d after sepsis did not have difference in Complex I plus Complex II respiration normalized to citrate synthase, mtDNA, and cytochrome c

ATP: Adenosine triphosphate; BCE: Biochemical coupling efficiency; ICU: Intensive care unit; qRT-PCR: Quantitative reverse transcriptase-polymerase chain reaction; mtDNA: Mitochondrion desoxyribonucleic acid; OXPHOS: Oxidative phosphorylation; PBMC: Peripheral blood mononuclear cells; ADP: Adenosine diphosphtate.

mitochondria is another important phenomenon[80]. Mitophagy (autophagic degradation) and mitoptosis (programmed destruction) are the processes by which cells deal with impaired mitochondria [12]. The efficiency of these processes may be an important contributing factor to the pathogenesis of various states of the disease. The process of mitophagy entails the targeted sequestration and subsequent degradation of damaged mitochondria, which occurs prior to their ability to activate cell death pathways and potentially jeopardize the viability of the entire cell. Thus, mitophagy operates as an initial protective response. Conversely, heightened levels of oxidative stress and apoptotic proteases can impede the function of mitophagy and stimulate additional inflammatory responses[81].

CONCLUSION

Alterations caused by acute inflammatory conditions, such as sepsis, is associated with impaired function of mitochondrial components including protein content, mtDNA concentration, oxidative complexes activity, and F1Fo-ATP synthase. Often, these alterations are associated with clinical outcomes. Given these features mitochondria deserve to be better explored regarding its role as potential biomarker in prognosis, sepsis rehabilitation, and its association with different spectrum of organ failure.

FOOTNOTES

Author contributions: Nedel W contributed to research, wrote the manuscript, reviewed the final version, and made the graphs and figures; Deutschendorf C contributed to write the manuscript and reviewed the final version; Portela LVC contributed to write the manuscript, reviewed the final version.

Supported by the Fundação de Amparo a Pesquisa do Estado do Rio Grande do Sul, No. 1010267.

Conflict-of-interest statement: The authors state that there was no conflict of interest.

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S-Editor: Chen YL
L-Editor: A
P-Editor: Xu ZH

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 June 9; 12(3): 153-164

DOI: 10.5492/wjccm.v12.i3.153

ISSN 2220-3141 (online)

MINIREVIEWS

Acute exacerbation of interstitial lung disease in the intensive care unit: Principles of diagnostic evaluation and management

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Juneja D, India; Wu J, China

Received: February 27, 2023
Peer-review started: February 27, 2023
First decision: March 28, 2023
Revised: April 18, 2023
Accepted: May 17, 2023
Article in press: May 17, 2023
Published online: June 9, 2023

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Abstract

Interstitial lung disease (ILD) is typically managed on an outpatient basis. Critical care physicians manage patients with ILD in the setting of an acute exacerbation (ILD flare) causing severe hypoxia. The principles of management of acute exacerbation of ILD are different from those used to manage patients with acute respiratory distress syndrome from sepsis, *etc*. Selected patients may be candidates for aggressive measures like extracorporeal membrane oxygenation and lung transplantation, while almost all patients will benefit from early palliative care. This review focused on the types of ILD, diagnosis, and management pathways for this challenging condition.

Key Words: Interstitial lung disease; Pulmonary fibrosis; Acute exacerbation of interstitial lung disease; Extracorporeal membrane oxygenation; Interstitial lung disease flare; Immunosuppression

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Core Tip: Interstitial lung disease (ILD) refers to a heterogeneous group of parenchymal lung disorders. Most patients with ILD receive management in outpatient clinics. Patients with acute exacerbation of ILD may experience significant respiratory distress, requiring urgent management in an intensive care unit. Timely diagnosis and management of these patients using a multimodality team approach may improve both morbidity and mortality. When acute exacerbation of ILD progresses to irreversible end-stage respiratory failure, lung transplantation and/or palliative care may be appropriate treatment options depending on the individual patient's clinical presentation.

Citation: Hayat Syed MK, Bruck O, Kumar A, Surani S. Acute exacerbation of interstitial lung disease in the intensive care unit: Principles of diagnostic evaluation and management. *World J Crit Care Med* 2023; 12(3): 153-164
URL: https://www.wjgnet.com/2220-3141/full/v12/i3/153.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i3.153

INTRODUCTION

Interstitial lung disease (ILD) is a heterogeneous group of approximately 200 disorders affecting lung parenchyma. The classification schema of this group of diseases has changed over time, with the most current iteration agreed upon in 2013 in a consensus statement from the American Thoracic Society and European Respiratory Society[1]. This classification system will be the basis for the nomenclature used in this review (Figure 1).

ILD can be more broadly categorized into those with a known cause and those without an identifiable etiology, also known as "idiopathic." Those ILDs with known causes can be due to drugs and toxins, rheumatic disease, granulomatous diseases such as sarcoidosis, and other forms such as lymphangioleiomyomatosis, eosinophilic pneumonia, or pulmonary Langerhans cell histiocytosis. The major idiopathic ILDs can be distributed into three categories: Chronic fibrosing [idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP)], acute/subacute fibrosing [cryptogenic organizing pneumonia, acute interstitial pneumonia (AIP)], and lastly smoking-related (delta sleep-inducing peptide, respiratory bronchiolitis-ILD)[1]. Notably, not all ILDs have the propensity to present as an acute exacerbation (AE). Moreover, common conditions like pulmonary edema, pneumonia, pulmonary embolism, and aspiration should be considered in the differential diagnosis of acute worsening. Furthermore, patients may present to the intensive care unit (ICU) with no known history of ILD.

An abnormal chest radiograph may be the initial finding in these patients[2]. Much attention is paid to the specific patterns noted on chest computed tomography (CT) that, when coupled with clinical history, can sometimes obviate the need for tissue sampling[3]. It is important to note that the lung has a limited and predictable response to injury; thus, a variety of disease processes may produce similar imaging findings[4]. Patients will almost universally present in a similar fashion, with dyspnea and acute hypoxemic respiratory failure. CT becomes an essential tool in the differentiation of the diagnosis.

AE-ILD

Definition

The definition of AE-ILD has evolved over time. AE-ILD was defined by 2007 IPFnet[5] as an "acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality typically less than 1-mo's duration with exclusion of alternative etiologies"[2]. The revised criteria in 2016[2] did not set a definite 30-d duration of onset of symptoms. The critical component of establishing a diagnosis of AE-ILD is excluding other etiologies that could be causing increased respiratory distress such as heart failure, pulmonary embolism, pneumothorax, and infection, *etc* (Table 1). However, in some cases infections and other pulmonary insults might act as a trigger for AE-ILD. It is difficult to lump all ILDs into one framework, and it is important to acknowledge that some of the acute presentations may be exacerbations of a previously unrecognized process[6]. AE-ILD symptoms tend to be shared across the spectrum of the disease. Commonly patients will present with worsening cough and dyspnea, but presentations may be more fulminant in the case of some AIP. However, given the non-specific nature of these symptoms, chest imaging and clinical history play an important role in discerning the diagnosis and thus the appropriate management.

Triggers

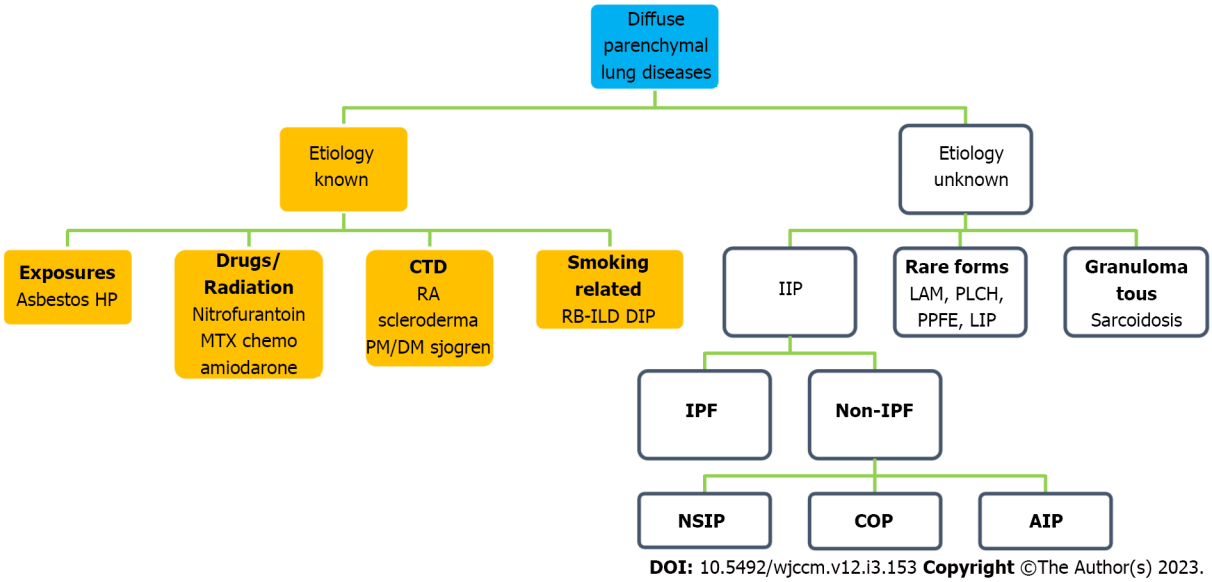
The incidence of AE-IPF ranges from 2% to 15% per year, depending on the cohort studied[7-10]. Nonetheless, AEs appear at a lower rate in non-IPF ILDs[11]. AEs are often devastating, with a median survival of usually about 4 mo[12]. If an IPF patient requires mechanical ventilation, mortality exceeds 75%[13]. Given that patients with ILD exist on the fringe between functionality and fulminant worsening, even the most minor perturbations in homeostasis can lead to a significant decline. Intuitively it makes sense that any of the common causes of respiratory failure in the general population also occur in the ILD population, with the implications of such in the latter being far more pronounced.

Risk factors for AE-IPF have been described in several studies but have not been validated in independent cohorts[11]. Whether the AE represents a progression of the underlying ILD or an aberrant response to external insults such as aspiration of gastric content, infection, or mechanical stretch remains unknown. Song *et al*[12] demonstrated that patients with lower baseline lung function as measured by

Table 1 Reversible causes of hypoxia in interstitial lung disease

No.	Potentially reversible (partial or complete) causes of worsening ILD
1	Pulmonary edema
2	Pneumonia
3	Aspiration
4	Pulmonary hemorrhage
5	Pulmonary embolism

ILD: Interstitial lung disease.



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Figure 1 Classification of interstitial lung disease/diffuse parenchymal lung disease. AIP: Acute interstitial pneumonia; COP: Cryptogenic organizing pneumonia; CTD: Connective tissue disease; DIP: Desquamative interstitial pneumonia; DM: Dermatomyositis; HP: Hypersensitivity pneumonitis; IIP: Idiopathic interstitial pneumonias; IPF: Idiopathic pulmonary fibrosis; LAM: Lymphangioleiomyomatosis; LIP: Lymphoid interstitial pneumonia; MTX: Methotrexate; NSIP: Non-specific interstitial pneumonia; PLCH: Pulmonary Langerhans cell histiocytosis; PM: Polymyositis; PPFE: Pleuroparenchymal fibroelastosis; RA: Rheumatoid arthritis; RB-ILD: Respiratory bronchiolitis-ILD.

forced vital capacity and those who never smoked had a greater risk for AE-IPF[12]. They described a subset of patients with AE-ILD as rapid deterioration of ILD, where the respiratory failure occurs in shorter duration (days to weeks) requiring hospitalization, with the presence of new radiographic abnormalities. Interestingly, within this cohort, many patients were found to have an infection as a trigger; more than half of those patients had opportunistic infections. The demonstration that AE is the most common cause of clinic deterioration in IPF patients is not a novel discovery[14]; thus, acceptance that disease progression may explain the patient's presentation can obviate the need for expensive and possibly morbid diagnostic investigations.

Other previously described exposures that can precipitate AE include bronchoalveolar lavage, cryobiopsy, lung resection surgery, pollution, aspiration, vaccination, and infection[15-21]. Churg *et al* [22] described the pathologic features found on lung biopsy in patients with fibrotic lung disease who were admitted with worsening respiratory failure. They noted three microscopic patterns found in these patients: Diffuse alveolar damage; organizing pneumonia; and a pattern of numerous very large fibroblast foci superimposed on underlying fibrosis. Ultimately, the onus on the admitting team is to differentiate idiopathic exacerbations from secondary ones, potentially more amenable to treatment. It has been shown to be related to mortality; that is, patients with suspected AE had worse in-hospital mortality as compared to those patients who had other causes for respiratory worsening[23].

Work-up

The diagnostic evaluation of patients with ILD admitted to the ICU is largely the same as that for all other patients admitted with acute hypoxemic respiratory failure. A caveat to this approach is for the patient with previously undiagnosed ILD, in which case, they will require a more thoughtful appraisal.

It is reasonable to exclude all the common, secondary causes of worsening that can be seen in ILD patients (Table 1).

Chest CT is now routinely utilized in all patients admitted to the ICU with AE-ILD. In those patients without a known diagnosis of ILD, a basic working knowledge of some of the classic radiographic findings can be helpful. As previously noted, ILDs are both a radiographic and histopathologic diagnosis.

There are several characteristics that can be used to quickly narrow the diagnosis: (1) Is increased attenuation present? *i.e.* reticulation, ground-glass, consolidation, nodules, or linear opacities; (2) Are cysts present?; and (3) Are areas of decreased attenuation (as is seen with honeycombing) a sign of lung fibrosis? While ILD is considered a rare family of diseases, IPF is the most common archetype of these rare diseases. The terms NSIP and usual interstitial pneumonia (UIP) are often encountered in the impression of CT scans of these patients. It should be mentioned that these are both descriptive of radiographic and histologic processes. With the advent of high-resolution chest CT, many ILDs can be diagnosed based on imaging alone. Radiologically, in UIP, honeycombing is the prototypical appearance of IPF (which represents areas of the destroyed and fibrotic lung) and is a predominant feature with an apical to basal gradient. It classically involves the subpleural region and is more often in the middle and lower lungs (Figure 2A). Ground glass opacities are minimal or absent, and traction bronchiectasis is often seen, which signifies architectural changes secondary to fibrosis[4]. NSIP refers to a pattern that is predominantly composed of diffuse, bilateral, ground-glass opacities and, at times, associated with peripheral irregular linear or reticular opacities. The distribution is mainly peripheral and basal and typically spares the subpleural region. Honeycombing, if present, is generally mild in comparison to UIP (Figure 2B).

However, there are some radiographic findings that are nearly pathognomonic and obviating the need for a tissue diagnosis[24]. While tissue sampling does provide a definitive diagnosis, surgical lung biopsy is generally not pursued in the setting of AE-ILD as it does not alter the course of treatment[25], and the procedure itself carries with it significant morbidity[26]. The typical UIP and NSIP CT patterns were outlined above. The findings seen during an AE may be of prognostic value. In AEs, the CT scan may show areas of consolidation, ground glass opacification, or a combination of the two (Figure 2C and D). In fact, Akira *et al*[27] were able to demonstrate Kaplan-Meir survival curve differences as it relates to the patterns found on CT scans in patients admitted with AE-UIP[27]. The chest CT will also exclude pulmonary embolism (if protocoled correctly) and pneumothorax.

Laboratory workups should follow the same standard of care as for patients admitted to the ICU with respiratory failure. Sputum and blood cultures should be drawn at the time of admission. Urine antigens for *Legionella* and *Streptococcus* and respiratory samples should be sent for PCR to assess for viral infection. Evidence exists that serum procalcitonin may be a helpful marker in differentiating bacterial pneumonia from AE-ILD[28,29]. Bronchoscopy likely has limited utility in the evaluation of these patients and if performed should be conducted with anticipation that further respiratory decompensation may occur. In the single-center cohort, it was demonstrated that bronchoscopy revealed potential causes of respiratory decline in 13% of patients and a change in management from the initial empiric regimen in 25% of patients. There was no difference in mortality between those with and without bronchoscopy findings. However, bronchoscopy in non-ICU patients led to immediate respiratory decompensation and the need for a higher level of care or invasive mechanical ventilation (IMV) in 25% of patients[30].

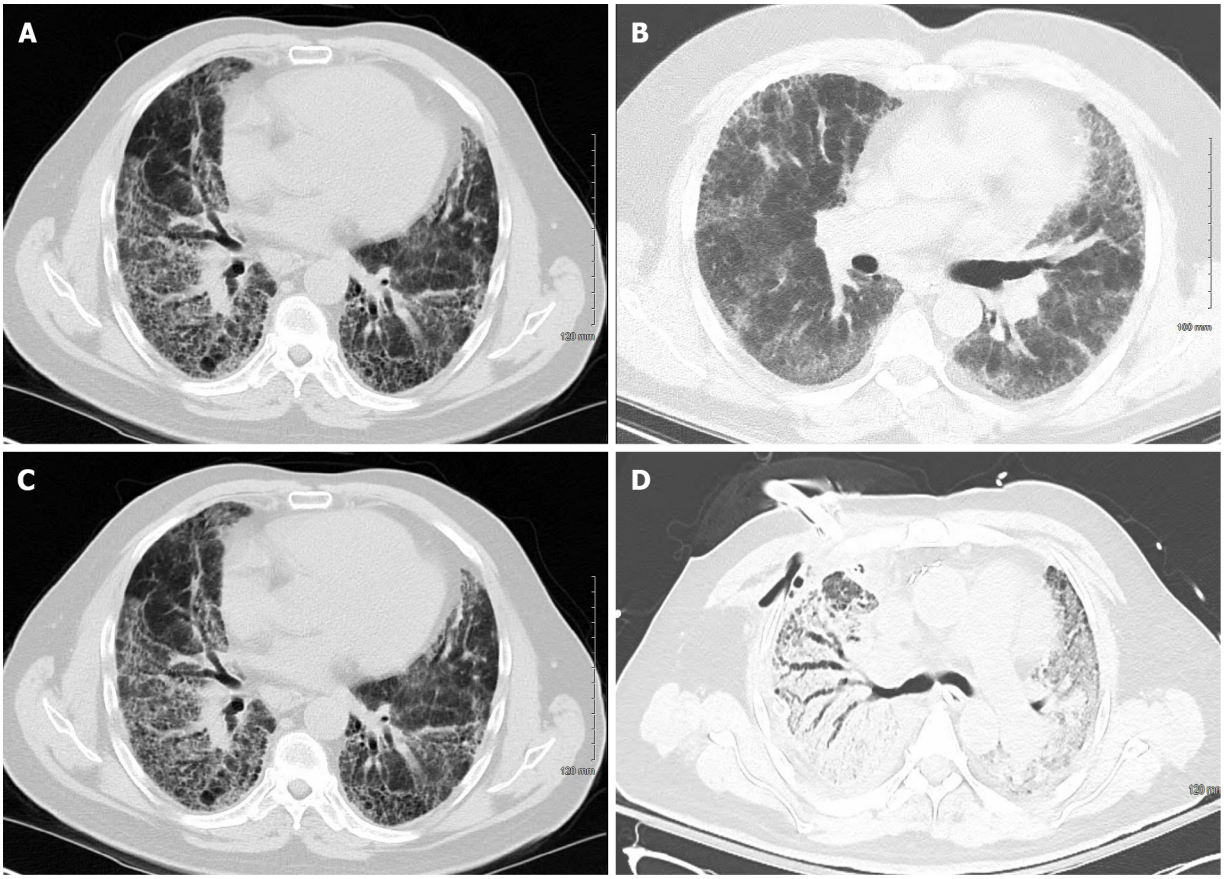
In patients without previously diagnosed ILD, there may be a role of assessing autoimmune serology for the purpose of differentiating between IPF and connective tissue disease-related ILD or pulmonary alveolar hemorrhage syndromes. The latter two are more likely to respond to high doses of immunosuppression[31].

Management

Management can be viewed as a multifaceted approach that is mainly comprised of supportive care for respiratory failure. Given the relative heterogeneity of disease processes, there is not one treatment plan that can be universally applied. Below we will outline the different considerations and treatment modalities that have been applied to patients with AE-ILD. It should be noted that much of this practice is done with a paucity of high-quality evidence and ultimately relies on expert opinion on consensus guidelines. Figure 3 is a generalized flowsheet that can be used to guide through the various steps of management of AE-ILD patients.

Immunosuppression

Presently there are no proven, effective therapies for the treatment of AE-IPF. Despite this, many patients with AE-IPF receive corticosteroids in accordance with the guidelines, which admit there are no controlled trials to judge efficacy and that the recommendation comes largely from anecdotal evidence of benefit[3]. Given the high mortality associated with AE-IPF, it is reasonable to administer corticosteroids to these patients. However, the dose, route, and duration are of unknown amounts. The same can be said for AIP, which is a rapidly progressing, lethal form of ILD with a dismal prognosis and is not responsive to steroids[6]. A general approach adopted is to use daily corticosteroid dosage in the 1-2 mg/kg range in divided doses. In patients who respond to this treatment, a gradual taper is attempted



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Figure 2 Chest computed tomography. A: Chest computed tomography (CT) of a patient with idiopathic pulmonary fibrosis with usual interstitial pneumonia pattern; B: A 54-year-old male with non-specific interstitial pneumonia. Chest CT showed faint ground glass opacity and mild reticulations (non-specific interstitial pneumonia); C: Idiopathic pulmonary fibrosis patient in Figure 2A during acute exacerbation showing ground glass opacities requiring extracorporeal membrane oxygenation as bridge to transplant; D: Chest CT of patient in Figure 2B during acute exacerbation of interstitial lung disease with areas of ground glass opacity and consolidation.

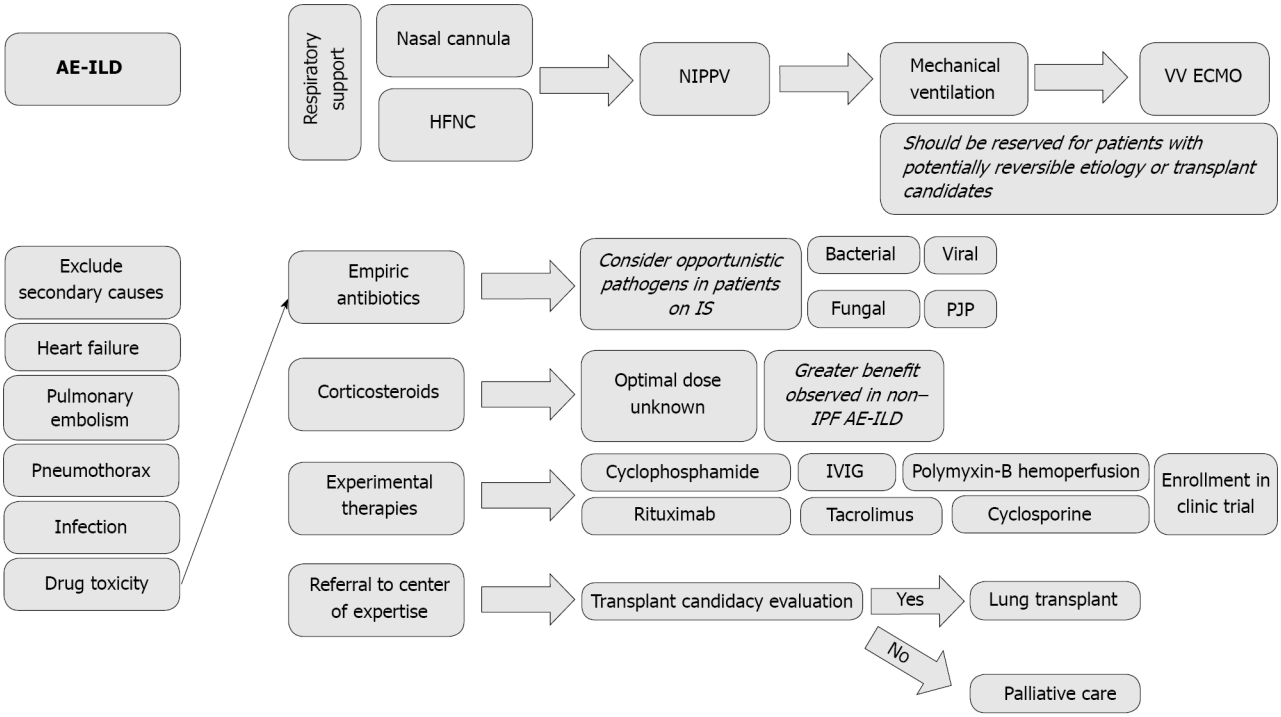
over the course of weeks.

A recent trial looked at the addition of cyclophosphamide to corticosteroids for the management of AE-IPF and showed that 3-mo mortality increased in the treatment arm, which provides further evidence against its use in this setting[32,33]. Another drug of interest is cyclosporine, which has been investigated in conjunction with corticosteroids in several non-randomized, retrospective studies in patients with AE-IPF and has shown potential benefits. However, larger randomized controlled studies are needed to confirm this[34]. It has been postulated that immune dysregulation may lead to autoantibody production, which may drive the progression of IPF or the development of AE. As such, rituximab, in conjunction with plasma exchange, has been investigated as a potential therapeutic with promising results[35].

Currently, there are ongoing, prospective, randomized controlled studies, STRIVE-IPF [NCT03-286556] and Europe Exchange-IPF [NCT03584802], testing the efficacy and safety of the combination of plasma exchange, rituximab, intravenous immunoglobulin, and corticosteroids for the treatment of AE-IPF based on the hypothesis that autoantibody reduction might help in its management. Regarding patients with AE of other ILDs, stronger evidence of benefits from corticosteroids exists, as is the case for fibrotic hypersensitivity pneumonitis, connective tissue disease-ILD, and organizing pneumonia, to name a few. We recommend the engagement of a pulmonologist familiar with the role of immunosuppression in connective tissue disease-ILD if this is suspected. Depending on the condition, the choice of agents may range from corticosteroids alone to consideration of agents like cyclophosphamide, rituximab, and even plasma exchange if alveolar hemorrhage is suspected. These decisions are best undertaken in a multidisciplinary discussion to facilitate the best outcome for the patient.

ANTIFIBROTIC THERAPY

Currently, there are two medications available on the market, nintedanib and pirfenidone, which are



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Figure 3 Flowsheet for management of acute exacerbation of interstitial lung disease. AE-ILD: Acute exacerbation of interstitial lung disease; HFNC: High-flow nasal cannula; IPF: Idiopathic pulmonary fibrosis; IS: Immunosuppressants; IVIG: Intravenous immunoglobulin; NIPPV: Noninvasive positive pressure ventilation; PJP: *Pneumocystis jiroveci* pneumonia; VV ECMO: Veno-venous extracorporeal membrane oxygenation.

classified as antifibrotics that are approved for the treatment of IPF. Nintedanib is a tyrosine kinase inhibitor that blocks the processes that propagate fibrosis. In the clinical trial, which ultimately led to its approval, it was shown to reduce the decline of lung function and thus slow disease progression[36]. Pirfenidone works by inhibiting transforming growth factor beta, which plays a role in collagen-directed fibroblast formation. While there is no reversal of disease, this medication has also shown the ability to slow the progression of lung decline. Both medications have been shown to reduce the rate of exacerbations[3]. Many patients with IPF will be on these medications at the time of hospitalization. Polke *et al*[33] looked at the management practices of AE-IPF in specialized and non-specialized ILD centers worldwide. They found that 80% of physicians in specialized centers continue antifibrotics during hospitalization, and 66% initiate therapy during the AE[33]. These therapies have not been investigated specifically for use in the setting of AE-IPF or other ILDs, for that matter. There is, however, a growing body of evidence for the use of these drugs in other fibrosing lung diseases other than IPF[37].

Antibiotics

Antimicrobial agents are used routinely in patients with AE-ILD in conjunction with a thorough infectious workup. Antimicrobial coverage should be tailored to the specific pathogens and sensitivities at each respective institution. Azithromycin is a familiar drug, and its use in the management of AEs of chronic obstructive lung disease is well documented. Azithromycin is postulated to exert its benefits through anti-inflammatory and immunomodulatory effects in the lung[38,39]. Evidence does exist that there may be a benefit to macrolide use in patients with AE-IPF. However, these studies are small and confounded by other therapies the patients received[40,41]. Other patient-specific considerations, such as recent hospitalization, prior culture data, and immunosuppression, should also play a role in determining the most appropriate therapy. In a Chinese cohort of patients with idiopathic inflammatory myopathy-related ILD, they found that roughly one-third of patients admitted with clinical worsening (mainly respiratory) had what they deemed to be concomitant infection and exacerbation of the idiopathic inflammatory myopathy. Nearly half of those patients with documented infections had a fungal infection with either *Aspergillus* or *Pneumocystis*[42]. This highlights the importance of considering opportunistic infections in patients with ILD who are admitted to the ICU.

Antacids

It is postulated that microaspiration might play a role in the incitement of lung fibrosis. Studies have frequently demonstrated a higher prevalence of gastroesophageal reflux disease in ILD patients; however, this association cannot be interpreted as causation[43,44]. The role of acid-reducing therapy in

AE has not been formally investigated. However, many physicians will continue antacids during hospitalization, and at the very least, the patients will qualify for alimentary prophylaxis based on mechanical ventilation and corticosteroid administration.

HIGH-FLOW NASAL CANNULA

The coronavirus disease 2019 pandemic has changed the way non-invasive ventilation (NIV) is viewed and utilized. With the popularization of high-flow nasal cannula (HFNC), the oxygen demands of severely hypoxemic patients can be met without the need for endotracheal intubation. IMV has a dismal prognosis for patients with AE-ILD[45], and a trial of HFNC is warranted. The benefit and feasibility of using HFNC for acute hypoxemic respiratory failure has been shown. However, patients with chronic hypoxemic respiratory failure were excluded from this study. While the patients that were randomized to HFNC *vs* continuous positive airway pressure (CPAP) or bi-level positive airway pressure devices did not result in a decreased need for intubation, there was a reduction in mortality at 90 d in the HFNC group. HFNC can deliver a fraction of inspired oxygen up to 100% with high flow rates that can match the patients' respiratory demands. Given the high flow rates, there is also a degree of dead-space washout that results in decreased work breathing. There is limited high-quality evidence regarding the matter, but it has been shown in several retrospective studies that it is a safe and well-tolerated modality with comparable outcomes to CPAP and bi-level positive airway pressure[46,47]. HFNC has been shown to have salutatory effects in IPF patients without an AE, specifically decreased minute ventilation and respiratory rate, and capillary carbon dioxide was seen. The minor increase in positive end-expiratory pressure seen with it is also considered beneficial[48,49]. Finally, there is the added advantage of the patient being able to eat and communicate with HFNC *vs* IMV.

NIV

NIV is often applied in patients with acute hypoxemic respiratory failure in the hopes of staving off endotracheal intubation. There is robust evidence for the utility of its use in respiratory failure secondary to chronic obstructive lung disease and congestive heart failure. However, the benefit is less certain in AE-ILD. Yokoyama *et al*[50] demonstrated that NIV might have potential benefits in patients with acute hypoxemic respiratory failure secondary to AE-ILD. Eleven patients received CPAP therapy. Of those patients, 6 failed and required IMV but did not survive. The remaining 5 patients survived and were alive at the 3-mo follow-up. Similar results were shown in another study that also used NIV for patients with IPF[51,52]. These studies are not without limitations, given small sample sizes and retrospective natures that may not be representative of the general AE-ILD population. Further, it may reflect a selection bias that patients who benefitted from the use of NIV may have had less severe diseases. Nonetheless, it is proof of concept that perhaps for a subset of AE-ILD patients, a trial of NIV is a potential alternative to an otherwise morbid intervention that in some cohorts see a mortality rate of up to 90% for ICU patients[51].

MECHANICAL VENTILATION

The outcomes for ILD patients that require IMV are so poor that outside of transplant candidates, some experts have advised against endotracheal intubation for these patients apart from those patients that have clearly reversible causes for respiratory decompensation[53]. The lungs of ILD patients are plagued by two detrimental factors: Significant V/Q mismatch and poor compliance. No specific guidelines dictate the optimal way to provide IMV to this subset of patients. The intrinsic substrate properties of ILD lungs make them especially prone to ventilator-induced lung injury with decreased compliance making the lung more prone to both barotraumas as well as atelecatrauma[54,55]. Therefore, it is reasonable to utilize strategies from the ARDSNET group for the management of patients with acute lung injury and acute respiratory distress syndrome (ARDS)[56]. Some authors use this fact as a caution against absolute denial of IMV for ILD patients, given that some of the data were collected before the publication of the landmark trial in 2000, which demonstrated the mortality benefit of low tidal volume ventilation[13].

There have been studies that looked at the lung mechanics of stable ILD patients and found that based on both static and dynamic lung compliance, the lung is less distensible than normal. Furthermore, it was demonstrated that the elastance of the mechanically ventilated IPF patient was four times higher than even those patients with ARDS[57]. This is further corroborated by retrospective studies that have shown that higher levels of positive end-expiratory pressure have been associated with higher mortality in AE-ILD patients[54].

In conclusion, the outcomes of ILD patients requiring IMV are extremely poor, with cohorts that report up to 100% mortality[58]. As such, the decision to proceed with endotracheal intubation should not be made lightly and should only occur after thoughtful discussion with the patient and family members. In the case of transplant candidates, IMV can be seen as a bridge therapy. Otherwise, early involvement in palliative services are advised.

EXTRACORPOREAL MEMBRANE OXYGENATION

Veno-venous extracorporeal membrane oxygenation (VV ECMO) is presently viewed as a salvage tool in the management of patients with refractory hypoxemic respiratory failure. When the known strategies, such as low-tidal volume ventilation, prone positioning, and neuromuscular blockade, all fail to improve oxygenation and/or refractory acidemia due to impossible ventilation in the capable centers, VV ECMO is often employed. ECMO helps to diminish ventilator-induced lung injury in these patients. There is no consensus recommendation on the use of VV ECMO for ARDS, and the data supporting its use leaves most intensivists with a great deal of uncertainty regarding the degree of and who will benefit[59,60].

There is even less certainty regarding its use in AE-ILD patients. Trudzinski *et al*[61] showed that ECMO is a viable option for patients who are suitable for a lung transplant. However, it should not be offered to those who are not, given that it does not reverse the otherwise poor prognosis faced by patients who are not transplant candidates. In an international poll, roughly 50% of physicians at specialized centers offered ECMO as a bridge to patients who were suitable for transplantation[33]. To summarize, ECMO should be considered for patients with AE-ILD with a clear reversible cause (*e.g.*, infection or pulmonary embolism) or as a bridging therapy for patients appropriate for lung transplant.

LUNG TRANSPLANTATION

ILD, particularly IPF, is now the most common indication for lung transplantation worldwide[62]. The median post-transplant survival for patients with idiopathic interstitial pneumonia, which includes IPF, is 5.2 years and 6.7 years for all other ILDs transplanted between 1992 and 2017[63]. Current guidelines recommend that transplant only be offered to those patients with a > 80% likelihood of 5-year post-transplant survival[64]. There are several relative contraindications to transplant, such as severe psychosocial problems or life-threatening extrapulmonary organ dysfunction. The latter may frequently be encountered in AE-ILD patients who require ICU admission. The need for IMV and/or ECMO for respiratory failure before the transplantation are associated with adverse post-transplant outcomes, which may prevent some of the sickest patients from undergoing transplantation[64]. For those patients who were already listed for transplantation and who experienced an AE, ECMO as a bridge to transplantation could be considered on a case-by-case basis. The emphasis in these patients is to avoid the development of critical illness myopathy and extrapulmonary organ damage. For de novo patients, performing invasive tests like heart catheterization and screening colonoscopies can be perilous. Ultimately, candidacy for an organ transplant will be a decision made in a multidisciplinary fashion incorporating the values of the patient and family, transplant surgeons, and transplant pulmonologists.

PALLIATIVE CARE

Palliative care (PC) medicine specialists are dedicated to improving patient quality of life during serious illnesses. In a recent survey, it was shown that the majority of ILD providers use PC and are comfortable discussing PC with their patients[65]. Given the poor prognosis that ILD patients face when they are admitted to the ICU, it warrants early involvement of PC services. Furthermore, the median life expectancy for all patients with IPF is between 2-7 years, which hastens in the AE setting. The American Thoracic Society/European Respiratory Society guidelines recommend that advanced directives and end-of-life issues be addressed in the ambulatory setting in all patients with IPF[3]. A subset of patients will require ICU level of care due to AE-ILD that was not previously diagnosed and will require more nuanced discussions given the emotional burden of a new, life-limiting diagnosis. In one IPF cohort, it was found that the hospital was the place of death for 80% of the patients, and most of these patients (93%) were hospitalized for an average of 30 d during the last 6 mo of their life. More striking was the statistic that 42% had a do not resuscitate order that was decided upon ≤ 3 d prior to their death[66]. This further confirms the importance of early and thoughtful communication with these patients and their families to ease the emotional and physical suffering they may endure at the end of their lives.

CONCLUSION

Flares or AEs of ILD have feared complications, owing both to their poor prognosis and uncertain management. The mainstay of therapy is supportive care and early recognition of a potentially reversible cause. Immunosuppression plays a role in a subset of patients; however, the optimal dosage and duration have not yet been defined. It behooves the intensivist to trial NIV forms on respiratory support to avoid the highly morbid effects of mechanical ventilation in these patients. The most aggressive therapies, such as IMV and ECMO, should be reserved for those patients who are potential transplant candidates. Early involvement in PC will assist in managing complex discussions and minimize suffering for patients with a high propensity for mortality.

FOOTNOTES

Author contributions: Hayat Syed MK contributed to idea origination, literature review, write-up, and revision; Bruck O and Kumar A contributed to the literature review and write-up; Surani S contributed to idea origination, review, revision, and supervision.

Conflict-of-interest statement: All the authors report having no relevant conflicts of interest for this article.

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S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

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World J Crit Care Med 2023 June 9; 12(3): 165-175

DOI: 10.5492/wjccm.v12.i3.165

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Case Control Study

Causative bacteria of ventilator-associated pneumonia in intensive care unit in Bahrain: Prevalence and antibiotics susceptibility pattern

Mohamed Eliwa Hassan, Safaa Abdulaziz Al-Khawaja, Nermin Kamal Saeed, Sana Abdulaziz Al-Khawaja, Mahmood Al-Awainati, Sara Salah Yusuf Radhi, Mohamed Hameed Alsaffar, Mohammed Al-Beltagi

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ewers A, Austria; Karim HMR, India

Received: December 23, 2022
Peer-review started: December 23, 2022
First decision: January 31, 2023
Revised: February 3, 2023
Accepted: March 24, 2023
Article in press: March 24, 2023
Published online: June 9, 2023

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Abstract

BACKGROUND

Ventilator-associated pneumonia (VAP) is defined as pneumonia that occurs two calendar days following endotracheal intubation or after that. It is the most common infection encountered among intubated patients. VAP incidence showed wide variability between countries.

AIM
To define the VAP incidence in the intensive care unit (ICU) in the central gove-rnment hospital in Bahrain and review the risk factors and the predominant bacterial pathogens with their antimicrobial susceptibility pattern.

METHODS
The research was a prospective cross-sectional observational study over six months from November 2019 to June 2020. It included adult and adolescent patients (> 14 years old) admitted to the ICU and required intubation and mechanical ventilation. VAP was diagnosed when it occurred after 48 h after endotracheal intubation using the clinical pulmonary infection score, which considers the clinical, laboratory, microbiological, and radiographic evidence.

RESULTS
The total number of adult patients admitted to the ICU who required intubation and mechanical ventilation during the study period was 155. Forty-six patients developed VAP during their ICU stay (29.7%). The calculated VAP rate was 22.14 events per 1000 ventilator days during the study period, with a mean age of 52 years ± 20. Most VAP cases had late-onset VAP with a mean number of ICU days before the development of VAP of 9.96 ± 6.55. Gram-negative contributed to most VAP cases in our unit, with multidrug-resistant Acinetobacter being the most identified pathogen.

CONCLUSION
The reported VAP rate in our ICU was relatively high compared to the international benchmark, which should trigger a vital action plan for reinforcing the implementation of the VAP prevention bundle.

Key Words: Ventilator-associated pneumonia; Intensive care unit; Antibiotics susceptibility pattern; Kingdom of Bahrain; Adults; Bacterial resistance; Acinetobacter

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Core Tip: Ventilator-associated pneumonia (VAP) is the most common infection among intubated patients. Early-onset VAP is usually caused by sensitive pathogens, while multidrug-resistant bacteria usually cause late-onset. Early, appropriate, and empirical antibiotics therapy for VAP is crucial to decreasing mortality risk. The VAP rate in Bahrain is relatively high compared to the international rates, which should trigger a vital action plan for reinforcing the implementation of the VAP prevention bundle. Gram-negative bacteria were the most common organisms that cause VAP in the current study, where *Acinetobacter baumannii* was the most common organism, followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Knowing the prevalent organisms helps choose the appropriate antibiotics until culture and sensitivity become available.

Citation: Hassan ME, Al-Khawaja SA, Saeed NK, Al-Khawaja SA, Al-Awainati M, Radhi SSY, Alsaffar MH, Al-Beltagi M. Causative bacteria of ventilator-associated pneumonia in intensive care unit in Bahrain: Prevalence and antibiotics susceptibility pattern. *World J Crit Care Med* 2023; 12(3): 165-175
URL: https://www.wjgnet.com/2220-3141/full/v12/i3/165.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i3.165

INTRODUCTION

Ventilator-associated pneumonia (VAP) is defined as pneumonia that occurs two calendar days following endotracheal intubation or after that. It is the most common infection encountered among intubated patients[1]. It occurs in 10%-30% of mechanically ventilated patients[2-4]. The VAP incidence showed wide variability, ranging from 10 to 41.7 per 1000 ventilator days in developing countries[5], while the rate is much lower in developed countries ranging between 1.2 and 8.5 per 1000 ventilator days[6].

Early-onset VAP is defined as pneumonia that occurs within four days of endotracheal intubation. It is usually attributed to sensitive pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and methicillin-sensitive *Staphylococcus aureus*. In contrast, late-onset VAP emerges after four days of intubation. It is caused by multidrug-resistant (MDR) bacteria such as methicillin-resistant *S. aureus* (MRSA), *Acinetobacter*, *Pseudomonas aeruginosa*, and extended-spectrum beta-lactamase-producing

bacteria. VAP caused by fungal and viral pathogens has a low contribution and tend to occur among immunocompromised host[5].

The risk for VAP is most significant during the first five days after intubation (3%), with the mean duration between intubation and development of VAP being 3.3 d. This risk declines to 2%/d between days 5 to 10 of ventilation and 1%/d after that[7]. Many previous studies showed that the related mortality for VAP ranges between 33%–50%, but this rate fluctuates and depends heavily on the underlying medical illness[5]. The diagnosis of VAP in the intensive care unit (ICU) remains challenging due to the absence of universally accepted gold-standard diagnostic criteria for VAP[8]. The clinical pulmonary infection score (CPIS) is one of the best diagnostic tools considering the clinical, physiological, microbiological, and radiographic evidence to allow a numerical value to predict the presence or absence of VAP[9,10].

Early, appropriate, and empirical antibiotics therapy for VAP is crucial as any delay in initiating proper antibiotics may increase the mortality risk with VAP. Consequently, selecting the appropriate regimen should be guided by the updated local antibiogram for each hospital and ICU. This study aimed to define VAP incidence in the ICU at Salmaniya Medical Complex, Bahrain's leading tertiary care government hospital. The study also reviewed the risk factors and the predominant pathogens that cause VAP, which helps choose the appropriate empiric antimicrobial therapy for VAP-related sepsis in adult ICU.

MATERIALS AND METHODS

The study was a prospective, observational, cross-sectional study conducted at the adult ICU in Salmaniya Medical Complex from November 2019 to June 2020 to determine the microbiological profile of adult patients with VAP and evaluate the magnitude of MDR microbes among those patients. We used patients who needed mechanical ventilation and did not develop VAP as a control group. The Research and Ethics Committee at Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain, approved the study. We did not collect consent, as the study was observational, without exposure to any personal data.

Sample size and inclusion criteria

We did not determine a preset sample size as we included all the patients admitted to the adult ICU during the study periods (November 2019-June 2020) when they met the inclusion criteria. We included adult and adolescent patients (> 14 years old) who were admitted to the ICU and required intubation and mechanical ventilation.

Diagnostic criteria of VAP

VAP was diagnosed when it occurs after 48 h after endotracheal intubation and mechanical ventilation based on the scoring system by using the CPIS, considering the clinical, laboratory, microbiological, and radiographic evidence to allow a numerical value to predict the presence or absence of VAP[7,11-13] as summarized in Table 1. We considered the VAP as early-onset when it occurred in the first four days following intubation and late-onset after the fourth day of intubation.

The laboratory parameters (leukocyte count and microbial profile) were obtained daily from the patient's laboratory data and documented in the study datasheets. The treating clinical teams assessed the radiological finding and oxygenation status. Temperature documentation and assessment of tracheal secretions were obtained from the assigned nurses' notes, which are part of their daily assessment of intubated patients. All culture reports were reviewed by the medical microbiologist and infectious diseases (ID) consultant. A summative score was calculated for each patient enrolled in the study. The scores range between 0 and 12, with a score of ≥ 6 showing a good correlation with the presence of VAP.

Microbiology

The microbial profile of endotracheal specimens isolated from the enrolled patients was identified as part of CPIS diagnostic criteria. Positive cultures (aerobic, anaerobic, and/or fungal) were further analyzed by full antibiotics sensitivity pattern with identification of MDR according to the standard definition of the Clinical Laboratory Standards Institute[14]. The medical microbiologist and the ID consultants reviewed all microbial data.

Calculation of VAP rate

VAP rate was calculated as a percentage of patients who developed VAP out of all intubated patients in the ICU during the study period.

VAP rate per 1000 ventilator days was also calculated according to the centers for disease control and prevention surveillance formula[15] by dividing the VAP cases (defined by CPIS ≥ 6) over the patient-ventilator days during the same period and multiplying by 1000.

Table 1 The clinical pulmonary infection score

Assessed parameter	Result	Score
Temperature (°Celsius)	36.5–38.4 °C	0
	38.5–38.9 °C	1
	≤ 36 or ≥ 39 °C	2
Leukocytes in blood (cells/mm^3)	4000–11000/mm^3	0
	< 4000 or > 11000/mm^3	1
	≥ 500 band cells	2
Tracheal secretions (subjective visual scale)	None	0
	Mild/non-purulent	1
	Purulent	2
Radiographic findings (on chest radiography, excluding CHF and ARDS)	No infiltrate	0
	Diff use/patchy infiltrate	1
	Localized infiltrate	2
Culture results (endotracheal aspirate)	No or mild growth	0
	Moderate or florid growth	1
	Moderate or florid growth and pathogen consistent with gram stain	2
Oxygenation status	> 240 or ARDS	1
	≤ 240 and absence of ARDS	2

CHF: Congestive heart failure; ARDS: Acute respiratory distress syndrome.

Risk factors and complications

To analyze the predisposing factors for VAP and the risk of complications, we evaluated the following variables among all enrolled patients and compared between the two groups: The VAP patients (case group) and non-VAP patients (control group) such as age, gender, presence of comorbidities, source of admission, and the number of ICU days before intubation, the outcome including the mortality, development of complication and the need for tracheostomy.

Statistical analysis

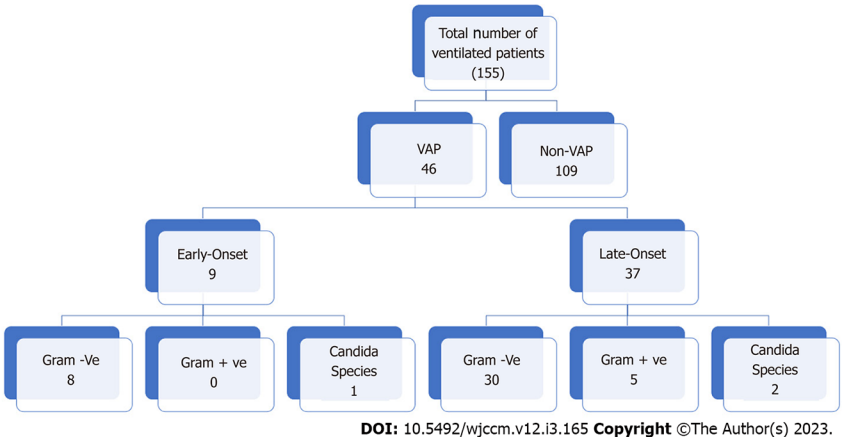
We performed a descriptive analysis, expressing the categorical variables in numbers and percentages and the quantitative variables in means and standard deviations. We compared the categorical variables as appropriate, using the χ^2 test or Fisher's exact test (when the expected n is less than 5). In addition, we used the *t*-test or Mann-Whitney U test to compare continuous variables. Statistical significance was established at 95% ($P < 0.05$). All statistical analyses were performed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY).

Ethical clearance

The investigation followed the latest version of the Declaration of Helsinki and was approved by the Secondary Research Committee of Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain. We did not get consent from the patients as it was a descriptive non-interventional study without disclosure of any patients' data.

RESULTS

Figure 1 shows the flow chart of the study. The total number of adult patients admitted to the ICU who required intubation and mechanical ventilation during the study period was 155. Forty-six patients developed VAP during their ICU stay (29.7%), with a VAP rate of 22.14 events per 1000 ventilator days. The mean age of patients who developed VAP was 52 ± 20 (range 27–88 years.), and 32 were male (69.6%). The mean number of ICU days before VAP development was 9.96 ± 6.55 d. Most VAP cases were late-onset, with a mean time interval between intubation and VAP diagnosis of 11.37 ± 6.67 d.



DOI: 10.5492/wjccm.v12.i3.165 **Copyright** ©The Author(s) 2023.

Figure 1 The flow chart of the study. VAP: Ventilator-associated pneumonia.

Thirty-seven cases (80.4%) were late-onset VAP that was developed after 96 h from intubation, while 9 cases (19.6%) were early-onset VAP (developed within initial 96 d post-intubation). The most common comorbidities among VAP cases were diabetes mellitus and hypertension (19 patients, 41.3 % of VAP cases). Other identified comorbid conditions include chronic kidney disease (7, 15.2%), ischemic heart disease (6, 13%), and neurological disorder (5, 10.9%). Less identified comorbidities included malignancy (4, 8.7%), chronic liver disease (3, 6.5%), and sickle cell disease (3, 6.5%).

Table 2 showed no statistically significant difference between VAP and non-VAP groups regarding age, sex, and the number of hospital or ICU stays before intubation. Hypertension was the only significant risk factor for VAP acquisition among ICU intubated patients regarding the underlying comorbidities. Complications differ significantly among the VAP and non-VAP groups, where the duration of mechanical ventilation and the length of ICU stay were significantly higher in the VAP group ($P = 0.009$, < 0.001, respectively).

The rate of septic shock, acute respiratory distress syndrome (ARDS), and acute kidney injury was significantly higher in the VAP group than in the non-VAP group. On the other hand, the rate of pneumothorax did not show a significant difference between both groups. Notably, the extubation failure and the rate of tracheostomy and reintubation among extubated patients were significantly higher among the VAP group than in non-VAP groups. The overall ICU mortality rate was 22.6% (35/155) in all mechanically ventilated patients. However, there was no significant difference in mortality between both groups.

Table 3 shows the most common organisms isolated from patients with VAP. The total number of isolates was 46. Twenty percent of the isolates were from early-onset VAP, while 80% were from late-onset VAP. About 58.7% of the total isolates showed MDR. In early-onset VAP, gram-negative bacteria formed 89% of the total isolates (75% were MDR), followed by candida (11%). No gram-positive isolates were detected. *Acinetobacter baumannii* was the most common isolated gram-negative bacteria (50%); all were MDR. *Klebsiella pneumoniae* was the second most common gram-negative bacteria (37.5%) isolated; two-thirds were MDR. In late-onset VAP, gram-negative bacteria formed 81% of the total isolates (70% were MDR), followed by gram-positive (13.5%) and candida (5.4%). *Acinetobacter baumannii* was the most common isolated gram-negative bacteria (50%); 93% were MDR. *Klebsiella pneumoniae* was the second most common gram-negative bacteria (16.6%) isolated; all were MDR. *Pseudonomas aeruginosa* was detected in 8% of late-VAP, 33% of them were MDR. We detected only one MRSA isolate in the samples collected from VAP (20% of all five gram-positive isolates). We also detected candida in 2 cases with late-onset VAP (5.4%).

Tables 4 and 5 showed the antibiotic susceptibility among the bacterial isolates from patients with VAP. *Acinetobacter baumannii,* which was the most common organism isolated from VAP, had 100% susceptibility to Colistin, 37% susceptibility to Trimethoprim/sulfamethoxazole, Gentamicin, and Amikacin, 21% susceptibility to Tigecycline, low susceptibility (5%) to Ciprofloxacin, Piperacillin-Tazobactam, Cefepime, Meropenem, Imipenem, and Ertapenem, and resistance to Levofloxacin. *Klebsiella pneumonia,* which was the second most common organism isolated from VAP, had 87.5% susceptibility to Tigecycline, 62.5% susceptibility to Colistin, 50% susceptibility to Trimethoprim/sulfamethoxazole, 37% susceptibility to Gentamicin, and Amikacin, 12.5% susceptibility to Levofloxacin, Cefepime, Meropenem, Imipenem, Ertapenem, Amoxiclav, Cefuroxime, and Ceftriaxone. However, it showed complete resistance to Ceftazidime and Piperacillin-Tazobactam. *Stenotrophomonas maltophilia* had 100% susceptibility to Trimethoprim/sulfamethoxazole, Levofloxacin, and Minocycline. It had 20% susceptibility to Ceftazidime. At the same time, *Pseudomonas aeruginosa* had 100% susceptibility to Ceftazidime, Piperacillin-Tazobactam, Cefepime, Colistin, Gentamicin, Amikacin, and Ciprofloxacin, 66.6% susceptibility to Meropenem, Imipenem, and Ertapenem. MRSA was 100% susceptible to Erythromycin, Clindamycin, Tetracycline, and Vancomycin.

Table 2 Comparison between ventilator-associated pneumonia and non-ventilator-associated pneumonia groups for risk factors and complications, *n* (%)

Risk factors and complications		VAP group, *n* = 46	Non-VAP group, *n* = 109	*P* value
Age, mean ± SD		52.74 ± 20.42	61.45 ± 65.05	> 0.5
Sex, males%		32 (69.57)	73 (66.97)	> 0.5
Number of hospital days before intubation, mean ± SD		5.39 ± 8.11	3.38 ± 6.37	> 0.5
Number of ICU days before intubation, mean ± SD		0.52 ± 1.94	0.47 ± 2.78	> 0.5
Presence of comorbidities	Diabetes mellitus	19 (41.30)	54 (49.54)	> 0.5
	Hypertension	19 (41.30)	67 (61.47)	> 0.5
	Chronic kidney disease	7 (15.22)	28 (25.69)	> 0.5
	Ischemic heart disease	6 (13.04)	25 (22.94)	> 0.5
	Neurological disorder	5 (10.87)	9 (8.26)	> 0.5
	Malignancy	4 (8.70)	3 (2.75)	> 0.5
	Liver disease	3 (6.52)	8 (7.34)	> 0.5
	Sickle cell disease	3 (6.52)	3 (2.75)	> 0.5
Hospital course	Length of ICU stay, mean ± SD	21.41 ± 11.89	11.01 ± 10.38	< 0.001[a]
	Duration of mechanical ventilation, mean ± SD	16.67 ± 8.70	12.03 ± 10.53	0.009[a]
	Extubation	18 (39.13)	79 (72.48)	< 0.001[a]
	Need of re-intubation	12 (26.09)	11 (10.09)	0.014[a]
	Tracheostomy	14 (30.43)	9 (8.26)	< 0.001[a]
Potential complication	Septic shock	28 (60.87)	31 (28.44)	< 0.001[a]
	ARDS	15 (32.61)	12 (11.01)	0.002[a]
	Acute kidney injury	24 (52.17)	36 (33.03)	0.031[a]
	Pneumothorax	1 (2.17)	2 (1.83)	> 0.5
	Mortality, deaths	14 (30.43)	21 (19.27)	> 0.5

[a]Means significant.

ARDS: Acute respiratory distress syndrome; VAP: Ventilator-associated pneumonia; ICU: Intensive care unit.

DISCUSSION

The Incidence of VAP among intubated patients in the current study was 29.7%; this figure is comparable to the incidence reported by other investigators in the developing region (15%–58%)[16,17]. The calculated VAP rate was 22.14 events per 1000 ventilator days which is high compared to the international standards[18] and to the rate reported by neighboring countries of the Gulf Cooperation Council, which reported a VAP rate of 4.8 per 1000 ventilator days[19]; but our rate was comparable to most data reported by other developing countries[20,21].

Such high incidence should trigger a vital action plan to reinforce healthcare workers' adherence to the recommended preventive VAP bundle.

The current study showed that age and gender were not essential risk factors for VAP development. This agrees with a recently published study by Zubair *et al*[22] in 2018, which demonstrated that age or gender was not a significant risk factor in developing VAP[22]. However, this finding contradicts many previous studies that defined age and gender as important independent risk factors in developing VAP [23-26].

The current study agrees with other previously published studies that VAP development significantly increases the need for re-intubation and tracheostomy and the risk of systemic complications such as septic shock, ARDS, and acute kidney injury, in addition to increasing the duration of mechanical ventilation and length of ICU stay in patients admitted to ICU[27]. Nevertheless, VAP was not a significant risk factor for the increased mortality rate among intubated patients. This finding agreed with other previously published studies, which noted that the mortality risk was not significantly high in VAP presence[27,28]. In the current study, gram-negative bacteria were the most common organisms that cause VAP, whereas *Acinetobacter baumannii* was the most common organism

Table 3 Most common organisms isolated among patients with ventilator-associated pneumonia, *n* (%)

Organism	Total	Early-onset VAP (Number 9)		Late-onset VAP (Number 37)	
		Number (of total)	MDR	Number (of total)	MDR
Total gram negative	38 (82.6)	8 (21)	6 (75)	30 (79)	21 (70)
Acinetobacter baumannii	19 (50)	4 (21)	4 (100)	15 (79)	14 (93)
Klebsiella pneumoniae	8 (21.1)	3 (37.5)	2 (66.6)	5 (62.5)	5 (100)
Pseudomonas aeruginosa	3 (9)	0	0	3 (100)	1 (33.3)
Stenotrophomonas maltophilia	5 (13.1)	0	0	5 (100)	0
Enterobacter asburiae	1 (2.6)	1 (100)	0	0	0
E coli	1 (2.6)	0	0	1	1 ESBL (100)
Hemophilus influenzae	1 (2.6)	0	0	1 (100)	0
Total gram positive	5 (11)	0	0	5 (100)	
Staph aureus	4 (80)	0	0	4 (100)	0
MRSA	1 (20)	0	0	1 (100)	0
	0	0	0	0	0
	0	0	0	0	0
Fungal infection					
Candida species	3 (100)	1 (33.3)	0	2 (66.6)	0
Total microorganisms	46 (100)	9 (19.6)	6 (13)	37 (80.4)	

VAP: Ventilator-associated pneumonia; MDR: Multidrug-resistant; ESBL: Extended spectrum beta-lactamase; MRSA: Methicillin-resistant *staphylococcus aureus*.

Table 4 Antibiotics sensitivity percentage of the common gram-positive causative organisms for patients with ventilator-associated pneumonia in our study, *n* (%)

Antimicrobial agent	MSSA, *n* = 4	MRSA, *n* = 1
Penicillin	0/4 = 0 (0)	0/1 = 0 (0)
Oxacillin	4 (100)	0/1 = 0 (0)
Erythromycin	4 (100)	1 (100)
Clindamycin	4 (100)	1 (100)
Tetracycline	4 (100)	1 (100)
Vancomycin	4 (100)	1 (100)

MSSA: Methicillin-sensitive *staphylococcus aureus*, MRSA: Methicillin-resistant *staphylococcus aureus*.

(50% of all VAP cases). This finding agrees with Ben Lakhal *et al*[29], who had 53% of their cases caused by *Acinetobacter baumannii*[29]. Staph aureus was the causative organism in 11% of all recorded VAP cases in our study, all isolated from late-onset VAP. However, this rate is much lower than in previous studies such as Jones[30] and Chi *et al*[31], who found that *Staphylococcus aureus* was the most common VAP-causing organism, followed by the gram-negative organism[30,31]. The increased prevalence of gram-negative over gram-positive organisms may indicate the changing pattern of the nosocomial infection's microbial profile, including VAP in our region. Unfortunately, we did not have previous studies in our country to compare.

In the current study, *Acinetobacter baumannii* was the most common organism isolated from patients with VAP, with a rate of 44.4% in patients with early-onset VAP (93% MDR) and 40.5% in patients with late-onset VAP (100% MDR). *Acinetobacter baumannii* is an opportunistic pathogen with a high incidence among immunocompromised individuals, particularly those who have experienced a prolonged hospital stay. It is *commonly* associated with high humidity, colonizing the skin, and isolated in high numbers from infected individuals' respiratory and oropharynx secretions[32]. Previous studies showed

Table 5 Antibiotics sensitivity percentage of the common gram-negative causative organisms for ventilator-associated pneumonia in our study, *n* (%)

Antimicrobial agent	*Acinetobacter baumannii*	*Klebsiella pneumoniae*	*Stenotrophomonas maltophilia*	*Pseudomonas aeruginosa*
Number of organisms	19 (50)	8 (42)	5 (26)	3 (16)
Ceftazidime	1 (5.2)	0	1 (20)	3 (100)
Trimethoprim/sulfamethoxazole	7 (37)	4 (50)	5 (100)	-
Levofloxacin	0	1 (12.5)	5 (100)	-
Minocycline	-	-	5 (100)	-
Piperacillin-tazobactam	1 (5.2)	0	-	3 (100)
Cefepime	1 (5.2)	1 (12.5)	-	3 (100)
Meropenem	1 (5.2)	1 (12.5)	-	2 (66.6)
Imipenem	1 (5.2)	1 (12.5)	-	2 (66.6)
Ertapenem	1 (5.2)	1 (12.5)	-	2 (66.6)
Colistin	19 (100)	5 (62.5)	-	3 (100)
Gentamicin	7 (37)	3 (37.5)	-	3 (100)
Amikacin	7 (37)	3 (37.5)	-	3 (100)
Ciprofloxacin	1 (5.2)	1 (12.5)	-	3 (100)
Tigecycline	4 (21)	7 (87.5)	-	-
Ampicillin	-	-	-	-
Amoxiclav	-	1 (12.5)	-	-
Cefuroxime	-	1 (12.5)	-	-
Ceftriaxone	-	1 (12.5)	-	-

that *Acinetobacter baumannii* is prevalent and even endemic in many Middle East and North African countries. A study from Tunisia showed that *Acinetobacter baumannii* caused 45% of ICU-related infections with an MDR-resistance rate of 39% during an epidemic from 2004 to 2005[33]. Another study from Saudi Arabia showed that *Acinetobacter baumannii* was the most common organism isolated from late-onset VAP, causing 26.65% of cases[34]. In our *Acinetobacter baumannii* isolates, the overall MDR rate was 95% (100% and 93% in early-onset and late-onset VAP, respectively). Our institute considers *Acinetobacter baumannii* a "red alert" human pathogen due to the high rate of MDR with almost resistance to all antibiotics except for Colistin. It becomes a cause for serious concern regarding nosocomially acquired infections[35].

Klebsiella pneumoniae was the second most common organism isolated from our patients, with a rate of 17.4% throughout the study with an MDR rate of 87.5%. We detected *Klebsiella pneumoniae* in 33.3% of patients with early-onset VAP (66.6% MDR) and 13.5 % in patients with late-onset VAP (100% MDR). Our results agree with the work from Iran by Bozorgmehr *et al*[36], which showed that *Klebsiella pneumoniae* was the second most common organism isolated from 29.82% of the patients with VAP after *Acinetobacter baumannii*[36]. Our results also agree with the finding observed from a Thailand study that found that *Klebsiella pneumoniae* was the second most common organism isolated from 17.3% of the patients with VAP after *Acinetobacter baumannii*[37]. However, a study from Egypt in 2020 showed that *Klebsiella* spp was the most frequently isolated microorganism, followed by *Pseudomonas aeruginosa* and *Acinetobacter baumannii*[38].

The guidelines for initial empiric antimicrobial therapy for VAP are highly dependent on the type of causative pathogen and the time of diagnosis. Knowing the prevalent organisms helps choose the appropriate antibiotics until culture and sensitivity are available. However, the development of rapid identification technologies and phenotypic methods would significantly help the proper choice to improve the treatment outcomes for VAP. As many hospitals may lack rapid identification technologies, knowing the most common bacterial types causing VAP and their antibiogram may help physicians make quick decisions in VAP management.

Limitations of the study

As the study was a single center-based study in the adult population, this may hinder us from generalizing the data to other public or private hospital settings and the pediatric population. However,

despite the study's limitation, it can provide valuable data concerning the incidence rates and the prevalence of VAP in Bahrain, reflecting the rest of the Arabian Gulf region's status.

CONCLUSION

VAP is a common serious complication among intubated patients in our ICU; our VAP rate is relatively high compared to the international benchmark, which should trigger a vital action plan for reinforcing the implementation of the VAP prevention bundle. Gram-negative bacteria were the most common organisms that cause VAP in the current study, where *Acinetobacter baumannii* was the most common organism, followed by *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Knowing the prevalent organisms helps choose the appropriate antibiotics until culture and sensitivity become available.

ARTICLE HIGHLIGHTS

Research background

Ventilator-associated pneumonia (VAP) is the most common infection encountered among intubated patients, occurring in 10%-30% of mechanically ventilated patients.

Research motivations

The lack of data from the Kingdom of Bahrain stimulated us to investigate VAP incidence, risk factors, and microbial profiles in the central hospital in the kingdom.

Research objectives

We aimed to define VAP incidence in the intensive care unit (ICU) at Salmaniya Medical Complex and review the risk factors and the predominant pathogens that cause VAP to choose the appropriate empiric antimicrobial therapy for VAP-related sepsis in adult ICU.

Research methods

The study was a prospective, observational, cross-sectional study done between November 2019 to June 2020 to determine the microbiological profile in adult patients with VAP and evaluate the magnitude of multidrug-resistant (MDR) microbes among those patients. We used patients who needed mechanical ventilation and did not develop VAP as a control group. We included adult and adolescent patients (> 14 years old) who were admitted to the ICU and required intubation and mechanical ventilation.

Research results

The incidence of VAP was 29.7% during the study period, with a calculated VAP rate of 22.14 events per 1000 ventilator days and a mean age of 52 years ± 20. Most VAP cases had late-onset VAP with a mean number of ICU days before the development of VAP of 9.96 ± 6.55. Gram-negative contributed to most VAP cases in our unit, with MDR Acinetobacter being the most identified pathogen.

Research conclusions

The VAP rate in our ICU was relatively high compared to the international benchmark.

Research perspectives

The high VAP rate in our hospital triggered us to initiate a vital action plan to reinforce the implementation of the VAP prevention bundle.

ACKNOWLEDGEMENTS

We thank the anonymous referees for their valuable suggestions.

FOOTNOTES

Author contributions: Hassan ME, Al-Khawaja S, and Radhi SSY designed the study; Hassan ME, Radhi SSY, Al-Awainati M, and Alsaffar M collected and analyzed data; Saeed NK performed microbiological testing, data, and analysis; Hassan ME wrote the manuscript draft; Al-Beltagi M wrote, revised, and edited the final draft; All authors have read and approved the manuscript and take full responsibility for the study.

Institutional review board statement: The study was ethically approved by the Research and Research Ethics Committee for Governmental Hospitals, Salmaniya Medical Complex, Bahrain.

Informed consent statement: Consent was unnecessary as the study was observational without exposure to the patient's data.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at mbelrem@hotmail.com. Participants gave informed consent for data sharing. No additional data are available.

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S-Editor: Li L
L-Editor: A
P-Editor: Li L

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World Journal of Critical Care Medicine

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World J Crit Care Med 2023 June 9; 12(3): 176-187

DOI: 10.5492/wjccm.v12.i3.176

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Observational Study

Knowledge and awareness of infection control practices among nursing professionals: A cross-sectional survey from South Asia and the Middle East

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bittner EA, United States; Marano L, Italy; Roilides E, Greece

Received: April 14, 2023
Peer-review started: April 14, 2023
First decision: May 9, 2023
Revised: May 15, 2023
Accepted: May 31, 2023
Article in press: May 31, 2023
Published online: June 9, 2023

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Abstract

BACKGROUND

The proficiency of nursing professionals in the infection prevention and control (IPC) practices is a core component of the strategy to mitigate the challenge of healthcare associated infections.

AIM

To test knowledge of nurses working in intensive care units (ICU) in South Asia and Middle East countries on IPC practices.

METHODS

An online self-assessment questionnaire based on various aspects of IPC practices was conducted among nurses over three weeks.

RESULTS

A total of 1333 nurses from 13 countries completed the survey. The average score was 72.8% and 36% of nurses were proficient (mean score > 80%). 43% and 68.3% of respondents were from government and teaching hospitals, respectively. 79.2% of respondents worked in < 25 bedded ICUs and 46.5% in closed ICUs. Statistically, a significant association was found between the knowledge and expertise of nurses, the country's per-capita income, type of hospitals, accreditation and teaching status of hospitals and type of ICUs. Working in high- and upper-middle-income countries (β = 4.89, 95%CI: 3.55 to 6.22) was positively associated, and the teaching status of the hospital (β = -4.58, 95%CI: -6.81 to -2.36) was negatively associated with the knowledge score among respondents.

CONCLUSION

There is considerable variation in knowledge among nurses working in ICU. Factors like income status of countries, public *vs* private and teaching status of hospitals and experience are independently associated with nurses' knowledge of IPC practices.

Key Words: Knowledge; Attitude; Policy compliance; Infection control; Infection control practices; Nurses

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Core Tip: The knowledge testing on infection prevention and control (IPC) practices among intensive care unit nurses in South Asia and the Middle East showed considerable variation. The higher economic status of the country and working experience were independently associated with better knowledge among respondents. Working in public or teaching hospital were inversely associated with knowledge of IPC practices. There is an urgent need for education and awareness among nurses regarding IPC practices, especially in lower-middle-income countries.

Citation: Sodhi K, Chanchalani G, Arya M, Shrestha GS, Chandwani JN, Kumar M, Kansal MG, Ashrafuzzaman M, Mudalige AD, Al Tayar A, Mansour B, Saeed HM, Hashmi M, Das M, Al Shirawi NN, Mathias R, Ahmed WO, Sharma A, Agarwal D, Nasa P. Knowledge and awareness of infection control practices among nursing professionals: A cross-sectional survey from South Asia and the Middle East. *World J Crit Care Med* 2023; 12(3): 176-187

URL: https://www.wjgnet.com/2220-3141/full/v12/i3/176.htm

DOI: https://dx.doi.org/10.5492/wjccm.v12.i3.176

INTRODUCTION

Healthcare-associated infections (HAI) pose a considerable threat to the patients who are admitted in hospitals, especially in intensive care units (ICU). According to the surveillance report published by the International Nosocomial Infection Control Consortium, despite appreciable efforts on prevention and control of HAI, the Device-Associated (DA)-HAI rates in the ICUs of developing countries are higher compared to the developed nations[1]. Though the device utilization rate is similar, the DA-HAI rates of the ICUs in the developing countries remain higher than the ones belonging to the Center for Disease Control and Prevention- National Healthcare and Safety Network[1,2]. Hence, a robust infection prevention and control (IPC) program involving multi-disciplinary stakeholders is essential to mitigate the threat of HAI[3]. However, the compliance with IPC practices has been a critical implication on the implementation of the IPC program. Nurses have frequent and direct contact with the patients due to which, their knowledge and awareness about the IPC practices are integral[4]. On the other hand, the nurses are also at-risk of self-infection when providing care to critically ill patients[5]. Several factors may affect the compliance with IPC practices, prominent of which are knowledge, education and training, and the experience of nurses[6]. The lack of knowledge among health care workers (HCWs) about the IPC practices or the occurrence of discrepancies when applying this knowledge in bedside has been linked to worsening healthcare delivery outcomes, especially in case of developing countries[6-8]. Recently, the global experts have recommended that the ICU nurses should be a part of the surveillance team that monitor adherence of IPC practices[9].

The countries in South Asia and the Middle East regions constitute one-third of the global population. In spite of such common neighborhoods and centuries of cultural and political exchange, these countries exhibit vast differences in terms of income, availability of the resources and healthcare dynamics[10].

Though studies have been conducted to evaluate the knowledge of the nurses from individual nations, the authors were unable to find any literature that compares the knowledge of the nurses across the South Asian and Middle Eastern nations[8,11,12]. So, the current study is aimed to analyse the knowledge of ICU nurses on various aspects of IPC practices across the countries in South Asia and the Middle East.

MATERIALS AND METHODS

The study was conducted over three weeks, from April 20 to May 10, 2022. An online-based, cross-sectional survey was conducted using a multiple-choice questionnaire to evaluate the knowledge of nurses on various aspects of the IPC program. A 20-member steering committee comprising of critical care physicians, infection control professionals, microbiologist and the nursing administrator was involved in framing the questionnaire and its pilot run. The questionnaire was examined, revised and validated internally among the steering committee. Internal consistency among the questionnaire items using Cronbach's alpha (α) was found to be 0.90, which was considered within the acceptable range. The study was approved by the Ethics Committee (DHEC-2057/2022) of the institute, where the principal investigator (Kanwalpreet Sodhi) is affiliated and is exempted from other participating hospitals.

The final questionnaire has two portions in which the first portion covered the aspects like country name, profile of the hospital such as the type of setup, hospital accreditation and their teaching status, the type, size and the operating model of the ICU, and the nurses' demographic data including their years of clinical experience. The operating model of the ICU had three options such as "Open ICU" in

which the patients are admitted under the care of a non-intensivist physician, with the intensivists providing their expertise consultation when required, "Closed ICU" in which the patients are admitted under an intensivist-led team, and is held responsible for the primary care, and "Semi-closed ICU" in which the intensivist-led team provides direct patient care in collaboration with the non-intensivist physicians with shared decision making[13]. The second portion of the questionnaire consisted of 25 single best response types, *i.e.*, multiple choice questions (MCQ) on different aspects of the IPC practices, categorized under five sections such as the general aspects of infection control, standard precautions, transmission-based precautions, care bundles, and severe acute respiratory syndrome coronavirus 2 transmission (Appendix). Each section had five MCQs, and respondents can score one mark for a correct response. The answers to the MCQs were decided *a priori* by the steering committee members (Kanwalpreet Sodhi, Muktanjali Arya Amandeep Sharma, Prashant Nasa). The knowledge level was categorized based on the mean overall score, secured by the participants, *i.e.*, more than 81% score as proficient, 61%-80% as above average, 41%-60% as average and less than 40% as poor knowledge (Table 1).

The survey was conducted using a web link circulated by the steering committee members of the respective participant countries. The study included around 4-5 tertiary care hospitals from each country. The questionnaire was distributed to the nurses who work full-time in ICUs, and they were asked to fill it anonymously and voluntarily. The nurse trainees were excluded from the study. The consent for participation in the study and the publication of the results was obtained from the respondents at the beginning of the online questionnaire. The STROBE checklist was used for reporting the results of this cross-sectional survey.

Statistical analysis

The data was described in terms of frequencies (number of cases) and relative frequencies (percentages) as appropriate. In order to compare the categorical data, the chi-square (χ^2) test was used. Both univariate and multivariate linear regression analyses were conducted to compare the covariates. A probability value (P value) less than 0.05 was considered to be statistically significant. The outcome variable for the linear regression analysis was the total score secured from the questionnaire and no continuous data sets were present. Collinearity was checked for each predictor variable whereas non-linear regression underwent the same analysis and yielded the same conclusions. (Appendix) Those variables obtaining a P value < 0.05 in the univariate analysis, were included in the multivariate linear regression analyses. The beta coefficient and the confidence intervals were used to present of the multivariate linear regression analysis. All the statistical calculations were done using (Statistical Package for the Social Science) SPSS version 21 (SPSS Inc., Chicago, IL, United States) statistical program for Microsoft Windows.

RESULTS

The questionnaire was filled out by 1376 nurses across 13 countries. Out of the total responses, 43 were excluded from the final analysis (11 with negative consent for participation, and 32 had missing information). The data from 1333 respondents (nurses) was considered for the study (Figure 1).

The demographic profile of the respondents' hospitals and the ICUs is provided in Table 2. For analysis, the countries of the respondents were divided according to the World Bank income classification criteria into high-income countries (HIC) (such as Bahrain, the United Arab Emirates, Oman, Qatar, Saudi Arabia, and Singapore); upper-middle-income countries (UMIC) (*i.e.*, Lebanon); and lower-middle-income countries (LMIC) (such as Bangladesh, Bhutan, India, Sri Lanka, Nepal, and Pakistan). Most of the respondents belong to HIC (608, 45.6%) and LMIC (656, 49.2%). The respondents had varying level of experience, with 232 (17.4%) nurses having less than two years of experience and 396 (29.7%) nurses with more than ten years of experience. Among the responding nurses, 524 (39%) worked in corporate or private hospitals, whereas 570(43%) were in public hospitals. Most of the respondents worked in a hospital, accredited either by an international agency like Joint Commission International (606, 45.5%), or a national level agency (442, 33.2%). Further, majority of the respondents (1056, 79.2%) were working in less than 25-bedded ICUs and 607 (45%) were in mixed medical and surgical ICUs. In terms of the operational model of ICU, 620 (46.5%) respondents were working in closed ICUs and nearly equal proportion (27%) were in open and semi-closed ICUs. Further most of the respondents (911, 68.3%) worked in teaching hospitals.

The average score of the respondents was 72.8% (Figure 2). In terms of knowledge level categories, 480 (36%) respondents were categorized as proficient, and 472 (35.4%) had above-average knowledge. Only 11% of the respondents with less than two years of experience, were found to be proficient, compared to 34% respondents who had 5-10 years of experience. The knowledge of 32% of nurses with > 10 years of experience was above average, compared to 18% nurses with < 2 years of experience (Table 1). A statistically significant difference was found between the respondents on knowledge testing based on the working experience of the nurses (P = 0.001). Further, there was also statistically significant difference in the knowledge of the nurses based on World Bank income status (P = 0.001). The

Table 1 Demographic profile of the respondents and scores achieved by the level of knowledge

	Number of respondents (%)		Number of respondents (%)
World Bank income classification		**Working experience (yr)**	
High-income countries	608 (45.6)	< 2 yr	232 (17.4)
Upper middle-income countries	69 (5.2)	2-5 yr	354 (26.6)
Lower middle-income countries	656 (49.2)	5-10 yr	351 (26.3)
		> 10 yr	396 (29.7)
Score attained by level of knowledge			
Proficient (81%-100%)	480 (36)	**Type of ICU**	
Above average (61%-80%)	472 (35.4)	Medical and Surgical ICU	607 (45.5)
Average (41%-60%)	296 (22.2)	Medical ICU	408 (30.6)
Below average (≤ 40%)	85 (6.4)	Others	318 (23.9)
Type of hospital		**Size of ICU (number of beds)**	
Corporate/private	524 (39)	< 25 bedded	1056 (79.2)
Medical college/university hospital	239 (18)	25-100 bedded	251 (18.8)
Public/government	570 (43)	> 100 bedded	26 (2.0)
Hospital accreditation		**Operating model of ICU**	
International	606 (45.5)	Closed ICU	620 (46.5)
National	442 (33.2)	Open ICU	355 (26.6)
None	285 (21.4)	Semi-closed ICU	358 (26.9)
Teaching status			
Non-teaching	422 (31.7)		
Teaching	911 (68.3)		

ICU: Intensive care unit.

performance of the respondents working in HIC and UMIC was found to be better than the LMIC. Further, 237 (38.9%) and 30 (43.5%) respondents from the HIC and UMIC, respectively, were found to be proficient, compared to 213 (32.4%) respondents from LMIC.

The difference in the knowledge of the respondents, based on the type of hospital was found to be statistically significant (P = 0.001). A more significant proportion of the nurses, working in corporate/private hospitals (231, 44.1%) and medical college/university hospitals (85, 35.6%) was found to be proficient than those working in public hospitals (164, 28.8%). There was also a statistically significant difference found in the knowledge of the nurses based on the accreditation status and teaching status of the hospital (P = 0.001).

In terms of the ICU setup, a difference was found in the knowledge of responding nurses for the type (P = 0.004) and size (P = 0.007) of the ICU. However, no significant difference was found in the knowledge of the respondents based on the operating model of ICU (P = 0.453) (Table 2).

In terms of multivariate analysis, the income status of the country (P < 0.001), type of the hospital (P < 0.001), teaching status (P < 0.001) and the experience of the nurses (P = 0.001) showed an independent association with a difference in knowledge among the nurses. Working in HIC and UMIC was found to be strongly associated with the high knowledge score secured by respondents (β = 4.89, 95%CI: 3.55 to 6.22). The teaching status of the hospital was inversely associated with the knowledge score secured by the respondents (β = -4.58, 95%CI: -6.81 to -2.36) (Table 3).

DISCUSSION

The cross-sectional survey results, on knowledge testing of the nurses working in 13 countries of South Asia and the Middle East, showed a considerable variation. About 3/4th of the respondents secured above average or proficient scores. Some of the factors like the higher economic status of the country and working experience were found to be independently associated with better knowledge among the

Table 2 Comparison of nurses' knowledge based on their experience and the demographic profile of the hospital and intensive care unit, *n* (%)

	Knowledge level categories				χ^2 value	*P* value
	Below average	Average	Above average	Proficient		
Working experience (yr)						
< 2 yr	24 (28.2)	69 (23.3%)	86 (18.2%)	53 (11%)	57.09	0.001[a]
2-5 yr	29 (34.1%)	84 (28.4%)	109 (23.1%)	132 (27.5%)		
5-10 yr	15 (17.6%)	48 (16.2%)	125 (26.5%)	163 (34.0%)		
> 10 yr	17 (20%)	95 (32.1%)	152 (32.2%)	132 (27.5%)		
World bank income classification						
High-income countries	14 (2)	119 (19.6)	238 (39.1)	237 (38.9)	46.47	0.001[a]
Lower-middle-income countries	68 (10.4)	164 (25)	211 (32.2)	213 (32.4)		
Upper-middle-income countries	3 (4.3)	13 (18.8)	23 (33.3)	30 (43.5)		
Type of hospital						
Corporate/private	42 (8)	98 (18.7)	153 (29.2)	231 (44.1)	60.53	0.001[a]
Medical college/university hospital	26 (10.9)	56 (23.4)	72 (30.1)	85 (35.6)		
Public/government	17 (2.9)	142 (24.9)	247 (43.3)	164 (28.8)		
Hospital accreditation						
International	30 (4.9)	120 (19.8)	220 (36.3)	236 (38.9)	30.56	0.001[a]
National	42 (9.5)	122 (27.6)	153 (34.6)	125 (28.3)		
None	13 (4.6)	54 (18.9)	99 (34.7)	119 (41.7)		
Teaching status						
Non-teaching	18 (4.2)	70 (16.6)	149 (35.3)	185 (43.8)	23.61	0.001[a]
Teaching	67 (7.3)	226 (24.8)	323 (35.5)	295 (32.4)		
Operating model of ICU						
Closed ICU	46 (7.4)	146 (23.5)	215 (34.7)	213 (34.4)	5.74	0.45
Open ICU	18 (5.1)	81 (22.8)	122 (34.4)	134 (37.7)		
Semi-closed ICU	21 (5.9)	69 (19.3)	135 (37.7)	133 (37.1)		
Type of ICU						
Medical-surgical ICU	30 (4.9)	113 (18.6)	221 (36.4)	243 (40)	19.39	0.004[a]
Medical ICU	30 (7.4)	98 (24)	134 (32.8)	146 (35.8)		
Other	25 (7.9)	85 (26.7)	117 (36.8)	91 (28.3)		
Size of ICU (number of beds)						
< 25	61 (5.8)	231 (21.9)	390 (36.9)	374 (35.4)	17.27	0.008[a]
25-100	18 (7.2)	59 (23.5)	77 (30.7)	97 (38.6)		
> 100	6 (23.1)	6 (23.1)	5 (19.2)	9 (34.6)		

[a]*P* value < 0.05 is significant.
ICU: Intensive care unit.

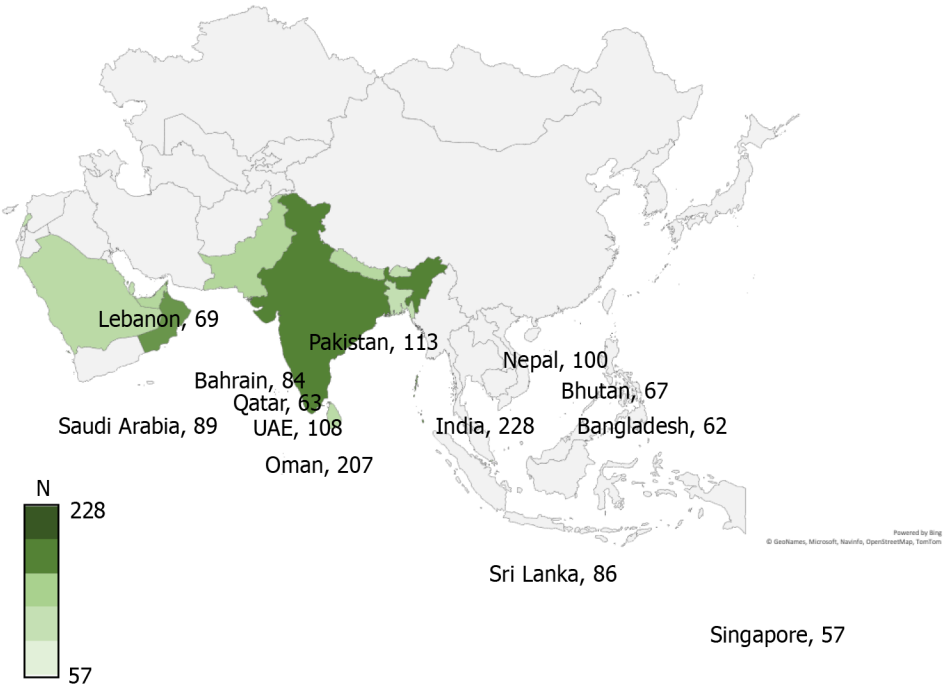
respondents. On the other hand, working in teaching or public hospitals was inversely associated with the knowledge level of IPC practices than the private and university hospitals.

In general, the ICUs show the highest prevalence of HAIs in a hospital setting. This may adversely affect the patients' clinical outcomes like length of stay in the hospital and ICU, quality of life after discharge, and mortality[14,15]. Nurses are the first and the foremost formidable line of defense against the HAIs. Hence their training, and awareness levels, knowledge, and compliance for the IPC practices are crucial in preventing the HAIs. The regional studies conducted earlier found gaps in the knowledge

Table 3 Multivariate analysis of demographic variables of respondents

Variables	Beta coefficient	*P* value	95%CI	
			Lower bound	Upper bound
Type of hospital	-3.76	< 0.001[a]	-5.03	-2.49
Hospital accreditation	0.89	0.24	-0.59	2.36
Teaching status	-4.58	< 0.001[a]	-6.81	-2.36
World bank income classification	4.89	< 0.001[a]	3.55	6.22
Type of ICU	-1.04	0.13	-2.40	0.32
Size of ICU	-2.01	0.07	-4.21	0.19
Working experience	1.71	0.001[a]	0.70	2.71

[a]$P < 0.05$ is significant.
CI: Confidence Interval, ICU: Intensive care unit.



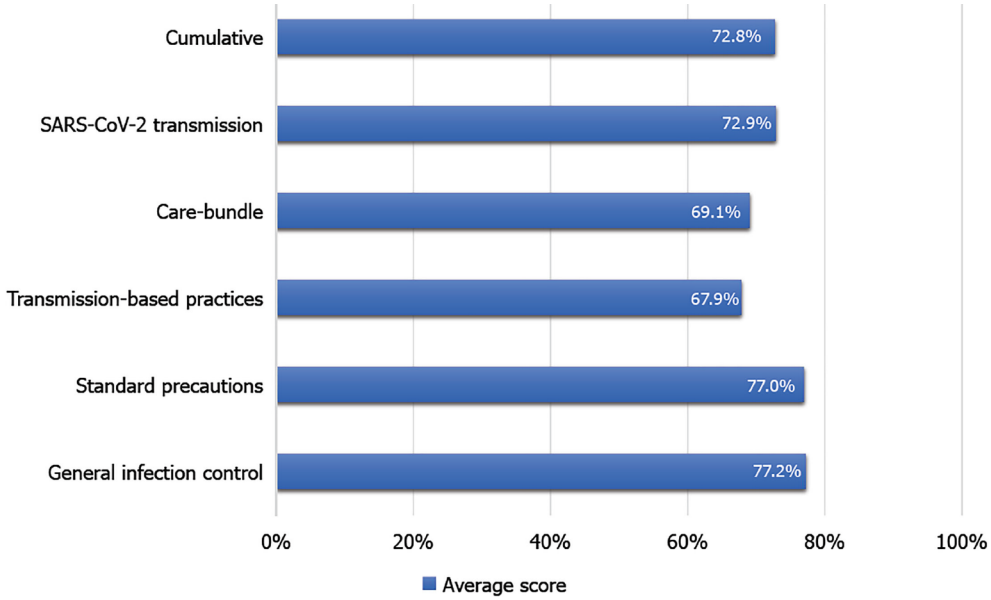
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Figure 1 Country-wise representation of the respondents of the survey. N: Number of respondents.

of HCWs upon the IPC practices, whereas training was found to be independently associated with better knowledge[16,17]. The literature showed a positive correlation between knowledge and better compliance with IPC practices among the HCWs[18,19].

Among five sections, the performance of the respondents was found to be worst in the section in transmission-based precautions. This reflects the knowledge deficiency of the nurses in understanding the microbiology aspect of IPC among nurses, which can be a focal point for future training programs. A systematic review of 30 studies also identified few gaps in the knowledge of HCWs among different IPC areas, such as vaccinations for HCWs, modes of transmission of infectious diseases, and the risk of infection from needle-stick and sharps injuries[6].

A recent review found that the structure and the skills of the ICU nurses vary according to the patient population, and availability of the resources, and treatments[20]. The current study found a strong association between the economic status of the countries (either UMIC or HIC *vs* LMIC) and better knowledge among the nurses. This finding infers about the impact caused by better resources, training, and surveillance opportunities on IPC practices in HIC or UMIC compared to LMIC. However, this finding is worrisome since the burden of HAIs is considerably higher in LMICs[21]. A recent global survey conducted by the World Health Organization on core components of the IPC programme and its



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Figure 2 Section-wise average score of the respondents in the questionnaire. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

implementation in healthcare facilities also highlighted the existence of critical gaps in LMIC and low-income countries[22]. The core components involving the workload, staffing, bed occupancy, education and training were scored the lowest in the survey.

The respondents working in private hospitals had significantly better knowledge about the IPC compared to their counterparts working in public hospitals. Though no direct studies compare different hospital settings on IPC practices, a few single-center studies have shown sound knowledge of the nurses working in private hospitals[23]. This can be attributed to resource constraints in terms of equipment, medications and the availability of the trained HCWs in public hospitals compared to private hospitals[24]. The current study finding with regards to teaching status of the hospital being negatively associated with knowledge of the nurses, is surprising. However, this can be explained by the fact that most of the teaching hospitals are public hospitals in UMIC and LMIC countries. Few studies conducted with the small number of samples in these countries from the region also found a deficiency in the knowledge among nurses working in teaching hospitals[25-27]. This suggests that education and training on IPC should be incorporated into medical teaching.

In the current study, a statistically significant difference was found in the knowledge of respondents based on their hospital accreditation status. Patient safety remains the centerpiece of hospital quality accreditation programs. Periodic training of the HCWs on various hospital-based policies, including IPC, is a core component of patient safety. In the current study, it is surprising to find the deficiency in knowledge of among the respondents working in hospitals with a national-level accreditation compared to their counterparts in international accreditation. However, the accreditation status was found to be not independently associated with better knowledge. This may reflect a difference in the standards of accreditation among the participating hospitals.

The working experience of the nurses was another factor, independently associated with a better knowledge. Since experience is the best teacher, it is expected that the knowledge of the nurses gets enhanced with increasing number of years of practice along with periodic trainings. In our previous multi-center study conducted in India, the working experience had a significant association with better knowledge among nurses[28]. Another single-center study from Saudi Arabia also found that the age (> 34 years), training and experience (> 6 years) were a predictor of good knowledge[17].

Strengths and limitations

The current study is a first-of-its-kind in this domain since the study conducted simultaneous knowledge testing of more than 1300 critical care nurses on IPC practices from 13 Asian countries. The survey intends to provide a snapshot of the knowledge of nursing professionals in terms of IPC practices, working in countries with a close cultural, social, and economic exchange. Besides testing the knowledge of the nurses on different aspects of IPC practices, the current study also tried to compare the knowledge based on a few factors such as the economic status of the country, working experience of the respondents; the type, accreditation, and the teaching status of the hospital, in which the respondents are working; and the type, size, and the operating model of ICUs by the respondents. The survey was participated by ICU nurses from large public and private hospitals with varying levels of accreditation and ICU setup.

The current study has a few limitations. Non-random convenience sampling method was followed for the study to obtain the data from only a set of selected hospitals from each participating nation. So, this data may not represent any individual country on the whole. We did make an effort to make the study population representative of nurses within respective countries with inclusion of public, corporate or university hospitals; teaching and non-teaching hospitals; and accredited as well as non-accredited hospitals, but still, this might not be an absolute representation. The number of entries received from each country varied from 57 to 228 which may have caused some statistical bias. The questionnaire did not include all the components of IPC as the intention was to evaluate only the knowledge of nurses working in the ICU. The questionnaire was made available to the study participants only in English and was not translated in their local language, due to concerns regarding accuracy and the misinterpretation of the questions. There is a potential for bias because of the gap in understanding the questions by the nurses due to language barrier. The knowledge testing of the IPC practices does not reflect the actual compliance with IPC practices and might not correlate with this self-answered knowledge evaluation. We did not capture the age, gender, qualification, and method of training rendered to the respondents, as these factors may have explained the variation in knowledge. Since the survey was an open-book and without any time restriction, the respondents might have answered the questions after taking external help, thus bringing a possible bias.

CONCLUSION

The current cross-sectional survey on testing the knowledge of nursing professionals on IPC practices from 13 Asian countries found a considerable variation. The higher economic status of the country and working experience were found to be independently associated with a better knowledge among the respondents. Working in public or teaching hospitals were found to be inversely associated with better knowledge about the IPC practices. There is an urgent need for periodic training and audits on the IPC practices of HCWs working in ICUs, especially in LMICs.

ARTICLE HIGHLIGHTS

Research background

Healthcare-associated infections (HAI) pose a significant threat to patients in hospitals, particularly in intensive care units (ICU). Despite efforts to prevent and control HAI, rates of device-associated (DA)-HAI in ICUs of developing countries remain higher than those in developed nations. Compliance with infection prevention and control (IPC) practices is crucial, and nurses play a key role due to their frequent contact with patients.

Research motivation

The lack of knowledge and awareness among healthcare workers about IPC practices, as well as discrepancies in applying this knowledge, have been linked to poor healthcare outcomes, especially in developing countries. ICU nurses' knowledge and awareness are integral to an effective IPC program. However, there is a lack of literature comparing the knowledge of ICU nurses across South Asian and Middle Eastern countries.

Research objectives

The current study aims to analyse the knowledge of ICU nurses regarding various aspects of IPC practices across countries in South Asia and the Middle East.

Research methods

The study conducted an online-based, cross-sectional survey using a multiple-choice questionnaire. The questionnaire was developed and validated by a 20-member steering committee comprising critical care physicians, infection control professionals, microbiologists, and nursing administrators. The survey was distributed to full-time ICU nurses in participating hospitals. The data were analysed using descriptive statistics, chi-square tests, and linear regression.

Research results

A total of 1333 nurses from 13 countries participated in the study. The average knowledge score was 72.8%, with 71.4% of respondents categorized as having above-average or proficient knowledge. Factors such as higher country income status, private hospital setting, and greater nursing experience were associated with better knowledge. Teaching hospitals and public hospitals showed lower knowledge levels.

Research conclusions

The study revealed significant variation in knowledge levels among ICU nurses across South Asian and Middle Eastern countries. Factors such as country income status, hospital type, teaching status, and nursing experience were associated with knowledge differences. These findings highlight the need for targeted interventions and training programs to improve IPC knowledge and practices, particularly in public and teaching hospitals.

Research perspectives

Future research should focus on developing comprehensive training programs and policies to enhance IPC knowledge and compliance among ICU nurses in South Asian and Middle Eastern countries. Comparative studies between different hospital settings and income groups can provide valuable insights into the factors influencing IPC practices and outcomes. Additionally, exploring the impact of improved IPC knowledge on healthcare delivery outcomes can further strengthen the evidence base for effective infection control strategies.

FOOTNOTES

Author contributions: Nasa P, Sodhi K, Arya M, Chanchalani G participated in the acquisition, and interpretation of the data and contributed equally to this work; Sodhi K designed the research and drafted the initial manuscript; Sodhi K and Nasa P, analyzed the data; Nasa P, Arya M, Chanchalani G, Shrestha G, Chandwani J, Kumar M, Kansal MG, Ashrafuzzaman M, Mudalige AD, Al Tayar A, Mansour B, Saeed HM, Hashmi M, Das M, Al Shirawi NN, Mathias R, Ahmed WO, Sharma A, Agarwal D performed the research, were involved in the recruitment of participants from their respective countries, revised the article critically for important intellectual content.

Institutional review board statement: The study was approved by the Ethics Committee (DHEC-2057/2022) of the institute of the principal investigator (KS) and exempted from other participating hospitals, as only healthcare professionals participated in the survey.

Informed consent statement: All study participants, provided informed written consent prior to study enrolment.

Conflict-of-interest statement: GPC reports receiving honorarium for advisory and consultancy services from Pneumocare Health Pvt Ltd. PN reports speaker honorarium from Tabuk Pharmaceuticals and MSD Pharmaceuticals. All other authors declare no competing interest in relation to the contents of this manuscript.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Ma YJ
L-Editor: A
P-Editor: Ma YJ

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ISSN 2220-3141 (online)

World Journal of

Critical Care Medicine

World J Crit Care Med 2023 September 9; 12(4): 188-235



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World Journal of Critical Care Medicine

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World Journal of Critical Care Medicine

Quarterly Volume 12 Number 4 September 9, 2023

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INDEXING/ABSTRACTING

The *WJCCM* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Li-Li Wang*.

NAME OF JOURNAL

World Journal of Critical Care Medicine

ISSN

ISSN 2220-3141 (online)

LAUNCH DATE

February 4, 2012

FREQUENCY

Quarterly

EDITORS-IN-CHIEF

Hua-Dong Wang

EDITORIAL BOARD MEMBERS

https://www.wjgnet.com/2220-3141/editorialboard.htm

PUBLICATION DATE

September 9, 2023

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INSTRUCTIONS TO AUTHORS

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STEPS FOR SUBMITTING MANUSCRIPTS

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ONLINE SUBMISSION

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World J Crit Care Med 2023 September 9; 12(4): 188-203

DOI: 10.5492/wjccm.v12.i4.188

ISSN 2220-3141 (online)

MINIREVIEWS

Biomarkers in sepsis-looking for the Holy Grail or chasing a mirage!

Neelmani Ahuja, Anjali Mishra, Ruchi Gupta, Sumit Ray

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Xie Q, China; Zaninotto M, Italy

Received: March 13, 2023
Peer-review started: March 13, 2023
First decision: April 28, 2023
Revised: May 12, 2023
Accepted: June 12, 2023
Article in press: June 12, 2023
Published online: September 9, 2023

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Abstract

Sepsis is defined as a life-threatening organ dysfunction caused by the dysregulated host response to infection. It is a complex syndrome and is characterized by physiologic, pathologic and biochemical abnormalities in response to an infection. Diagnosis of sepsis is based on history, physical examination and other investigations (including biomarkers) which may help to increase the certainty of diagnosis. Biomarkers have been evaluated in the past for many diseases and have been evaluated for sepsis as well. Biomarkers may find a possible role in diagnosis, prognostication, therapeutic monitoring and anti-microbial stewardship in sepsis. Since the pathophysiology of sepsis is quite complex and is incompletely understood, a single biomarker that may be robust enough to provide all information has not been found as of yet. However, many biomarkers have been studied and some of them have applications at the bedside and guide clinical decision-making. We evaluated the PubMed database to search for sepsis biomarkers for diagnosis, prognosis and possible role in antibiotic escalation and de-escalation. Clinical trials, meta-analyses, systematic reviews and randomized controlled trials were included. Commonly studied biomarkers such as procalcitonin, Soluble urokinase-type plasminogen activator (Supar), presepsin, soluble triggering receptor expressed on myeloid cells 1, interleukin 6, C-reactive protein, *etc*., have been described for their possible applications as biomarkers in septic patients. The sepsis biomarkers are still an area of active research with newer evidence adding to the knowledge base continuously. For patients presenting with sepsis, early diagnosis and prompt resuscitation and early administration of anti-microbials (preferably within 1 h) and source control are desired goals. Biomarkers may help us in the diagnosis, prognosis and therapeutic monitoring of septic patients. The marker redefining our view on sepsis is yet a mirage that clinicians and researchers continue to chase.

Key Words: Sepsis; Sepsis biomarkers; Procalcitonin; Presepsin; Omics

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Core Tip: Sepsis is defined as life threatening organ dysfunction caused by a dysregulated host response to infection. Early diagnosis of sepsis and prompt initiation of antimicrobials is essential. Biomarkers may be helpful in early diagnosis, prognostication and monitoring of response to therapy in septic patients. We review commonly used biomarkers such as procalcitonin, presepsin, soluble urokinase plasminogen activator, *etc*., and their utility in clinical practice.

Citation: Ahuja N, Mishra A, Gupta R, Ray S. Biomarkers in sepsis-looking for the Holy Grail or chasing a mirage! *World J Crit Care Med* 2023; 12(4): 188-203
URL: https://www.wjgnet.com/2220-3141/full/v12/i4/188.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i4.188

INTRODUCTION

Sepsis is defined as a life-threatening organ dysfunction caused by the dysregulated host response to infection. It is a complex syndrome and is characterized by physiologic, pathologic and biochemical abnormalities in response to an infection. It is a leading cause of mortality across the world and is a major healthcare concern[1]. Septic shock is a subset of sepsis in which the underlying cellular/metabolic abnormalities are profound enough to increase mortality. These patients are identified with the help of clinical criteria of hypotension requiring vasopressors to maintain a mean blood pressure of more than 65 mmHg and a serum lactate level of more than 2 mmol/L despite adequate fluid resuscitation. Initially, sepsis was defined in 1991 as infection or suspected infection leading to the onset of systemic inflammatory response syndrome (SIRS) where SIRS was defined as the presence of any two out of four criteria-tachycardia (heart rate > 90/min), tachypnoea (respiratory rate > 20 breaths per min), fever or hypothermia (temperature > 38 C or < 36 C), leukocytosis or leukopenia (Total Leukocyte Count > 12000/mm^3 or < 4000/mm^3 or immature forms or bands > 10%. Rudd *et al*[2] have attempted to estimate the global, regional and national incidence of sepsis and associated mortality using the Global Burden of Diseases, Injuries and Risk Factor Study estimates. They estimated an incidence of 48.9 million cases [95% uncertainty interval (UI): 38.9-62.9] of sepsis recorded worldwide in 2017. Almost 11 million (10.1-12) deaths were recorded as related to sepsis which is approximately 19.7% (18.2-21.4%) of all global deaths. In comparison from 1990 to 2017, age-standardized sepsis incidence decreased by 37% (95%UI: 11.8-54.5) and mortality decreased by 52.8% (47.7-57.5). The highest burden of sepsis was estimated to be in sub-Saharan Africa, Oceania, south Asia, East Asia, and Southeast Asia. Markwart *et al*[3] in their study have estimated that around 23.6 % of cases (95%CI: 17%-31.8%, range 16%-36.4%). Among the patients with sepsis associated with organ dysfunction in intensive care unit (ICU), 24.4% (95%CI: 16.7%-34.2%, range 10.3%-42.5%) were acquired during ICU stay while 48.7% (95%CI: 38.3%-59.3%, range 18.7%-69.4%) had a hospital origin. In ICU patients, with hospital-acquired sepsis associated with organ dysfunction, a mortality of 52.3% (95%CI: 43.4%-61.1%, range 30.1%-64.6%). With this huge burden of sepsis worldwide, there is a pressing need for early and accurate diagnosis of sepsis to allow early initiation of therapy.

The pathophysiology of sepsis is complex and is poorly understood. It involves the activation of various pro-inflammatory and anti-inflammatory pathways in response to a pathogen and its effects on the host. These pathways tend to disrupt the metabolomic profile and the identification of these metabolites can be helpful in diagnosis, therapy modification, and prognostication in sepsis patients.

Early recognition of sepsis and prompt management is essential and can help to reduce mortality in such patients. Differentiation of septic patients from other patients with a systemic inflammatory response due to non-infectious causes is difficult. Diagnosis of sepsis is based on history, physical examination and other investigations (including biomarkers) may help to increase the certainty of diagnosis. Early initiation of antibiotics is one of the cornerstones of the management of septic patients. However prudent antimicrobial therapy is required to prevent the emergence of drug-resistant organisms and hence an increased certainty in the diagnosis of sepsis will help to rationalize initiation of anti-microbials and also might help to de-escalate or discontinue them in critically ill patients, thereby reducing the chances of resistance. Biomarkers may serve as an aid for diagnosis, prognosis and therapy modification in septic patients. In the plethora of biomarkers, only a few have been recognized for their diagnostic abilities, but none have marked their presence as the absolute indicator of sepsis diagnosis.

A biological marker or a biomarker is defined as a character that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention. They may be used for diagnosis, staging of disease, prognostication, and for prediction and monitoring of clinical response to therapy. An ideal biomarker for sepsis should have the following characteristics: (1) Early identification of sepsis to initiate timely antibiotics; (2) High specificity to differentiate from noninfective causes of SIRS; (3) Identify bacterial sepsis from other causes of infection; (4) Prognostication of the patient's condition; and (5) Guide antibiotic therapy-escalation and de-escalation of antibiotics

A few biomarkers for sepsis have been described in Table 1. Our review aims to assess the role of biomarkers in diagnosis, prognosis and antibiotic stewardship in septic patients.

Table 1 Biomarkers in sepsis

Biomarker	Description
Procalcitonin	Precursor of hormone calcitonin secreted by C cells of thyroid gland
C-reactive protein	Acute phase protein secreted by hepatocytes in response to pathogen or tissue damage
IL6	A cytokine, mainly produced by macrophages and lymphocytes in response to infection and it can affect the activation of B and T lymphocytes
suPAR	A protein derived from cleavage and release of cell membrane bound urokinase plasminogen activator receptor
sTREM1	Mainly expressed on the surface of polymorphonuclear cells and mature monocytes
Presepsin (sCD14-ST)	sCD14 is cleaved by proteases during inflammation, to form an N terminal fragment-the sCD14 subtype (sCD14-ST)
Adrenomedullin	A 52 amino acid peptide initially isolated from phaeochromocytomas. It is secreted by mammalian tissues and endothelial cells in response to various stimuli such as hypoxia, angiotensin 2, inflammatory cytokine such as TNF-α, IL-1β, *etc.*
Mid regional Proadrenomedullin (MR-proADM)	A peptide secreted by multiple tissues in order to stabilize the microcirculation and protect against endothelial permeability

IL: Interleukin; sTREM1: Soluble triggering receptor expressed on myeloid cells 1; suPAR: Soluble urokinase plasminogen activator receptor; TNF: Tumor necrosis factor.

BIOMARKERS FOR DIAGNOSIS OF SEPSIS

In our review for biomarkers for the diagnosis of sepsis, we searched the PubMed database for sepsis biomarkers for diagnosis and narrowed the search by selecting biomarkers which have been studied in at least 300 patients or had a meta-analysis done with at least 1000 patients. Biomarkers with an area under the receiver operator characteristic curve (AUC) of at least 0.80 were then individually researched and included (Table 2). Few of the biomarkers and their utility in diagnosing sepsis, have been explained in our review.

C-REACTIVE PROTEIN

C-reactive protein (CRP) is an acute phase reactant which rises early in any inflammatory response including sepsis. Though its specificity has been challenged repeatedly, it is still among the most frequently included parameter in clinical studies[4].

PROCALCITONIN

Procalcitonin (PCT) demonstrated better diagnostic accuracy and specificity compared to CRP[5,6]. Alongside CRP, it is the most extensively studied marker and the most common marker against which most other markers have been compared for their diagnostic and prognostic role in sepsis. It is now well established that its levels rise in sepsis. However, the increase in PCT levels is significantly influenced by the type of infection, the site of infection, the severity of the patient's illness and post-operative status and the type of surgery. It increases within 4 h of injection of endotoxin, so it has the potential to recognize Gram-negative sepsis early. Higher procalcitonin levels are seen in Gram-negative bloodstream infections compared to Gram-positive infections and candidemia[7,8].

Patients with Gram-negative bacteremia had higher procalcitonin levels than Gram-positive bacteremia or candidemia [9]. However, Goodlet *et al*[10] found that PCT failed to rule out bacteremia.

In burn patients, PCT has been shown to be effective for early diagnosis of sepsis (AUC: 0.92)[11].

PCT like many other sepsis biomarkers [CRP, interleukin 6 (IL6)] increases in response to surgery in the first 24 h. Major cardiac and abdominal surgeries have been found to have higher PCT values. Unlike CRP, PCT levels rapidly fall and any subsequent rise has been shown to corroborate with post-operative sepsis.

Dong *et al*[12] found in post-cardiac surgery that PCT was able to identify infective SIRS compared to CRP and white blood cell count (WBC) ($P < 0.0001$)[12].

Procalcitonin-based antibiotic initiation failed to show any short-term mortality benefit rather than a delay in antibiotic initiation in sepsis. Procalcitonin-based antibiotic protocol, though, has shown its role in the de-escalation of antibiotics [13]. Hence it is imperative to use procalcitonin within a clinical context rather than as a sole marker for the diagnosis of sepsis.

Table 2 Biomarkers for diagnosis of sepsis

Ref.	Study characteristics		Results and inference			
	Study type	Patient characteristics	Variables	AUC/95%CI	Sensitivity/specificity/PPV/NPV	Inference
Tan *et al* [5], 2019	Meta-Analysis; 9 studies	Pooled data. Total: 1368 patients. Sepsis: 495. Non sepsis: 873	CRP; PCT	0.73 (95%CI: 0.69-0.77), 0.85 (95% CI: 0.82-0.88)	Sensitivity 0.80 (95%CI: 0.63-0.90); spec: 0.61 (95%CI: 0.50-0.72) DOR: 6.89 (95%CI: 3.86-12.31); sensitivity 0.80 (95%CI: 0.69-0.87); specificity: 0.77 (95%CI: 0.60-0.88) DOR: 12.50 (95%CI: 3.65-42.80)	Diagnosis accuracy and specificity of PCT are higher than those of CRP
Thomas-Rüddel *et al*[9], 2018	Randomised control trial, Prospective, Secondary analysis	Gram negative *vs* Gram positive bacteremia and candidemia	PCT (Gram negative bacteremia)	0.72 (95%CI: 0.71-0.74)	Value was 10 ng/mL sensitivity 69%, specificity 35% for Gram negative bacteraemia	Streptococci, *E. coli* and other Enterobacteriaceae detected from BC were associated with three times higher PCT values. Urogenital or abdominal foci of infection were associated with twofold increased PCT
Lai *et al* [7], 2020	Meta-Analysis; 25 studies	GNBSI	CRP	0.85 (0.81–0.87)	Sens: 0.75 (0.56–0.87); Spec: 0.80 (0.68–0.88)	PCT was helpful in recognizing GNBSI, but the test results should be interpreted carefully with knowledge of patients' medical condition and should not serve as the only criterion for GNBSI
			PCT	0.87 (0.84–0.90)	Sens: 0.80 (0.60–0.91); Spec: 0.82 (0.72–0.89)	
			IL6	0.83 (0.80-0.86)	Sens: 0.76 (0.58–0.88); Spec: 0.79 (0.71-0.85)	
Zhao *et al* [29], 2014	Prospective; Observational, single centre	Total: 652; Sepsis: 452; Non sepsis SIRS: 200	PCT	0.803	Sens: 75.2%, Spec: 80.0%, PPV: 89.5%, NPV: 58.8%	Combination of PCT, IL6 and D-dimer enhances the diagnostic ability for sepsis and severe sepsis
			IL6	0.770	Sens: 81.0%, Spec: 61.0%, PPV: 82.4%, NPV: 58.7%	
			D-Dimer	(0.737)	Sens: 79.9%, Spec: 59.0%, PPV: 81.5%, NPV: 56.5%	
			PCT + IL6 + D-Dimer	0.866	Sens: 81.6%, Spec: 73.6%, PPV: 56.0%, NPV: 90.6%	
Kondo *et al*[14], 2019	Meta-Analysis; 19 studies	Adult. Tot: 3012	Presepsin	0.87	Sens: 0.84 (95% 0.80-0.88); Spec: 0.73 (0.61-0.82)	Diagnostic accuracy of procalcitonin and presepsin in detecting infection was similar
			PCT	0.84	Sens: 0.80 (0.75-0.84); spec 0.75 (0.67-0.81)	
Kang *et al* [16], 2019	Adult	Infected trauma: 89; Non infected trauma: 68; Healthy controls: 60	Presepsin	0.853 (0.784-0.922)	321.5 pg/mL; Sens: 67.2%; Spec: 91.9; PPV: 87.5; NPV: 78.2; LR+: 4.89; LR-: 0.39	Presepsin might be a superior biomarker for early differentiation of infection in trauma patients
			PCT	0.771 (0.682-0.859)	0.923 ng/mL; Sens: 61.1%; Spec: 88.2%; PPV: 79.1; NPV: 74.7; LR+: 5.21; LR-: 0.47	
			Presepsin + ISS	0.939 (0.9-0.977)		
Liu *et al* [15], 2013	Prospective, adult consecutive, emergency department	Total: 859; Control: 100; SIRS: 372; Sepsis: 372; Severe sepsis: 210; Septic shock: 98	Presepsin	0.820 (0.784-0.856)	317 pg/mL; Sens: 70.8%; Spec: 85.8%; PPV: 93.2%; NPV: 51.6%; LR+: 4.99; LR-: 0.34	Presepsin is a valuable biomarker for early diagnosis of sepsis. trauma stress elevates PCT, CRP, and WBCs even in the absence of infection
			PCT	0.724 (0.680 to 0.769)	0.25 ng/mL; Sens: 60%; Spec: 77.7%; PPV: 93.2%; NPV: 28.4%; LR+: 2.69; LR-: 0.51	
Cong *et al* [20], 2021	Meta-Analysis	Adult 20 studies	CD 64	0.94 (0.91-0.96)	Sens: 0.88 (0.81-0.92); Spec: 0.88 (0.83-0.91); LR+: 7.2; LR-: 0.14; DOR-51 (25-101)	Neutrophil CD64 test has a high sensitivity and specificity in adult sepsis patients, and was superior to the traditional biomarkers PCT and IL6
			PCT	0.87 (0.83-0.89)	Sens: 0.82 (0.78-0.85); Spec-: 0.78 (0.74-0.82); LR+: 3.7; LR-: 0.23; DOR-16 (11-23)	
			IL6	0.77 (0.73-0.80)	Sens: 0.72 (0.65-0.78); Spec: 0.70 (0.62-0.76); LR+: 2.4; LR-: 0.40; DOR-6 (4-9)	
Gámez-Díaz *et al*	Prospective, cohort	Emergency, total 631 pts; based on	nCD-64	NA	Sens: 65.8% (95%CI: 61.1%-70.3%); Spec: 64.6% (95%CI: 57.8%-70.8%); LR+: 1.85	Patients suspected of having any infection in the ED, the

[25], 2011		expert consensus, Sepsis- 416			(95%CI: 1.52-2.26); LR-: 0.52 (95%CI: 0.44-0.62)	accuracy of nCD64, sTREM1, and HMGB-1 was not significantly sensitive or specific for diagnosis of sepsis
			HMGB-1		Sens: 57.5% (95%CI: 52.7%-62.3%); Spec: 57.8% (95%CI: 51.1%-64.3%); LR+: 1.36 (95%CI: 1.14-1.63); LR-: 0.73 (95%CI: 0.62-0.86)	
			s-TREM-1		Sens: 60% (95%CI: 55.2%-64.7%). Spec: 59.2% (95%CI: 52.5%-65.6%). LR+: 1.47 (95%CI: 1.22-1.76). LR-: 0.67 (95%CI: 0.57-0.79)	
Yeh *et al* [19], 2019	Metaanalysis. 14 studies	Adult, pooled data: Total: 2471; Control: 1167; Sepsis: 1304	Neutrophilic CD 64	0.89 (0.87–0.92)	Sens: 0.87 (0.80-0.92); spec 0.89 (0.82-0.93)	Neutrophil CD64 levels are an excellent biomarker with moderate accuracy outperforming both CRP and PCT determinations
			PCT	0.84 (0.79–0.89)	Sens: 0.76 (0.61-0.86); spec 0.79 (0.70-0.86)	
			CRP	0.84 (0.80–0.88)	Sens: 0.83 (0.78-0.86); spec 0.71 (0.56-0.85)	
Dimoula *et al*[22], 2014	Prospective observational study	548 adult ICU patients. Sepsis: 103; Non sepsis: 445	nCD64	NR	230 MFI. sens: 89% (81%-94%); spec: 87% (83%-90%).	Combining CRP and nCD64 expression, an abnormal result for both was associated with a 92% probability of sepsis, whereas sepsis was ruled out with a probability of 99% if both were normal. In nonseptic patients, an increase in nCD64 expression ≥ 40 MFI predicted ICU-acquired infection (n = 29) with a sensitivity of 88% and specificity of 65%
Wang *et al*[23], 2021	Metaanalysis: 7 articles	Neonatal, paediatric and adults	IL27	0.88 (0.84-0.90)	Sens: 0.85 (95%CI: 0.72-0.93); Spec: 0.72 (95%CI: 0.42-0.90); DOR-15 (95%CI: 3-72)	IL27 is a reliable diagnostic biomarker for sepsis and should be evaluated with other clinical tests
Wong *et al*[24], 2013	Prospective	Adults, infective (n = 145) and non-infective (n = 125) critically ill	IL27	0.68 (0.62-0.75)		IL27 inferior to PCT in sepsis diagnosis
			PCT	0.84 (0.79-0.89)		
Uusitalo-Seppälä *et al*[27], 2012	Prospective cohort	525 adult patients in emergency. Severe sepsis: 49; Sepsis: 302; SIRS: 58. Sirs with no bacterial infection: 53. Bacterial infection no SIRS: 63	PLA(2)GIIA	NA	OR: 1.48 (1.20-1.81, P < 0.001)	Differences in AUC between these parameters were not significant. On multivariate logistic regression analysis only PLA(2)GIIA could differentiate patients with severe sepsis from others (OR: 1.37, 95%CI: 1.05-1.78, P = 0.019
			BPI		OR: 2.66 (1.54-4.60, P = 0.001)	
			CRP		OR: 1.35 (1.02-1.77, P = 0.036)	
			WBC		OR: 2.81 (1.48-5.34, P = 0.002)	
Aksaray *et al*[26], 2016	Prospective	ICU, Adult, Sepsis (52), SIRS (38)	STREM1	0.78 (0.69–0.86)	sTREM1 cut-off value ≥ 133 pg/mL. Sens: 71.1%; Spec: 67.33%; PPV: 80.43; NPV: 65.91	sTREM1, APACHES II higher in patients with positive culture than negative cultures. sTREM1, PCT and CRP levels, or WBC count performed equally to differentiate
			PCT	0.65 (95%CI: 0.53–0.76)	PCT cut-off value of 1.57 ng/mL. Sens: 67.31; Spec: 65.79%; PPV: 72.92; NPV: 70	

AUC: Area under the receiver operator characteristic curve; BPI: Bactericidal/permeability-increasing protein; CRP: C-reactive protein; GNBSI: Gram negative blood stream infection; HMGB: High mobility group box 1; IL: ICU: Intensive care unit; Interleukin; NA: Data not available; NPV: Negative predictive value; NR: Data not reported; OR: Odds ratio; PCT: Procalcitonin; PPV: Positive predictive value; sens: Sensitivity, specificity.

PRESEPSIN (SCD14-ST)

Presepsin is released from monocytes following infection and in a recent meta-analysis, it is as good as procalcitonin for diagnosis of sepsis with an AUC of 0.87 and sensitivity and specificity of 0.84 and 0.73, respectively. The major limitation was the inclusion of only observational studies and no randomized controlled trials (RCTs)[14].

Liu *et al*[15] evaluated 859 patients in a single center presenting in emergency and found that compared to SIRS, patients with sepsis had significantly presepsin values (P < 0.0001). The value increased with the severity of sepsis. Presepsin had significantly higher AUC than PCT in diagnosing sepsis (P < 0.01).

Following trauma; PCT, CRP, and total blood count[15] increase irrespective of infective status, unlike presepsin which was found to be significantly increased in infected trauma cases only[16].

Halıcı *et al*[17] found presepsin to be effective in differentiating chronic obstructive pulmonary disease exacerbation with and without pneumonia[17].

Thus, presepsin has the potential to diagnose sepsis early and also to differentiate sepsis from non-infective SIRS, thereby optimising antibiotic initiation. Further randomised control trials are needed.

SOLUBLE UROKINASE-TYPE PLASMINOGEN ACTIVATOR RECEPTOR

Soluble urokinase-type plasminogen activator receptor (SuPAR) is normally present in blood and various other body fluids and is increased in states of inflammation. In the recent meta-analysis by Huang *et al*[18] SuPAR had a moderate diagnostic ability for sepsis similar to procalcitonin, but was inferior to PCT in differentiating from non-infective SIRS[18].

NEUTROPHILIC CD 64

Neutrophilic CD 64 (NCD64) is a surface receptor on the antigen-presenting cells which increases in response to infections and exposure to endotoxins.

In adult patients, Yeh *et al*[19] and Cong *et al*[20] found NCD64 outperformed procalcitonin, CRP and IL6 for sepsis diagnosis[19,20].

Liu *et al*[21] in their observational study found NCD64 to be significantly increased in bacterial and viral infections compared to fungal infections ($P < 0.0005$), and in DNA virus infections compared to RNA virus infections($P < 0.0071$) [21]. Further studies may be needed to establish its role to distinguish bacteremia.

In critically ill patients, NCD64 when combined with other markers like CRP is useful for diagnosing sepsis, especially when combined with CRP. A normal CRP and NCD64 [cut off 230 mean fluorescence intensity (MFI)] ruled out sepsis with a 99% probability. An increase of ≥ 40 MFI may indicate ICU-acquired infection in a previously non-infected patient as per their results[22].

OTHER BIOMARKERS

Various markers like IL27, Soluble triggering receptor expressed on myeloid cells 1 (sTREM1), and high mobility group box 1 (HMGB-1) failed to perform as diagnostic markers in larger trials[23-26].

Group IIA secretory phospholipase A2 (sPLA2-IIA) in a prospective cohort analysis could differentiate severe sepsis but needs further studies. Bactericidal/permeability-increasing protein in the same study did not show a significant benefit[27].

COMBINATION OF BIOMARKERS

Recent researchers are now also focusing on using a combination of markers with promising results[28]. Novel markers when used with traditional/time-tested clinical tools like neutrophil count, CRP, *etc*. increases the probability of differentiating sepsis from non-infective SIRS and initiates timely management.

PCT when combined with CRP and IL6 significantly increased its diagnostic accuracy for sepsis[29]. NCD64 combined with CRP have shown similar results[22,30].

Timely antibiotic initiation remains the most important factor determining patient survival. At present, most biomarkers act as an aid to clinical judgement and not its replacement in the diagnosis of sepsis and antibiotics administration (Table 3).

BIOMARKERS FOR SEPSIS PROGNOSIS

Apart from diagnosis, biomarkers may also be used for prognostication in septic patients. We searched the PubMed database for biomarkers that have been previously described commonly in the literature. We searched for the biomarker in question in the context of prognosis in septic patients. Only clinical trials, meta-analyses, systematic reviews and randomized controlled trials were included. Some of the biomarkers studied in sepsis patients have been evaluated for prognostication in such patients and results have been promising.

Table 3 Biomarkers for diagnosis of sepsis-current understanding in diagnosis of sepsis

Biomarker	Diagnosis of sepsis	Differentiating sepsis and SIRS	Guiding antibiotic initiation	Organism identification
Procalcitonin	Better than CRP; cannot be used independently; diagnosis based on clinical context	Better than CRP; cannot be used independently; diagnosis based on clinical context	Delays antibiotic administration; No short term mortality benefit	Higher in Gram negative bacteremia than Gram positive. Higher in bacteremia than in candidemia. No defined cutoffs. Treatment to be based on clinical judgement
Presepsin	Possible role	Possible role	No significant data	No significant data
nCD64	Possible role; when combined with CRP, higher diagnostic accuracy and high negative predictive value	No significant data	No significant data	Increased in bacterial and viral infection more than fungal
suPAR	Possible role	Performed poorly	No significant data	No significant data
IL6	Inferior to PCT, CRP	Inferior to PCT, CRP	No significant data	No significant data

CRP: C-reactive protein; IL6: Interleukin 6; PCT: Procalcitonin; SIRS: Systemic inflammatory response syndrome; suPAR: Soluble urokinase plasminogen activator receptor.

PROCALCITONIN

In a meta-analysis conducted by Arora *et al*[31], procalcitonin levels were found to be significantly lower in survivors of sepsis than non-survivors. Another meta-analysis by Patnaik *et al*[32] that had 1974 patients evaluated for procalcitonin clearance had an overall mortality of 37.54%. They concluded that procalcitonin non-clearance can be used as a marker for mortality. However, optimal cutoff points for the same for septic patients in the ICU are unknown. An overall AUC of 0.708 (95%CI: 0.648-0.769) was observed for the same under the random effect model as a result of moderate variation (50.80%) in the studies included. So, procalcitonin clearance could be used as a predictor for mortality and prognostication in septic patients with non-clearance suggesting a higher risk of death (Table 4).

PRESEPSIN

Masson *et al*[33] evaluated presepsin (a soluble CD 14 subtype) and its relation with mortality in patients with septic shock enrolled in the multicenter ALBIOS trial. 997 patients were evaluated and their results showed that baseline presepsin concentrations increased with SOFA score, the number of prevalent organ dysfunction failures, and the incidence of new failures of respiratory, coagulation, liver and kidney systems. A rise in the concentration of presepsin from day 1 to day 2 predicted a significantly higher ICU and 90-d mortality. They concluded that presepsin is an early predictor of host response and mortality in septic patients (Table 5).

ADRENOMEDULLIN (ADM) AND PRO ADRENOMEDULLIN

Adrenomedullin (ADM) and Pro adrenomedullin (proADM) are other markers that could be used for prognostication in septic patients and it is one of the biomarkers that has been evaluated for prognostication in community acquired pneumonia (CAP) patients (apart from IL6). Christ-Crain *et al*[34] have described its prognostic significance in CAP patients and concluded that proADM could be used as a risk stratification marker in patients with CAP. Ortqvist *et al*[35] in their observational trial found that higher IL6 levels were associated with higher mortality and bacterial pneumonia patients had the highest IL6 levels as compared to pneumonia of other aetiologies. Li *et al*[36] evaluated the ability of Adm and proADM for prognosis in septic patients in a meta-analysis and their results showed that increased AM or Pro ADM levels are associated with increased mortality (pooled RR: 3.31; 95%CI: 2.31-4.75) (Table 6).

SuPAR

suPAR has been evaluated in multiple trials and systematic reviews[18] to assess for prognostication in septic patients and has been validated to be a useful prognostic marker in adult septic patients (Table 7).

sTREM1 could also be useful in predicting mortality in septic patients at an initial stage of infection and has also been used for prognostication in neonatal septic patients[37] (Table 8).

Various biomarkers as described above and, in the table, have been evaluated for prognostication in septic patients. Sepsis biomarkers by themselves can provide valuable information for prognostication and in conjunction with organ dysfunction scores and severity scoring systems for critically ill patients, can provide an improved assessment for mortality and prognosticating in such patients. However, costs associated with their use, limited availability and limited knowledge about them are a hindrance in the clinical application of these markers. The optimal cut-off for prediction for

Table 4 Procalcitonin for prognosis of sepsis

Ref.	Type of study	Patient population	Aim	No. of patients/studies	Results	Conclusion of study
Ryu *et al* [52], 2015	Observational	Adults	To compare changes in PCT and CRP concentration in critically ill septic patients to determine which marker better predicts outcome	157 patients; 171 episodes	CPCTc and CRPc are significantly associated with treatment failure (P = 0.027 and P = 0.03 respectively) and marginally significant with 28 d mortality (P = 0.064 and 0.062 respectively). AUC for prediction of treatment success-PCTc-0.71 (95%CI: 0.61-0.81); CRPc-0.71 (95%CI: 0.61-0.81); AUC for survival prediction-PCTc-0.77 (95%CI: 0.66-0.88); CRPc-0.77 (95%CI: 0.67-0.88)	Changes in PCT and CRP concentrations were associated with outcomes of critically ill septic patients. CRP may not be inferior to PCT in predicting outcomes in these patients
Patnaik *et al*[32], 2020	Meta-Analysis	Adults	To evaluate the results of all non-clearance of serial PCT as a mortality predictor	10 studies, 1974 patients	AUC varied between the studies between 0.52 and 0.86. Overall AUC-0.711 (95%CI: 0.662-0.760) under fixed effect model and 0.708 (95%CI: 0.648-0.769) under random effect model. Overall proportion of mortality-37.54%	PCT non clearance is a marker for increased mortality. Optimal cut off points for PCT non clearance in septic patients admitted to ICU are not known
Park *et al* [53], 2013	Observational	Adults	To evaluate the value of PCT in women with APN at ED	240	AUC for predicting 28 d mortality for PCT-0.68. For predicting mortality, a cut off value of 0.42 ng/mL, sensitivity was 80% and specificity was 50%. Disease classification systems were predicted to be superior to PCT in predicting 28 d mortality	By distinguishing the severity of sepsis related to APN mortality, PCT levels help clinicians in disease severity classification and treatment decisions at ED
Oberhoffer *et al*[54], 1999	Observational	Adults	To predict outcome with traditional and new inflammatory markers in septic patients	242	AUC for PCT was 0.878 which was highest as compared to other markers	PCT may be a better marker than other inflammatory markers, CRP, leukocyte count, body temperature to identify patients endangered by severe infection or sepsis
Arora *et al* [31], 2015	Meta-Analysis	Adults	To study the procalcitonin levels in survivors and non survivors of sepsis	25 studies; 2353 patients	Mean difference in procalcitonin levels between survivors and non survivors on day 1 (P = 0.02) and day 3 (P = 0.03) was statistically significant	Significantly lower levels of procalcitonin were observed in survivors as compared to non survivors in early stages of sepsis

APN: Acute pyelonephritis; AUC: Area under the receiver operator characteristic curve; CRP: C-reactive protein; CRPc: Clearance of CRP; PCT: Procalcitonin; PCTc: Clearance of PCT.

prognosis has not been well defined and there is considerable heterogeneity in the literature. Site-specific values of these biomarkers (such as urine, cerebrospinal fluid, *etc*.) have not been adequately studied. Procalcitonin is a biomarker that has been used relatively more frequently in many countries and its non-clearance is associated with a higher mortality. The domain of biomarkers for sepsis prognosis is a promising field and many new biomarkers are expected to be discovered with the use of omics technologies.

ROLE OF BIOMARKERS IN ANTIBIOTIC STEWARDSHIP/DE-ESCALATION

Longer and injudicious use of broad-spectrum antibiotics has been associated with a higher frequency of adverse effects and interference with the microbiome, more treatment costs and the emergence of antibiotic resistance. Ruling out sepsis with certainty and withholding antibiotics, especially in critically ill patients is a challenging task even for a highly experienced physician. Although a shorter treatment course instead of longer has been recommended by the current Surviving Sepsis guidelines, a definitive duration of treatment for different sites and severity of infection has not been clearly defined[38]. CRP and PCT have been studied extensively in the biomarker-based algorithmic approach including antibiotic initiation and discontinuation.

Table 5 Presepsin for prognosis of sepsis

Ref.	Type of study	Patient population	Aim	No. of studies/patients	Results	Conclusion of study
Masson *et al* [33], 2015	Retrospective case control study	Adults	To evaluate the prognostic value of presepsin and comparison with procalcitonin	100	Presepsin levels at day 1 were higher in decedents (2269 pg/mL, median-1171 to 4300 pg/mL) than in survivors (1184 pg/mL, median-875 to 2113 pg/ml); $P = 0.002$) whereas PCT was not different (18.5 mcg/L, median 3.4 to 45.2) and 10.8 mcg/L (2,7 to 41.9 mcg/L) $P = 0.13$). The evolution of presepsin levels over time was significantly different in survivors compared to non survivors (P for time-survival interaction-0.03)	Presepsin showed better prognostic accuracy than procalcitonin in the range of SOFA. (AUC: 0.64-0.75 *vs* AUC: 0.53-0.65)
Behnes *et al* [55], 2014	Prospective cohort study	Adults	Evaluation of diagnostic and prognostic value of presepsin in sepsis and septic shock patients during the 1st wk of ICU treatment	116	AUC- 0.64 TO 0.71; Presepsin cut off values-Sepsis-530 pg/mL; Severe sepsis-600 pg/mL; Septic shock-700 pg/mL	Presepsin has good prognostic value in terms of prognosis for 30 d and 6 mo all cause mortality throughout the 1st wk of ICU stay and its prognostic value for all cause mortality is comparable to that of IL6 and better than that of PCT, CRP or WBC
Yang *et al*[56], 2018	Meta-Analysis	Adults	To evaluate the mortality prediction value of presepsin in septic patients	10 studies; 1617 patients	Initial prespesin levels (within 24 h) were significantly lower in survivors as compared to non survivors. Pooled SMD (standardized mean difference) between survivors and non survivors-0.92 (95%CI: 0.62–1.22)	Some mortality prediction of presepsin; further studies may be needed to define optimal cut off points for presepsin to predict mortality in sepsis
Wang *et al*[57], 2020	Observational	Elderly patients	To investigate the prognostic value of presepsin for elderly septic patients in ICU	142	Presepsin levels were significantly higher in infected patients. Day 3 presepsin levels showed a significant prognostic value for 30 d mortality but was not found to be superior to other biomarkers	Early diagnostic ability comparable to that of PCT; however not a perfect biomarker for prognosis of 30 d mortality in elderly patients
Koh *et al*[58], 2021	Observational	Adults	Estimation of prognostic value of presepsin in septic patients	153	AUC for presepsin- 0.656; Presepsin levels > 1176 pg/mL (odds ratio 3.352, $P < 0.001$) was a risk factor for in hospital mortality	Non survivors had higher presepsin levels; presepsin may have prognostic value
Endo *et al*[59], 2014	Prospective study	Adults	To compare presepsin with other conventional biomarkers (PCT, CRP, IL6) for evaluating the severity of sepsis	103	In patients with unfavorable prognosis: (1) Presepsin levels did not decrease significantly during follow up; (2) Higher duration of antibiotic therapy was used ($P < 0.05$); and (3) Higher 28 day mortality ($P < 0.05$)	Presepsin levels correlated with severity during follow up as compared to other conventional biomarkers
Masson *et al* [33], 2015	Observational	Adults	Evaluating the relationship between presepsin levels and host response, appropriateness of antibiotics, and mortality in severe sepsis patients	997 patients with severe sepsis or septic shock in ALBIOS trial	Baseline Presepsin concentrations increased with SOFA score, number of organ failures, and incidence of new organ failures; An increasing concentration of presepsin from day 1 to day 2 predicted higher ICU ($P < 0.0001$) and 90 d mortality ($P < 0.01$)	Presepsin is an early predictor of host response and mortality in patients with sepsis

AUC: Area under the receiver operator characteristic curve; CRP: C-reactive protein; IL6: Interleukin 6; PCT: Procalcitonin; WBC: White blood cell count.

PROCALCITONIN

Based on the multiple RCTs that evaluated PCT to guide antimicrobial treatment in patients with lower respiratory tract infections (LRTI), the current guidelines by IDSA recommend a shorter treatment course for pneumonia under PCT guidance[39]. The ProHOSP trial conducted at tertiary care hospitals in Switzerland included 1359 patients with severe LRTIs and studied the role of PCT in the initiation and discontinuation of antibiotics. The trial concluded a lower mean duration of antibiotic exposure and less frequent antibiotic-associated adverse effects in the PCT group as compared to the control group [standard of care (SOC)] within 30 d from the time of presentation[40].

Table 6 Adrenomedullin and pro adrenomedullin for prognosis of sepsis

Ref.	Type of study	Patient population	Aim	No. of patients	Results	Conclusion of study
Christ-Crain *et al*[34], 2006	Prospective observational	Adult patients with CAP	To evaluate the value of Pro ADM levels for severity assessment and outcome prediction in CAP	302	Pro ADM levels (as compared to CRP and leukocyte count) increased with increasing severity of CAP (calculated through PSI score). Pro ADM levels at admission significantly higher 2.1 (1.5 to 3) nmol/L compared to survivors 1 (0.6 to 1.6) nmol/L; P < 0.001. AUC for proADM was 0.76 (95%CI: 0.71–0.81)-significantly higher than PCT, CRP, TLC	Pro ADM is a useful biomarker for risk stratification in patients with CAP
Charles *et al*[60], 2017	Prospective cohort	Adults	To assess the prognostic value of PCT, MR pro ADM, copeptin and CT proendothelin1 concentrations	173	Day 1 MR-ProADM levels significantly higher in non survivors [8.6 (5.9) *vs* 4.4 (3.9)] nmol/L; P < 0.0001	Day 1 MR-ProADM is a good predictor of short term clinical outcome as compared with others
Li *et al* [36], 2018	Meta-Analysis	Adults	To evaluate the ability of adrenomedullin and Pro Adm to predict mortality in septic patients	13 studies; 2556 patients	Increased AM or Pro ADM levels are associated with increased mortality (pooled RR = 3.31; 95%CI: 2.31-4.75); AUC 0.8 (95%CI: 0.77-0.84)	AM and Pro ADM may be used as prognostic markers in sepsis
Chen and Li [61], 2013	Observational	Adults	To evaluate the prognostic value of adrenomedullin in septic patients and compare it with PCT and MEDS	837	Mean levels (at admission of AM were 28.66 ± 6.05 ng/L in 100 healthy controls, 31.65 ± 6.47 ng/L in 153 systemic inflammatory response syndrome patients, 33.24 ± 8.59 ng/L in 376 sepsis patients, 34.81 ± 8.33 ng/L in 210 severe sepsis patients, and 45.15 ± 9.87 ng/L in 98 septic shock patients. The differences between the 2 groups were significant. ADM levels significantly higher in non survivors; AUC for in hospital mortality-AM-0.773; PCT-0.701; MEDS-0.721	Adrenomedullin is valuable prognostic biomarker for septic patients in ED
Caironi *et al*[62], 2017	Observational	Adults	To evaluate the role of Bio ADM	956	Plasma bio ADM (day 1) was higher in and associated with higher 90 d mortality, multi organ failures, extent of haemodynamic support and serum lactate time course over the 1st wk. Bio ADM trajectory during the 1st wk of treatment predicted 90 d mortality; Reduction to levels below 110 pg/ml at day 7 was associated with reduction in 90 d mortality	Bio ADM levels may help individualize haemodynamic support therapy in septic patients
Elke *et al* [63], 2018	Secondary analysis of RCT	Adults	To evaluate role of MR Pro Adm compared to conventional biomarkers (PCT, CRP, lactate) and clinical scores to identify disease severity in sepsis	1089	MR Pro Adm had strongest association with mortality and high disease severity; A decreasing concentration of PCT by ≥ 20 % from baseline to day 1 or ≥ 50 % from baseline to day 4 but a persisting high level of Pro Adm had significantly increased mortality risk [HR (95%CI)-19 (8-45.9) and 43.1 (10.1-184)]	MR Pro Adm assesses disease severity and treatment response more accurately than conventional biomarkers and scores

AM: Adrenomedullin; AUC: Area under the receiver operator characteristic curve; Bio ADM: Bio adrenomedullin; CAP: Community acquired pneumonia; CRP: C-reactive protein; MEDS: Mortality in Emergency Department Score; MR pro ADM: Mid Regional Pro adrenomedullin; PCT: Procalcitonin; Pro ADM: Pro adrenomedullin; PSI: Pneumonia severity Index; TLC: Total leukocyte count.

The PRORATA trial, which was a large trial conducted on 630 critically ill patients with a suspected bacterial infection in France aimed at studying the effectiveness of a procalcitonin-based algorithm to decrease antibiotic exposure. The algorithm included initiation of antibiotic if serum PCT was ≥ 0.5 ng/mL and continuation until the serial measurements showed levels less than 0.5 ng/mL or reduction by at least 80% of the baseline value. The trial results showed a statistically significant decrease in the duration of antibiotic treatment from 11.6 d in the PCT group to 14.3 d in the control arm (P < 0.0001). The rate of relapse and re-infection were comparable between the two arms but a trend towards higher mortality in the PCT group at 60 d[41]. On similar grounds, the SAPS trial was designed to study the discontinuation of antibiotic protocol based on serial PCT measurements. The results were similar to the PRORATA trial with a significant reduction in antibiotic exposure days in the PCT group [5 d *vs* 7 d in the SOC (P < 0.0001)]. However, in contrast to the PRORATA trial, the SAPS trial also found a reduction in 28-d (19.6% *vs* 25%, P = 0.0122) and 1-year mortality (34.8% *vs* 40.9%, P = 0.0158)[42].

CRP

A systematic review and meta-analysis published by Petel *et al*[43] evaluated the efficacy of CRP in septic patients. Based

Table 7 Soluble urokinase plasminogen activator receptor for prognosis of sepsis

Ref.	Type of study	Patient population	Aim	No. of patients	Results	Conclusion of study
Backes *et al*[64], 2012	Systematic review	Adults	To assess the usefulness of suPAR levels in critically ill patients with sepsis, SIRS, bacteraemia, focusing (diagnostic and prognostic value)	10 studies	Little diagnostic value in critically ill septic patients. Superior prognostic value in such patients as compared to other markers. Improved mortality prediction by combining suPAR with other markers or disease severity classifications. suPAR levels correlate positively with markers of organ dysfunction and severity of disease classification system scores	suPAR has a low diagnostic value for septic patients. It may add to prognostication with other markers and organ dysfunction scores
Huang *et al*[18], 2020	Systematic review	Adults	To evaluate the value of suPAR for diagnosis and prognosis of sepsis	30 studies, 6906 patients	Pooled sensitivity and specifity for predicting mortality-0.74 (95%CI: 0.67-0.8) and 0.7 (95%CI: 0.63-0.76) with AUC of 0.78 (95%CI: 0.74-0.82)	suPAR is a good maker for prognostication of sepsis
Pregernig *et al*[65], 2019	Meta-Analysis	Adults	To assess the prognostic value of suPAR and 6 other biomarkers in predicting mortality in adult septic patients	28 studies included	Pooled mean differences in marker concentrations (survivors-non survivors) at onset of sepsis for suPAR-5.2 ng/mL; 95%CI: 4.5-6; $P < 0.01$)	suPAR can provide prognostication information about mortality in adult septic patients
Ni *et al* [66], 2016	Meta-Analysis	Adults	To evaluate the usefulness of suPAR for diagnosis and prognosis of bacterial infections	17 studies included	High suPAR levels were related with a significantly increased risk of death with a pooled risk ratio of 3.37 (95%CI: 2.6-4.38). Pooled sensitivity and specificity for predicting mortality were 0.7 and 0.72 respectively, with AUC of 0.77	suPAR can be used for prognosis of bacterial infection

AUC: Area under the receiver operator characteristic curve; SIRS: Systemic inflammatory response syndrome; suPAR: Soluble urokinase plasminogen activator receptor.

Table 8 Soluble triggering receptor expressed on myeloid cells 1 for prognosis of sepsis

Ref.	Type of study	Patient population	Aim	No. of patients/studies	Results	Conclusion of study
Su *et al* [67], 2016	Systematic review	Adults	To determine prognostic value of sTREM1 in predicting mortality at the initial stage of infection	9 studies	High sTREM1 level was associated with higher risk of death in infection, with pooled RR 2.54 (95%CI: 0.61-0.86) using a random effects model; Pooled sensitivity and specificity of sTREM1 to predict mortality in infection were 0.75 (95%CI: 0.61-0.86) and 0.66 (95%CI: 0.54-0.75), respectively	Higher sTREM1 levels had a moderate prognostic significance in assessing the mortality of infection in adult patients; however sTREM1 alone is not sufficient to predict mortality as a marker
Su *et al* [68], 2012	Observational	Adults	To study the association of sepsis prognosis with dynamic changes in sTREM1 and its polymorphisms	160	sTREM1 levels were significantly raised in non survivors than in survivors ($P < 0.001$); Logistic regression showed that sTREM1, APACHE 2, and rs2234237 polymorphisms are risk factors for prognosis	Dynamic changes in sTREM1 and rs2234237 polymorphism could be used for prognostication in septic patients
Wang *et al* [69], 2011	Observational	Adults	To observe dynamic changes in plasma sTREM1 levels and to study its effect on predicting outcome of septic patients combined with SOFA score	57	Non survivors-sTREM1 levels were highest on Day 1 and a gradual elevation was seen over days 1, 3 and 7). Survivor-sTREM levels were highest on day 1 and then showed a gradual reduction over days 1, 3 and 7. sTREM levels were significantly higher in non survivors as compared to survivors ($P < 0.01$)	High plasma levels of sTREM1 are detected at initial stages in septic patients and sTREM1 level combined with SOFA score may be helpful in predicting outcomes in septic patients

RR: Risk ratio; sTREM1: Soluble triggering receptor expressed on myeloid cells 1.

on the results of this analysis, the CRP cut-off recommended for antibiotic discontinuation was < 10 mg/L for neonatal sepsis. The majority of the studies on adults included patients with respiratory tract infection and cut-offs used were similar, with most of them withholding antibiotics if CRP was < 20 mg/L and initiating or continuing the use of CRP was > 100 mg/L. The physician's discretion was followed for CRP values between 20 mg/L and 100 mg/L. The meta-analysis

concluded that CRP based algorithmic approach reduced the rate of antibiotic initiation with no significant differences in mortality, infection relapse and hospitalization rates[43].

A recent trial conducted in the critical care unit of a university hospital in Brazil by Borges *et al*[44] compared the days of antibiotic therapy between a CRP-guided protocol and an evidence-based judicious use strategy (not using the marker). The decision of antibiotic discontinuation in the intervention arm was based on serial CRP measurements (if CRP < 35 mg/dL or decrease to decrease ≥ 50%). The trial illustrated the efficacy of the CRP-based strategy in reducing the median duration of antibiotic use by 1 day for the index infection episode [6 (5-8) d in the CRP arm *vs* 7 (7-10) d in the control arm; $P = 0.011$]. However, despite such promising results, no significant differences were found in terms of antibiotic-free days and survival outcomes between the two arms[44].

Another multicenter RCT, including patients with Gram-negative bacteremia with randomization in a 1:1:1 ratio, compared an individualized CRP-guided antibiotic treatment (Duration based on the decrease in CRP levels ≥ 75% from its peak along with the absence of fever for 48 h) with a fixed 7-d and 14-d therapy. The primary outcomes of this trial in terms of incidence of clinical failure occurred in 2.4% of patients in the CRP arm, 6.6% in the 7-d arm, and 5.5% in the 14-d arm (difference in CRP *vs* 14-d arm was -3.1%; $P < 0.001$). The median duration of antibiotic therapy in the CRP-guided group was 7 d. The findings of this study hence concluded that antibiotic duration should not be predefined in the initial phase of illness and use of a biomarker-guided approach may prevent prolonged antibiotic exposure without increasing the failure rates[45].

Considering the results of these trials and meta-analysis, it may be inferred that CRP-guided protocolized therapy allows a lower antibiotic exposure and comparable rates of infection relapse and mortality with the control group.

NEWER BIOMARKERS WITH A ROLE IN ANTIBIOTIC STEWARDSHIP

Presepsin

Presepsin is a soluble form of CD14 that takes part in pathogen recognition by innate immunity. Masson *et al*[33] analyzed a subset of data from the ALBIOS trial and studied the relation between the circulating presepsin levels, the host response and mortality in patients with severe sepsis. The study concluded a direct correlation between a rise in presepsin concentration and a rise in SOFA score and the number of organ failures. Baseline levels of presepsin were found to be higher in patients who subsequently tested positive for bacterial infection (particularly with Gram-negative sepsis). The levels declined gradually in patients with negative cultures and appropriate antibiotic therapy[33]. Xiao *et al* [46], published a trial recently, comparing presepsin guidance to SOC in sepsis. In the intervention group, antibiotics were discontinued at serum presepsin concentration of < 350 pg/mL or a decline of more than 80% from baseline. Despite more antibiotic-free days in the presepsin group, there was no significant difference in mortality between the two arms [46]. These findings suggest a potential role of this biomarker in guiding antibiotic escalation and de-escalation strategies.

IL-1β and IL-18

The VAPrapid2 trial published in 2020 was the first trial to use biomarkers (IL-1β and IL-18 from the bronchoalveolar lavage fluid) to improve antibiotic stewardship by the early exclusion of infection in patients with suspected ventilator-associated pneumonia (VAP). Although the trial illustrated the efficacy of studied biomarkers (IL-1β and IL-18) in accurately excluding VAP, it could not achieve the endpoint of showing any statistically significant difference in the number of antibiotic-free days. Certain factors such as reluctance to BAL and non-adherence to the discontinuation protocol by treating clinicians could have contributed to the lack of difference in antibiotic duration between the intervention and control groups[47].

OMICS (GENOMICS, TRANSCRIPTOMICS, PROTEOMICS AND METABOLOMICS) IN SEPSIS

The host inflammatory response leads to the generation of by-products or metabolites and these have been used as the traditional biomarkers in sepsis. However, omics technology, including genomics, transcriptomics, proteomics and metabolomics are referred to as the systematic measurement at the level of DNA, RNA, protein and metabolite levels and the omics technology has resulted in the delineation of newer biomarkers in sepsis and sub-phenotyping in sepsis patients. We will explain omics in sepsis in a nutshell as a more comprehensive detail of omics in sepsis is beyond the scope of this review.

Genomics is the study of the genome to explain physiological or pathological processes. Variable response and susceptibility of individual patients to infection are different because of genetic factors. Genomics can be used to determine genetic polymorphisms and epigenetic markers that may be used as bioindicators in septic patients. Single Nucleotide Polymorphism (SNP) are a common type of genetic polymorphism and SNP genotyping of various genes may provide important information relevant to sepsis.

Tightly regulated gene expression leads to the regulation of pro and anti-inflammatory responses in septic patients and gene expression study forms the basis of transcriptomics. Micro RNAs (miRNAs) are short RNAs of 18 to 25 nucleotides that regulate gene expression in target mRNA. miRNA profiling of leukocytes and plasma in septic patients may be used to detect molecules that may be used as biomarkers. Similarly, long non-coding (involved in epigenetic control of gene expression) may be useful to detect diagnostic and therapeutic classes of biomarkers.

All sets of proteins expressed by an organism constitute a proteome and proteomics is the study of the expression, localization, function and interaction of the proteome. Proteomics may thus provide the basis for determining newer biomarkers in sepsis[48].

Metabolomics was defined way back in the 1990s and defines techniques aimed at measuring metabolites present within a cell, tissue or organism. The underlying principle in genetics describes the flow of information from DNA through mRNA transcripts and the subsequent translation of it into proteins. These proteins take part in tightly controlled metabolic pathways. Metabolome is the terminal downstream product of the genome and consists of all the low molecular weight molecules (metabolites) in a cell, tissue or organism required for growth, maintenance, or normal function in a specific physiological state. These metabolites generate the phenotype in an organism and these can be detected and measured to provide information about the particular process in question[49]. The pathophysiological pathways of sepsis may lead to inflammatory and anti-inflammatory metabolites being produced and identification of these metabolic products can help to detect sepsis early, and may also help to assess treatment response and estimate recovery[50].

Su *et al*[51] identified metabolic biomarkers that can be useful to differentiate sepsis from SIRS. They assessed 65 patients (35 patients with sepsis, 15 patients with SIRS, and 15 normal individuals). They used liquid chromatography-mass spectrometry to analyze metabolites in serum samples. They reported significantly lower levels of lactitol dehydrate and S-phenyl-D cysteine and increased S-(3-methylbutanoyl)-dihydrolipamide-E and N-nonanoyl glycine in septic patients as compared to SIRS patients. Patients with severe sepsis and septic shock had low glyceryl-phosphoryl-ethanolamine, Ne, Ne dimethyllysine, phenylacetamide and D-cysteine ($P < 0.05$) in serum. S-(3-methylbutanoyl)-dihydrolipoamide-E, phosphatidylglycerol (22:2 (13Z,16Z)/0:0), glycerlophosphocholine and S-succinyl glutathione were significantly lower ($P < 0.05$) in serum (collected 48 h before death) of patients who died. These metabolites are reflective of the ongoing metabolome during sepsis and may be used to diagnose sepsis and estimate severity and mortality. However, larger studies are needed for validation.

CONCLUSION

Sepsis and septic shock are life-threatening conditions requiring prompt resuscitation and antibiotic administration. The sepsis biomarkers are still an area of active research with newer evidence adding to the knowledge base continuously. Sepsis is the result of a complex interplay of various pathways. A single biological marker may not be an answer for diagnosis, prognostication, follow up and guide to antibiotic escalation/de-escalation in sepsis. Regardless, understanding these sepsis biomarkers and their role in the sepsis pathway can help to further rationalize sepsis management alongside clinical judgement. Early targets for sepsis treatment would be to administer anti-microbials within 1 h of presentation and source control as early as possible. The 2021 surviving sepsis campaign guidelines suggest against using procalcitonin and clinical judgement to start initial antibiotic *vs* clinical judgement alone as waiting for procalcitonin may delay antibiotic administration. However, it is suggested to use procalcitonin in addition to clinical evaluation as compared to clinical evaluation alone to discontinue antimicrobials in patients with septic shock with adequate source control. The values of the biomarkers (like procalcitonin, Supar, nCD64, presepsin, *etc*.) may help guide the therapy by differentiating noninfective SIRS from infective SIRS. A combination of biomarkers has been found to increase their diagnostic accuracy.

The marker redefining our view on sepsis is yet a mirage that clinicians and researchers continue to chase. Many have become redundant and many more are still in the running to prove their worth. "Omics" (including genomics, transcriptomics, proteomics and metabolomics) will lead to the discovery of newer biomarkers and their applications in diagnosis, prognosis and therapeutic monitoring are going to increase.

FOOTNOTES

Author contributions: All the authors were equally involved in the designing, research methodology, data collection and writing of the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Fan JR

L-Editor: Filipodia

P-Editor: Cai YX

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 September 9; 12(4): 204-216

DOI: 10.5492/wjccm.v12.i4.204

ISSN 2220-3141 (online)

MINIREVIEWS

Should we initiate vasopressors earlier in patients with septic shock: A mini systemic review

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Bittner EA, United States; Karim HMR, India; Shelat VG, Singapore

Received: March 20, 2023
Peer-review started: March 20, 2023
First decision: June 14, 2023
Revised: June 28, 2023
Accepted: July 17, 2023
Article in press: July 17, 2023
Published online: September 9, 2023

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Abstract

Septic shock treatment remains a major challenge for intensive care units, despite the recent prominent advances in both management and outcomes. Vasopressors serve as a cornerstone of septic shock therapy, but there is still controversy over the timing of administration. Specifically, it remains unclear whether vasopressors should be used early in the course of treatment. Here, we provide a systematic review of the literature on the timing of vasopressor administration. Research was systematically identified through PubMed, Embase and Cochrane searching according to PRISMA guidelines. Fourteen studies met the eligibility criteria and were included in the review. The pathophysiological basis for early vasopressor use was classified, with the exploration on indications for the early administration of mono-vasopressors or their combination with vasopressin or angiotensinII. We

found that mortality was 28.1%-47.7% in the early vasopressors group, and 33.6%-54.5% in the control group. We also investigated the issue of vasopressor responsiveness. Furthermore, we acknowledged the subsequent challenge of administration of high-dose norepinephrine *via* peripheral veins with early vasopressor use. Based on the literature review, we propose a possible protocol for the early initiation of vasopressors in septic shock resuscitation.

Key Words: Septic shock; Resuscitation; Vasopressor; Norepinephrine; Vasopressin; Timing

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Core tip: It remains unclear whether vasopressors should be used early in the course of treatment of septic shock. Here, we provide a systematic review of the literature on the timing of vasopressor administration. The pathophysiological basis for early vasopressors use was classified, with the exploration on indications for the early administration of mono-vasopressors or their combination with vasopressin or angiotensinII. We also investigated the issue of vasopressor responsiveness and the subsequent challenge of administrating high-dose norepinephrine *via* the peripheral vein with early vasopressor use. Based on the literature review, we propose a possible protocol for the early initiation of vasopressors in septic shock resuscitation.

Citation: Zhou HX, Yang CF, Wang HY, Teng Y, He HY. Should we initiate vasopressors earlier in patients with septic shock: A mini systemic review. *World J Crit Care Med* 2023; 12(4): 204-216
URL: https://www.wjgnet.com/2220-3141/full/v12/i4/204.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i4.204

INTRODUCTION

Sepsis and septic shock are still considered a major challenge in healthcare, associated with significant morbidity and mortality[1-3]. Septic shock is the most severe form, and considered one of the most prominent challenges in critical care medicine, characterized by persistent hypotension and the presence of tissue hypoperfusion, with a mortality of 28.6%[4-6].

The primary therapies to resuscitate septic shock are to hold the systemic blood pressure and promote the regional and microcirculatory perfusion. According to the Surviving Sepsis Campaign (SCC) guidelines, it is recommended to increase blood pressure with intravenous fluids and vasopressors, and fluid resuscitation without vasopressors is not recommended until a lack of hypotension correction is confirmed. However, recent studies have proposed that early initiation of vasopressors such as norepinephrine with fluid loading may allow for early resolve of hypotension by reaching the target arterial pressure[7]. Therefore, the timing of vasopressor therapy is speculated to be crucial to optimize the outcomes of septic shock patients[8]. Furthermore, adding other vasopressors such as vasopressin and angiotensinII to norepinephrine may decrease the norepinephrine dosage by raising arterial pressure[9-12]. Recent studies have also been focused on whether an early initiation of vasopressin or angiotensinII to norepinephrine as a combined therapy could lead to a better outcome in septic shock patients compared to norepinephrine monotherapy[13,14].

Here, we conducted a systematic review of the available evidence regarding the physiological and clinical effects of early initiation of single or combined vasopressors during septic shock treatment in adults, aiming to provide evidence on optimal timing and protocol for vasopressors administration during septic shock resuscitation.

RATIONALE FOR EARLY INITIATION OF VASOPRESSORS IN SEPTIC SHOCK

An early administration of vasopressors may exert several potential beneficial effects in septic shock. According to clinical and experimental studies, several possible mechanisms may support the idea to initiate vasopressors early in septic shock, mainly focused on perfusion improvement, blood flow increase and fluid overload prevention.

Early vasopressors can improve perfusion in septic shock

The early initiation of vasopressors could reduce the time of insufficient perfusion caused by hypotension. Previous studies have suggested a relation of risks for mortality and acute kidney injury with a long duration and a high severity of hypotension in septic patients[15-17]. As a result, the earlier administration of vasopressor, the quicker relief of the hypotension, and the shorter duration of organ hypoperfusion, thus achieving a better outcome[16].

Early initiation of vasopressor therapy raises the mean arterial pressure (MAP) to a contributing level to facilitate tissue perfusion and prevent the onset or progression of organ dysfunction[18]. It is widely recognized that organs require a critical MAP to allow an adequate perfusion. When the MAP is maintained below to organ's critical perfusion pressure, organ injury may occur[19].

Early initiation of vasopressors may promote the microcirculatory perfusion in septic shock[20-23]. Traditionally, the administration of vasopressors at the early phase of septic shock is concerned to potentially lead to the worsened microcirculation through excessive vasoconstriction of precapillary microvessels[24]. However, if the MAP is below the threshold of autoregulation of organ blood flow, severe hypotension can theoretically worsen organ hypoperfusion. When norepinephrine is added to fluid infusion on the basis of a low diastolic pressure, the increased MAP with norepinephrine significantly increases the tissue oxygen saturation (StO_2) recovery slope[22]. The StO_2 recovery slope reflects the capacity that microvessels are recruited in response to local hypoxia, as well as serving as a prognostic factor in septic shock patients. Furthermore, restoring arterial pressure with norepinephrine could significantly improve the microvascular reactivity during ischemia-reperfusion in severely hypotensive septic patients[22,25].

Early initiation of vasopressors modifies the coronary artery perfusion in septic patients by maintaining a proper diastolic arterial pressure[26]. Diastolic arterial pressure refers to the upstream pressure for the perfusion of the left ventricle. Indeed, the left ventricle is perfused only during the diastole, unlike the right ventricle during the whole cardiac cycle. Therefore, the low diastolic arterial pressure, as frequently the case in early septic shock due to arterial tone depression, induces an increased risk of myocardial ischemia[26]. Early regain of a target diastolic blood pressure could be recommended for patients with unstable coronary artery disease or chronic pulmonary hypertension at risk of low coronary perfusion pressure[27].

Early vasopressors can increase blood flow in septic shock

Vasopressors can allow a higher blood flow by enlarging the stroke volume and cardiac output in the early stage of septic shock[28]. In a study covering 105 patients with severely hypotensive septic shock, early administration of norepinephrine achieved an increase in stroke volume and cardiac output, which were revealed by an elevation of cardiac preload and systemic venous return in patients with preload responsiveness, through the α1-adrenergic-mediated effects of norepinephrine[23,29].

Early initiation of vasopressors increases organ blood flow and improves blood flow distribution. The improvement in MAP by norepinephrine was associated with maintenance of aortic and mesenteric blood flow, achieving a better tissue oxygenation compared with fluid alone[30]. Norepinephrine may optimize the distribution of blood flow to the mesenteric region with an earlier administration[31].

Early vasopressors can prevent fluid overload during resuscitation in septic shock

Early initiation of vasopressors was related to the decreased infused fluid volume. Two recent studies have demonstrated it in association with less fluid treatment volumes and the improved outcomes[32,33], and multiple studies have shown that large amounts of resuscitation fluids and positive cumulative fluid balance have correlation to the increased mortality in sepsis[32,34-38], and the increased incidence of pulmonary edema[39].

Early administration of vasopressors induces endogenous fluid recruitment by promoting venous return[40]. Vasodilation results in reduced mean systemic filling pressure, thus limiting venous return during septic shock. Vasopressors raise blood pressure through increased systemic vascular resistance. The venoconstrictive effect also contributes to increasing the venous return through mobilizing non-stress volume to stress volume[41,42]. Administration of vasopressors can therefore simulate a fluid bolus through endogenous fluid recruitment[29].

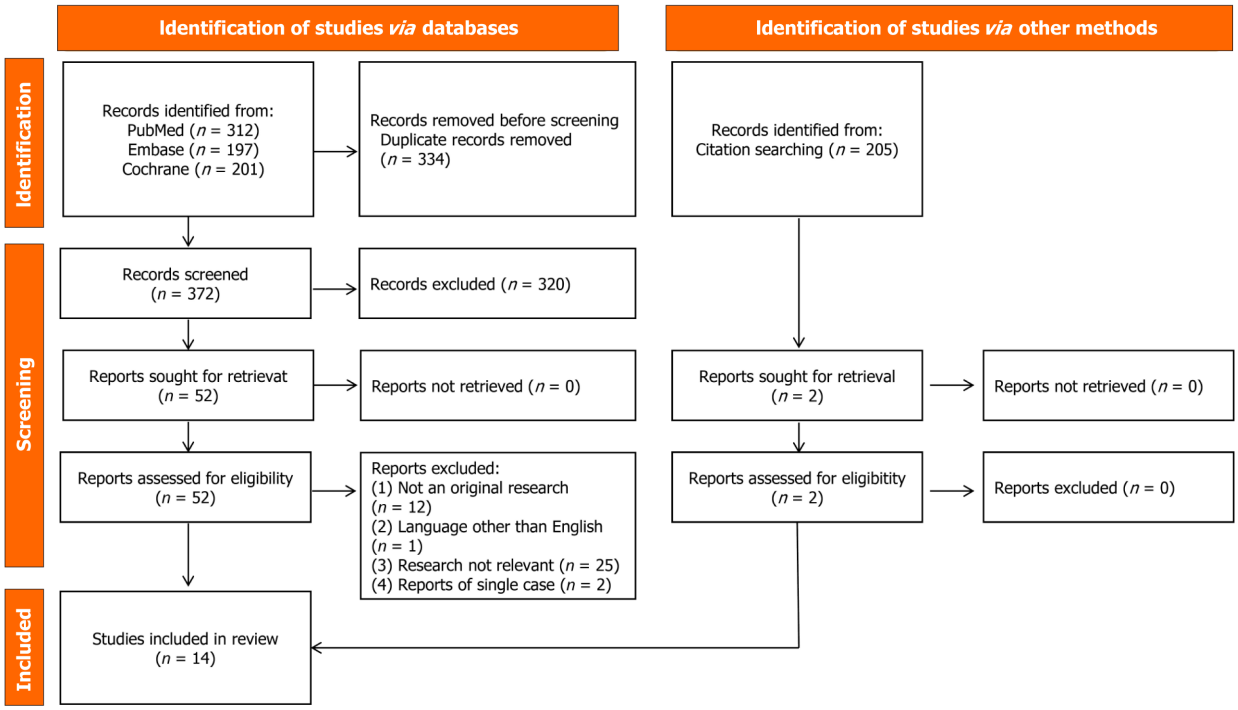
Early administration of vasopressors can diminish the capillary permeability by inhibiting inflammation. In one experiment, norepinephrine prominently reduced the endothelial permeability resulting from agonists of multiple Toll-like receptors *in vitro*, suggesting that both β1- and β2-adrenergic receptors mediate the stabilizing effects of norepinephrine on the endothelial barrier[43].

EVIDENCE THAT SUPPORTS EARLY INITIATION OF VASOPRESSORS: SYSTEMIC REVIEW OF CLINICAL STUDIES

Literature search

In accordance with the 2020 guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, www.prisma-statement.org/PRISMAStatement), a systematic review was conducted. Pubmed, Medline, Embase, and Cochrane database from 2012 to September 28, 2022 were searched using the following search terms: ("early"[All Fields] OR "Time Factors"[MeSH Terms] OR ("timely"[All Fields] OR "timing"[All Fields] OR "timings"[All Fields]) OR "delay*"[All Fields]) AND ("vasopressor*"[All Fields] OR ("noradrenalines"[All Fields] OR "norepinephrin"[All Fields] OR "norepinephrine"[MeSH Terms] OR "norepinephrine"[All Fields] OR "noradrenalin"[All Fields] OR "noradrenaline"[All Fields] OR "norepinephrines"[All Fields]) OR "vasopressin*"[All Fields] OR "Vasoconstrictor Agents"[MeSH Terms]) AND "shock, septic"[MeSH Terms]).The search was slightly adjusted to different databases. We also reviewed the references listed in the identified articles, which were manually searched for the related articles to identify all relevant and eligible articles and to minimize publication bias.

Two researchers independently screened and evaluated the eligibility of all studies, and a third reviewer intervened if a disagreement emerged. Original research reports of septic shock patients, and studies in which patients were treated with vasopressors early were enrolled. The exclusion criteria were: (1) Languages other than English; (2) study protocols, review articles, abstracts, and editorials; (3) research on children or animals; and (4) case reports. The flow chart of the search strategies is depicted in Figure 1.



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Figure 1 The PRISMA flow diagram of literature search, screen, and selection criteria.

The primary outcome assessed was mortality, while the other endpoints included shock control rate, time to achieve target MAP, incidence of organ failure and lactate clearance rate.

Study characteristics

The characteristics of the included trials are summarized in Tables 1 and 2. A total of 14 studies were included in this systematic review, including three randomized controlled trials (RCTs) and 11 observational studies, covering 11327 patients. The 14 studies were conducted in the USA (*n* = 5), Canada (*n* = 1), China (*n* = 1), Thailand (*n* = 1), Egypt (*n* = 1), Colombia (*n* = 1), Korea (*n* = 1), France (*n* = 1), and two were international studies.

Definition of early initiation of vasopressors in septic shock: There were two definitions for early initiation of vasopressors in septic shock used in previous studies.

First, in most studies, early initiation was defined as the initiation of a vasopressor such as norepinephrine during the early stage of hypotension or shock onset as a mono-vasopressor therapy, and at the same time (< 1 h) or even before administration of loading fluid in three studies. Initiation of vasopressors after a short time (within 2, 3or 6 h) of hypotension or shock onset was used in other studies. Three studies defined the early start of vasopressors at an average of 30 or 90 min after emergency room arrival or even before hospital. The studies above were summarized in Table 1.

Second, in other recent studies, early initiation stood for early addition of a second vasopressor such as vasopressin or angiotensinII to the first-line norepinephrine as multi-vasopressor therapy in severe septic shock (Table 2).

Major outcomes and findings of studies for early administration of single vasopressors in septic shock: Mortality was 28.1%–47.7% in the early group and 33.6%–54.5% in the control group. In five studies, norepinephrine was used as a first-line vasopressor early in septic shock. The 28–30-day mortality and hospital survival were reported as the primary outcome in six and two studies, respectively. Lower mortality was reported in the early vasopressor group in seven studies. Other findings for early vasopressor initiation associated with lower occurrence of organ failure were reported in two studies; shorter time to MAP achievement in three studies; better lactate clearance in four studies; lower volume of fluid use in two studies; and less norepinephrine use (shorter duration or lower dose) in two studies (Table 1).

Major outcomes and findings of studies for early administration of a second vasopressor as a combination therapy in septic shock: A total of five studies involved vasopressin or angiotensinII as an early second vasopressor for catecholamine-resistant septic shock. In three studies, vasopressin was added at 4–6 h after addition of norepinephrine or one type of catecholamine. In two other studies, angiotensinII was added when the dose of norepinephrine reached >0.2 μg/kg/min. A lower mortality was reported in the angiotensinII group in one study. Three studies reported that early administration of the second vasopressor for septic shock contributed to achieving the target MAP (Table 2).

Table 1 Basic characteristics of studies on early initiation of vasopressors included in the systematic review

No.	Ref.	Study design and period	No.of patients/early/late group	Agents	Time 0	Definition for early initiation	Primary outcome reported	Primary outcome	Other points	Comments
1	Beck *et al* [31], 2014, Canada	Multicenter, retrospective cohort study 1996-2008	6514/-/-	NE, Dopamine, Phenyleph-rine, VP, Epinephrine			Survival to hospital discharge	A weak correlation between vasopressor delay and hospital mortality (adjusted OR 1.02/h, $P < 0.001$)	The significance was found between the delay to vasopressor initiation (> 14 h post hypotension) and the occurrence of organ failure	1 Markedly delayed initiation of vasopressor (> 14 h after hypotension) in septic shock patients is associated with a small increase in mortality risk. 2 Delays in vasopressor initiation is only weakly associated with mortality, while delays in antimicrobial is more higher
2	Bai *et al* [61], 2014, China	Two centers, retrospective cohort study, Jan. 2011-Dec. 2012	213/86/127	NE	Septic shock onset	NE administered within 2 h after onset of septic shock	28 d mortality	The early group was lower than the late group, 29.1% *vs* 43.3%, $P < 0.001$	1 Duration of NE was significantly shorter in the early-NE group (2.6 ± 0.6 d *vs* 2.9 ± 1.0 d, $P = 0.001$). 2 Serum lactate levels at 2, 4, 6 and 8 h after septic shock onset were significantly lower in the early-NE group ($P < 0.05$)	1 Early administration (within 2 h after the septic shock onset) of NE in septic shock patients is associated with an increased survival rate. 2 Early NE initiation can increase MAP, shorten the duration of hypotension and, improve vital organ perfusion and decrease serum lactate levels
3	Permpikul *et al*[39], 2019, Thailand	Single center, RCT, Oct. 2013-Mar. 2017	310/155/155	NE	ED arrival	Median time from emergency room arrival to NE administration was 93 min	Shock control rate	Early NE adminis-tration resulted in significant higher shock control rate than standard treatment, 76.1% *vs* 48.8%, $P < 0.001$	1 Achievement of target MAP (> 65 mmHg), urine output (> 0.5 mL/kg) and lactate clearance (> 10%) were all significantly higher in the early-NE group (all $P < 0.05$). 2 There was no difference between groups for the rates of mechanical ventilator support or RRT. 3 patients in the early-NE group had a lower rate of cardiogenic pulmonary edema (14.4% *vs* 27.7%, $P = 0.004$) and new-onset arrhythmia (11% *vs* 20%, $P = 0.03$)	This study confirms that the early use of NE, can enable septic shock patients to benefit in short-term endpoints, such as shock control rate, urine output and lactate clearance, represented both macro- and micro-circulation restoration
4	Colon *et al* [62], 2019, United States	Single center, retrospective cohort study Jan. 2017-Jul. 2017	119/76/43	Vasopress-ors	Initial hypotension	Received vasopressor within 6 h from initial hypotension	30 d mortality	Vasopressor initiation after 6 h from shock onset is associated with a significant increase in 30 d mortality, 25% *vs* 51.1%, $P < 0.01$	1 Logistic regression analysis: adminis-tration of vasopressors after 6 h from hypotension were independently associated with increased 30 d mortality. 2 The time to target MAP was shorter in the early vasopressor group (1.5 h *vs* 3 h, $P < 0.01$)	1 Demonstrates that there is a mortality benefit with early use of vasopressor. 2 Early adminis-tration of vasopressor in septic shock patients (< 6 h from initial hypotension) is associated with decreased mortality, that is likely secondary to faster achievement of MAP goals
5	Elbouhy *et*	Single center,	101/57/44	NE	ED admission	NE infusion started	In-hospital	Early NE in septic	1 MAP of 65 mmHg was achieved after 2 h	1 They found that early use of

	al[63], 2019, Egypt	RCT Jan. 2017-Dec. 2018				after 25 (20-30) min from ED admission, simultaneous administration of crystalloid fluids	survival	shock improved in-hospital survival, 71.9% *vs* 45.5%, P = 0.007	in the early group compared to 3 h in the late group (P = 0.003). 2 Post-resuscitation serum lactate level was 2 mmol/L in the early group and 2.9 mmol/L in the late group (P = 0.037). 3 Acute kidney injury developed in 24 of the early group (42%) compared to 23 of the late group (52%) (P = 0.3). 4 Patients in the early group were resuscitated by significantly lower volume of fluids, 25 mL/kg compared to 32.5 mL/kg in the late group (P = 0.000). 5 The in-hospital survival rate in the early group was 71.9% compared to 45.5% in the late group (P = 0.007)	NE initiated simultaneously with fluids was associated with earlier achievement of target MAP, earlier lactate clearance with earlier achievement of lactate < 2 mmoL/L and consequently higher in-hospital survival. 2 The significantly lower volume required for fluids resuscitationin the early-NE than in the late-NE group
6	Ospina-Tascón *et al* [64], 2020, Colombia	Single center, prospective cohort study, Jan.2015-Feb.2017	186/93/93	NE, VP	First resuscitative fluid load	Vasopressor support initiated within the next hour or even before the first fluid load with resuscitative intention (FRLoad)	Association between early vasopressor and 28 d mortality	Early vasopressor was associated with a significant reduction in the risk of death compared to delayed vasopressor (HR 0.31, 95%CI 0.17-0.57, P < 0.001) at day 28	1 Patients in the early vasopressor group received less resuscitation fluids in the first 8 h of resuscitation (P < 0.001). 2 There were no significant differences regarding the maximal dose of NE, steroids and VP use, or requirement of RRT. 3 No cases of severe digital or severe vasopressor-induced splanchnic ischemia were documented	1 Early vasopressor support is associated with less use of resuscitation fluids, less fluid accumulation, and shortening of hypotension time. 2 Early vasopressor was not associated with increased kidney injury or ischemia-related adverse effects, and it might decrease mortality in patients with septic shock
7	Yeo *et al* [65], 2021, Korean	Multicenter, prospective observational study Sep. 2019-Feb. 2020	298/149/149	NE, VP, epinephrine, dopamine	First resuscitative fluid load	Vasopressor was initiated within 1 h of the first resuscitative fluid load	28 d mortality	Vasopressor initiation within 1 h was associated with higher 28 d mortality, 47.7% *vs* 33.6%, P = 0.013	1 Volume of fluid given within the initial 6 h was significantly lower in the early group (P = 0.046). 2 The total SOFA score on day 3 in ICU was significantly lower in the late group than that in the early group (P = 0.045). Lactate levels were significantly lower on day 3 in the late group than that in the early group (P = 0.014)	1 Use of a vasopressor within 1 h of the first fluid loading was related to higher mortality in patients with septic shock. 2 Less fluid was administered to the early group, but inadequate fluid resuscitation exhibited worse organ function and lactate clearance 3 d after septic shock onset
8	Jouffroy *et al*[50], 2022, France	Multicenter, retrospective study, Apr. 2016-Dec. 2020	478/143/335	NE	Prehospital	Patients with prehospital NE administration (early NE)	30 d mortality	Prehospital NE infusion (early NE) is associated with a decrease in 30 d mortality	N/A	A strength of this study is that NE administration is started within 1 h after septic shock onset and before the completion of the fluid resuscitation
9	Xu *et al*[7], 2022, United States	Single center, retrospective observational cohort study 2008-2019	2862/1431/1431	NE	Septic shock onset	Receiving NE within the first 3 h	28 d mortality	Early group had lower 28 d mortality, 30.0% *vs* 37.8%, P < 0.001	Patients in the early-NE initiation group had a significantly shorter duration of ICU and hospital stay, shorter duration of supportive NE and invasive mechanical ventilation, lower incidence of acute kidney injury, and lower proportion of organ failure progression than patients in the delayed NE initiation group	NE initiation within the first 3 h, regardless of preload dependency, was associated with longer survival time and shorter duration of supportive NE and invasive mechanical ventilation and may delay or partially reverse rapid onset organ failure

Sum	USA 2, other countries 1	2 RCTs	11081/2190/2377	NE 5	Shock onset 3, ED arrival 2, First fluid 2, Prehospital 1	Within 2, 3 and 6 h after shock, Within 0, 0.5, 1 h of fluid start, Prehospital	28 d mortality 4 and 30 d mortality 2 hospital survival 2	Mortality was lower in early group in 7 studies; mortality in early group was 28.1%-47.7%, in control group was 33.6%-54.5%

ED: Emergency department; MAP: Mean arterial pressure; NE: Norepinephrine; RRT: Renal replacement therapy; SOFA: Sequential organ failure assessment; ICU:Intensive care unit; VP: Vasopressin; N/A: Not applicable.

MARKERS PREDICTING OR SUGGESTING VASOPRESSOR RESPONSIVENESS

A key point is which markers or indexes could provide a clue for selecting the most appropriate population from septic shock patients who could mostly benefit from an early initiation of vasopressors. Several potential markers predicting vasopressor requirements were proposed in previous studies, such as diastolic arterial blood pressure[26,44] and dynamic elastance to identify early initiation of norepinephrine in first-line mono-vasopressor therapy. The kinetics of norepinephrine dose increment, and serum lactate and rennin levels were used to identify the timing for early administration of vasopressin or angiotensinII based on a norepinephrine multi-vasopressor therapy.

Norepinephrine responsiveness predictors

Diastolic arterial pressure: Physiologically, a low diastolic arterial pressure can result from depression of arterial tone, bradycardia, or arterial stiffness. In case of tachycardia, diastolic arterial pressure < 40 mmHg strongly suggests a markedly depressed arterial tone and the requirement to prompt initiation of a vasopressor[24]. Therefore, a low diastolic arterial pressure could serve as a simple indicator to identify patients requiring norepinephrine urgently at the early stage of septic shock[26].

Dynamic arterial elastance: Dynamic arterial elastance (Ea_{dyn}) is defined as the pulse pressure variation/stroke volume variation ratio. Arterial pressure in a hypotensive patient is increased, if Ea_{dyn} is high and the cardiac output is increased. In contrast, low Ea_{dyn} does not elicit a proportionally increased arterial pressure despite the increased cardiac output in response to volume challenge. In such hypotensive cases, the addition of vasopressors should be considered to correct hypotension. Ea_{dyn} has been demonstrated to be superior to diastolic arterial pressure as a marker of early initiation of vasopressors in septic shock patients[45].

Vasopressin responsiveness predictors

Norepinephrine-equivalent dose: Norepinephrine-equivalent dose may serve as an easily accessible marker to utilize with a consideration of an early vasopressin initiation before doses higher than 10–15 μg/min (0.1–0.2 μg/kg/min in a patient weighing 80 kg)[14].

Norepinephrine dose escalating kinetics: Clinically, two dose-requirement profiles, refractory and controlled, can be observed at the patient's bedside. A refractory profile meets the requirements of exposure to an exponential increase in norepinephrine dose, and a controlled profile with a gradual increase in norepinephrine dose to a plateau does not reach toxic levels of norepinephrine. In the refractory profile, the earlier vasopressin is started, the greater the chance of avoiding norepinephrine surge and exposure to harmful norepinephrine doses. In the controlled profile, it may not be

Table 2 Basic characteristics of studies on early combination with another vasopressor included in the systematic review

No.	Ref.	Study design and period	No. of patients	Agents	Time 0	Definition for early combination	Primary outcome reported	Primary outcome	Other points	Comments
1	Reardon *et al* [56], 2014, United States	Single center, retrospective study Jan. 2010-Dec. 2011	71, 35 (early)/36 (late)	VP	Catecholamine initiation	VP was initiated within 6 h of catecholamine therapy	Impact of VP on catecholamine dose and duration	No difference in dose and duration of catecholamine or VP therapy between the 2 groups	1 There was a significant difference in incidence of new-onset arrhythmias between the early VP and late groups (P < 0.001). 2 There was a trend toward worsening troponin T and CK-MB in the late VP group	1 Early VP therapy was associated with no difference in total catecholamine requirements but decreased incidence of new-onset arrhythmias. 2 There was also a trend toward improvement in cardiac biomarkers in the early VP group
2	Hammond *et al*[11], 2018, United States	Single center, prospective trial Nov. 2015-Jun. 2016	82, 41 (VP)/41 (NE)	VP	NE initiation	VP was initiated within 4 h of NE	Time to target MAP	Early VP to NE achieved target MAP faster than those receiving initial NE alone (P = 0.058)	-	Early concomitant VP and NE achieved and maintained a target MAP faster than initial NE alone, particularly in those in whom absolute or relative VP deficiency is suspected or confirmed
3	Hammond *et al*[13], 2019, United States	Single center, retrospective cohort study, May 2014-Oct. 2015	93, 48 (VP)/48 (NE)	VP	NE initiation	VP was initiated within 4 h of NE	Time to target MAP	Early VP to NE achieved target MAP sooner than later or no initiation (P = 0.023)	1 Changes in SOFA at 76 h since septic shock onset, the early VP saw a significant decrease of 4 compared to a decrease of 1 for NE alone (P = 0.012). 2 Early VP were discharged from the hospital 10 d sooner than those in the NE alone (14.3 *vs* 25.2 d, P = 0.014). 3 Incidence and duration of RRT were comparable between groups (17% *vs* 25% and 6.7 *vs* 11.2 d, respectively)	Early VP in combination with NE achieved a target MAP faster than the NE alone and may be more likely to resolve organ dysfunction at 72 h, although the in-hospital and 28-d mortalities were similar between groups, patients who survived benefited from earlier achievement and maintenance of goal MAP
4	Khanna *et al* [66], 2017, International	Multicenter, RCT May. 2015-Jan 2017	321/163/158	ATII	NE initiation	> 0.2 μg/kg/min of NE	Response to MAP at 3 h	More patients in the ATII response to MAP at 3 h (69.9% *vs* 23.4%, P < 0.001)	1 At 48 h, mean doses of background vasopressors were consistently less in the AT II group. 2 At 48 h, the mean improvement in the cardiovascular SOFA score was greater in the ATII group (-1.75 *vs* -1.28, P = 0.01). 3 No difference between the two groups for serious adverse reactions. 4 No difference between the two groups for 28 d mortality	1 Demonstrates the safety and efficacy of widespread clinical use of ATII. 2 ATII reduces the need for catecholamines in patients with catecholamine-resistant vasodilatory shock (CRVS), while reducing the cardiovascular injury it causes
5	Bellomo *et al* [49], 2020, International	Multicenter, Retrospective study	255/127 (low)/119 (high)	ATII	NE initiation	> 0.2 μg/kg/min of NE	Renin kinetic changes and their prognostic value in CRVS	In patients with higher renin concentrations, ATII significantly reduced 28-d mortality compared with placebo (P = 0.012)	1 Baseline serum renin concentration was above the upper limits of normal in 194 of 255 (76%) patients with a median renin concentration of 172.7 pg/mL. 2 At 3 h after initiation of ATII therapy, there was a 54.3% reduction in renin compared with a 14.1% reduction with placebo (P < 0.0001)	Serum renin concentrations are significantly higher in CRVS and may identify patients in whom early combination with ATII has a beneficial effect on clinical outcome
Sum	United States 3, International 2	RCT 1, Retrospective study 3	822, 414/402	VP 3, ATII 2	Vasopressors initiation 5	Within 4, 6 h of catecholamine, > 0.2 μg/kg/min of NE	Time to target MAP 2	1 VP, Achieved target MAP faster 2, No difference 1. 2 ATII response to MAP 1		

	reduced mortality 1

ATII: Angiotensin-II; CRVS: Catecholamine-resistant vasodilatory shock; MAP: Mean arterial pressure; NE: Norepinephrine; RRT: Renal replacement therapy; SOFA: Sequential organ failure assessment; VP: Vasopressin.

necessary to add vasopressin at the norepinephrine threshold of 0.5 μg/kg/min[46].

Angiotesin-II responsiveness predictors

It appears that a subgroup of patients with an impaired endogenous renin-angiotensin system[47] exhibit a pronounced response to angiotensinII and may derive benefits from earlier administration. Therefore, due to the robust relationship between hyper-reninemia and favorable angiotensinII response, renin is rapidly emerging as a promising prognosticator for the early initiation of angiotensinII in septic shock[14,48]. Bellomo *et al*[49] investigated the role of angiotensinII in patients with catecholamine-resistant vasodilatory shock and revealed the high renin levels in most of these patients (76%). Using a cutoff of 173 pg/mL, angiotensinII administration improved mortality in the subset of patients with high renin levels, suggesting that measurement of renin levels may contribute to identifying patients who might benefit from angiotensinII therapy. Median renin level of 173 pg/mL in the study cannot be directly applied in clinical practice; therefore, further prospective trials are required to confirm these findings.

POSSIBLE ADVERSE EFFECTS OF EARLY INITIATION OF VASOPRESSORS

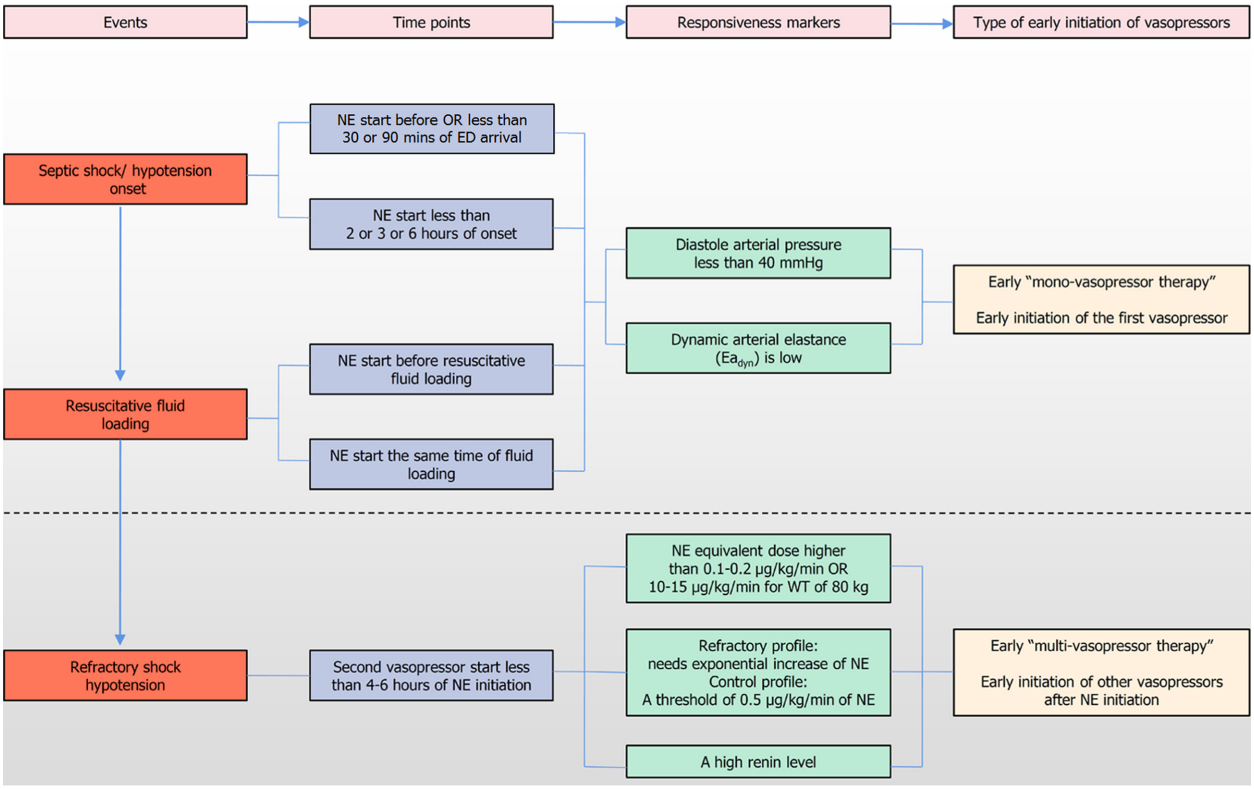
Feasibility and safety of peripheral infusion of high concentration of norepinephrine

The application of high concentrations of norepinephrine *via* the peripheral vein is considered an option for the early administration of vasopressors in patients with septic shock who meet the indications. Considering the strong vasoconstriction due to norepinephrine, the most appropriate approach is to administer the drug in intensive care units (ICUs) after placing a central venous catheter. However, if the timing of norepinephrine administration is advanced to admission to ICUs, emergency departments, or even prehospital[50], central venous catheter placement may not be generally feasible.

A previous study[51] has systematically reviewed the literature on the peripheral infusion of norepinephrine and noted that the available data failed to reveal a correlation between the occurrence of adverse events and the application of peripheral vein access. The administration of norepinephrine through the peripheral vein requires knowledge of concentration, dose, duration, and infusion site. In a study by Nguyen *et al*[52], the concentration of norepinephrine administered *via* the peripheral vein was 64 μg/mL, and the median dose as 10 μg/min, which was considered to be a high dose; the anterior elbow/external jugular vein was considered the site of infusion, with a median duration of infusion of 62 min; and the incidence of adverse events was 4.5%.

Myocardial ischemia in septic shock with early initiation of vasopressors

Septic shock is complicated by myocardial ischemia, which exacerbates diastolic shock symptoms such as tachycardia and hypotension. Norepinephrine can be administered after adequate fluid resuscitation. An RCT[53] comparing the efficacy of norepinephrine and epinephrine in patients with diastolic shock complicated by acute myocardial infarction revealed no significant difference in cardiac index. It does, however, show a notable disparity in heart rate; epinephrine



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Figure 2 A possible protocol for early administration of vasopressors in septic shock patients. During septic shock resuscitation, although not mentioned in the protocol, volume status and responsiveness should be assessed repeatedly and titrated crystalloids. NE: Norepinephrine.

results in a faster heart rate, which is particularly unfavorable for patients with myocardial ischemia. Additionally, dobutamine also elevates heart rate and directly contributes to increased morbidity and mortality[54], and should be avoided in these patients. An RCT[55] also compared early use of vasopressin *versus* norepinephrine, revealing a higher incidence of life-threatening arrhythmia in the norepinephrine group (0.98% *vs* 2.5%), and a higher incidence of acute coronary syndrome in the vasopressin group (3.4% *vs* 1.0%). These findings suggest that patients with coronary artery disease may benefit from avoiding vasopressin, while those with tachyarrhythmia may consider early co-administration of this drug. In contrast, Reardon *et al*[56] found a trend toward improvement in cardiac biomarkers in the early vasopressin group; however, no specific etiology was identified and the research was limited to a single-center retrospective analysis.

POSSIBLE PROTOCOL FOR CONSIDERING EARLY INITIATION OF VASOPRESSORS IN SEPTIC SHOCK

A possible protocol for early administration of vasopressors in septic shock patients is depicted in Figure 2, based on the literature reviewed above.

The timing of vasopressor initiation was the primary focus of our protocol, control of the source of infection in sepsis, use of albumin, and early steroid use are not included in the figure. However, four prominent RCTs investigated the administration of corticosteroids in patients with septic shock, but they yielded contradictory results. The enrollment time across the four studies was from 8 h[57] to 24 h[58,59] and 72 h[60]. Two trials demonstrated that early addition of corticosteroids to vasopressors significantly reduced all-cause mortality among patients with septic shock. Additionally, it is noteworthy that the majority of these trials initiated hydrocortisone administration concurrently with norepinephrine at a dose range of 0.5-1 μg/kg/min. The Surviving Sepsis Campaign guidelines recommend administering intravenous corticosteroids to septic shock patients who require ongoing vasopressor therapy, commencing as early as 4 h after the initiation of vasopressors and at a minimum norepinephrine dose of 0.25 μg/kg/min.

Control of the source of infection should be required as an emergency intervention as soon as a specific anatomical diagnosis of infection is identified. Early albumin infusion also should be considered when patients receive large volumes of crystalloids.

CONCLUSION

In septic shock, early initiation of vasopressors may exert several potential beneficial effects. Several mechanisms support

initiation of vasopressors early in septic shock, mainly focused on perfusion improvement, blood flow enlargement and fluid overload prevention. Clinical evidence has suggested possible benefits of early initiation of single or combined vasopressors in the resuscitation of septic shock. Several potential markers predicting vasopressor requirements were mentioned. Diastolic arterial blood pressure and dynamic elastance indicated early initiation of norepinephrine in first-line mono-vasopressor therapy. Kinetics of norepinephrine dose increment, serum lactate and rennin levels were applied to identify the timing of early initiation of vasopressin or angiotensin II based on norepinephrine multi-vasopressor therapy. Administration of high concentrations of norepinephrine *via* the peripheral vein is considered an option for the early administration of vasopressors in patients with septic shock.

FOOTNOTES

Author contributions: Zhou HX, Yang CF, and Wang HY drafted the manuscript; Teng Y and He HY designed and reviewed the manuscript, and revised it for critical intellectual content; all authors have read and approved the final version.

Conflict-of-interest statement: All authors declare that they have no competing interests.

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S-Editor: Liu JH
L-Editor: Kerr C
P-Editor: Zhang YL

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World Journal of Critical Care Medicine

Submit a Manuscript: https://www.f6publishing.com

World J Crit Care Med 2023 September 9; 12(4): 217-225

DOI: 10.5492/wjccm.v12.i4.217

ISSN 2220-3141 (online)

MINIREVIEWS

Improving environmental sustainability of intensive care units: A mini-review

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Juneja D, India; Kvolik S, Croatia

Received: April 24, 2023
Peer-review started: April 24, 2023
First decision: July 4, 2023
Revised: July 8, 2023
Accepted: July 17, 2023
Article in press: July 17, 2023
Published online: September 9, 2023

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Abstract

The carbon footprint of healthcare is significantly impacted by intensive care units, which has implications for climate change and planetary health. Considering this, it is crucial to implement widespread efforts to promote environmental sustainability in these units. A literature search for publications relevant to environmental sustainability of intensive care units was done using PubMed. This mini-review seeks to equip intensive care unit practitioners and managers with the knowledge necessary to measure and mitigate the carbon cost of healthcare for critically ill patients. It will also provide an overview of the current progress in this field and its future direction.

Key Words: Carbon footprint; Critical care; Global warming; Greenhouse effect; Greenhouse gases; Plastics

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Core Tip: To achieve environmental sustainability in the intensive care unit (ICU), healthcare professionals must have the knowledge and tools to measure and mitigate the carbon cost of healthcare for critically ill patients. Two complementary methods have been used in the ICU to measure the environmental cost of critical care: Life cycle assessment and material flow analysis. Various methods can decrease waste generation in the healthcare industry, such as preventing the progression of illnesses and inpatient admissions, avoiding unnecessary ICU admissions, minimizing overdiagnosis and over-investigation, and curtailing overtreatment. Interventions can also focus on reducing energy consumption and reusing/recycling products.

Citation: See KC. Improving environmental sustainability of intensive care units: A mini-review. *World J Crit Care Med* 2023; 12(4): 217-225
URL: https://www.wjgnet.com/2220-3141/full/v12/i4/217.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i4.217

INTRODUCTION

Slowing down the harmful effects of climate change and improving planetary health are crucial for humankind[1]. Sustainability involves protecting ecosystems and staying within planetary boundaries[2], which are limits that, if exceeded, could lead to catastrophic environmental changes. One of these boundaries relates to climate change and is measured by atmospheric carbon dioxide concentration, with a threshold of 350 ppm proposed, which has already been exceeded[2]. This highlights an urgent need to reduce greenhouse gas emissions.

It is important for healthcare professionals to promote environmental sustainability, with intensive care units (ICUs) being in a unique position to implement solutions due to their intersection with healthcare and high resource use for critically ill patients. For instance, a life cycle assessment conducted in a United States hospital showed that compared to acute care units, an ICU generates 1.3 times more solid waste (7.1 kg *vs* 5.5 kg) and 3.1 times more greenhouse gases [138 kg *vs* 45 kg CO2-equivalents (CO2e)] per bed day[3]. The major contributors to emissions were consumable goods, building energy consumption, capital equipment purchases, food services, and staff travel.

While ICU staff may be familiar with the need for environmental sustainability, the ability to implement improvements requires knowledge regarding measuring and mitigating the carbon cost of healthcare for critically ill patients. To equip ICU practitioners and managers with such knowledge, this mini-review was therefore done to provide an overview of the current progress in this field and its future direction.

METHODS

An updated search on 8 July 2023 of PubMed® (pubmed.ncbi.nlm.nih.gov) using the search term ("environmental sustainability" OR "ecological sustainability" OR "planetary health" OR "waste recycling" OR "recyclable waste" OR "climate change" OR "climate action" OR "carbon footprint" OR "carbon cost" OR "environmental footprint" OR "life cycle assessment" OR "life cycle analysis" OR “plastic waste”) AND ("ICU" OR "intensive care" OR "critical care") yielded 269 publications. This search was done to update the author's personal library of articles. When they were relevant to environmental sustainability of ICUs, articles were included in this narrative review.

IMPACT OF THE ENVIRONMENT ON HEALTH

The burning of fossil fuels results in the release of greenhouse gases, which include carbon dioxide, methane, and nitrous oxides, as well as particulate matter and sulphur dioxides. The accumulation of these gases in the atmosphere contributes to global warming, which is estimated to cause a rise in temperature of 1 degree Celsius per decade. This increase in temperature can lead to heat-related injuries, dehydration, renal dysfunction, skin cancer, mental health issues, pregnancy complications, allergies, cardiorespiratory illnesses, and an elevated risk of death from cardiovascular causes such as ischemic heart disease, stroke, and heart failure[4]. Additionally, there may be changes in vector-related diseases, rising sea levels, and an increase in wildfires[5,6]. Regions that experience warmer climates such as central and south America, central and south Europe, and southeast Asia may experience an increase in mortality[7]. Burning fossil fuels also generate particulate matter, which further damage the respiratory system, worsen respiratory and cardiovascular diseases, have various non-cardiorespiratory health effects, and increase the number of excess deaths[8].

Plastics, which are widely used in healthcare, are derived from fossil fuels and their extraction, refining, and manufacturing processes contribute to greenhouse gas emissions and global warming. In addition to their impact on global warming, plastics can also harm human health through the presence of microplastics. These are tiny plastic particles with a diameter of less than 5 mm, which can be synthetic or formed from the natural breakdown of larger plastic pieces. Microplastics can be found in air, water, and soil, and can enter plants and animals, including humans, where they have been found in the lungs, blood, stool, and placenta[9]. Per- and polyfluoroalkyl substances (PFAS) are a type of plastic material that is resistant to water, oil, and fire and are commonly used in a wide range of products, including containers, wrapping, and personal protective equipment. However, these chemicals are long-lasting and can accumulate in the blood, brain, liver, and kidneys, leading to adverse health effects. PFAS exposure has been linked to decreased antibody response, dyslipidaemia, decreased growth in infants and foetuses, neurotoxicity in developing brains, and an increased risk of kidney and breast cancer[10,11]. These chemicals are poorly excreted from the body and can persist for years or decades.

IMPACT OF HEALTHCARE ON PLANETARY HEALTH

Health systems are responsible for 1%-5% of the world's carbon footprint[12]. Within health systems, there are several sources of carbon emissions within the ICU. For instance, in patients receiving treatment for septic shock, a carbon footprint evaluation conducted in two ICUs located in Australia and the United States found that energy consumption related to heating, ventilation, and air conditioning accounted for 76%-87% of the carbon footprint, while the use of single-use materials and other consumables were less significant contributors[13].

On a related note, the use of plastics in healthcare has a significant negative impact on the environment, as it contributes to various harmful effects at different stages of the plastic life cycle[11]. These include the extraction of coal, oil, and gas, which are the primary raw materials for plastic production, the energy-intensive manufacturing process, and the inefficient disposal methods, which involve landfilling, controlled burning, and uncontrolled incineration. The use of single-use plastic products, which now make up 35%-40% of plastic production, has contributed to the growing plastic use trend. However, the global recovery and recycling rates for plastics are below 10%, which exacerbates the harmful effects of plastic waste. Plastic production is estimated to be responsible for 3.7% of global greenhouse gas emissions, and this figure is projected to increase to 4.5% by 2060 if no action is taken to curb plastic use.

MEASURING THE ENVIRONMENTAL COST OF HEALTHCARE

Two complementary methods have been used in the ICU to measure the environmental cost of critical care: life cycle assessment (LCA)[13] and more recently, material flow analysis (MFA)[14]. An LCA involves analysing the environmental impact of products or processes, at every stage of a product or process life cycle[13]. This life cycle includes natural resource extraction, manufacturing, packaging, transport, use/reuse, and recycling/waste disposal. In other words, an LCA is a scientific approach that evaluates the environmental impact of a product or process from the beginning of its life cycle to its disposal.

Two main types of LCAs are relevant to healthcare, namely process-based LCAs and Environmentally Extended Economic Input Output (EEIO) LCAs. Process-based LCAs directly measure the environmental impact of a product or activity by assessing material inputs and emissions. These LCAs are useful for comparing related products or processes, such as reusable *vs* disposable equipment. On the other hand, EEIO LCAs are suitable for analysing large data sets where process-based LCA is not feasible. These LCAs rely on nationally reported economic input output tables and pollution emissions tables to estimate the environmental impact of a system. By assigning an environmental footprint to monetary value spent, approximations of entire healthcare systems' CO2e emissions are possible. For example, the UK-MRIO (multi-region input-output) model of Greenhouse Gas emissions[15] and the Eora multiregional input-output database [12] are commonly used in multiregional input-output analysis. This approach covers the entire supply-chain network underpinning the operation of healthcare services and yields comprehensive estimates for environmental footprints. The use of international input-output tables (MRIO in terms of nations/countries as regional units) in EEIO LCA allows for the expansion of the system boundaries from a single country to surrounding regions.

While LCAs focus on a particular product or patient pathway, MFAs provide a broader perspective on all materials entering and leaving the ICU. MFAs quantify all goods and waste flows, making them useful for waste management and raising awareness among ICU staff. They also identify environmental hotspots, which are areas that cause significant environmental impacts and require urgent attention. These hotspots often include products with the highest mass and environmental footprint assessment. By highlighting these hotspots, ICU personnel can then target areas for improvement. In a 2019 case study of a Dutch ICU, 2839 patients were admitted, with an average stay of 4.6 d and a material mass inflow of 247000 kg. Of this, 50000 kg were incinerated as hazardous hospital waste. MFA analysis showed that each patient had an environmental impact of 17 kg of mass, 12 kg CO2e, 300 L of water usage, and 4 m^2 of agricultural land occupation per day. The five identified hotspots were non-sterile gloves, isolation gowns, bed liners, surgical masks, and syringes (including packaging)[14].

PRACTICAL SOLUTIONS FOR IMPROVING ENVIRONMENTAL SUSTAINABILITY IN ICU

Reduce

Categories of interventions include reduce, reuse, and recycle[16]. The category that has the most significant impact is reduction of waste generation since it prevents the creation of environmental pollution from the outset. A review of 54 studies revealed that there is substantial waste in the US healthcare system, with a cost ranging from USD 760-935 billion, representing 25% of all spending[17]. Among this waste, USD 75.7-101.2 billion is attributed to overtreatment or low-value care. Efforts to reduce overtreatment or low-value care could save USD 12.8-28.6 billion.

There are various methods to decrease waste generation in the healthcare industry, such as preventing the progression of illnesses and inpatient admissions, avoiding unnecessary ICU admissions through accurate triage and avoiding futile care, reducing overdiagnosis by not detecting harmless conditions that could be safely left undiagnosed and untreated [18], minimizing over-investigation by avoiding routine blood tests[19], changing central venous catheter infusion sets not earlier than 7 d[20], and curtailing overtreatment such as routine use of proton pump inhibitors for low-risk patients or continued thromboprophylaxis in ambulatory patients. Other solutions for reducing healthcare resources include managing the supply chain prudently to reduce unused medical waste, replacing intravenous drug use with oral altern-

atives, avoiding unnecessary vehicular transport by utilizing telepresence enabled by medical robots[21], reducing facility energy consumption for HVAC (heating, ventilation, and air conditioning) by setting a moderate room temperature[13], improving first-pass success of procedures through better training, decarbonizing energy sources by using natural rather than artificial lighting, reducing paper printouts and forms, minimizing plastic use, and reducing healthcare-associated infections and iatrogenic complications.

Another example of reducing waste generation in healthcare involves avoiding the routine use of supplemental oxygen, which can prevent harmful gas emissions during the production of medical oxygen and disposable plastic masks and tubing[22]. Although avoiding unnecessary computed tomography (CT) or magnetic resonance imaging (MRI) is ideal[23], when necessary, chest X-ray (CXR) or point-of-care ultrasound could also help reduce the carbon footprint. A study showed that the mean CO2e emissions were much higher for MRI and CT scans compared to CXR and ultrasound (17.5 kg/scan for MRI and 9.2 kg/scan for CT, compared to 0.8 kg/scan for CXR and 0.5 kg/scan for ultrasound[24]). In some paediatric ICUs, isolation rooms contribute to over 75% of unused medical waste, which includes endotracheal tubes, diapers, disposable under pads, and flexible suction catheters[25]. Interventions for reducing this waste include stocking fewer items inside patient rooms and keeping them in supply carts outside patient rooms, protecting bedside resuscitator bags, positive end-expiratory pressure valves, and oropharyngeal airways in plastic bags for re-use. Another interesting intervention is to reduce the use of super-pollutants such as inhalational anaesthetics[26,27] (*e.g.*, replace with total IV anaesthesia) and hydrofluorocarbon-containing MDI[28] (*e.g.*, replace with mesh nebulizer), which have high global warming potential.

Reuse

If direct reduction of waste generation is not possible, then indirect methods of reusing and recycling are important. Choosing reusable equipment over single-use disposable ones is one such method[29]. Examples of reusable equipment include stethoscopes, procedural kits, laryngoscope blades, bronchoscopes, laryngeal mask airways, and metal scissors [30]. In one hospital, reusable flexible bronchoscopes were preferred over single-use devices due to their lower environmental impact, lower cost, and technical reliability for tracheal intubation. Another approach to reducing waste is single-use device reprocessing, where used single-use devices are sent to a third-party facility for cleaning, sterilization, and sale back to hospitals. Investing in durable equipment with modular components that are repairable and upgradable can also reduce waste. When making procurement decisions, factors such as energy efficiency and equipment quality must be considered. Extending product lifespans through repairing and upgrading equipment as much as possible can also be effective.

Recycle

The final approach to reducing waste is recycling used fluid bags and non-sharps, with appropriate segregation of registered medical waste (*i.e.*, biohazard waste, which is expensive to process) and non-medical waste. However, recycling has the lowest impact because most life cycle emissions occur during the upstream manufacturing and distribution of products, and recycling requires additional energy and materials, which can create emissions. While there are many practical solutions for reducing, reusing, and recycling (Table 1), few have been validated and peer-reviewed (Table 2).

IMPLEMENTATION OF ENVIRONMENTAL SUSTAINABILITY IN ICU

The COM-B model of behaviour change identifies three essential conditions: capability, opportunity, and motivation[31]. Education can improve motivation among staff, but simply having willpower is not sufficient. Health systems must also provide the opportunity (space), logistics (stuff), and capability (system) for sustainability interventions. Batcup and colleagues conducted a recent systematic review of behavioural change interventions designed to encourage clinicians to reduce carbon emissions in clinical activity. They analysed six full-text studies and 14 conference abstracts and found that the most common behaviour change techniques used were social support, highlighting the consequences, restructuring the physical environment, using prompts and cues, providing feedback on behaviour outcomes, and sharing information about environmental consequences[32].

Education has played a significant role in decreasing the usage of inhalational anaesthetics with high global warming potential (GWP). According to the GWP100 (100 year time horizon GWP), which is used as the standard comparison of long-lived effects, carbon dioxide has a GWP of 1, while desflurane has a GWP100 of 2540, sevoflurane 130, isoflurane 510, and nitrous oxide approximately 265 (nitrous oxide also having ozone-depleting potential)[33]. In one example, staff education on desflurane-sparing practices and distribution of posters has allowed for a gradual removal of desflurane from operating theatres, resulting in a 95.63% reduction in desflurane bottles purchased (from 800 bottles in January 2016 to 35 bottles in December 2021). In contrast, the number of sevoflurane bottles purchased (which has a low global warming potential) increased by 6.13% from 1191 bottles to 1264 bottles, leading to an overall 87.9% decrease in carbon emissions[34].

Improving environmental sustainability in critical care involves the concepts of "greening" and environmental stewardship. "Green" teams, made up of critical care leaders and frontline staff, can be formed to undertake these measures[16,25]. Change management is important, which involves convincing others, obtaining leadership support, and acquiring necessary resources, time, and staffing. Audit, feedback, and continuous improvement cycles are also crucial. Multidisciplinary team members can help reduce waste, such as pharmacists who can review drug charts to identify unnecessary medications and implement antimicrobial stewardship. Ultimately, reducing waste in healthcare is crucial

Table 1 Clinical practices which may aid in reducing the environmental impact of intensive care unit

Category	Clinical practices
Reduce	Avoid unnecessary ICU admissions through accurate triage
	Avoid futile care
	Avoid overdiagnosis
	Avoid over-investigation and routine testing
	Avoid overtreatment
	Avoid overuse of supplemental oxygen
	Avoid routine prophylaxis (*e.g.*, proton pump inhibitors, thromboprophylaxis) for low-risk patients
	Change central venous catheter infusion sets not earlier than 7 d
	Manage supply chain to reduce unused medical waste
	Replace intravenous drug use with oral alternatives
	Avoid unnecessary vehicular transport by utilizing telepresence
	Reduce facility energy consumption for heating, ventilation, and air conditioning, by setting a moderate room temperature
	Improve first-pass success of procedures through better training
	Decarbonize energy sources by using natural rather than artificial lighting
	Reduce paper printouts and forms
	Minimize plastic use
	Reduce healthcare-associated infections and iatrogenic complications
	Stock fewer items inside patient rooms and keep them in supply carts outside patient rooms
	Replace inhalational anaesthetics with total intravenous anaesthesia
	Replace hydrofluorocarbon-containing metered dose inhaler with mesh nebulizer
Reuse	Choose reusable equipment over single-use disposal ones
	Consider single-use device reprocessing
	Extend product lifespans through repairing and upgrading equipment as much as possible
Recycle	Recycle used fluid bags and non-sharps

ICU: Intensive care unit.

for better patient care, improved efficiency, and a healthier planet.

FUTURE DIRECTION

Improving environmental sustainability in healthcare is not only good for the planet but may also reduce healthcare costs. However, it is important to validate interventions to ensure their effectiveness and avoid unintended consequences, such as limiting patients' access to necessary products[35,36]. Education on planetary health and sustainability should be included in medical education[37] and training for all stakeholders[38,39]. Education platforms include virtual learning spaces like the Virtual Health Academy, which provides lectures and workshops on transformative planetary health education in Germany[40]. Education for sustainable healthcare should also be included in faculty development to improve knowledge and teach community-building and leadership skills[41].

Collaboration between humans and artificial intelligence (AI)[42] can contribute to environmental sustainability. Clinicians can input clinical data into electronic health records, while AI can use big data to accurately triage patients for ICU admission[43], potentially reducing unnecessary ICU utilization and healthcare waste. Additionally, ICU staff members can use Radio Frequency Identification systems or AI-driven contactless visual systems[44] to provide real-time data on consumable and equipment usage. Predictive AI models can then assist with forecasting resource utilization[45] and optimizing inventory management, reducing losses from expired consumables and equipment. In other words, AI-enabled effective supply chain management and stocking systems may help minimize overstocking and waste of expired equipment.

Table 2 Published environmental sustainability efforts done in intensive care unit

Category	Method	Outcome	Ref.
Reduce	Redesign pharmaceutical doses and packaging; install waste containers for non-recyclables and chemical wastes; educate staff	Decreased solid waste generation by 39% (13.7 to 8.4 kg/patient/d)	Furukawa *et al* [47], 2016
Reduce	Four-step action plan: (1) Audit local practice; (2) develop clinical guideline for rational ordering; (3) educate stakeholders; and (4) measure impact through re-audit	Comparing July-December 2017 *vs* July-December 2018 in a 58-bed ICU, number of ABG tests decreased by 31.3%, saving A$770000, 100 L of blood, and reducing emissions of 1038 kg CO2e (akin to driving 6782 km in an average Australian car). Inappropriate ABG testing decreased by 47.3%, and the number of inappropriate tests per bed-day decreased by 71%, without worsening patient mortality	Walsh *et al* [48], 2020
Reduce	Relocating in-room disposable equipment to supply carts situated outside the patient rooms, while using small baskets for basic admissions with expected short lengths of stay. Additionally, instead of refilling all items to quota, daily room restocking was customized based on nursing requirements	A Canadian ICU with 16 beds implemented a strategy to reduce the amount of unused equipment waste, resulting in a large 80% decrease. This reduction translated to an approximate annual saving of Can$110000	Yu *et al*[49], 2021
Recycle	Recycling program in ICU	An Australian ICU produced 540 kg total waste/week in 2008, which reduced to 505 kg after introducing a recycling program in 2013, with 14% of the total waste being recycled	McGain *et al* [50], 2009; Kubicki *et al* [51], 2015

ABG: Arterial blood gas; ICU: Intensive care unit.

Promoting environmental sustainability requires the active participation of stakeholders beyond the ICU, *e.g.*, manufacturers and healthcare regulators. On the one hand, manufacturers should strive to prioritize sustainability in their product designs and production processes, aiming for environmentally friendly alternatives whenever feasible. For non-recyclable products, these should offer substantial advancements in device performance compared to their recyclable counterparts, to justify their purchase. On the other hand, healthcare regulators should preferentially approve products that can be reusable or recycled, lessening waste accumulation and environmental degradation. For instance, the World Health Organization has recommended that when purchasing equipment and supplies, environmentally friendly products should be prioritized, such as those with minimal packaging, reusable and recyclable parts, and minimal hazardous chemicals and non-degradable plastics[46].

CONCLUSION

Promoting environmental sustainability in healthcare, specifically in the ICU, is essential for mitigating the environmental impact of critical care and improving planetary health. Sustainability involves staying within planetary boundaries, which if exceeded, could lead to catastrophic environmental changes. One of these boundaries relates to climate change, and the atmospheric carbon dioxide concentration has already exceeded the proposed threshold of 350 ppm. Therefore, reducing greenhouse gas emissions is urgent.

To achieve environmental sustainability in the ICU, healthcare professionals must have the knowledge and tools to measure and mitigate the carbon cost of healthcare for critically ill patients. Two complementary methods have been used in the ICU to measure the environmental cost of critical care: LCA and MFA. Various methods can decrease waste generation in the healthcare industry, such as preventing the progression of illnesses and inpatient admissions, avoiding unnecessary ICU admissions, minimizing overdiagnosis and over-investigation, and curtailing overtreatment. Interventions can also focus on reducing energy consumption and reusing/recycling products.

ICU staff should take a lead role in implementing solutions due to their intersection with healthcare and high resource use for critically ill patients. However, reducing the environmental footprint of critical care requires a collective effort from healthcare providers, patients, policymakers, and other stakeholders. Collaborative efforts, including those with artificial intelligence, can result in more sustainable healthcare systems and better health outcomes for individuals and the planet.

FOOTNOTES

Author contributions: See KC collected the data, wrote the paper, read and approved the final manuscript.

Conflict-of-interest statement: The author reports no relevant conflicts of interest for this article.

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Country/Territory of origin: Singapore

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World Journal of Critical Care Medicine

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World J Crit Care Med 2023 September 9; 12(4): 226-235

DOI: 10.5492/wjccm.v12.i4.226

ISSN 2220-3141 (online)

ORIGINAL ARTICLE

Retrospective Study

Delayed inflammatory pulmonary syndrome: A distinct clinical entity in the spectrum of inflammatory syndromes in COVID-19 infection?

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gupta MK, Germany; Luo W, China

Received: May 11, 2023
Peer-review started: May 11, 2023
First decision: June 15, 2023
Revised: June 24, 2023
Accepted: July 6, 2023
Article in press: July 6, 2023
Published online: September 9, 2023

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Abstract

BACKGROUND

During the second wave of the coronavirus disease 2019 (COVID-19) pandemic, a subset of critically ill patients developed delayed respiratory deterioration in the absence of new infection, fluid overload or extra-pulmonary organ dysfunction.

AIM

To describe the clinical and laboratory characteristics, outcomes, and management of these patients, and to contrast this entity with other post COVID-19 immune dysregulation related inflammatory disorders.

METHODS

This was a retrospective observational study of adult patients admitted to the medical intensive care unit of a 2200-bed university affiliated teaching hospital, between May and August 2021, who fulfilled clearly defined inclusion and exclusion criteria. Outcome was assessed by a change in PaO_2/FiO_2 ratio and levels of inflammatory markers before and after immunomodulation, duration of mechanical ventilation after starting treatment, and survival to discharge.

RESULTS
Five patients developed delayed respiratory deterioration in the absence of new infection, fluid overload or extrapulmonary organ dysfunction at a median interquartile range (IQR) duration of 32 (23-35) d after the onset of symptoms. These patients had elevated inflammatory markers, required mechanical ventilation for 13 (IQR 10-23) d, and responded to glucocorticoids and/or intravenous immunoglobulin. One patient died (20%).

CONCLUSION
This delayed respiratory worsening with elevated inflammatory markers and clinical response to immunomodulation appears to contrast the well described Multisystem Inflammatory Syndrome – Adults by the paucity of extrapulmonary organ involvement. The diagnosis can be considered in patients presenting with delayed respiratory worsening, that is not attributable to cardiac dysfunction, fluid overload or ongoing infections, and associated with an increase in systemic inflammatory markers like C-reactive protein, inteleukin-6 and ferritin. A good response to immunomodulation can be expected. This delayed inflammatory pulmonary syndrome may represent a distinct clinical entity in the spectrum of inflammatory syndromes in COVID-19 infection.

Key Words: COVID-19; ARDS; Multisystem Inflammatory Syndrome in Adults; Long COVID; Organizing pneumonia

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Core Tip: Delayed respiratory deterioration in critically ill coronavirus disease 2019 (COVID-19) in the absence of new infection, fluid overload, pneumothorax, or lung collapse is seen in a subset of patients admitted to the intensive care unit. This presentation does not fit in to the definition of Multisystem Inflammatory Syndrome Adults, owing to the predominance of pulmonary symptoms and the notable absence of cardiac, gastrointestinal, and mucocutaneous manifestations. In the current study, five patients developed worsening respiratory function requiring escalation of ventilatory support after the third week of COVID-19 illness. This was accompanied by elevated inflammatory markers. All five patients showed clinical response to immunomodulation. This delayed inflammatory pulmonary syndrome contrasts Multisystem Inflammatory Syndrome Adults where extrapulmonary organ involvement predominates.

Citation: Bose P, Chacko B, Arul AO, Robinson Vimala L, Thangakunam B, Varghese GM, Jambugulam M, Lenin A, Peter JV. Delayed inflammatory pulmonary syndrome: A distinct clinical entity in the spectrum of inflammatory syndromes in COVID-19 infection? *World J Crit Care Med* 2023; 12(4): 226-235
URL: https://www.wjgnet.com/2220-3141/full/v12/i4/226.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i4.226

INTRODUCTION

While much has been written about coronavirus disease 2019 (COVID-19) Associated Acute Respiratory Distress Syndrome (CARDS)[1], less is known about the clinical presentations that evolve after the acute infection has subsided. The Centre for Disease Control (CDC) has grouped a cluster of organ failure syndromes under the umbrella of multisystem inflammatory syndrome (MIS). This entity is characterised by dysregulated host immune response causing widespread organ dysfunction and usually follows the period of viremia[2]. MIS was first described in COVID-19 in the paediatric population and was termed MIS-C (Children)[2]. Although a similar phenomenon was subsequently reported in adults (MIS-A) in 2021[3], the MIS-A criteria, in contrast to the MIS-C, is strikingly bereft of respiratory involvement. It has encompassed primarily an extrapulmonary syndrome with cardiac, neurologic, and gastrointestinal manifestations [3].

While managing COVID-19 patients in the intensive care unit (ICU), we observed that a small subset of patients with CARDS developed worsening respiratory function after an initial period of improvement that could not be attributed to the usual causes such as superadded infection, lung collapse, pleural effusion, pulmonary embolism, or fluid overload. Unlike CARDS or the fibrotic phase of ARDS which are a continuum of the initial insult, this phenomenon was observed in patients with increasing ventilatory requirements between the third and fourth weeks after the diagnosis of COVID-19. Respiratory deterioration was associated with an increase in inflammatory markers with minimal or no extrapulmonary organ involvement. This clinical picture suggested an entity not fitting into the classical MIS-A definition but nevertheless befitting a distinct position in the spectrum of inflammatory syndromes in COVID-19.

The study was thus aimed to describe the clinical and laboratory characteristics of this delayed inflammatory pulmonary syndrome (DIPS) through a retrospective review of cases admitted in the ICU during the second wave of the pandemic, along with clinical outcomes and caveats in management.

MATERIALS AND METHODS

Study setting and design

This was a retrospective observational study of adult patients admitted to the medical ICU of a 2200-bed university affiliated teaching hospital, between May and August 2021.

Study approval

The study was approved by the Institutional Review Board of the institution. In view of the retrospective nature of the study and the large number of COVID-19 patients admitted in the ICU, informed consent waiver was obtained from the institutional review board.

Data harvesting

Computerised records of patients admitted in the medical ICU during the period of study was accessed and those fulfilling the following diagnostic criteria for delayed inflammatory pulmonary syndrome were included in the analysis.

Criteria for the diagnosis of delayed inflammatory pulmonary syndrome (modified from CDC criteria for MIS-A)

Patients were considered to have DIPS if they fulfilled ALL the following clinical and laboratory criteria.

Clinical criteria: Documented fever (≥ 38.0°C) along with evidence of respiratory involvement in the form of:

(a) Development of respiratory failure or worsening respiratory failure following a period of initial improvement, occurring after the third week of COVID illness and requiring either non-invasive or invasive mechanical ventilation, with documented acute drop in PaO_2/FiO_2 (PF) ratio, resulting in a change in the respiratory Sequential Organ Failure Assessment (SOFA) score by at least one point over 24 h.

(b) New or worsening bilateral diffuse infiltrates on chest radiograph or computed tomography (CT) scan, not due to pleural effusion, lobal collapse, pulmonary nodules, or pulmonary embolism.

(c) Respiratory failure not explained by left atrial hypertension or cardiac failure or fluid overload.

(d) Exclusion of infection as the cause of worsening lung function.

Laboratory evidence: The presence of laboratory evidence of inflammation AND SARS-CoV-2 infection.

(a) Elevated levels (exceeding the upper limit of normal specific to age and gender) of at least TWO of the following: C-reactive protein (CRP), ferritin, interleukin-6 (IL-6), or erythrocyte sedimentation rate.

(b) A positive SARS-CoV-2 test by reverse transcriptase polymerase chain reaction (RT-PCR), serology, or antigen detection in the current admission or in the previous 12 wk[3].

(c) Negative blood culture and endotracheal aspirate cultures collected at the time of worsening of lung function and not fulfilling the CDC definition of ventilator associated pneumonia (VAP)[4].

Management protocol

Adult patients aged ≥ 18 years fulfilling criteria for CARDS received as part of the protocol, dexamethasone 6 mg once daily for 10 d and therapeutic anticoagulation if D-Dimer was more than 1000 ng/mL. Following the diagnosis of DIPS, patients were treated with intravenous immunoglobulins (IVIG) at a dose of 2 g/kg over three to five days, or with steroids (6 mg dexamethasone once or twice daily or hydrocortisone 50 mg every six hours, as per the treating clinician's assessment and discretion). The decision on the use of IVIG was left to the treating physician and also guided by financial feasibility. Daily clinical monitoring and blood gas analysis was done to track improvement in respiratory function.

Statistical analysis

The data was tabulated and analysed using Microsoft Excel version Office 365. Continuous variables were presented as mean, standard deviation (SD) for normally distributed data and as median, interquartile range, (IQR) for skewed data. Categorical data were reported as proportions. Paired-t test was done to analyse the change in PF ratio before and after the onset of DIPS.

Main outcomes and measures

The outcome measures that were assessed were survival to discharge, change in the PF from the onset of DIPS to after immunomodulation, change in inflammatory markers before and after DIPS and duration of mechanical ventilation after the onset of DIPS.

RESULTS

Five patients, with mean (SD) age of 48.2 (14.2) years and median (IQR) Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score of 19 (IQR 10-21), fulfilled the case definition of DIPS. One patient who was included had a positive endotracheal aspirate culture (patient 4) but did not fulfil the CDC criteria for VAP[4]. All five patients underwent point of care echocardiography for assessment of left ventricular function. There was no evidence of left ventricular dysfunction; in addition, 3 of the 5 patients in whom an NT pro-BNP was done had values of 449, 132 and 146 pg/mL (reference range: Up to 125 pg/mL). There was a male preponderance (80%); the lag time from symptom onset to

deterioration was a median 32 d (IQR 23-35 days). One patient (patient 2) had received 2 doses of vaccination with the Oxford-AstraZeneca ChAdOx1 nCoV-19 recombinant vector Corona Virus Vaccine (Brand: Covishield™, manufactured by the Serum Institute, India) prior to admission. Two patients (patients 3 and 5) were not vaccinated. The vaccination history of the remaining two patients (patient 1 and 4) could not be ascertained as contact could not be established through telephone.

Clinical and laboratory characteristics at baseline and at the time of respiratory deterioration are summarised in Table 1. Figure 1 illustrates that respiratory SOFA scores contributed predominantly to the total SOFA score in all subjects on the day of deterioration. Representative chest radiographs and high-resolution CT scan images taken before the onset of symptoms, at the nadir of PF ratio and during recovery show the evolution of diffuse infiltrates and resolution following treatment (Figure 2).

There was a significant drop in the PF ratio from a peak of 323 ± 96.2 (mean ± SD) prior to DIPS to 169.8 ± 33.7 (mean ± SD) after the onset of DIPS (P = 0.043). There was an increase in the levels of inflammatory markers (CRP, Ferritin) at the onset of DIPS when compared with baseline (Table 1); IL-6 levels were also elevated (Table 1). The median duration of mechanical ventilation prior to the onset of DIPS was 9 (2-16) d.

At the time of deterioration of respiratory function, of the 5 patients, two patients (patients 2 and 4) deteriorated while on a spontaneous mode of invasive ventilation to require high ventilatory support. Both these patients were subsequently weaned off the ventilator following immunomodulation and extubated; at the time of discharge, they were on room air. Two other patients (patients 1 and 3) were on intermittent non-invasive ventilation (NIV) at the time of deterioration, worsening to require continuous NIV with increased oxygen support and higher positive end-expiratory pressure. Following immunomodulation, patient 3 improved and was discharged stable while patient 1 developed a tension pneumothorax, and subsequently a nosocomial infection and succumbed. Patient 5 who was initially admitted for moderate COVID-19 infection and discharged home re-presented on day 36 with worsening respiratory failure needing intubation and mechanical ventilation. She improved with immunomodulation and was discharged stable.

All 5 patients were on anticoagulation at the time of respiratory deterioration. Of these, 2 were on therapeutic anticoagulation with low molecular weight heparin (enoxaparin) at a dose of 1 mg/kg every 12 h (monitoring of anti- factor Xa levels was done on one patient) while the other 3 patients were on unfractionated heparin with monitoring of activated partial thromboplastin time.

Following the diagnosis of DIPS, two patients received IVIG at 2 g/kg over 5 days, while one received dexamethasone at 6 mg twice daily for 5 d followed by once daily for 5 d, one received dexamethasone 6 mg once daily for 10 d, and the fifth received hydrocortisone 50 mg every six hours for 5 d. Following immunomodulation there was a significant improvement in the PF ratio from 169.8 ± 33.7 at the onset of DIPS to 349.2 ± 57.6 (P = 0.001) over time. The trends of PF ratios over time for the 5 individual patients is shown in Figure 3. Mechanical ventilation was required for a median duration of 13 (10-23) d after the onset of DIPS. Four out of the five patients (80%) survived to hospital discharge.

DISCUSSION

This series describes five critically ill patients with CARDS who developed unexplained worsening respiratory function after a median interval of 32 d (IQR 23-35 d) from the onset of symptoms of COVID-19. These patients had increased inflammatory markers and responded to immunomodulation. This syndrome of worsening gas exchange appears to be part of a dysregulated host immune response; however, the clinical characteristics of our subset of patients did not fit in to criteria described for the diagnosis of MIS-A.

Lung hyperinflammation is an established phenomenon in the context of CARDS and occurs as part of the initial presentation of COVID-19 infection, generally in the second week following onset of symptoms[5]. Our novel observation of ventilated CARDS patients developing delayed pulmonary hyperinflammation three to four weeks after of the onset of initial symptoms, which improved with immunomodulation, has hitherto not been reported.

In a large cohort of MIS-A, patients developed MIS-A at a median time of 28 d from the onset of COVID-19–like illness [6]. The time of presentation in our cohort was similar (median 32 d). However, the paucity of extrapulmonary organ dysfunction and the predominance of lung involvement sets it apart from MIS-A cohorts[6]. It is unclear if DIPS represents a distinct clinical entity or is part of the spectrum of MIS-A. The differences between DIPS, CARDS and MIS-A are summarised in Table 2[2,6-12].

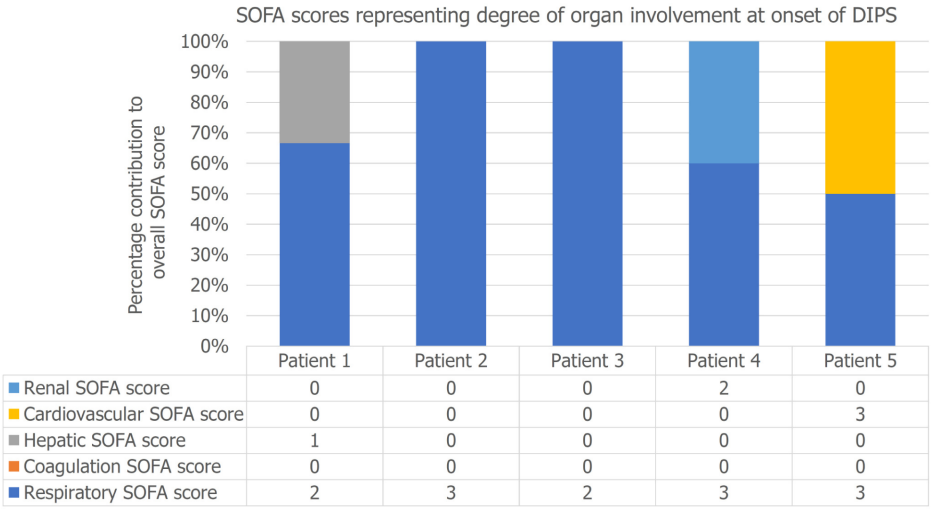
Deteriorating lung function occurring beyond 4 wk after COVID-19 illness, in the absence extra-pulmonary organ involvement has also been previously reported from a few centres either as persistent post COVID-19 interstitial lung disease (ILD), organising pneumonia, secondary organising pneumonia[7-9] or pulmonary fibrosis[13]. Although the time of onset of symptoms may imply a similar pathology in our cohort, there are several differences that merit consideration. All the 35 patients described in the ILD case series[9] were reviewed 4-weeks after discharge following a telephone interview, in the outpatient clinic, for persistence of respiratory symptoms. In another report[7], two patients presented two months after discharge: one with new onset breathlessness for 3 d and the other with a 1-week history of worsening cough and right sided pleuritic chest pain. The case report of a 36-year-old male with diffuse large B-cell lymphoma[8] was an acute presentation with high fever and fatigue, 40 d after a COVID infection. All the patients described in these publications were discharged from hospital after the initial illness and on review reported persistence of respiratory symptoms[7,9] or presented with new symptoms after recovery[8] that were not severe enough to warrant ventilatory support. In contrast, all the patients in our cohort barring one, developed worsening symptoms while in hospital, occurring as a continuum after the initial improvement following treatment for CARDS, were much sicker, and required ventilatory support. The radiological features in the reports[7-9] ranged from focal consolidation, ground-glass

Table 1 Patient characteristics

Baseline characteristics of the study cohort (*n* = 5)	
Age (mean ± SD) yr	48.2 (14.2)
Male: Female ratio	4: 1
APACHE-II score at admission (median, IQR)	19 (10-21)
Day of worsening from date of onset of symptoms (Median, IQR)	32 (23-35)
Oxygenation parameters (median, IQR) PF ratio	
Peak PF ratio prior to onset of DIPS	326 (243-329)
PF ratio at onset of DIPS	182 (156-190)
Peak PF ratio after immunomodulation	353 (327-353)
Ventilation data (median, IQR) d	
Duration of mechanical ventilation[a] prior to the onset of DIPS	9 (2-16)
Duration of mechanical ventilation after the onset of DIPS	13 (10-23)
Inflammatory markers (median, IQR)	
CRP (mg/L) at baseline	142 (113-182)
CRP (mg/L) at onset of DIPS	165.5 (157-212)
Ferritin (ng/mL) at baseline	270.2 (191-349)
Ferritin (ng/mL) at onset of DIPS	677.5 (382-1893)
IL-6 (pg/mL) at onset of DIPS (median, IQR)	207.4 (163-311)

[a]Mechanical ventilation includes both invasive and non-invasive ventilation.

SD: Standard deviation; APACHE: Acute Physiology and Chronic Health Evaluation; PF: (PaO_2/FIO_2); IQR: Interquartile range; DIPS: Delayed inflammatory pulmonary syndrome; CRP: C reactive protein (reference range: < 6 mg/L). Ferritin reference range (male: 22-322 ng/mL; female: 10-291 ng/mL); IL: Interleukin (reference range: < 7 pg/mL);



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Figure 1 Sequential Organ Failure Assessment score representing degree of organ involvement in Delayed Inflammatory Pulmonary Syndrome. The contribution of respiratory Sequential Organ Failure Assessment (SOFA) to the overall SOFA score is depicted for all the five patients. It is evident that in all patients, respiratory SOFA contributed to > 50% of the total SOFA score. In two patients, there was no extrapulmonary organ dysfunction, while in the remaining three patients, there was some hepatic, renal and cardiovascular dysfunction. DIPS: Delayed Inflammatory Pulmonary Syndrome; SOFA: Sequential Organ Failure Assessment.

attenuation, and linear opacities[7] to extensive pulmonary infiltrates[8] and peri-bronchial and peri-lobar dense consolidation with traction bronchiectasis in the ILD series[9]. In the ILD series, 21 patients with pure ground glass opacities involving < 15% of the lung and 3 patients with fixed minor ground glass opacities were excluded and offered follow-up

Table 2 Comparison of characteristics of coronavirus disease 2019 (COVID-19) associated acute respiratory distress syndrome, multisystem inflammatory syndrome Adults, multisystem inflammatory syndrome Children, post COVID-19 secondary organising pneumonia, post COVID-19 interstitial lung disease and Delayed Inflammatory Pulmonary Syndrome

Syndrome	Time of onset (Median, IQR) d	Primary organ affected	Other organs affected	Inflammatory markers	Treatment	Intensive care required (%)	Mortality, %
CARDS[11,12]	8 (5-13) d from onset of infection	Lungs	Gastro-intestinal	Elevated IL-2, IL7, TNF-α	Corticosteroids, Baricitinib (JAK-2 inhibitor) and Tocilizumab (IL-6 inhibitor) in severe hypoxia and evidence of hyperinflammation	Yes (17)	39
MIS-A[6]	28 (20-36) d after SARS-CoV-2 infection	Cardio-vascular	Gastro-intestinal, muco-cutaneous, haematological	Fibrinogen, D-dimer, CRP, ferritin, IL-6 elevated in > 90%	IVIG (55%), corticosteroids (74%), IL-6 inhibitors (21%)	Yes (57)	7
MIS-C[2]	Within 4 wk of SARS-CoV-2 infection (13)	Gastro-intestinal tract	Muco-cutaneous	CRP, ferritin, procalcitonin, IL-6 elevated	IVIG (76.4%) and corticosteroids (52.3%), IL-1ra inhibitor (8.5%) and IL-6 inhibitors (6%)	Yes (73.8)	1.9
Secondary OP[7,8]	Beyond 4 wk of SARS-CoV-2 infection	Lungs	Nil	CRP (mild elevation: 3.45 to 11.7 mg/dL)	Corticosteroids	No	Nil
Secondary ILD[9]	6 wk after discharge from hospital	Lungs	Uncommon	CRP and ferritin significantly elevated	Corticosteroids	No	Nil
DIPS (Current study)	32 (23-35) d after symptom onset	Lungs	Uncommon	Elevated CRP, ferritin, and IL-6	Good response to IVIG/steroids	Yes (100)	20

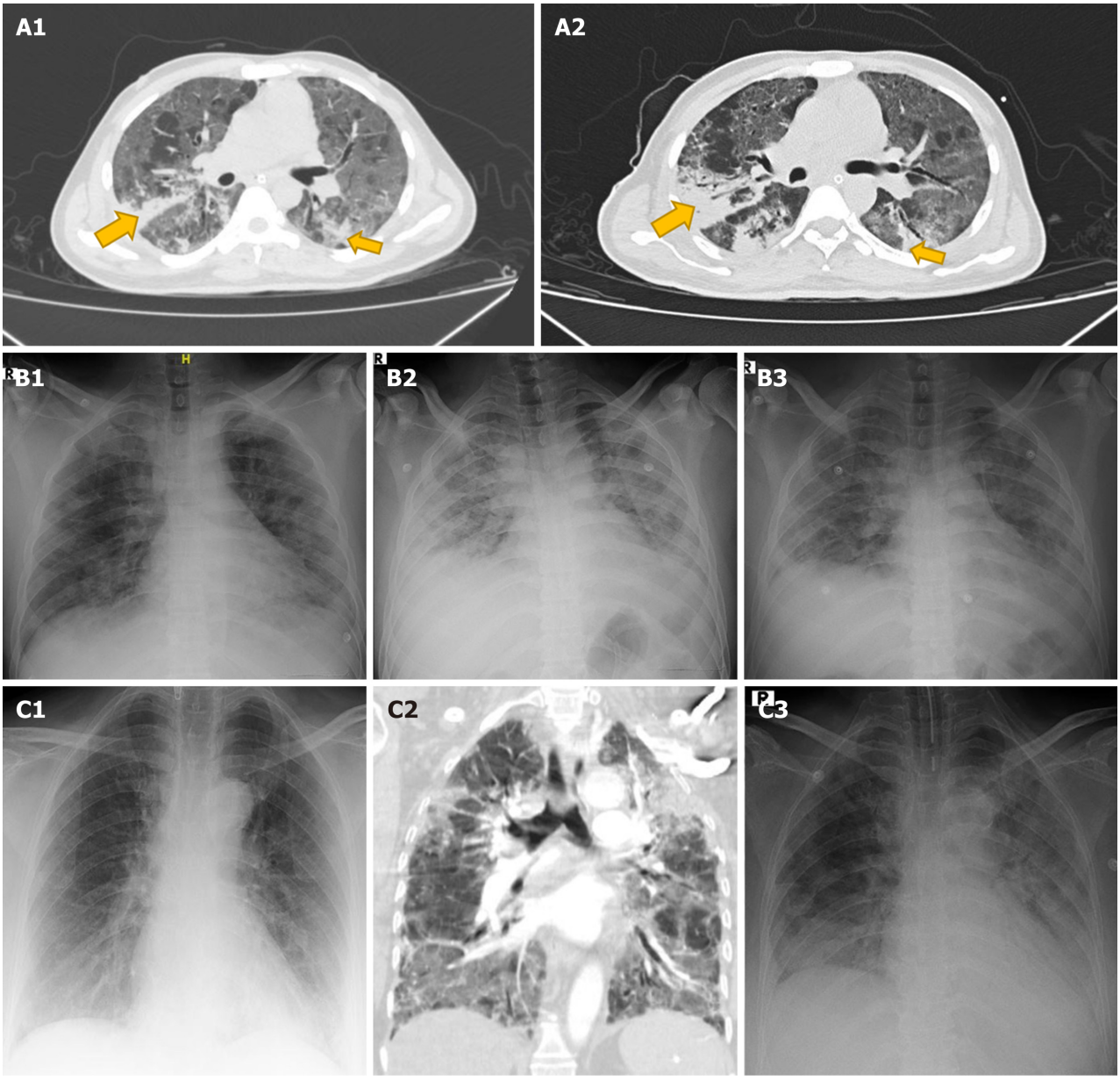
CARDS: COVID-19 associated acute respiratory distress syndrome; MIS-A: Multisystem inflammatory syndrome Adults; MIS-C: Multisystem inflammatory syndrome Children; OP: Organising pneumonia; ILD: Interstitial lung disease; DIPS: Delayed inflammatory pulmonary syndrome; IQR: Interquartile range; equivalent of dexamethasone 6 mg once daily recommended in hypoxic patients; IVIG: Intravenous immunoglobulin; CRP: C-reactive protein.

[9]. The patients in our cohort had radiological features of focal or diffuse ground glass opacities in addition to pulmonary infiltrates and tractional bronchiectasis. The radiological features in our series may thus reflect mixed pathology or evolution from one pathological phase of the illness to another, as occurs in ARDS and may not be pathognomonic of a specific diagnosis. Although histopathology would have helped characterise the syndrome further, this was not done in our series due to concerns of performing lung biopsy in patients on high ventilatory support. In the other case reports, the histological features were consistent with organising pneumonia[7,8]; biopsy was not done in the ILD series[9].

Pulmonary fibrosis as a cause for clinical deterioration is unlikely in our patients for the following reasons. The rapid deterioration of symptoms correlated with an increase in serum inflammatory markers and imaging (ground glass opacification) that was consistent with an inflammatory process. This clinical picture contrasts the more subacute presentation and imaging characteristics of pulmonary fibrosis of architectural distortion in the form of irregular reticulation, traction bronchiectasis and honeycombing[14]. The rapid resolution of symptoms and radiological opacities with immunomodulation also makes pulmonary fibrosis less likely.

Other causes for worsening lung function need to be considered. It is possible that prior vaccination could have contributed to ARDS[15]. Vaccination history could not be obtained for all patients and hence association or lack of it could not be ascertained. There is also evidence that microvascular thrombosis contributes to the pathophysiology of COVID-19 infection[16,17]. Although it is possible that micro-thrombosis may have contributed to the manifestations, worsening of respiratory function cannot be explained only by ongoing thrombosis given that all patients received anticoagulation, and the observation that patients responded rapidly to immunomodulation. However, the debate on the appropriate level of anticoagulation for COVID-19 patients remains unresolved.

The number of patients described in this cohort as well as on persistent post-COVID-19 ILD[9] or post COVID organising pneumonia[8] is small in relation to the proportion of COVID-19 infected patients; however, subsets with varying clinical presentation and course of illness is not unique to COVID-19 and needs to be documented and reported for better understanding of any disease. The response to immunomodulation in our patients highlights the importance of considering this syndrome among the differential diagnosis for delayed respiratory deterioration. Various biomarkers that have been postulated to correlate with increased incidence of the post-acute sequelae of SARS-CoV-2 infection are TNF-α, IP-10 (Interferon-inducible protein-10) and IL-6, also need to be explored further[18]. Although larger studies are required to provide additional insights on these preliminary observations, awareness of this clinical entity will help in



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Figure 2 Representative Cross sectional computed tomography and plain radiograph images of patients with Delayed Inflammatory Pulmonary Syndrome. A: High resolution transverse computed tomography (CT) sections of patient 4, showing the evolution of infiltrates from day -2 of Delayed Inflammatory Pulmonary Syndrome (DIPS) (A1) till day +15 (A2). The diffuse ground glass opacities seen in A1 have reduced, while the areas of consolidation (marked with yellow arrows) have increased slightly, along with features of tractional bronchiectasis, suggestive of coronavirus disease (COVID) sequelae. The overall improvement in clinical status from A1 to A2 could suggest that the ground glass opacities were part of the inflammatory changes in the lungs and responded to immunomodulation; B: Representative plain radiographs (portable) of patient 1 showing the evolution of infiltrates from day -7 of DIPS (B1) till day 0 (B2), followed by improvement on day +1 (B3), after the initiation of glucocorticoids; C: Representative chest radiograph and coronal high resolution CT sections on day -26 (C1, taken in the index admission for mild COVID on day 10 of symptom onset) before the onset of DIPS, significant increase in diffuse ground glass opacities on day 0 of DIPS (C2), followed by improvement on day +1 of DIPS (C3).

timely diagnosis and treatment of a potentially lethal cause of respiratory failure in the ICU.

CONCLUSION

Delayed inflammatory pulmonary syndrome is a serious and life-threatening complication of long COVID, occurring commonly in the fourth week of illness and characterised by a predominance of pulmonary hyperinflammation in the absence of secondary infections or fluid overload or extrapulmonary organ system involvement. This entity can be considered in the differential diagnoses in a patient with delayed deterioration in pulmonary function, after a period of initial improvement. The diagnosis is supported by raised inflammatory markers. Treatment with immunomodulation (systemic glucocorticoids or intravenous immunoglobulin) can be considered and a good response expected.

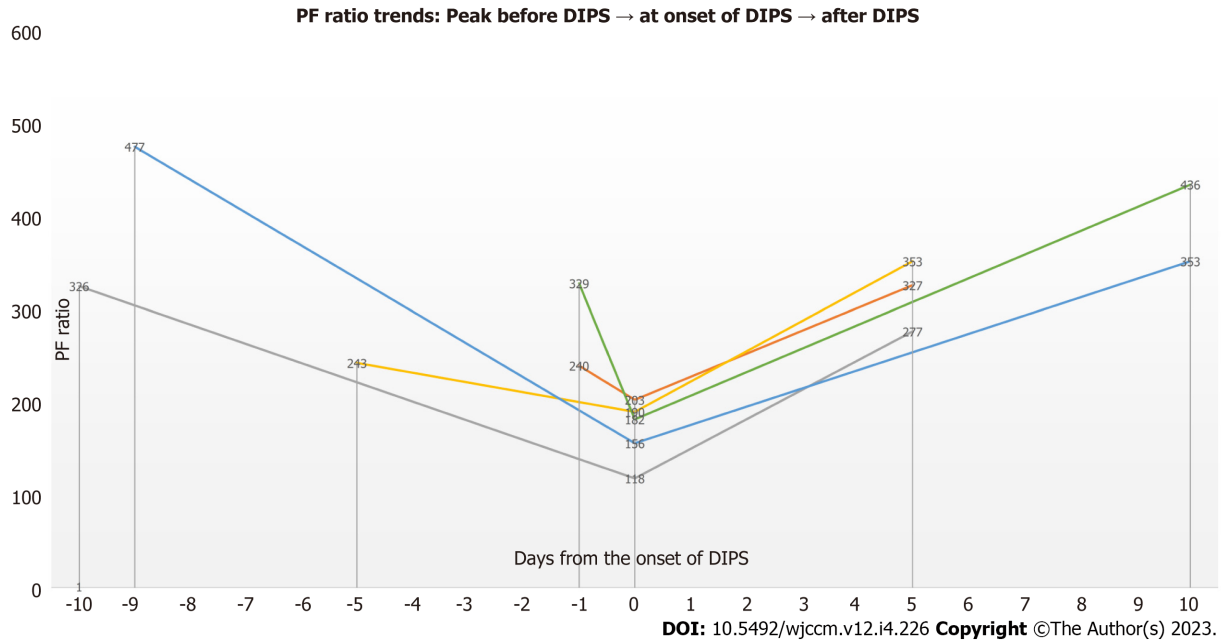


Figure 3 PaO_2/FiO_2 ratio trends of patients prior to, during and post Delayed Inflammatory Pulmonary Syndrome. The PaO2/FiO2 (PF) ratio of the individual patients is shown in the y-axis. The x-axis depicts day 0 as the day of onset of Delayed Inflammatory Pulmonary Syndrome (DIPS). The highest PF ratio of each patient in the period prior to DIPS and following recovery from DIPS is plotted. The figure shows that the respiratory deterioration occurred gradually over several days in 3 patients and acutely over a day in 2 patients. Recovery was gradual over 5 to 10 d. DIPS: Delayed Inflammatory Pulmonary Syndrome; SOFA: Sequential Organ Failure Assessment.

ARTICLE HIGHLIGHTS

Research background

Delayed deterioration in pulmonary function, following initial improvement, was seen in a subset of patients admitted to the intensive care unit (ICU) during the coronavirus disease 2019 (COVID-19) pandemic. These patients had no evidence of ongoing infection, fluid overload or cardiac dysfunction, but had elevated systemic inflammatory markers. They did not satisfy the diagnostic criteria for Multisystem Inflammatory Syndrome- Adults (MIS-A) due to the paucity of extra-pulmonary organ manifestations (mainly cardiac, gastrointestinal and mucocutaneous), but responded well to immunmodulation.

Research motivation

Delayed worsening of respiratory function in the ICU is generally attributable to infection, cardiac dysfunction, or fluid overload. But non-infectious inflammatory complications of post COVID-19 immune dysregulation is a distinct clinical entity that may play a role in worsening organ dysfunction in patients who have no evidence of the above.

Research objectives

The objectives of the current study were to describe the clinical and laboratory characteristics of post COVID-19 delayed inflammatory pulmonary syndrome (DIPS), the outcomes and management caveats encountered in the management of these patients, and to contrast DIPS with other post COVID-19 immune dysregulation related inflammatory disorders.

Research methods

This was a retrospective observational study of adult patients admitted to the medical ICU of a 2200-bed university affiliated teaching hospital, between May and August 2021, who fulfilled clearly defined inclusion and exclusion criteria. Outcome was assessed by a change in PaO_2/FiO_2 ratio and levels of inflammatory markers before and after immunomodulation, duration of mechanical ventilation after starting treatment, and survival to discharge.

Research results

Five patients developed delayed respiratory deterioration in the absence of new infection, fluid overload or extra-pulmonary organ dysfunction at a median interquartile range (IQR) duration of 32 (23-35) d after the onset of symptoms. These patients had elevated inflammatory markers, required mechanical ventilation for 13 (IQR 10-23) d, and responded to glucocorticoids and/or intravenous immunoglobulin. One patient died (20%).

Research conclusions

This delayed respiratory worsening with elevated inflammatory markers and clinical response to immunomodulation

appears to contrast the well described MIS-A by the paucity of extrapulmonary organ involvement. The diagnosis can be considered in patients presenting with delayed respiratory worsening, that is not attributable to cardiac dysfunction, fluid overload or ongoing infections, and associated with an increase in systemic inflammatory markers like C-reactive protein, inteleukin-6 and ferritin. A good response to immunomodulation can be expected. This delayed inflammatory pulmonary syndrome may represent a distinct clinical entity in the spectrum of inflammatory syndromes in COVID-19 infection.

Research perspectives

Larger prospective studies are required to validate these preliminary observations and formulate treatment guidelines for this inherently reversible entity.

ACKNOWLEDGEMENTS

The authors acknowledge the contributions of the healthcare team in the management of patients during the COVID-19 pandemic.

FOOTNOTES

Author contributions: Bose P, Chacko B, Oliver A, and Peter JV designed and performed the research and wrote the paper, performed literature search, reviewed the final manuscript, and approved for publication; Leena RV, Balamugesh T, George MV, Mohan J, and Audrin L provided clinical advice, literature review, reviewed the final manuscript and approved the manuscript for publication; Peter JV designed the research and supervised the report.

Institutional review board statement: The study was approved by the Institutional Review Board of the institution, (CDSCO- Ethics Committee Registration number: ECR/326/INST/TN/2013/RR-2019; DHR provisional registration number: EC/NEW/INST//2020/818; IRB Min No. 14513, approval date 23.02.2021, study title: "Pulmonary hyperinflammation syndrome in survivors of critically ill COVID-19 Long stayers in ICU – a case series").

Informed consent statement: In view of the retrospective nature of the study, the large number of COVID-19 patients admitted in the ICU, and deidentification of clinical data, informed consent waiver was obtained from the institutional review board.

Conflict-of-interest statement: There was no conflict of interest or any financial disclosure for all the authors listed in the manuscript.

Data sharing statement: No additional data are available.

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S-Editor: Liu JH
L-Editor: A
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ISSN 2220-3141 (online)

World Journal of

Critical Care Medicine

World J Crit Care Med 2023 December 9; 12(5): 236-285



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INDEXING/ABSTRACTING

The *WJCCM* is now abstracted and indexed in PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database.

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Production Editor: *Yi-Xuan Cai*; **Production Department Director:** *Xu Guo*; **Editorial Office Director:** *Jia-Ping Yan.*

NAME OF JOURNAL
World Journal of Critical Care Medicine

ISSN
ISSN 2220-3141 (online)

LAUNCH DATE
February 4, 2012

FREQUENCY
Quarterly

EDITORS-IN-CHIEF
Hua-Dong Wang

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3141/editorialboard.htm

PUBLICATION DATE
December 9, 2023

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https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
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ONLINE SUBMISSION
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World Journal of Critical Care Medicine

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World J Crit Care Med 2023 December 9; 12(5): 236-247

DOI: 10.5492/wjccm.v12.i5.236

ISSN 2220-3141 (online)

MINIREVIEWS

New-onset atrial fibrillation among COVID-19 patients: A narrative review

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Batta A, India; Mahmoud MZ, Saudi Arabia; Yu L, Singapore

Received: May 30, 2023
Peer-review started: May 30, 2023
First decision: August 2, 2023
Revised: August 20, 2023
Accepted: September 11, 2023
Article in press: September 11, 2023
Published online: December 9, 2023

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Abstract

Over the last three years, research has focused on examining cardiac issues arising from coronavirus disease 2019 (COVID-19) infection, including the emergence of new-onset atrial fibrillation (NOAF). Still, no clinical study was conducted on the persistence of this arrhythmia after COVID-19 recovery. Our objective was to compose a narrative review that investigates COVID-19-associated NOAF, emphasi-

zing the evolving pathophysiological mechanisms akin to those suggested for sustaining AF. Given the distinct strategies involved in the persistence of atrial AF and the crucial burden of persistent AF, we aim to underscore the importance of extended follow-up for COVID-19-associated NOAF. A comprehensive search was conducted for articles published between December 2019 and February 11, 2023, focusing on similarities in the pathophysiology of NOAF after COVID-19 and those persisting AF. Also, the latest data on incidence, morbidity-mortality, and management of NOAF in COVID-19 were investigated. Considerable overlaps between the mechanisms of emerging NOAF after COVID-19 infection and persistent AF were observed, mostly involving reactive oxygen pathways. With potential atrial remodeling associated with NOAF in COVID-19 patients, this group of patients might benefit from long-term follow-up and different management. Future cohort studies could help determine long-term outcomes of NOAF after COVID-19.

Key Words: COVID-19; SARS-CoV-2; New-onset atrial fibrillation; Atrial fibrillation

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Core Tip: In this literature review, we have observed resemblances between the fundamental pathophysiology of coronavirus disease 2019 (COVID-19)-related new-onset atrial fibrillation (NOAF) and the mechanisms proposed for the persistence of AF, particularly those involving oxidative stress and reactive oxygen species. The mechanisms responsible for the development of AF following a COVID-19 infection could potentially contribute to atrial remodeling, further perpetuating AF. However, while short-term outcomes of COVID-19-related NOAF have been well-studied, as we transition into an endemic era of COVID-19, there is a need for more research to investigate the long-term outcomes of patients who develop NOAF after COVID-19 infection.

Citation: Talaei F, Banga A, Pursell A, Gage A, Pallipamu N, Seri AR, Adhikari R, Kashyap R, Surani S. New-onset atrial fibrillation among COVID-19 patients: A narrative review. *World J Crit Care Med* 2023; 12(5): 236-247
URL: https://www.wjgnet.com/2220-3141/full/v12/i5/236.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i5.236

INTRODUCTION

Background

As atrial fibrillation (AF) incidence was approaching an epidemic proportion[1], in January 2020, the world health organization announced the preliminary determination of a novel coronavirus in Wuhan, China. By March 2020, the novel virus was recognized as a global pandemic[2,3]. AF was reported as the most common arrhythmia in a multicenter review of coronavirus disease 2019 (COVID-19) cases in 76 countries, with a prevalence of 19% to 21% of all hospitalized cases[4]. The new onset of AF (NOAF) among COVID-19 patients (referred to as COVID-19-related NOAF) raises concerns for unfavorable outcomes, especially in critically ill patients, regarding in-hospital mortality, length of stay in the intensive care unit, and survival[5,6].

In individuals whose AF has progressed, it has previously been observed that various factors, such as oxidative stress, atrial dilatation, calcium overload, inflammation, and myofibroblast activation, interact in a way that significantly contributes to the remodeling of the atrial extracellular matrix (ECM) and electrical properties. This ultimately results in the continuous presence of AF. Nevertheless, the possibility of AF persisting following a COVID-19 infection has not undergone comprehensive investigation, and there is currently a dearth of prolonged studies that evaluate the consequences of COVID-19-related NOAF[7,8]. Furthermore, maintaining sinus rhythm is generally more challenging in patients with persistent AF compared to those with paroxysmal AF, and persistent AF is associated with higher thromboembolic risks [9]. However, there is a paucity of the data regarding persistence of AF after COVID-19 infection. The innate tendency of COVID-19 for coagulopathy, characterized by elevated D-dimer and a significant increase in peripheral thromboembolic events observed in NOAF patients, calls for further investigation of the management of COVID-19-related NOAF[10,11].

Similar to past pandemics in history, the COVID-19 pandemic presents a chance to broaden our knowledge despite the challenges it poses[3]. Our objective was to explore the underlying mechanisms of NOAF in COVID-19 patients, with a particular emphasis on factors that could sustain the occurrence of this arrhythmia. To peruse this, a comprehensive, structured literature search was conducted through EMBASE and MEDLINE for articles published between December 2019 and May 20, 2023, that reported the pathophysiology of NOAF after COVID-19 and those persisting AF. Also, the latest data on incidence, morbidity-mortality, and management of NOAF in COVID-19 were investigated. The search terms include each of the following terms individually and in combination: "new-onset atrial fibrillation", "NOAF", "AF persistence", "persistent atrial fibrillation", "SARS-CoV-2", "COVID-19", "SARS", coronavirus as described in the Supplementary Table 1[12]. Two investigators (Talaei F and Banga A) independently screened studies for eligibility. We focused primarily on published research articles, systematic reviews, and observational cohorts. The title, abstract, and keywords were checked for relevance initially. Studies were excluded if not written in English.

NOAF

NOAF is defined as AF detected after diagnosis of COVID-19 without a prior history[13]. In the course of the disease, AF might indefinitely appear as short (< 7 d) self-limiting episodes (*i.e.*, paroxysmal). However, it is more likely to transform into long-lasting forms of AF[14]. AF is considered persistent when perpetually lasting more than seven days[15,16].

Epidemiology

An October 2021 meta-analysis involving over 21000 hospitalized COVID-19 patients revealed that NOAF had a prevalence of 11%. Elderly COVID-19 patients (aged ≥ 60) had a higher NOAF prevalence (13%) compared to younger patients (5%). Among different ethnic subgroups, Europeans (15%) and Americans (11%) had the highest NOAF prevalence, while Africans had the lowest (2%). Additionally, NOAF was significantly linked to a higher risk of all-cause mortality among COVID-19 patients (odds ratio = 2.32)[17].

A report from the American Heart Association COVID-19 Cardiovascular Disease Registry revealed that 5.4% of patients hospitalized for COVID-19 infection developed NOAF during their hospital stay. Moreover, NOAF was associated with higher rates of death (45.2% *vs* 11.9%) and major adverse cardiovascular events of cardiovascular death, myocardial infarction, cardiogenic shock, and heart failure (23.8% *vs* 6.5%) compared to those who did not develop NOAF. The unadjusted hazard ratio for mortality was 1.99 [95% confidence interval (CI): 1.81-2.18], and for major adverse cardiovascular events was 2.23 (95%CI: 1.98-2.53) for patients with *vs* without new-onset AF[18].

COVID-19-related NOAF was demonstrated to be an independent prognostic factor for in-hospital embolic events, irrespective of anticoagulant use and prolonged hospital stay. Potential co-factors contributing to the development of NOAF could include older age, arterial hypertension, a history of myocardial infarction, renal dysfunction, and elevated D-dimers[19], which align with previously reported risk factors associated with the emergence of NOAF in critically ill patients[20].

Etiology and pathophysiology

There are ongoing debates regarding underlying mechanisms involved in provoking arrhythmias in COVID-19 infection. While some attribute arrhythmias and hence AF directly to the virus itself[21]; others highlight the connection between inflammatory markers and arrhythmias, considering it as a consequence of a systemic illness not exclusive to COVID-19 [11,22]. A third group points towards the long-term changes required to make atrial structural abnormalities and the relatively short incubation period of COVID-19 and concludes that it might be a symptom of prior undetected structural heart diseases[23,24].

There are limited studies concerning the pathophysiology of NOAF in COVID-19; nonetheless, several of them are built upon earlier research conducted on severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) or Middle East respiratory syndrome coronavirus (MERS-CoV). Considering the resemblances in structure and potential pathogenicity among MERS-CoV, SARS-CoV-1, and SARS-CoV-2[25], various mechanisms have been suggested to elucidate the processes that might trigger arrhythmia in the context of COVID-19[26,27].

Angiotensin-converting enzyme-2 (ACE2)-related signaling pathways, endothelial dysfunction, spike protein interaction, cytokine storm, hypoxia, alteration in the autonomous nervous system, and metabolic disarray in the setting of viral infection are some proposed mechanisms[21,23].

Modulation of myocardial ACE2 expression: ACE2 is found in abundance in the lungs. It is thought to play an essential role in the pathogenesis of SARS-CoV-2-associated severe acute respiratory syndrome by acting as a receptor for this family of viruses. However, this enzyme is not exclusive to the lungs, as it is also highly expressed in the heart and kidneys[19,28].

The catalytic action of this enzyme in the heart leads to the degradation of angiotensin-II (Ang II) to cardioprotective Ang1-7. In doing so, ACE2 plays a cardioprotective counterbalance role in the renin-angiotensin-aldosterone system (RAAS)[19].

Binding the viral spike protein to the ACE2 receptor activates catalytic processes that lead to ACE2 shedding, decreasing antifibrotic Ang1-7. Consequently, the Ang II/Ang1-7 ratio will move toward Ang II production, which is a growth factor for fibroblasts, and promote inflammation, fibrosis, oxidative stress, and vasoconstriction[19,29,30]. Decreasing Ang1-7 also leads to an increase in disintegrin and metalloproteinase 17, which will prompt further cardiac injury and subsequent potential AF[23,27].

Endothelial dysfunction: The cardioprotective role of ACE2 has been discussed, yet it extends beyond that by serving as a regulator of the kallikrein-bradykinin pathway, imparting a significant vasodilator effect. This effect acts as a counterbalance to the vasopressor effect of RAAS[19,31]. Declined vascular levels of ACE2 in COVID-19 patients lead to overactivation of the kallikrein-bradykinin system and increased permeability[31]. The heightened permeability leads to the recruitment of diverse immune cells, inflammatory cytokines, and vasoactive molecules to the site. Consequently, the production of reactive oxygen species (ROS) and other cytotoxic mediators by activated neutrophils synergizes with the release of vasoactive molecules, including thrombin, histamine, bradykinin, thromboxane A2, and vascular endothelial growth factor. This, in turn, enhances the contractility of endothelial cells and the loosening of inter-endothelial junctions, ultimately leading to vascular leakage[32]. Also, interleukin (IL)-1β and tumor necrosis factor (TNF)-α are recognized for their ability to promote fluid retention by increasing glycocalyx degradation and upregulating hyaluronic acid synthesis, the ultimate result of which is an increased deposition of hyaluronic acid in the compromised ECM, promoting fluid retention[32]. Both mechanisms ultimately converge on vascular impairment as an endpoint.

While the impact of AF on the vasculature has been better studied, recent discoveries indicate a bidirectional relationship between the two[33,34]. Endothelial dysfunction would further increase oxidative stress, proinflammatory cytokines, and impaired nitric oxide-dependent vasorelaxation[29]. Excessive production of endothelial ROS has been linked to atrial oxidative injury, resulting in structural and electrical remodeling, contributing to AF. Interestingly, there is evidence that patients with coronary endothelial dysfunction are at increased risk for developing persistent AF[33,34]. Up to date, no similar human studies are available, and the current pandemic could present an opportunity to investigate this link.

Spike protein binding to cardiomyocyte: Spike protein of COVID-19 plays an essential role in host cell invasion, including cardiomyocytes[35]. Viral spike protein interacts with CD147 as an ECM metalloproteinase inducer. CD147 is a potent stimulator of several cytokines, including IL-18, *in vitro,* and IL-18 is an essential element of the inflammatory cascade, acts as a cardiotropic metalloproteinase, and correlates with cardiac remodeling and AF[36,37].

Spike protein also binds to N-acetylneuraminic acid (Neu5Ac), the predominant sialic acid in human cells, including cardiomyocytes. Higher levels of Neu5Ac are associated with left atrial enlargement, and it plays a crucial role in severe coronary artery diseases (CAD) and cardiac fibrosis[38], but how this cardiac fibrosis could lead to AF is under study[23].

Cytokine storm: The sustained infiltration of neutrophils, macrophages, and CD4+ T-lymphocytes associated with the COVID-19 cytokine storm can promote the transformation of fibroblasts to myofibroblasts, which in the long run could lead to pathological cardiac remodeling and fibrosis[39].

On the other hand, atherosclerotic plaques in the coronary artery are more prone to rupture in the state of inflammation anticipated by cardiac injury and arrhythmias. Production of several cytokines, either by inducing direct myocardial necrotic effect or releasing pro-atherogenic cytokines like IL-6, will develop proliferation in vascular smooth muscle accompanied by endothelial cell and platelet activation[40,41].

Hypoxemia: COVID-19 causes hypoxia by several different mechanisms that can transform into acute respiratory syndrome[42]. Pneumonia in COVID-19 deteriorates gas exchange and complicates cell metabolism. This enhances anaerobic fermentation, resulting in intracellular acidosis and oxygen free radicals destroying the phospholipid layer of the cell membrane. Meanwhile, the hypoxia-induced influx of calcium ions also leads to injury and subsequent apoptosis of injured cardiomyocytes[43]. Also, COVID-19 systemic infection, being a situation of increased cardiometabolic demand, collaterals with hypoxia caused by an acute respiratory illness. This coincidence leads to an unmatched myocardial demand-supply ratio and subsequent acute myocardial injury[44].

The above should also add hypoxemia-induced dynamic changes in transmural pressure gradients, promoting increased pulmonary pressure, which leads to tricuspid regurgitation and further impairment in the right atrium, followed by possible changes in atrial conduction properties and refractoriness[45].

Gramley *et al*[46] previously observed a close association between prolonged hypoxic and increased angiogenic markers in the atrium with AF. With the persistence of hypoxia, an endoglin called CD105 would up-regulate, which is a homolog to the type III receptor of transforming growth factor-β, leading to ECM formation. It was hypothesized that cardiac hypoxia could provoke AF through the hypoxia-inducible factor pathway and over-expression of connective tissue growth factor and angiogenic genes like vascular endothelial growth factor[46].

Autonomic nervous system alteration: Severe infections generally activate the sympathetic nervous system (SNS), which also relates to AF[23]. Among cytokines released in COVID-19 infection, IL-6 can hyperactivate SNS, either centrally by a hypothalamus-mediated mechanism or peripherally *via* the left stellate ganglia[47].

SNS activation likely increases calcium influx into the cardiomyocytes and calcium overload in the sarcoplasmic reticulum, further increasing the frequency of spontaneous diastolic calcium releases, resulting in delayed afterdepolarizations and triggered action potentials, increasing the likelihood of AF induction[48].

On the other hand, hypoxemia might activate the parasympathetic system. Combined sympathetic and vagal activation creates a more pronounced AF substrate than sympathetic or parasympathetic stimulation alone. In an experimental animal model, changes in intrathoracic pressure, dynamic hyperinflation, and obstructive respiratory events that were followed by hypoxia-activated the parasympathetic nervous system, reducing the right atrial effective refractory period and increasing the susceptibility to AF. Autonomic nervous system (ANS) activity and AF have a reciprocal interaction that could help the arrhythmia continue to evolve[49].

Fluid and electrolyte abnormality: Renal dysfunction in COVID-19 can lead to a decrease in serum potassium levels due to increased excretion[50]. Increased ACE/ACE2 ratio imbalance would also affect the RAS and potassium metabolism [51]. Increased ACE2 degradation augments RAS activity, increasing sodium and water reabsorption and collateral increase potassium excretion[52]. Hypokalemia frequently happens in hospitalized patients with COVID-19, with reported rates ranging from 41% to 55% of cases[53]. The occurrence of hypokalemia, which increases resting potential, leads to cell membrane hyperpolarization, thus accelerating atrial conduction and potentially creating a susceptibility to AF. Hypokalemia, by increasing resting potential, leads to cell membrane hyperpolarization, thus accelerating atrial conduction, which could possibly predispose to AF[54]. Hypokalemia frequently happens in hospitalized patients with COVID-19, reported in 41% to 55% of cases[55].

Association with CAD

Growing evidence highlights a strong link between CAD and AF, and several observational studies have indicated that CAD and AF aggravate each other. Shared risk factors encompassing hypertension, diabetes mellitus, and obesity substantiate this linkage. Notably, AF incidence has been found to be higher in people with CAD compared to age-matched

adults without CAD[56].

Evidence points to an intricate relationship between atrial tissue excitability and neuronal remodeling with ischemia at the microcirculatory level. CAD adversely affects AF by promoting progression *via* re-entry and increasing the excitability of atrial tissue as a result of ischemia and electrical inhomogeneity. AF, in turn, accelerates atherosclerosis and, together with enhanced thrombogenicity and hypercoagulability contribute to micro and macrothrombi throughout the cardiovascular system. Inflammation and endothelial dysfunction remain central to both disease processes[57].

Patients with CAD associated with NOAF or persistent AF have significantly higher morbidity and mortality, predisposing to heart failure, life-threatening ventricular arrhythmias, and major adverse cardiovascular events[57]. A recent comprehensive analysis supports heightened AF risk in CAD patients, yet a causal AF-to-CAD link remains unestablished[56]. Management of concurrent CAD and AF centers on anti-thrombotic strategies, balancing stroke prevention and stent thrombosis avoidance while cautiously mitigating bleeding risk. Current guidelines recommend up to one year of combined oral anticoagulant (OAC) and antiplatelet therapy, preferably P2Y12 inhibitors or OAC monotherapy. However, the limited quality of evidence in these guidelines and persistently high bleeding risk constrain their clinical applicability[50,52].

Management of NOAF

Recognition: NOAF recognition in patients with COVID-19 can be done with electrocardiography, telemetry, or implantable device interrogation. Close observation of vital signs and regular electrocardiograms help monitor for dysrhythmias such as AF in patients with COVID-19[51].

Evaluation: The initial evaluation of COVID-19-related NOAF parallels the standard management for AF. This involves conducting a routine two-dimensional transthoracic echocardiogram to assess for structural irregularities. However, if indications of heart failure, hemodynamic instability, unexplained clinical deterioration, or planned cardioversion are pre-sent, expedited evaluation is warranted[15].

Transesophageal echocardiography should be obviated by the early start of anticoagulation in NOAF to detect left atrium thrombi as a potential source of systemic embolism in AF and can be used to guide the timing of cardioversion or catheter ablation procedures[53].

Treatment goals: Treatment goals are regardless of the type, treatment goals encompass three primary objectives: Managing heart rate during episodes of AF; and achieving the restoration, sustained maintenance of normal sinus rhythm (rhythm control), and mitigating the risk of systemic or cerebral embolism linked to the heightened embolic risk associated with AF all while minimizing the impact of drug interactions[15,58].

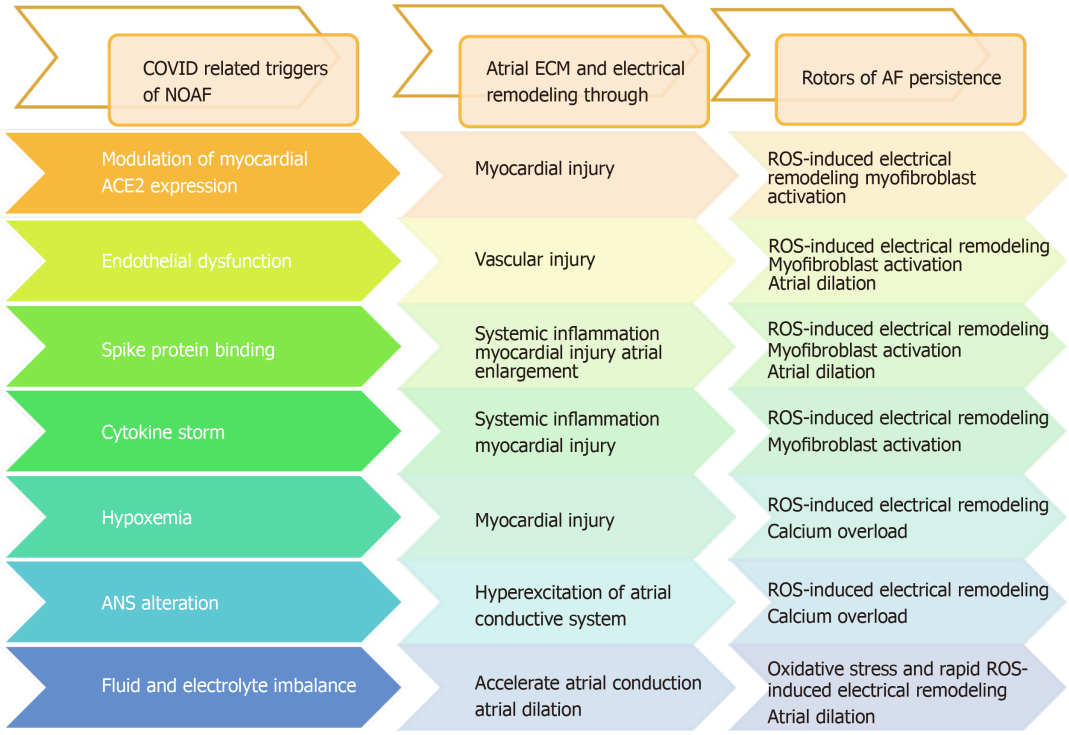
Rate and rhythm control: The contemporary therapy of AF with rate control *vs* rhythm control strategies is still disputed, there is a scarcity of data regarding the effectiveness of rhythm and rate control approaches for COVID-19-related AF. Current recommendations are based on acute management of AF in COVID-19 disease and long-term data is not available[53,58]. Enhancing the treatment of underlying factors such as hypoxemia, inflammation, and potentially reversible triggers (like hypokalemia, hypomagnesemia, and acidosis) seems to form the empirical foundation for managing these cases. As with other setting, if NOAF is suspected to be a contributing factor to hemodynamic instability immediate cardioversion should be considered. Although, for the remaining patients who do not urgently require cardioversion, the decision to proceed should be weighed against the availability of necessary equipment and medical personnel, as well as the potential risk of virus transmission with intubation. In critically ill patients with compromised hemodynamics due to NOAF, intravenous amiodarone is the preferred antiarrhythmic medication for rhythm control[59].

Hospitalized patients who have developed COVID-19-related NOAF and are undergoing antiviral treatment while maintaining hemodynamic stability should give precedence to discontinuing their anti-arrhythmic medications. Instead, the preferred approach involves initiating rate control therapy using beta-blockers or non-dihydropyridine calcium channel blockers, along with or without digoxin, unless contraindicated[58]. This approach ensures the safe administration of antiviral medication without the potential risk of QT prolongation[53,58].

Amidst a COVID-19 infection, the potential for QT interval-related risks could be heightened due to the simultaneous utilization of anti-arrhythmic medications with other QT-prolonging medications (such as hydroxychloroquine, azithromycin, lopinavir/ritonavir), along with factors like myocardial inflammation and electrolyte imbalances (like hypokalemia, hypomagnesemia, and/or hypocalcemia)[60]. It's crucial to assess potential drug interactions, including those between antiviral and antiarrhythmic drugs, prior to initiating therapy[53].

Unless dealing with highly symptomatic AF cases, such as individuals with AF-related heart failure or those experiencing medically refractory AF resulting in frequent emergency room visits, all AF ablation procedures ought to be delayed for a minimum of three months after recovering from a COVID-19 infection[53].

Prevention of thromboembolic events: As a general guideline, for patients with a history of prior stroke, transient ischemic attack, or a CHA2DS2-VASc score > 2 who subsequently develop AF, oral anticoagulation is recommended[15]. Given that hospitalized COVID-19 patients are generally over the age of 65 and often have multiple underlying health conditions, a significant proportion of individuals with AF necessitate prolonged anticoagulation therapy[11]. Hemodynamically stable COVID-19 patients presenting with atrial AF during their hospitalization have treatment including unfractionated heparin, low molecular weight heparin, or direct OACs (DOACs). The specific choice among these options is influenced by factors like the suitability of oral administration, renal function, and additional clinical aspects. It's important to highlight that certain medications for COVID-19 treatment could potentially interact with DOACs. Lopinavir/ritonavir may create a potential interaction with DOACs through cytochrome P450 CYP3A4 interaction, and antimalarial drugs could influence DOACs *via* P-glycoprotein inhibition. If such interactions are pertinent, there may be



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Figure 1 Comparing available studies on new-onset atrial fibrillation pathophysiology in coronavirus disease 2019 patients and rotors of atrial fibrillation persistence (including oxidative stress, calcium overload, atrial dilation, micro-RNA, inflammation, and myofibroblast activation. COVID: Coronavirus disease; ECM: Extracellular matrix; NOAF: New-onset atrial fibrillation; AF: Atrial fibrillation; ROS: Reactive oxygen species; ACE2: Angiotensin-converting enzyme-2; ANS: Autonomic nervous system.

an increased risk of bleeding, underscoring the need to avoid DOACs. Given this scenario, DOACs are favored over vitamin K antagonists (VKAs) due to their more favorable safety profile and standardized dosing schedule[58].

VKAs are also considered for specific subsets of patients, including individuals with mechanical prosthetic valves or antiphospholipid syndrome. While VKAs typically induce a temporary deficiency of vitamin K, the observed lower levels of vitamin K in patients with COVID-19 compared to healthy individuals suggest a need for additional investigation regarding the utilization of VKAs in COVID-19 patients[61]. The precise mechanisms driving this connection are yet to be fully understood.

The innate tendency of COVID-19 for coagulopathy, characterized by elevated D-dimer and a significant increase in peripheral thromboembolic events observed in NOAF patients, calls for further investigation of the management of COVID-19-related NOAF[10,11]. Since heparins are unlikely to interact with drugs used in COVID-19 treatment, they represent a safe and attractive option for stroke prevention in AF patients who are hospitalized due to COVID-19. Remarkably, beyond their antithrombotic effects, heparins also possess anti-inflammatory properties that could be pertinent in this context[53]. Following recovery from COVID-19, the continuation of long-term anticoagulation should be based on the CHA2DS2-VASc score.

Discussion

COVID-19-related NOAF is still not well studied. Mechanisms involved in the development of NOAF after COVID-19 infection could potentially lead to atrial remodeling and fibrosis, which can further perpetuate AF, as shown in Figure 1. Clinical studies suggested that the majority of the patients with AF remain paroxysmal, though the electrophysiological substrate underlying AF in those who progress to sustained forms may differ from that of those who remain paroxysmal [62]. However, in this study, a sizable overlap was noted in mechanism inducing COVID-19 associated NOAF and those persisting AF.

The mechanism involved in the progression of AF is a constellation of oxidative stress, inflammation, atrial dilatation, calcium overload, and myofibroblast activation, all of which are likely to be involved in one way or another in AF-induced ECM and electrical remodeling[7,8]. Interestingly, many of these mechanisms seem to be mutual with suggestive models of COVID-19-related NOAF (Figure 2), and looking back to the mutual mechanisms of persistent AF and COVID-19-related NOAF could explain the possible risk of developing persistent AF after NOAF in COVID-19 patients (Table 1 and Figure 2).

In the working model of AF perpetuation by Jalife and Kaur[8], oxidative stress and ROS are the cornerstones of maintaining AF. In that model, a putative mechanism of AF perpetuation involves Ang II stimulation, which triggers the release of ROS from activates nicotinamide adenine dinucleotide phosphate oxidases 2/4. This process leads to a rapid reduction in L-type Ca^{2+} current and an increase in inward rectifier K^{+} current within a short timeframe (*i.e.*, hours or

Table 1 Comparing coronavirus disease 2019-related new-onset atrial fibrillation and persistent atrial fibrillation in terms of etiology, pathophysiology, contributing risk factors, outcome, and management

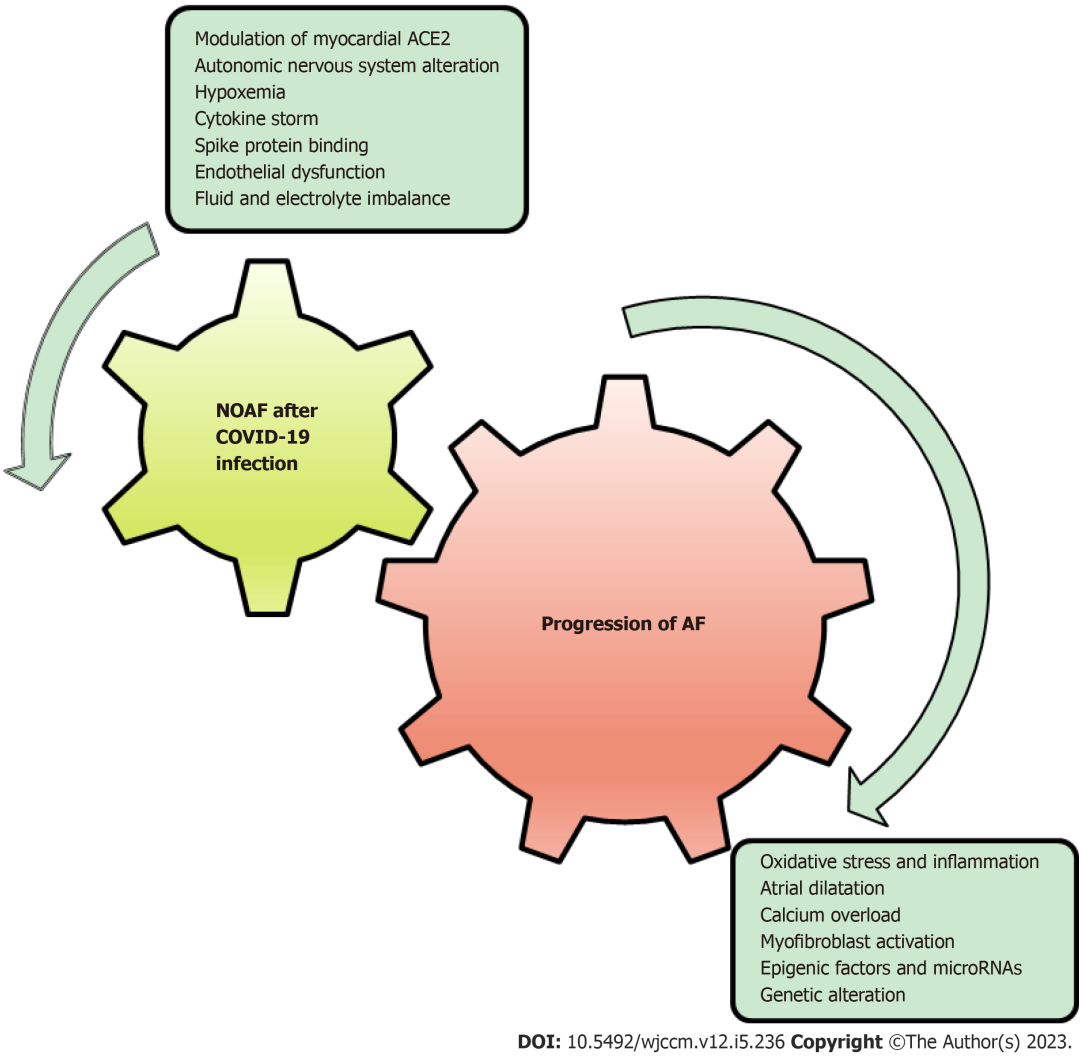
	COVID-19-related NOAF	Persistent AF
Etiology and pathophysiology	(1) Diminished availability of ACE-2 receptors contributes to myocardial hypertrophy, vasoconstriction, ROS production, oxidative stress, tissue inflammation, and fibrosis, all of which play a role in the development of AF; (2) Endothelial dysfunction leads to increased vascular permeability and leakage culminating in an overproduction of ROS leading to structural and electrical remodeling predisposing to AF; (3) CD147- and myocyte's sialic acid-spike protein interaction upregulate the expression of several cytokines and ROS that induce extracellular matrix degradation, cardiac remodeling, and fibrosis; (4) Excessive release of proinflammatory cytokines in cytokine storm leads to ROS production, progressive myocardial cell apoptosis or necrosis, which may lead to conduction disturbances leading to AF; (5) Impaired gas exchanges and intrathoracic pressure swings lead to cardiomyocyte injury and increased frequency of premature atrial beats and induce AF; (6) ANS alteration: SNS-mediated calcium influx increases the frequency of delayed afterdepolarization and triggers AP; PNS activation mediated by intrathoracic pressure swing leads to shortening of right atrial ERP, and APD both induce AF; and (7) Sodium and water resorption increases blood pressure and excretion of potassium increase the resting membrane and enhances depolarization predisposing to AF	Steady generation of ROS triggered by sustained high-electrical activity, followed by intracellular Ca^{2+} overload together with atrial dilatation, mitochondrial ROS and activation of inflammatory and pro-fibrotic pathways progressively alters gene expression clinically relevant sheep model of persistent AF, leading to myocyte hypertrophy, interstitial fibrosis, and ion channel remodeling, all of which would occur relatively slowly but reach critical levels when AF becomes persistent at a median time of about 2 mo: (1) Oxidative stress by ROS released either by NOX2/4 or mitochondria is the first consequence, the persistence of which leads to shortened APD and RF through reducing rapid L-type Ca^{2+} current and increasing inward rectifier K^{+} current promoting the formation and stabilization of rotor that world in a vicious cycle to preserve sustained high electrical activity; and (2) Inflammation leads to profibrotic signaling in response to cardiac injury by promoting fibroblast-to-myofibroblast trans-differentiation leading to either through increased expression of TRP channels or miR-21 resulting in structural remodeling by atrial dilation and fibrosis that maintains AF
Risk factors	(1) Older age; (2) A history of myocardial infarction; (3) Renal dysfunction; (4) Raised D-dimer levels; and (5) Hypertension	Risk factors for progression to more persistent forms of AF among patients with paroxysmal AF and varying degrees of CVD per HATCH score is[62]: (1) Heart failure; (2) Older age; (3) Previous transient ischemic attack or stroke; (4) Chronic obstructive pulmonary disease; and (5) Hypertension
Outcomes	Among patients hospitalized with COVID-19 infection, 5.4% could develop NOAF. All-cause mortality rates are 45.2% *vs* 11.9% and MACE is 23.8% *vs* 6.5% for patients with *vs* without NOAF[67]	Among patients with persistent AF all-cause mortality rate is 4.41% and MACE is 5.09%[67]
Treatment	The initial approach is to enhance the treatment of underlying factors. Hemodynamic instability warrants immediate cardioversion, provided that the risk of embolism is low	Hemodynamic instability warrants immediate cardioversion provided that the risk of embolism is low[15]
	Rate control therapy is preferred over rhythm control unless hemodynamic instability warrants the addition of rhythm control *e.g.*, with amiodarone	A similar efficacy of rate *vs* rhythm control in all-cause mortality and MACE had been noted. Thus, current guidelines recommend an individualized decision taking into consideration that a rhythm control is most likely to fail in patients with long-term persistent AF (> 1 yr), in whom atrial substrate alteration is greatest
	Anticoagulation: Unfractionated heparin, LMWH is safe to use. Use DOACs with caution as interact with some antiviral medications. VKAs induce a state of vitamin K deficiency that could potentially influence susceptibility to contracting COVID-19	The choice of anticoagulation should be individualized based on the patient's comorbidities, like other indications for anticoagulation and renal function

COVID-19: Coronavirus disease 2019; ECM: Extracellular matrix; NOAF: New-onset atrial fibrillation; AF: Atrial fibrillation; ROS: Reactive oxygen species; ACE2: Angiotensin-converting enzyme-2; SNS: Sympathetic nervous system; AP: Action potential; PNS: Peripheral nervous system; ERP: Effective refractory period; APD: Action potential duration; TRP: Transient receptor potential; CVD: Cardiovascular disease; MACE: Major adverse cardiovascular events; LMWH: Low molecular weight heparin; DOAC: Direct oral anticoagulant; VKA: Vitamin K antagonist; ANS: Autonomic nervous system.

days). These alterations result in the shortening of the atrial action potential duration and refractory period, promoting the formation and stabilization of rotors of persistent AF. Subsequently, intracellular Ca^{2+} overload ensues, promoting triggered activity and apoptosis[63,64].

Nevertheless, Ca^{2+} overload, together with atrial dilatation, mitochondrial ROS, and activation of inflammatory and pro-fibrotic pathways, progressively alters gene expression. The eventual outcomes of these persistent alterations entail myocyte hypertrophy, interstitial fibrosis, and ion channel remodeling. When these processes collectively escalate to a critical threshold, it could lead to the persistence of AF. In an animal study, after two months of tachypacing, the arrhythmia progressed to persistent AF[65]. However, no study is available on the same time frame in COVID-19 patients.

In addition to Ang II, sustained AF is fostered by the release of proinflammatory cytokines and tissue injury mediators such as TNF-α, IL-6, and IL-8. While the initial purpose of this cascade is to facilitate a beneficial "self-destroy and rebuild" process[66], its continuous activation is a widely recognized initiator of fibroblast-to-myofibroblast transformation leading to atrial remodeling[8]. Therefore, the prolonged presence of inflammatory cascades and myocyte apoptosis, whether through spike protein binding to cardiomyocyte, cytokine storm, prolonged hypoxemia, or altered ANS, could also potentially lead to ion channel dysfunction and excessive matrix production, likely generating electrical and structural remodeling and predisposing persistent AF.



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Figure 2 Long-term studies needed to assess progression from coronavirus disease 2019-related new-onset atrial fibrillation to more sustained forms of atrial fibrillation. COVID-19: Coronavirus disease 2019; NOAF: New-onset atrial fibrillation; ACE2: Angiotensin-converting enzyme-2; AF: Atrial fibrillation.

Conversely, potential risk factors associated with COVID-19-related NOAF, such as advanced age, hypertension, and a previous myocardial infarction, exhibit resemblances to independent factors that are linked with the progression toward persistent AF[62].

Progression from paroxysmal to more sustained forms of AF is associated with increased adverse events, including thromboembolic events, although the long-term outcomes of COVID-19-related NOAF infection are unknown (Figure 1) [67]. Early recognition of COVID-19-related NOAF is essential due to the high mortality risk associated with it. It is unknown if the management of COVID-19-related NOAF should follow the same pattern as routine management of paroxysmal or persistent AF. The disturbed coagulation system resulting from COVID-19 infection appears to elevate the potential for thromboembolic events in individuals with NOAF, although this necessitates additional research and confirmation.

While the conclusions drawn from this review are limited due to its non-experimental nature, it is evident that among various factors contributing to the development of COVID-19-related NOAF, some have the potential to perpetuate AF. These factors include modulation of myocardial ACE2 expression, spike protein binding, cytokine storm, endothelial dysfunction, increased permeability, and hypoxemia, which have the potential to induce atrial, ECM, or electrical remodeling, thereby perpetuating AF. To gain a more comprehensive understanding, further fundamental studies are required to explore the interplay between these factors. Additionally, prospective long-term studies are necessary to investigate the outcomes of patients who develop NOAF after experiencing COVID-19 infection in the long run (Figure 1).

CONCLUSION

Among several mechanisms that contribute to COVID-19-related NOAF, those exerting oxidative stress, such as modu-

lating myocardial ACE2 expression, endothelial dysfunction, spike protein binding, and cytokine storms, have the potential to contribute to changes in atrial structure, ECM, and electrical characteristics, which are common factors perpetuating AF. The electrophysiological substrate underlying AF in those who progress to sustained forms may differ from that of those who remain paroxysmal as maintaining sinus rhythm is generally more challenging in patients with persistent AF compared to those with paroxysmal AF, and persistent AF is associated with higher thromboembolic risks. The long-term outcomes of NOAF, including the persistence of AF after COVID-19 infection, remain unknown. Long-term prospective studies are needed to follow up on patients with COVID-19-related NOAF to address this knowledge gap.

FOOTNOTES

Author contributions: Talaei F and Kashyap R contributed to the conceptualization and methodology of this manuscript; Banga A, Adhikari R, and Kashyap R involved in the validation of this study; Talaei F, Banga A, Pursell A, Adhikari R, and Kashyap R participated in the formal analysis; Talaei F, Banga A, Pallipamu N, and Kashyap R investigated the article; Talaei F, Banga A, Pursell A, Gage A, Pallipamu N, Seri AR, Adhikari R, and Surani S contributed to the writing-original draft preparation of this study; Talaei F, Banga A, Pursell A, Seri AR, Adhikari R, Kashyap R, and Surani S involved in the writing-review and editing of this manuscript; Adhikari R, Kashyap R and Surani S participated in project administration.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang JJ

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World Journal of Critical Care Medicine

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World J Crit Care Med 2023 December 9; 12(5): 248-253

DOI: 10.5492/wjccm.v12.i5.248

ISSN 2220-3141 (online)

MINIREVIEWS

Narrative review of traumatic pneumorrhachis

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ferreira GSA, Brazil; Md Reazaul Karim H, India

Received: July 9, 2023
Peer-review started: July 9, 2023
First decision: August 24, 2023
Revised: August 31, 2023
Accepted: October 30, 2023
Article in press: October 30, 2023
Published online: December 9, 2023

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Abstract

Pneumorrhachis (PR) is defined as presence of free air in the spinal canal. Traumatic PR is very rare, and its exact incidence and pathogenesis is unknown. A comprehensive literature search was performed using the PubMed, Cochrane Library, Google Scholar and Scopus databases to identify articles relevant to traumatic PR published till January 2023. A total of 34 resources were selected for inclusion in this narrative review. Traumatic PR can be classified anatomically into epidural and intradural types. In the epidural type, air is present peripherally in the spinal canal and the patients are usually asymptomatic. In contrast, in intradural PR, air is seen centrally in the spinal canal and patients present with neurological symptoms, and it is a marker of severe trauma. It is frequently associated with traumatic pneumocephalus, skull fractures or thoracic spine fracture. Computed tomography (CT) is considered to be the diagnostic modality of choice. Epidural PR is self-limited and patients are generally managed conservatively. Patients with neurological symptoms or persistent air in spinal canal require further evaluation for a potential source of air leak, with a need for surgical intervention. Differentiation between epidural and intradural PR is important, because the latter is an indication of severe underlying injury. CT imaging of the entire spine must be performed to look for extension of air, as well as to identify concomitant skull, torso or spinal injuries Most patients are asymptomatic and are managed conservatively, but a few may develop neurological symptoms that need further evaluation and management.

Key Words: Pneumorrhachis; Trauma; Intraspinal air; Spinal emphysema

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Core Tip: Traumatic Pneumorrhachis (PR) is defined as presence of free air in the spinal canal, and is very rare. Differentiation between epidural and intradural PR is important, because the latter is an indication of severe underlying injury. Computed tomography imaging of the entire spine must be performed to look for extension of air, as well as identify concomitant skull, torso or spinal injuries. Most patients are asymptomatic and are managed conservatively, but a few may develop neurological symptoms that need further evaluation and management.

Citation: Pothiawala S, Civil I. Narrative review of traumatic pneumorrhachis. *World J Crit Care Med* 2023; 12(5): 248-253
URL: https://www.wjgnet.com/2220-3141/full/v12/i5/248.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i5.248

INTRODUCTION

Pneumorrhachis (PR) is defined as presence of free air in the spinal canal. The term was coined by Newbold *et al*[1] in 1987, but the pathology was first described by Gordon in 1977[1,2]. The etiology of PR could be iatrogenic, non-traumatic or traumatic[3]. Iatrogenic causes include lumbar puncture, epidural anesthesia or spinal surgery. Non-traumatic causes include violent coughing or vomiting, spinal dural arteriovenous fistula, gas-producing infections, epidural abscess, malignancy, radiotherapy or drug use[4-6].

Traumatic PR is very rare, and its exact incidence is not known[7]. It has been mainly described in the radiology and spine surgery literature, and the emergency medicine specialists are less familiar with this rare presentation. This clinical review discusses the etiology, pathogenesis and management of traumatic PR.

METHODOLOGY

A comprehensive literature search was performed using the PubMed, Cochrane Library, Google Scholar and Scopus databases to identify articles and case reports relevant to traumatic PR published till January 2023. The following search terms were used: "traumatic pneumorrhachis", "spinal emphysema", "epidural emphysema", "intraspinal air", "spinal pneumatosis" and "pneumomyelogram". Studies published in English were included, and the reference lists of relevant articles were also searched. A total of 34 resources were selected for inclusion in this narrative review. Of these, there was 1 systematic review, 2 retrospective studies, 2 narrative reviews and 29 case reports/series. Publications due to non-traumatic or iatrogenic causes were excluded from this review.

DISCUSSION

Classification and etiology

Traumatic PR is very rare. Blunt trauma accounted for 80% of cases of traumatic PR, while the remaining were secondary to penetrating trauma. PR can be classified anatomically into epidural and intradural (subdural/subarachnoid) types, based on location of air in the spinal canal. In the epidural type, air is present peripherally in the spinal canal (Figure 1), while in intradural PR, the air is seen centrally within the spinal canal in the subarachnoid space[8].

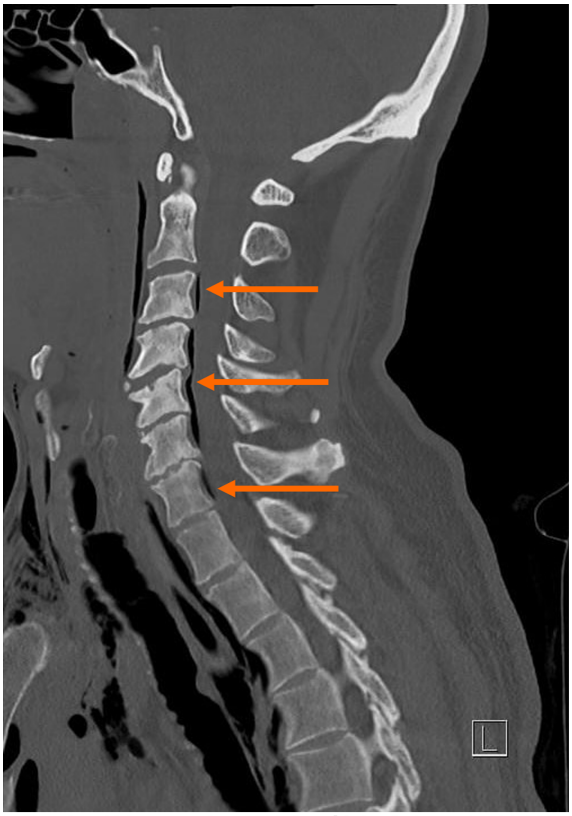
There was no correlation between the type of PR and the mechanism of injury, with 60%-65% of the traumatic PR cases being epidural PR, and the remaining 35%-40% cases had intradural PR[4]. Traumatic PR is often localized to isolated cervical, thoracic or lumbar regions, but there are have been limited case reports of PR in two contiguous spinal regions, or even along the entire spinal canal[3].

The location of air within the spinal canal depends on the site of injury causing the air leak, volume of air, capacity of the intraspinal space, and patient position. In epidural PR, air usually collects in the posterior epidural space as result of reduced resistance from the connective tissue, compared to the rich vascular network in the anterior epidural space[9]. But epidural air can also be present in the anterior or lateral epidural space (Figure 2).

There has been a reported case of PR secondary to penetrating spinal injury without an associated skull fracture[10]. In absence of penetrating injury, it can be seen in patients with head injury and basal skull fracture, likely secondary to accompanying tear in the dura mater[11]. PR was reported in a paediatric patient with associated T3 spine fracture, highlighting the need for evaluation for occult spinal fractures in patients without a clear etiology of PR[12]. The presence of traumatic PR is associated with significant injury of the skull, chest, abdomen, pelvis or spine[13], and the patient may have concomitant pneumocephalus, pneumothorax, pneumomediastinum, or subcutaneous emphysema.

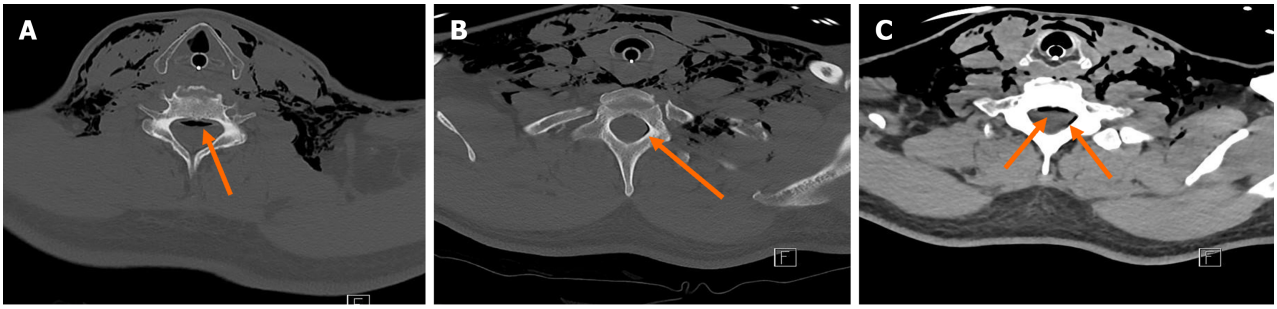
Pathophysiology

The exact pathophysiology of traumatic PR is not known. One of the possible mechanisms is that in patients with base of skull fracture, air in the cranial cavity (pneumocephalus) extends inferiorly through the foramen magnum in the spinal canal leading to PR[14]. In patients with pneumothorax or pneumomediastinum, air migrates along fascial planes of mediastinum into the epidural space through the neural foramina alongside the neurovascular bundle. Due to lack of a



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Figure 1 Sagittal computed tomography scan demonstrating peripheral pneumorrhachis in the spinal canal from the level of C3 to C7 (marked by arrows), suggestive of epidural pneumorrhachis.



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Figure 2 Axial computed tomography scan demonstrating epidural pneumorrhachis (marked by arrows) in the anterior spinal canal, left lateral spinal canal and both anterior and lateral part of spinal canal. A: Anterior spinal canal; B: Left lateral spinal canal; C: Both anterior and lateral part of spinal canal.

fascial barrier between the posterior mediastinum and the spinal canal, air can enter the epidural space without any significant trauma to the surrounding structures[15,16]. Another proposed theory is entry of air in the epidural venous plexus due to embolization of small mediastinal veins[3]. It could also occur due to dural tear following blunt trauma to the trachea or the lungs[17,18]. Air can reach the spinal canal *via* the intervertebral veins which anastomose with the lumbar veins which are damaged due to pelvic fracture[19,20]. Hollow viscus injuries, like oesophageal perforation associated with cervical spine fractures, or duodenal or jejunal rupture after seat belt injuries and associated spine fracture can also result in PR[21,22]. There has also been a report of intradural PR secondary to subarachnoid- pleural fistula after blunt thoracic trauma[23].

Clinical presentation

Although challenging, it is important to differentiate between epidural and intradural PR, because the etiology, pathogenesis and clinical presentations are different[15]. Epidural PR is relatively less common, and is associated with traumatic pneumothorax, pneumomediastinum or subcutaneous emphysema[24]. These patients are usually asymptomatic, with only two cases reported in the literature who suffered from neurological deficits[25]. In contrast, intadural PR is frequently associated with traumatic pneumocephalus, skull fractures or thoracic spine fracture, and is a

marker of severe trauma. These patients often experience associated neurological symptoms like radicular pain, limb weakness, paraesthesia, and sphincter dysfunction. Some authors suggest that the presence of PR with neurological deficit suggests a focal spinal instability due to an initial fracture-dislocation which reduced spontaneously[14,26,27]. These patients may suffer from potential complications such as tension pneumocephalus or meningitis[28]. Although tension PR has not been reported in trauma patients, intraspinal air can be trapped in the spinal canal due to a one-way valve mechanism, leading to increased pressure, which in turn causes progressive worsening of the neurological deficits.

Diagnosis

The majority of the cases of traumatic PR are asymptomatic, thus making its clinical diagnosis extremely challenging. It is usually diagnosed incidentally during radiological evaluation for other injuries[4]. On plain radiography, PR appears as a linear lucency along the spinal canal in the lateral views of cervical and thoracic spine or chest radiographs. It has a sensitivity of about 48% and is only able to detect large volume PR[29]. Computed tomography (CT) is considered to be the diagnostic modality of choice, with a sensitivity of 100%[11]. Even on CT scan, it may sometimes be difficulty to differentiate between intradural and extradural PR, and additional testing with magnetic resonance imaging or intrathecal contrast CT can help in this differentiation[8,29].

Management

As the incidence of traumatic PR is rare with varied underlying etiology, there are no definitive guidelines for its management, and the current management strategies are based on individual case reports[30]. Upon identification of this condition on the initial CT scan, PR is usually managed conservatively if patients are asymptomatic. Traumatic PR usually resolves spontaneously in 96% of the cases[4]. However, the patient requires monitoring for development of any new neurological symptoms[30]. There is no indication for repeat imaging as air in the spinal canal absorbs spontaneously in majority of the patients.

If PR is detected, the physician should evaluate the patient for major underlying injuries such as base of skull fracture, pneumocephalus, pneumothorax, pneumomediastinum or hollow abdominal viscera[4]. Also, in a rare instance, if the patient develops neurological symptoms or signs of raised intracranial pressure, further evaluation for a potential source of air leak is needed. Early surgical or neurosurgical consultation for surgical intervention may be required in these patients to treat the underlying causes of traumatic PR. Routine use of prophylactic antibiotics with an aim to prevent meningitis in these patients is not recommended in both epidural and intradural PR[4,13]. Rarely, traumatic PR can serve as a potential entry point for infection in the spinal canal, and antibiotics should be initiated if the patient shows any signs or symptoms of systemic infection (meningitis) or sepsis[5].

Epidural PR is generally benign and self-limiting, and the air gets spontaneously reabsorbed into the blood without any recurrence. Patients are generally managed conservatively, and they recover without any neurological sequelae[4,31]. The management of epidural PR depends on management of the underlying cause like pneumothorax or pneumomediastinum. In the case of traumatic pneumothorax, the patient may need to be undergo chest tube insertion or surgery in case of persistent air leak[32].

Presence of intradural/subarachnoid air in the spinal canal is a marker of concomitant major trauma like base of skull fracture, spinal fracture, or lung or hollow abdominal viscus injury[32]. These cases need to be referred promptly to the relevant specialty like neurosurgery or cardio-thoracic surgery for definitive management of the associated serious injuries. Persistent cerebrospinal fluid leak can be treated by repair of dural tears or placement of a lumbar spinal catheter [12]. Intradural PR may be complicated by tension pneumocephalus and meningitis[33]. Tension PR can occur rarely due to the unidirectional valve mechanism, wherein the air can occupy a significant portion of the intradural space increasing the intraspinal pressure, and by extension leading to raised intracranial pressure as well[27]. This can lead to increasing pain or development of neurologic deficits in the patient, requiring urgent treatment by neurosurgery or interventional radiology, with interventions such as air decompression using a Tuohy needle, surgical decompressive laminectomy or repair of the dural tear[34].

CONCLUSION

Traumatic PR is a rare phenomenon, often found incidentally on CT scan. Differentiation between epidural and intradural PR is important, because the latter is an indication of severe underlying injury, with potential complications of tension pneumocephalus or meningitis. CT imaging of the entire spine must be performed to look for extension of air, as well as identify concomitant skull, torso or spinal injuries. Traumatic PR is usually self-limiting, with most patients being managed conservatively, but a few may develop neurological symptoms that need further evaluation and management.

FOOTNOTES

Author contributions: Pothiawala S conceptualized and drafted the initial and revised versions of the manuscript; Civil I reviewed and edited the manuscript; All authors accept the final version of the manuscript.

Conflict-of-interest statement: All authors declare that they have no conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers.

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S-Editor: Fan JR
L-Editor: A
P-Editor: Cai YX

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World Journal of Critical Care Medicine

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World J Crit Care Med 2023 December 9; 12(5): 254-263

DOI: 10.5492/wjccm.v12.i5.254

ISSN 2220-3141 (online)

MINIREVIEWS

Advances in post intensive care unit care: A narrative review

Nishant Kumar

Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Boots RJ, Australia; Sánchez JIA, Colombia

Received: July 9, 2023
Peer-review started: July 9, 2023
First decision: August 16, 2023
Revised: September 29, 2023
Accepted: November 8, 2023
Article in press: November 8, 2023
Published online: December 9, 2023

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Abstract

As the treatment options, modalities and technology have grown, mortality in intensive care unit (ICU) has been on the decline. More and more patients are being discharged to wards and in the care of their loved ones after prolonged treatment at times and sometimes in isolation. These survivors have a lower life expectancy and a poorer quality of life. They can have substantial familial financial implications and an economic impact on the healthcare system in terms of increased and continued utilisation of services, the so-called post intensive care syndrome (PICS). But it is not only the patient who is the sufferer. The mental health of the loved ones and family members may also be affected, which is termed as PICS-family. In this review, we shall be reviewing the definition, epidemiology, clinical features, diagnosis and evaluation, treatment and follow up of PICS. We shall also focus on measures to prevent, rehabilitate and understand the ICU stay from patients' perspective on how to redesign the ICU, post ICU care needs for a better patient outcome.

Key Words: Post intensive care syndrome; Post intensive care syndrome-family; Guidelines; Post intensive care syndrome clinics; Impediments

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Core Tip: Core priorities of critical illness survivors should be a part of the stakeholder-driven clinical guidelines and quality measures for post-intensive care unit (ICU) care. Future research should extend these findings among other stakeholders (*e.g.*, family members and healthcare providers) and determine barriers and facilitators to patient-centered post-ICU care. It is not too far-fetched to think of a multi-professional patient centric critical care team that provides the right care to the right patient at the right time throughout and after the acute illness is over. What we need to change to bring in the future is how we use data, devices, and new technologies to continue to strive toward that goal.

Citation: Kumar N. Advances in post intensive care unit care: A narrative review. *World J Crit Care Med* 2023; 12(5): 254-263
URL: https://www.wjgnet.com/2220-3141/full/v12/i5/254.htm
DOI: https://dx.doi.org/10.5492/wjccm.v12.i5.254

INTRODUCTION

As the treatment options, modalities and technology have grown, mortality in intensive care unit (ICU) has been on the decline[1]. More and more patients are being discharged to wards and in the care of their loved ones after prolonged treatment and sometimes in isolation. These survivors have a lower life expectancy and a poorer quality of life. They can have substantial familial financial implications and an economic impact on the healthcare system in terms of increased and continued utilisation of services[2].

Though the intensivists may have cured the underlying disease, the process and time spent in the ICU far from family and loved ones predispose them to a new set of diseases which warrant special attention in terms of prevention, recognition, diagnosis, treatment and support of the so-called post intensive care syndrome (PICS)[1,2]. But it is not only the patient who is the sufferer. The mental health of the loved ones and family members may also be affected, which is termed as PICS-family (PICS-F)[1,2].

In this review, we shall be reviewing the definition, epidemiology, clinical features, diagnosis and evaluation, treatment and follow up of PICS. We shall also focus on measures to prevent, rehabilitate and understand the ICU stay from patients' perspective on how to redesign the ICU, post ICU care needs for a better patient outcome.

Definitions

PICS may simply be defined as a new or worsening function in one or more following domains: Cognitive, psychiatric and/or physical. This includes all adult patients who after being discharged from the ICU reside in acute rehabilitation units, nursing facilities or at home. Patients with traumatic brain injury and stroke are excluded, and since this is a relatively new concept, the timeline for the occurrence after discharge is not defined[1].

PICS-F encompasses the acute and chronic psychological effects among a patient's family members that occur during the critical care or following death or discharge of the patient from the ICU[1,2]. An expansion of PICS has been proposed with a focus on the contributing factors, addition of potential new components which include: Osteopenia, metabolic disorders, endocrine dysfunction, vulnerability, fatigue, sleep disorders and chronic pain, and consequences thereof (Figures 1-3)[2].

Epidemiology

Approximately 50% of ICU survivors, while out of those requiring life support, 64% at three months and 56% at 12 mo, suffer from either one or more of the three components of PICS[3-8]. Impairment of the cognitive domain has been reported with an incidence of 25%-78%[4]. The BRAIN-ICU study has reported that while 6% had cognitive impairment at baseline, 40% had impairment similar to traumatic brain injury and 26% similar to mild dementia at three months. These deficits persisted for most patients at 12 mo post discharge[6].

Depression, anxiety and post-traumatic stress disorder (PTSD) are the most common psychiatric disorders reported among survivors of critical illness. The absolute risk varies from 1%-62% in literature, with higher rates in acute respiratory distress syndrome (ARDS) survivors[9]. The reported incidence of depression is 28% and that of PTSD is 22% respectively in systematic reviews[10-12].

Twenty five percent or more ICU survivors are left with ICU acquired weakness as the most common form of physical impairment. Mobility at six months was problematic in 64%[3], while 73% complained of moderate or severe pain. As much as 26% of patients could not perform normal daily activities fully and this persisted in most patients at the end of one year[5,6]. The presence of neuropsychological and functional disability that occurs after survival leads to substantial public health burden and a negative impact on the family income[3].

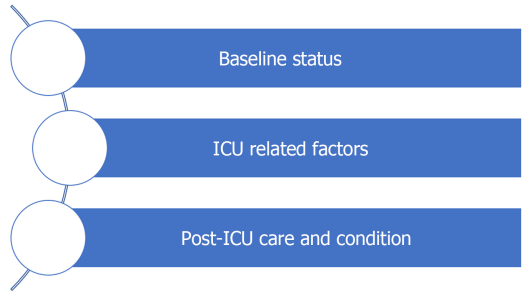
Risk factors

These can be broadly classified into either pre-existing or ICU specific factors. Any of the factors responsible may be preexisting or acquired during or after the ICU stay[8]. It is not clear however, whether ICU related factors introduce morbidity or merely enhance the pre-existing neuropsychological and functional decline and to what extent[13].

Risk factors for the cognitive domain are: delirium[5], prior cognitive deficit[14], sepsis[15], ARDS[16] and others such as alcoholism, hypoxemia, hypotension, glucose dysregulation, respiratory failure, blood transfusions, benzodiazepines, transfusions and renal replacement therapy[5,15-20]. The possible mechanisms include ischemia, neuroinflammation and disruption of white mater integrity in areas involved in memory[16,21-23].

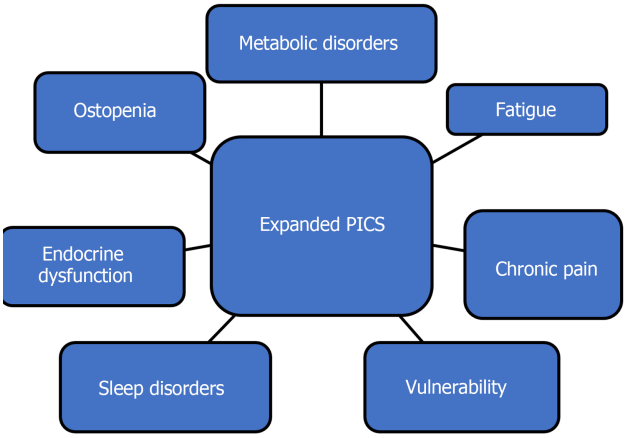
The psychiatric factors are similar to cognitive dysfunction, pre-existing anxiety, depression and PTSD. Female sex, tall stature in males, age < 50 years and low level of education increase the risk. Glucocorticoid administration during critical illness may reduce the levels of cortisol, hence offering protection against development of PTSD[16,24-30].

The physical factors include pre-existing functional disability, fraility, cognitive impairment, prolonged mechanical ventilation (> 7 d), sepsis, multi-organ failure, prolonged bed rest[31-33], and others like ARDS, hyperoxia, use of vasoactive agents and steroids[15,30,34]. The role of neuromuscular blockers in developing physical component of PICS is under suspicion and more studies are required to prove it conclusively[31,35,36].



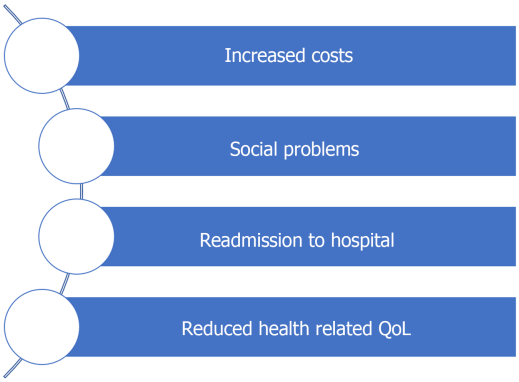
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Figure 1 Contributing factors for post intensive care syndrome. ICU: Intensive care unit.



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Figure 2 Potential new components of post intensive care syndrome. PICS: Post intensive care syndrome.



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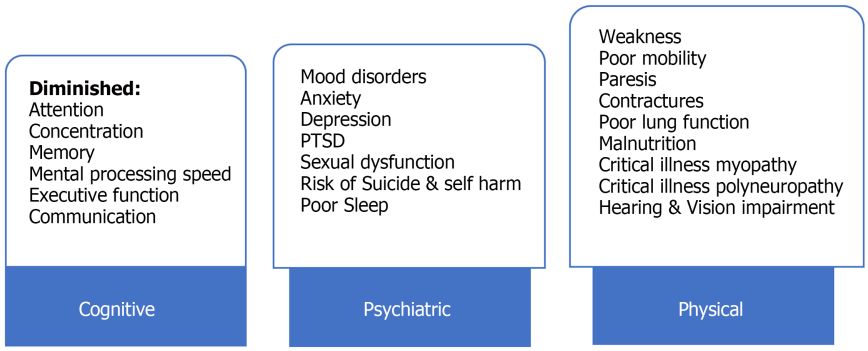
Figure 3 Consequences of post intensive care syndrome. QoL: Quality of life.

Clinical presentation

The common symptoms include weakness, poor mobility, poor concentration, fatigue, anxiety, and depressed mood. These symptoms are either new or represent worsening after the critical illness. The clinical features are depicted in Figure 4[1,7,16,31,32,37].

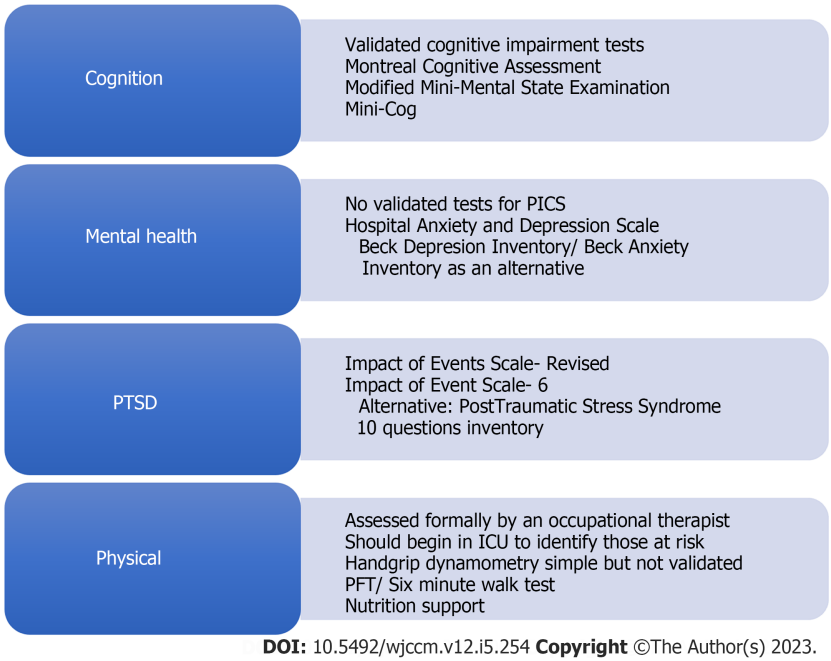
Diagnosis

A high index of suspicion is required for its identification. There are no formal screening or definitive tests available for its diagnosis[38,39]. The society of critical care medicine advocates an early and serial assessment which begins at admission to ICU, as a part of ICU to ward over and involves predischarge functional assessment, followed by 2-4 wk post discharge and throughout recovery. Those at high risk due to pre-existing or ICU related risk factors should be prioritised for evaluation[40]. All three domains are evaluated using a systematic screening approach beginning two to four weeks after hospital discharge (Figure 5)[33,40-44].



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Figure 4 Clinical features of post intensive care syndrome. PTSD: Post-traumatic stress disorder.



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Figure 5 Evaluation tools for diagnosis of post intensive care syndrome. PTSD: Post-traumatic stress disorder; PICS: Post intensive care syndrome; ICU: Intensive care unit; PFT: Pulmonary Function Test.

It is also important to rule out other causes which may cause disability and loss of function after ICU discharge. Most important of these include pre-existing illness which may persist and remain unchanged, thus excluding a diagnosis of PICS. The worsening or appearance of new illness may be difficult if the pre-existing illness is not known. Help may be sought from family members to obtain an extended history and pre admission status may help confirm the diagnosis. Apart from above, certain conditions may mimic PICS, including but not limited to stroke, hypo/hyper-thyroidism, vitamin B12 deficiency, anaemia, malignancy and obstructive sleep apnoea. These can usually be detected by routine laboratory testing or imaging, but should be directed based on history and examination findings. Rhabdomyolysis, cachetic myopathy and Guillain Barre syndrome may be mistaken for ICU acquired weakness, but usually obvious on admission[40].

A transient hospital- associated disability (post-hospital syndrome) may be confused with PICS. However, this is transient, seen in elderly and associated with a number of functional disabilities. PICS, on the other hand, may afflict all ages and runs a protracted course[45].

Prevention

All patients being admitted into the ICU facility should undergo a psychological evaluation that includes pre-admission history, ability to adapt to stress in past, medication history, current mental and clinical status and environmental and family factors[46].

An ABCDEF bundle approach is warranted to prevent PICS especially in patients receiving mechanical ventilation. This approach includes: (1) Awakening (minimal, light sedation, daily interruption, minimising use of benzodiazepines); (2) Breathing (disease appropriate ventilation, ventilator liberation practices including spontaneous breathing trails); (3) Coordination of care and communication among various disciplines; (4) Delirium monitoring and management; (5) Early

ambulation/exercise; and (6) Family empowerment and engagement[47-49].

Additional interventions to prevent PICS include avoiding hypoglycaemia and hypoxemia, maintenance of ICU diary prospectively by the family members, health care providers, or both during the patient's ICU stay, has shown to decrease symptoms of PTSD, and can be used as a holistic tool to provide support and care to the patient and family[50]. Creating post-ICU clinics to provide follow-up counselling and support to the patients and family[51]. Maintaining good nutritional status and adequate sleep of the patient. Progressive feeding in the early phase for both proteins and calories is essential to prevent overfeeding and high caloric intake. After 4-7 d, high-protein intake and sufficient calories, essential to prevent further loss of muscle mass and function, should be initiated. High-protein targets either by prolonged tube feeding or by enhanced high-protein oral nutrition (supplement) intake should be ensured post discharge [52].

The different phases of critical illness and recovery can be classified as acute illness, hospital recovery, and early and late post discharge recovery. Table 1 summarizes the various phases of critical illness and its consequences, which may be amenable to interventions that attempt to prevent, ameliorate, or treat the underlying impairments of PICS. Identification of the issues associated with each phase encourages development of targeted strategies to mitigate the impediments to complete recovery[53].

Treatment

The clinician should endeavour to treat each component and seek appropriate post ICU discharge services such as cognitive, mental health, physical therapy, occupational rehabilitation and social/family support. Early physical rehabilitation and nutrition along with psychological and familial support right from the early recovery phase within the ICU itself may improve outcomes (Figure 6)[54-57]. Of late, the primary involvement of rehabilitation therapists and psychosocial support have emerged to be the mainstay of the treatment. While the intensivist may ameliorate and prevent the development of PICS, therapy beyond the walls of ICU lies outside the domain of the intensivist[40].

Follow up

The exact period for follow up is not known, but may extend up to years every 2-3 mo post discharge. There is no set protocol and it should be individualised to the disease and needs of each patient. The multidisciplinary team should include specialist providers, social services, occupational and physical therapists[40].

Communication between the care givers and patients should be optimised. PICS clinics are specialised clinics which recognise the need for the care of patients and families with medical, mental health, social support and counselling requirements. Post pandemic, e surveys and tele-medicine have been incorporated for far to reach areas or where expert consultation is required in the absence of available specialists[40]. Peer support groups much like alcoholic anonymous, is being attempted to mitigate PICS and may go a long way in providing help and therapy to these patients[58,59].

PICS-F

Family provides an unyielding and strong support to the individual. Just as the family has an effect on individual, the family itself cannot remain unaffected by the suffering of the individual. Over half of the family can be affected psychologically by the critical illness in of a member, which may persist for months to years. This is termed as PICS -F.

The risk factors may be lower educational level, being the decision maker, child or spouse of the patient, long term stay, less social and financial support, death of the patient and poor communication between the staff[60,61]. Usually family members present with anxiety, depression, PTSD, sleep deprivation, complicated grief, and financial stress[60]. Diagnosis is based on presence of any psychological sequelae that is directly attributable to the critical illness of a loved one. This can however be prevented while the patient in still in ICU by liberalised family presence, structured communication approaches and increasing access to information[62-64]. Additional measures which may reduce the incidence are use of a trained nurse though that may induce additional financial burden, participation in bedside care and keeping a diary to reduce PTSD[65]. The treatment modalities remain the same as for the patients suffering from PICS.

FUTURE TRENDS

Seamless care integration appears to be a key factor in ensuring optimal continuum of care for survivors of critical illness. With growing ICU survivorship and increasing burden of PICS, it is imperative to integrate post-acute care services targeting residual impairments into the discharge process. It may aid post-discharge recovery, but also optimize resource use utilising bundled episode-based care[66].

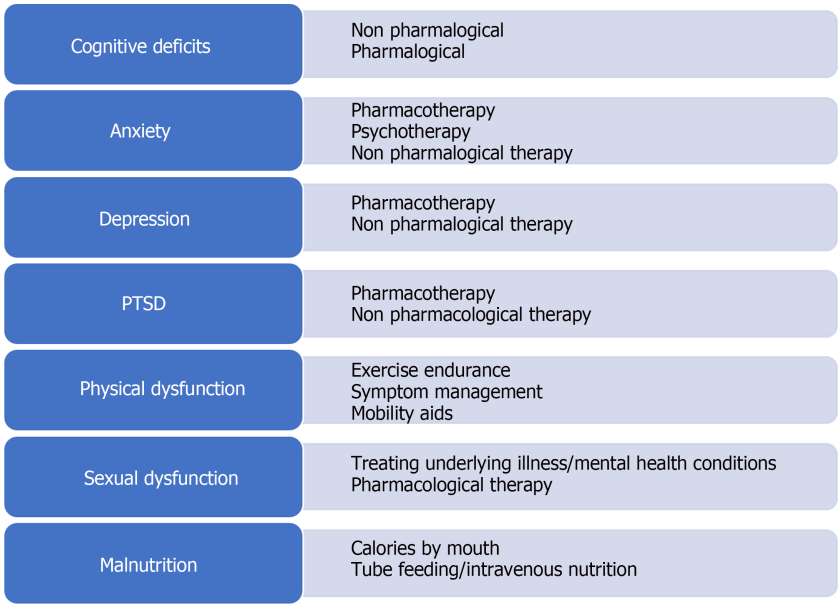
Patients' ICU and post-ICU experiences are challenging, with little or no preparation or support. There are no evidence-based, patient-centered guidelines for the interdisciplinary care teams to develop and execute care plans meeting patients' medical, social, and rehabilitation needs. Before these guidelines can be developed, it is necessary to understand patients' priorities during recovery. The patients want to feel safe, be comfortable, engage in mobility, participate in self-care, resume normal roles and routines, connect with people, assert personhood, ensure family well-being, go home, restore physical and psychological health and seek new experiences[66].

These core priorities of critical illness survivors should be a part of the stakeholder-driven clinical guidelines and quality measures for post-ICU care. Future research should extend these findings among other stakeholders (*e.g.*, family members and healthcare providers) and determine barriers and facilitators to patient-centered post-ICU care[66].

Table 1 Various phases of critical illness, its consequences amenable to interventions[53]

Phase of critical illness	Acute illness	Recovery	Early post-discharge recovery	Late post-discharge recovery
Desired outcome	Survival	Discharge home	Stay home and improving	Return to baseline
Location	ICU	Hospital ward	Home	Home
Impediments	(1) Late antibiotics or source control for sepsis; (2) Hospital-onset infection (*e.g.*, VAP, CABSI, CAUTI); (3) Lack of venous thromboembolism prophylaxis; and (4) High-tidal volume ventilation for ARDS	(1) Immobility; (2) Delirium; (3) Lack of rehabilitation; (4) Polypharmacy; (5) Prolonged catheterization; and (6) Disruption of circadian rhythm	(1) Post-intensive care syndrome; (2) Caregiver misinformation; (3) Fragmented care or inadequate follow-up; (4) Vague or incomplete discharge instructions; (5) Non-compliance to medication; (6) Absence of ME; (7) Inadequate rehabilitation; (8) Lack of subspecialist follow-up; and (9) Polypharmacy	(1) Post-intensive care syndrome; (2) Inadequate vocational rehabilitation; (3) Disrupted employment; (4) Patient and family financial burden; (5) Socioeconomic barriers to care (insurance, transport); (6) Fragmented or inadequate family support; and (7) Polypharmacy

The table was adapted from Brown SM *et al*[53]. VAP: Ventilator associated pneumonia; CABSI: Catheter associated blood stream infection; CAUTI: Catheter associated urinary tract infection; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit; ME: Medical equipment.



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Figure 6 Treatment modalities for post intensive care syndrome. PTSD: Post-traumatic stress disorder.

Some of the barriers that are needed to be crossed before a critical care team of the future can be created are: Enhancing collaboration and communication, evolving technologies, enhanced security of health data, evolving research techniques, provider responsibilities to improve patient care and innovative educational models[67]. To achieve this, the role of professional societies would be equally important to improve outcomes for a diverse population of critically ill and injured patients, expand and support a global network of critical care professionals and advocate for patients, families, and critical care professionals[67].

CONCLUSION

It is not too far-fetched to think of a multi-professional patient centric critical care team that provides the right care to the right patient at the right time throughout and after the acute illness is over. What we need to change to bring in the future is how we use data, devices, and new technologies to continue to strive toward that goal.

FOOTNOTES

Author contributions: Kumar N performed the literature search and wrote the article; the final manuscript has been read and approved by the author.

Conflict-of-interest statement: The author reported no relevant conflicts of interest for this article.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Cai YX

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World J Crit Care Med 2023 December 9; 12(5): 264-285

DOI: 10.5492/wjccm.v12.i5.264

ISSN 2220-3141 (online)

META-ANALYSIS

Systematic review and meta-analysis of seroprevalence of human immunodeficiency virus serological markers among pregnant women in Africa, 1984-2020

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Specialty type: Critical care medicine

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Hedayati-Moghaddam MR, Iran

Received: July 29, 2023
Peer-review started: July 29, 2023
First decision: September 14, 2023
Revised: September 19, 2023
Accepted: November 8, 2023
Article in press: November 8, 2023
Published online: December 9, 2023

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Abstract

BACKGROUND

Human immunodeficiency virus (HIV) is a major public health concern, particularly in Africa where HIV rates remain substantial. Pregnant women are at an increased risk of acquiring HIV, which has a significant impact on both maternal and child health.

AIM

To review summarizes HIV seroprevalence among pregnant women in Africa. It also identifies regional and clinical characteristics that contribute to study-specific estimates variation.

METHODS

The study included pregnant women from any African country or region, irrespective of their symptoms, and any study design conducted in any setting. Using electronic literature searches, articles published until February 2023 were reviewed. The quality of the included studies was evaluated. The DerSimonian and Laird random-effects model was applied to determine HIV pooled seroprevalence among pregnant women in Africa. Subgroup and sensitivity analyses were conducted to identify potential sources of heterogeneity. Heterogeneity was assessed with Cochran's Q test and I^2 statistics, and publication bias was assessed with Egger's test.

RESULTS

A total of 248 studies conducted between 1984 and 2020 were included in the quantitative synthesis (meta-analysis). Out of the total studies, 146 (58.9%) had a low risk of bias and 102 (41.1%) had a moderate risk of bias. No HIV-positive pregnant women died in the included studies. The overall HIV seroprevalence in pregnant women was estimated to be 9.3% [95% confidence interval (CI): 8.3-10.3]. The subgroup analysis showed statistically significant heterogeneity across subgroups ($P < 0.001$), with the highest seroprevalence observed in Southern Africa (29.4%, 95%CI: 26.5-32.4) and the lowest seroprevalence observed in Northern Africa (0.7%, 95%CI: 0.3-1.3).

CONCLUSION

The review found that HIV seroprevalence among pregnant women in African countries remains significant, particularly in Southern African countries. This review can inform the development of targeted public health interventions to address high HIV seroprevalence in pregnant women in African countries.

Key Words: Human immunodeficiency virus; Pregnant women; Africa; Prevalence; Review; Meta-analysis

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Core Tip: A meta-analysis reveals a 9.3% Human immunodeficiency virus (HIV) seroprevalence among pregnant women in Africa, with regional variations. Southern Africa reports the highest rates at 29.4%, whereas Northern Africa shows the lowest at 0.7%. These findings underscore the need for targeted public health interventions to tackle high HIV seroprevalence in pregnant women, especially in Southern African countries.

Citation: Ebogo-Belobo JT, Kenmoe S, Mbongue Mikangue CA, Tchatchouang S, Robertine LF, Takuissu GR, Ndzie Ondigui JL, Bowo-Ngandji A, Kenfack-Momo R, Kengne-Ndé C, Mbaga DS, Menkem EZ, Kame-Ngasse GI, Magoudjou-Pekam JN, Kenfack-Zanguim J, Esemu SN, Tagnouokam-Ngoupo PA, Ndip L, Njouom R. Systematic review and meta-analysis of seroprevalence of human immunodeficiency virus serological markers among pregnant women in Africa, 1984-2020. *World J Crit Care Med* 2023; 12(5): 264-285

URL: https://www.wjgnet.com/2220-3141/full/v12/i5/264.htm

DOI: https://dx.doi.org/10.5492/wjccm.v12.i5.264

INTRODUCTION

Human immunodeficiency virus (HIV) treatment guidelines, increased use of testing and counselling have resulted in a significant decrease in HIV rates in the general population during the 2010s, including in Africa[1-4]. Unfortunately, the impact of these interventions on pregnant women is less clear. According to the UNAIDS report (2023), 39 million people globally were living with HIV in 2022, and around 65% of these people lived in sub-Saharan Africa[5]. According to the same report, women and girls accounted for 63% of all new HIV infections in sub-Saharan Africa. A meta-analysis of participants recruited from 1984 to 2012 showed that HIV acquisition during pregnancy and postpartum was estimated at

3.8 [95% confidence interval (CI): 3.0, 4.6] per 100 person-years[6]. HIV incidence was higher during pregnancy and in Africa. A more recent meta-analysis revealed HIV incidence among pregnant women in sub-Saharan Africa remained significant at 3.6 (95%CI: 1.2-11.1)[7]. HIV causes maternal deaths between 5.9% and 17.9%[8-10]. HIV-positive pregnant and postpartum women are more likely to die than those without HIV. Moreover, the study estimated that 994 deaths per 100000 were caused by HIV in pregnant and postpartum women[11]. A more rapid progression of HIV-related illness or obstetric complications may contribute to this higher morbidity in HIV-positive pregnant women[12,13]. Besides health risks for mothers, HIV infection also increases the risks of mother-to-child transmission. HIV transmission from mother to child is also increased during pregnancy and after delivery[6,7]. A study has shown that the risk of mother-to-child HIV transmission during pregnancy is higher than that of chronic infections during pregnancy and postpartum[6]. A separate study found that mothers infected with HIV who don't receive antiretroviral therapy have an increased chance of having a preterm birth, a low birth weight, a small for gestational age, and a stillbirth in sub-Saharan Africa[14]. Several studies have explored the HIV seroprevalence among pregnant women in Africa, but a comprehensive review is needed. A meta-analysis of 15 studies found that 5.74% (95%CI: 3.96-7.53%) of pregnant women in Ethiopia had HIV with a high level of regional heterogeneity[15]. To guide future research and policy, it is essential to better understand the characteristics contributing to variations in HIV estimates among pregnant women. Furthermore, it is vital to develop effective strategies to reduce horizontal and vertical transmission of HIV during pregnancy and breastfeeding. We have summarized estimates of HIV seroprevalence among pregnant women in Africa and identified regional and clinical characteristics that contribute to variation in study-specific estimates.

MATERIALS AND METHODS

Study design

This study complied with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [16]. Study protocol was registered in PROSPERO (CRD42021272440). The registered protocol specifies objectives, inclusion and exclusion criteria, search strategy, data extraction, and statistical analysis plan.

Eligibility criteria

This systematic review and meta-analysis assessed the seroprevalence of HIV serological markers among pregnant women in 54 African countries up to February 2023. The study included pregnant women from any African country or region, irrespective of their symptoms, and any study design (cross-sectional, cohort, clinical trial, or case-control) conducted in any setting (hospital-based, antenatal clinics, or community-based). All laboratory diagnostic methods using any sample type to detect HIV serological markers were eligible. Studies with a sample size greater than 10, with enough data available, written in English and French were included. We chose studies with more than 10 samples for statistical robustness and reliability. When overlapping data appeared in different articles, the most recent or complete study was used. Review articles, comments, case reports, and studies with inaccessible full-text or abstracts were excluded from the study.

Article search strategy

Using Pubmed and Web of Science, African Index Medicus, and African Journal online, we reviewed the electronic bibliography for articles published till February 2023. Search terms related to HIV, pregnant women, and Africa were used (Supplementary Table 1). The reference lists of all relevant articles were reviewed to complete searches in the bibliographic database and identify possible additional data sources.

Article selection

Two investigators (Ebogo-Belobo JT and Kenmoe S) independently screened titles and abstracts of articles retrieved from electronic literature searches, and full texts of those eligible were obtained and assessed further for final inclusion. A PRISMA flow diagram was used to document the screening process. Consensus was reached between reviewers to resolve disagreements.

Data extraction from the included articles

Data extraction for this systematic review was conducted using a Google form by 14 study authors and verified by Ebogo-Belobo JT. The extracted data included information on the first author's name, year of publication, and participants' inclusion period. We also collected information about the study design and countries. A number of websites were used to obtain the WHO region, United Nations region, and World Bank Income Group from country information [17,18]. Other extracted information included single HIV diagnostic methods or algorithms of diagnostic methods, parity, gravidity, gestational age, educational level, sample size, HIV positive number, and type of HIV. In studies reporting results with undetermined HIV status, we excluded these patients from our estimations. In cases where detection algorithms were used, we considered the number of positives from the group of detection methods constituting the algorithm, not the results of the individual detection methods. Discrepancies encountered during data extraction were resolved through discussion and consensus among the authors.

Assessment of study quality

The risk of bias assessment was conducted using the Hoy *et al*[19], tool, which is designed to assess the risk of bias in

prevalence studies (Supplementary Table 2). This tool includes ten items related to the study's external and internal validity. Each item is scored as either low risk, high risk, or unclear risk of bias. Scores range from 0 to 10, with higher scores indicating lower bias risk. Each study included in the review was assessed for bias using the tool, with disagreements resolved through discussion and consensus.

Statistical analysis

This meta-analysis used the DerSimonian and Laird random-effects model to determine pooled HIV seroprevalence among pregnant women in Africa[20]. This was done by inputting numerators (HIV positive) and denominators (HIV tested) extracted from selected studies. Using the Clopper-Pearson method, we calculated 95%CI for individual studies. The results of individual studies were summarized using forest plots. The analysis was conducted with the 'meta' package in R v4.0.3 (R Foundation for Statistical Computing, Vienna, Austria), and the 'metaprop' function was applied to conduct the meta-analysis of single proportions to obtain HIV pooled seroprevalence[21,22].

Sub-group, metaregression, and sensitivity analyses

A subgroup meta-analysis and metaregression analysis were conducted to identify potential sources of heterogeneity. Several covariates were considered, including: (1) Regional characteristics such as countries, United Nations regions, WHO regions, and World Bank Income Groups; (2) HIV characteristics such as type of HIV and HIV diagnostic method; (3) participant characteristics such as gestational age, parity, gravidity and educational level; and (4) studies characteristics such as sample size, risk of bias, and study period. Only covariates with at least three data points were considered in the subgroup analyses. We included only cross-sectional studies and those with low bias risks in the sensitivity analyses.

Heterogeneity and publication bias

Heterogeneity was assessed using Cochran's Q test and I^2 statistics[23]. A statistically significant Cochran's Q test ($P < 0.05$) was indicative of true heterogeneity of effect sizes between studies. The I^2 statistic was calculated as an estimate of between-studies variance using the maximum likelihood method. I^2 values of 50% or higher indicate substantial heterogeneity. Publication bias was assessed with Egger's test, with a statistically significance ($P < 0.05$) suggesting evidence of funnel plot asymmetry[24].

RESULTS

Selection of included articles

We conducted a comprehensive search of relevant databases for studies on HIV seroprevalence and case fatality rates in pregnant women. After deduplication and initial screening, 619 full-text articles were evaluated. Ultimately, 248 articles met our inclusion criteria and were incorporated into the meta-analysis (Figure 1)[25-272].

Included article characteristics

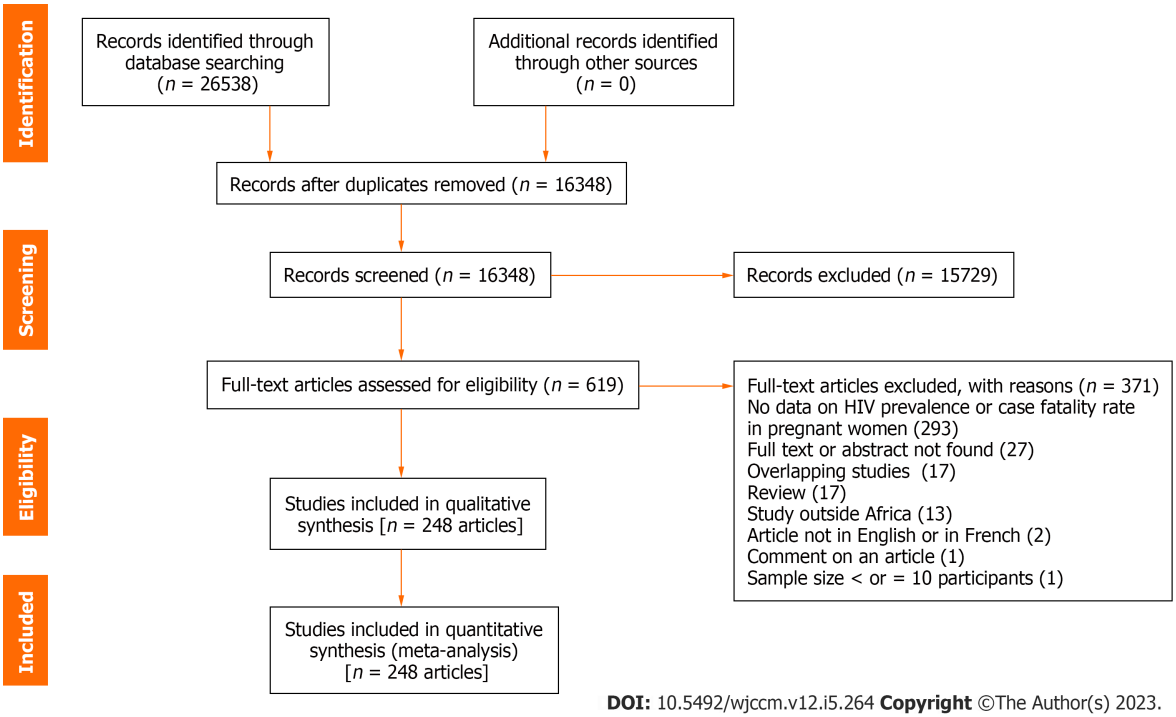
We conducted a systematic review of studies published from 1987 to 2023 and reviewed 248 studies. The selected studies encompassed a total of 1374392 participants, with individual studies ranging from 11 to 243302 participants. There were no cases reported of HIV-positive pregnant women dying in the included studies, which only reported HIV seroprevalence among pregnant women. Included studies recruited participants between 1984 and 2020, with unclear inclusion periods in 25 studies (Supplementary Table 3). The studies were conducted in 37 African countries, with the majority being from Nigeria (23.0%), followed by Tanzania (8.5%), Ethiopia (7.3%), and South Africa (7.3%). The studies were mostly conducted in lower-middle-income countries (58.5%), followed by low-income countries (32.3%) and upper-middle-income countries (8.9%). Most studies were hospital-based (99.2%), with only one community-based study. The HIV diagnostic methods used in the studies varied, with the most common methods being algorithm of rapid antibody tests (29.0%), single rapid antibody test (14.9%), and indirect enzyme-linked immunosorbent assay (ELISA) (11.7%).

Risk of bias in the included studies

Out of the total number of studies included in the review (248), 146 (58.9%) were deemed to have a low risk of bias, while 102 (41.1%) were categorized as having a moderate risk of bias (Supplementary Table 4).

Meta-analysis

A meta-analysis was performed to estimate the overall HIV seroprevalence in pregnant women, as well as the seroprevalence among cross-sectional studies, among studies with sample size ≥ 100 and those with a low risk of bias. The overall HIV seroprevalence in pregnant women was estimated to be 9.3% (95%CI: 8.3-10.3). The seroprevalence among cross-sectional studies and among studies with a low risk of bias were slightly lower at 8.8% (95%CI: 7.7-9.8) and .8% (95%CI: 7.5-10.2) respectively, while the seroprevalence among studies with sample size ≥ 100 was 9.1% (95%CI: 8.1-10.2). All three analyses exhibited high heterogeneity ($P < 0.001$). The analysis of publication bias using the Egger test indicated evidence of significant publication bias ($P < 0.001$) in the meta-analysis (Supplementary Figure 1).



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Figure 1 Study selection.

Metanalysis by United Nation regions

Subgroup analysis was conducted to explore the difference in seroprevalence among different United Nation regions (Figure 2). The results showed statistically significant heterogeneity across subgroups ($P < 0.001$). The seroprevalence of the disease varied across different regions with the highest observed in Southern Africa (29.4%, 95%CI: 26.5-32.4) and the lowest in Northern Africa (0.7%, 95%CI: 0.3-1.3). Eastern Africa had a relatively high seroprevalence (11.7%, 95%CI: 10.2-13.2), while that in Western Africa was relatively low (6.2%, 95%CI: 5.2-7.3). Middle Africa had a moderate seroprevalence (4.8%, 95%CI: 4-5.8). The difference in seroprevalence between United Nation regions was statistically significant ($P < 0.001$).

Meta-analysis of other regional categories

HIV seroprevalence in pregnant women varied among different countries (Table 1). The highest seroprevalence was reported in South Africa (29.9%, 95%CI: 26.7-33.2), followed by Zimbabwe (25.7%, 95%CI: 16.4-36.3) and Malawi (18.7%, 95%CI: 14.2-23.8) (Figure 3). The lowest seroprevalence was reported in Sudan (1.0%, 95%CI: 0.4-1.7) and Senegal (0.7%, 95%CI: 0.5-0.9). The difference was statistically significant ($P < 0.001$). HIV seroprevalence in pregnant women varied significantly among WHO regions ($P < 0.001$) (9.5%, 95%CI: 8.4-10.6 in Africa *vs* 1.4%, 95%CI: 0.6-2.4 in Eastern Mediterranean) (Table 1). HIV seroprevalence during pregnancy was significantly different among World Bank Income Groups ($P < 0.001$) (Table 1). The highest seroprevalence was observed in upper-middle-income countries (24%, 95%CI: 19.9-28.3), followed by low-income countries (8.4%, 95%CI: 6.9-10.1) and lower-middle-income countries (8.1%, 95%CI: 7.2-9.1).

Meta-analysis by HIV characteristics

The HIV-1 seroprevalence was 8.7% (95%CI: 7.5-10) with a 95% prediction interval of 0.5-25.4%, while the HIV-2 seroprevalence was 1.2% (95%CI: 0.7-1.9) with a 95% prediction interval of 0-5.2% (Table 1). HIV-1 seroprevalence was significantly higher than HIV-2 ($P < 0.001$) (Figure 3). Regarding the HIV diagnostic method, the highest seroprevalence was found in the combination of rapid antibody test and indirect ELISA subgroup (15.9%; 95%CI: 1.3-42.1) (Table 1). The lowest seroprevalence was found in the algorithm (rapid antibody test, indirect ELISA, and enzyme immunoassay) subgroup (3.3%; 95%CI: 1.9-4.9). There was a statistically significant difference between subgroups ($P < 0.001$).

Meta-analysis by pregnant women's characteristics

The subgroup analysis by gestational age included 17 studies involving 36935 participants (Table 1). The HIV seroprevalence was highest in the second trimester with 9.6% (95%CI: 5.2-15), followed by the third trimester with 8.7% (95%CI: 5.2-13.1) and the least during the first trimester with a prevalence of 7.3% (95%CI: 3.5-12.2) but without statistical significance ($P = 0.902$). Ten studies were included in the parity subgroup analysis, involving 18015 participants. HIV seroprevalence was 6.7% (95%CI: 4-10) among nulliparous women, 6.5% (95%CI: 4.5-8.8) among multiparous women, and 5% (95%CI: 2.8-7.8) among primiparous women. There was no statistically significant difference between the different categories ($P = 0.690$). The subgroup analysis by gravidity included 17 studies with 53860 participants. HIV seroprevalence was 9.2% (95%CI: 5.5-13.7) among multigravidae and 6.5% (95%CI: 4.2-9.2) among primigravidae. HIV

Table 1 Summary of meta-analysis results for human immunodeficiency virus seroprevalence among pregnant African women from 1984 to 2020

	Prevalence (95%CI, %)	95% prediction interval	N Studies	N Participants	H (95%CI)	I^2 (95%CI)	*P* heterogeneity	*P* difference subtypes
Study design								< 0.001
Cohort	21.6 (15.5-28.4)	(2.6-51.8)	12	95334	19.6 (18.4-21)	99.7 (99.7-99.8)	< 0.001	
Cross-sectional	8.8 (7.7-9.8)	(0-30.6)	236	1276343	20.7 (20.4-21)	99.8 (99.8-99.8)	< 0.001	
Sampling								0.554
Non probabilistic	9.1 (8.1-10.2)	(0.1-29.9)	225	1228039	19.7 (19.5-20)	99.7 (99.7-99.8)	< 0.001	
Probabilistic	10.5 (6.4-15.5)	(0-45.1)	26	146353	24.4 (23.5-25.4)	99.8 (99.8-99.8)	< 0.001	
Timing of samples collection								0.936
Prospectively	9.2 (8.1-10.5)	(0-32.1)	205	942978	19.3 (19-19.6)	99.7 (99.7-99.7)	< 0.001	
Retrospectively	9.2 (6.9-11.8)	(0-31.2)	43	428329	26.6 (25.9-27.3)	99.9 (99.9-99.9)	< 0.001	
Countries								< 0.001
Angola	4.9 (0.6-13.2)	(0-100)	3	3008	7.8 (5.8-10.4)	98.3 (97-99.1)	< 0.001	
Burkina Faso	7.6 (5.6-9.9)	(1.6-17.5)	10	55644	6 (5.1-7.1)	97.2 (96.2-98)	< 0.001	
Cameroon	6.6 (5.4-7.9)	(2.5-12.3)	13	55429	5.5 (4.7-6.4)	96.7 (95.5-97.5)	< 0.001	
Democratic Republic of the Congo	3 (2-4)	(0.5-7.3)	6	21268	3.8 (2.9-5.1)	93.2 (87.9-96.2)	< 0.001	
Ethiopia	5.6 (3.1-8.8)	(0-25.1)	18	25412	9.2 (8.4-10.1)	98.8 (98.6-99)	< 0.001	
Ghana	3.4 (0.4-9)	(0-46.7)	4	4736	6.7 (5.2-8.8)	97.8 (96.3-98.7)	< 0.001	
Ivory Coast	13 (12.1-13.8)	(10.2-16)	9	74677	2.9 (2.2-3.8)	88.3 (80-93.2)	< 0.001	
Kenya	14.4 (10.4-18.8)	(1.8-36)	14	51495	13.2 (12.2-14.3)	99.4 (99.3-99.5)	< 0.001	
Malawi	18.7 (14.2-23.8)	(3.9-41.2)	12	130923	17.6 (16.4-18.9)	99.7 (99.6-99.7)	< 0.001	
Nigeria	6.1 (5-7.3)	(0.4-17.2)	57	84396	6.6 (6.2-7)	97.7 (97.4-98)	< 0.001	
Republic of the Congo	5 (4.1-6)	(2.3-8.7)	7	12841	2.4 (1.7-3.4)	82.8 (66-91.3)	< 0.001	
Rwanda	14.5 (6.9-24.2)	(0-70.4)	4	28796	18.4 (16.1-21)	99.7 (99.6-99.8)	< 0.001	
Senegal	0.7 (0.5-0.9)	(0-4.5)	3	23529	1.6 (1-3.1)	62.9 (0-89.4)	0.068	
South Africa	29.9 (26.7-33.2)	(16.7-45.1)	18	134840	10 (9.2-10.9)	99 (98.8-99.2)	< 0.001	
Sudan	1 (0.4-1.7)	(0-3.2)	4	1296	1.1 (1-2.7)	12.2 (0-86.6)	0.332	
Tanzania	7.3 (5.9-8.8)	(1.9-15.8)	21	157211	10 (9.3-10.9)	99 (98.8-99.2)	< 0.001	
Uganda	11.4 (6.9-16.8)	(0.2-35)	8	50585	14.6 (13.2-16.2)	99.5 (99.4-99.6)	< 0.001	

Zambia	18.6 (14.7-22.8)	(6.3-35.3)	8	326966	20.3 (18.7-22)	99.8 (99.7-99.8)	< 0.001	
Zimbabwe	25.7 (16.4-36.3)	(0.7-68.5)	10	33198	17.6 (16.3-19.1)	99.7 (99.6-99.7)	< 0.001	
WHO Region								< 0.001
Africa	9.5 (8.4-10.6)	(0-31.3)	244	1366377	20.8 (20.5-21.1)	99.8 (99.8-99.8)	< 0.001	
Eastern Mediterranean	1.4 (0.6-2.4)	(0-5.7)	6	7651	2.1 (1.4-3.2)	78.3 (52.3-90.2)	< 0.001	
UN Regions								< 0.001
Eastern Africa	11.7 (10.2-13.2)	(1.2-30.3)	99	813901	20.1 (19.7-20.5)	99.8 (99.7-99.8)	< 0.001	
Middle Africa	4.8 (4-5.8)	(0.9-11.5)	33	101346	6.6 (6-7.1)	97.7 (97.3-98)	< 0.001	
Northern Africa	0.7 (0.3-1.3)	(0-2.8)	5	4328	1.4 (1-2.3)	46.4 (0-80.4)	0.113	
Southern Africa	29.4 (26.5-32.4)	(16.5-44.2)	21	136338	9.3 (8.6-10.1)	98.8 (98.6-99)	< 0.001	
Western Africa	6.2 (5.2-7.3)	(0.2-19.2)	92	317532	11.5 (11.2-11.9)	99.3 (99.2-99.3)	< 0.001	
Sustainable Development Goal regions								< 0.001
Northern Africa and Western Asia	0.7 (0.3-1.3)	(0-2.8)	5	4328	1.4 (1-2.3)	46.4 (0-80.4)	0.113	
Sub-Saharan Africa	9.5 (8.5-10.6)	(0-31.4)	246	1370064	20.7 (20.4-21)	99.8 (99.8-99.8)	< 0.001	
World Bank Income Groups								< 0.001
Low-income countries	8.4 (6.9-10.1)	(0-28.5)	81	712218	23.3 (22.8-23.9)	99.8 (99.8-99.8)	< 0.001	
Lower-middle-income countries	8.1 (7.2-9.1)	(0.5-23.2)	147	521930	12.7 (12.4-13)	99.4 (99.3-99.4)	< 0.001	
Upper-middle-income countries	24 (19.9-28.3)	(6.9-47.2)	22	139297	14.8 (13.9-15.7)	99.5 (99.5-99.6)	< 0.001	
Study period								0.255
(1987-2001)	9.9 (8.1-11.8)	(0.4-29)	62	238301	14.7 (14.2-15.3)	99.5 (99.5-99.6)	< 0.001	
(2001-2016)	8 (6.8-9.4)	(0-27.7)	128	919743	21.7 (21.3-22.1)	99.8 (99.8-99.8)	< 0.001	
(2016-2020)	9.5 (5.9-13.8)	(0-41.9)	30	189325	26.6 (25.8-27.5)	99.9 (99.8-99.9)	< 0.001	
Parity								0.69
Multiparous	6.5 (4.5-8.8)	(0.9-16.1)	10	18015	4.6 (3.8-5.5)	95.2 (92.9-96.8)	< 0.001	
Nulliparous	6.7 (4-10)	(0.1-21.1)	9	14035	5.3 (4.4-6.4)	96.5 (94.9-97.6)	< 0.001	
Primiparous	5 (2.8-7.8)	(0-16.6)	9	8581	4 (3.2-5)	93.8 (90.3-96)	< 0.001	
Gravidity								0.276
Multigravidae	9.2 (5.5-13.7)	(0-35.1)	17	53860	14.2 (13.2-15.2)	99.5 (99.4-99.6)	< 0.001	
Primigravidae	6.5 (4.2-9.2)	(0-21)	16	22946	6.6 (5.9-7.5)	97.7 (97.1-98.2)	< 0.001	
Gestational age								0.902

First trimester	7.3 (3.5-12.2)	(0-32.7)	17	6164	4.1 (3.5-4.8)	94 (91.8-95.6)	< 0.001	
Second trimester	9.6 (5.2-15)	(0-40.7)	18	15874	7.8 (7.1-8.6)	98.4 (98-98.7)	< 0.001	
Third trimester	8.7 (5.2-13.1)	(0-39.4)	27	16897	8.5 (7.8-9.2)	98.6 (98.4-98.8)	< 0.001	
Residence								0.789
Rural	8.1 (5.8-10.6)	(0-29.9)	43	103272	13.5 (12.9-14.1)	99.5 (99.4-99.5)	< 0.001	
Urban	8.5 (7-10.2)	(1.6-20.2)	32	92657	8.5 (7.9-9.1)	98.6 (98.4-98.8)	< 0.001	
Education								0.804
None	5.8 (3.8-8.2)	(0-18)	18	29175	6 (5.3-6.8)	97.2 (96.5-97.8)	< 0.001	
Primary	6.6 (4.1-9.6)	(0-24.6)	21	26835	7.9 (7.2-8.7)	98.4 (98.1-98.7)	< 0.001	
Secondary	7.3 (5.4-9.6)	(0.8-19.1)	20	13337	4.1 (3.5-4.7)	94 (92-95.5)	< 0.001	
Tertiary	6.2 (4.3-8.5)	(0.3-17.6)	18	4744	2.8 (2.3-3.3)	86.8 (80.6-91)	< 0.001	
Type of HIV								< 0.001
HIV-1	8.2 (6.6-10)	(0.2-25.7)	58	279778	15.9 (15.4-16.5)	99.6 (99.6-99.6)	< 0.001	
HIV-2	1.2 (0.7-1.9)	(0-5.2)	16	143453	9.7 (8.8-10.6)	98.9 (98.7-99.1)	< 0.001	
Sample size								0.097
< 100	19.5 (7-36.1)	(0-82.2)	6	425	3.8 (2.9-5.1)	93.2 (87.9-96.2)	< 0.001	
≥ 100	9.1 (8.1-10.2)	(0-30.8)	242	1371252	21 (20.7-21.3)	99.8 (99.8-99.8)	< 0.001	
Risk of bias								0.205
Low risk of bias	8.8 (7.5-10.2)	(0-31)	146	1159206	25.3 (24.9-25.6)	99.8 (99.8-99.8)	< 0.001	
Moderate risk of bias	10 (8.6-11.5)	(0.6-28.5)	102	212471	10.6 (10.3-11)	99.1 (99.1-99.2)	< 0.001	

HIV: Human immunodeficiency virus.

seroprevalence was not significantly higher among multigravidae than among primigravidae (P = 0.276).

The metaregression analysis revealed an association between different factors and HIV seropositivity, with an overall variability of 63.07% observed in our multivariate model (Supplementary Table 5).

DISCUSSION

Participants were recruited in 248 studies between 1984 and 2020 from 39 African countries, with 1374392 participants in total. The overall HIV seroprevalence among pregnant women in Africa was estimated to be 9.3% (95%CI: 8.3-10.3), which suggests that a significant proportion of pregnant women in the region live with HIV. However, it is worth noting that no HIV-positive pregnant women died in any of the included studies. The study also found significant differences in HIV seroprevalence by United Nation region, WHO region, World Bank Income Groups, and individual countries. United Nation regions showed Southern Africa had the highest seroprevalence, followed by Eastern Africa, Western Africa, Middle Africa, and Northern Africa. The WHO region with the greatest seroprevalence was Africa compared to the Eastern Mediterranean. There were significant differences in HIV seroprevalence among World Bank Income Groups, with upper-middle-income countries having the highest seroprevalence, followed by low-income countries, and lower-middle-income countries. The analysis presented data on HIV seroprevalence in different African countries, with South Africa having the highest seroprevalence, followed by Zimbabwe, Malawi, Zambia, and Rwanda. The lowest seroprevalence was observed in Senegal and Sudan. The study found significantly higher HIV-1 seroprevalence (8.2%)

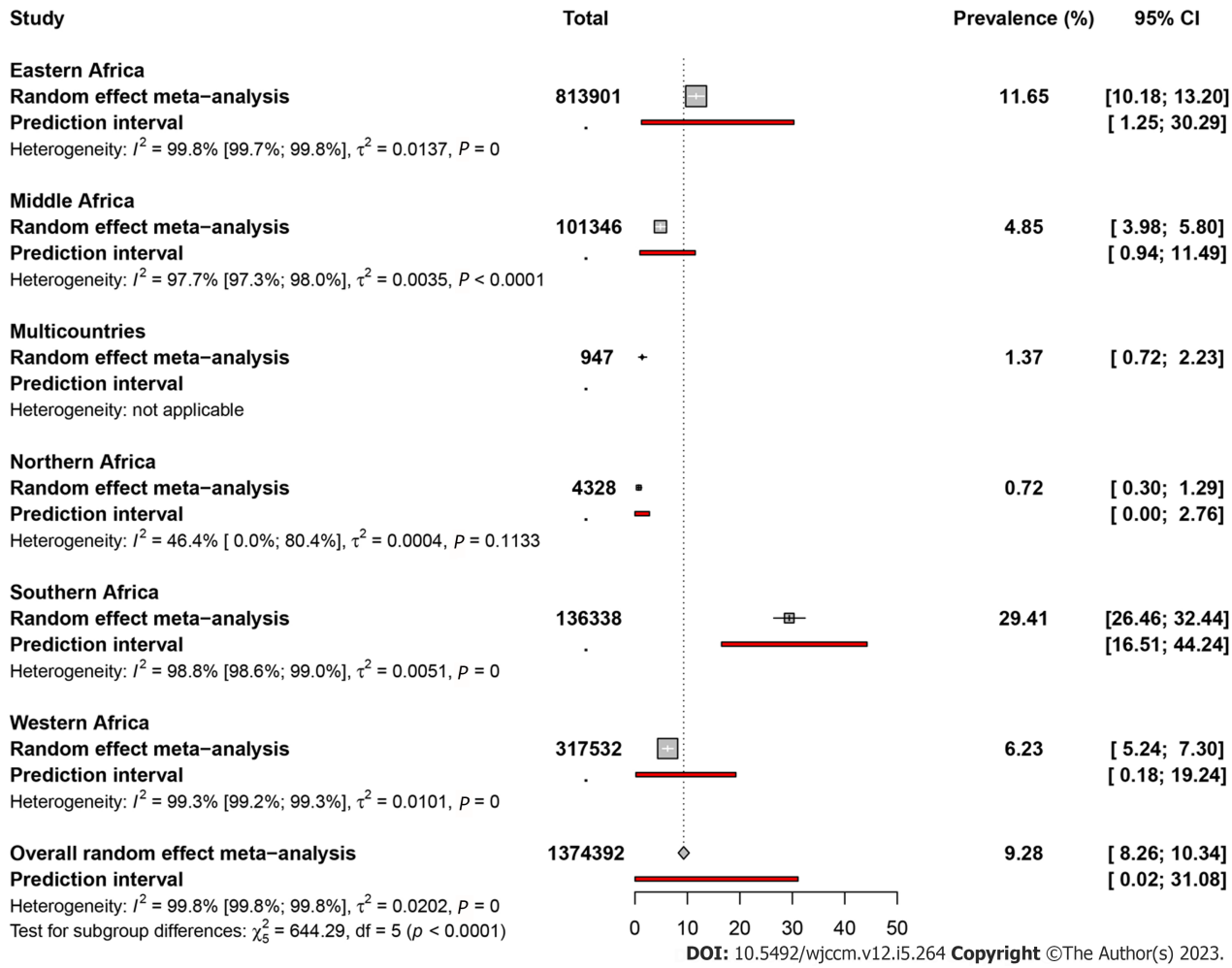


Figure 2 Human immunodeficiency virus seroprevalence among pregnant African women according to United Nation regions from 1984 to 2020.

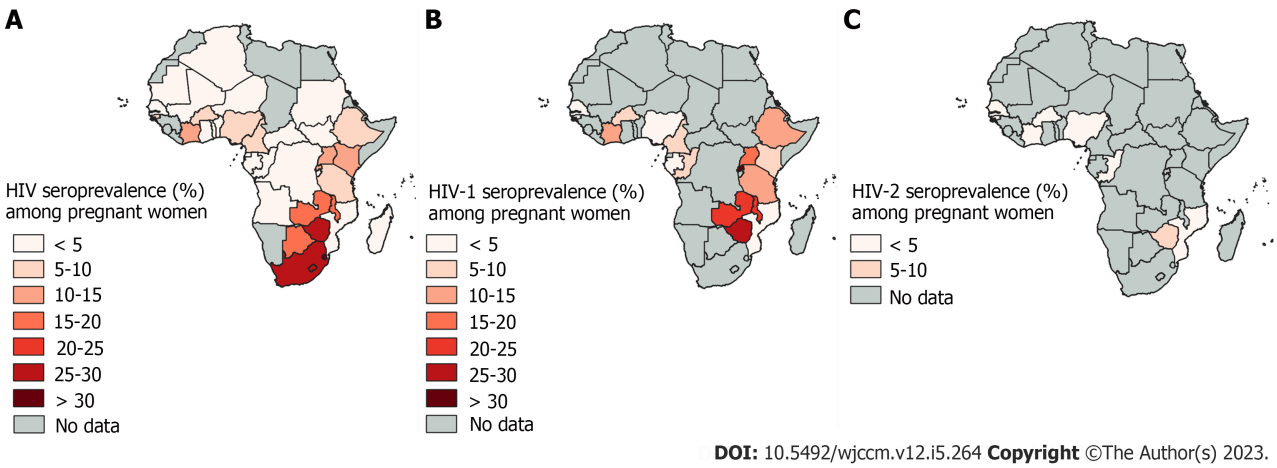


Figure 3 Map of the distribution seroprevalence data among pregnant women in Africa. A: Human immunodeficiency virus; B: Human immunodeficiency virus-1; C: Human immunodeficiency virus-2. The base map was taken from (https://www.naturalearthdata.com/) and modified with Qgis software. HIV: Human immunodeficiency virus.

than HIV-2 (1.2%). No significant differences were observed in seroprevalence based on gestational age, parity, and gravidity.

It is concerning to find that the overall HIV seroprevalence among pregnant women in Africa was estimated to be 9.3% (95%CI: 8.3-10.3), which indicates that the HIV epidemic continues to have a high impact on the continent. Previous studies show pregnant women in Africa are at higher risk of HIV infection[6,7]. There have been previous reports of death in African pregnant and postpartum women, primarily in longitudinal studies[11,13,273]. It is noteworthy that none of the included studies reported the death of HIV-positive pregnant women. As previously reported[274,275], Southern Africa had the highest HIV seroprevalence among pregnant women, followed by Eastern Africa, Western Africa, Middle Africa, and Northern Africa. This highlights the urgent need for continued efforts to prevent HIV transmission and provide effective care and treatment to HIV-positive pregnant women in these regions. The high HIV seroprevalence in Southern Africa is well documented, with countries like South Africa being among the highest HIV seroprevalence in the world[276,277]. This can be attributed to a range of factors, including data availability, poverty, violence against women, cultural restrictions promoting intergenerational sex, unprotected sex, multiple sexual partners, political barriers, recreational drug use, stigma, and discrimination[276,277]. Eastern and Western Africa also have high HIV seroprevalence, with countries like Zimbabwe, Malawi, Zambia, Rwanda, Uganda, and Kenya reporting significant numbers of HIV infections each year[278]. These findings suggest that efforts to prevent HIV transmission and provide care and treatment to HIV-positive pregnant women need to be targeted towards these high-prevalent regions. This may include scaling up prevention interventions such as condom use and pre-exposure prophylaxis (PrEP), as well as increasing access to HIV testing and treatment services[279-281]. In addition, addressing social and economic factors that contribute to HIV transmission, such as poverty, gender inequality, and stigma, is crucial to reducing HIV seroprevalence in these regions.

HIV-1 seroprevalence was significantly higher than HIV-2 seroprevalence, which has implications for HIV prevention and treatment. HIV-1 and HIV-2 are two distinct types of the virus that cause HIV infection, and they differ in their transmission, clinical presentation, and response to treatment[282-284]. HIV-1 is more prevalent globally and is the predominant HIV type in sub-Saharan Africa, where the HIV burden is highest. In contrast, HIV-2 is primarily found in West Africa and is less prevalent globally[282,283]. This has significant implications for prevention efforts, as HIV-1 is more easily transmitted than HIV-2 and associated with faster AIDS progression. Prevention efforts must therefore focus on reducing HIV-1 transmission through strategies such as condom use, pre-exposure PrEP, and promoting HIV testing and treatment for people living with HIV. Antiretroviral therapy is the cornerstone of HIV treatment, and it suppresses both HIV-1 and HIV-2. However, HIV-2 is less responsive to some antiretroviral therapy regimens and may require different treatment strategies[282,283,285]. The high HIV-1 seroprevalence in the study population suggests that healthcare providers should know the HIV-1 predominance and tailor treatment accordingly.

There was no significant difference in seroprevalence based on gestational age, parity, or gravidity, indicating that HIV infection does not discriminate against these demographic characteristics. This finding is consistent with previous research that shows that HIV can affect anyone, regardless of their age, parity, or gravidity[286-288].

This systematic review and meta-analysis of HIV seroprevalence among pregnant women in Africa has some limitations. We acknowledge that not searching the grey literature might introduce a potential limitation to our review. The lack of uniformity in testing methods and cutoffs used in included studies may have affected the results comparability. However, this systematic review and meta-analysis of HIV seroprevalence among pregnant women in Africa has several strengths. The comprehensive search strategy and pre-defined inclusion and exclusion criteria minimized the risk of missing relevant studies and ensured that only appropriate studies were considered. The large sample size and broad time frame of the review increased generalizability. Finally, meta-analysis allowed for the estimation of overall seroprevalence rates and identification of factors associated with HIV seroprevalence among pregnant women in Africa, providing significant insights for clinicians, researchers, and policymakers.

CONCLUSION

This study reports that HIV seroprevalence in pregnant African women was estimated to be 9.3%, highlighting the substantial burden of HIV in Africa. Southern Africa had the highest HIV seroprevalence among pregnant women, followed by Eastern, Western, Middle, and Northern Africa, emphasizing the need for targeted efforts to prevent transmission and provide care and treatment in these regions. HIV-1 seroprevalence was considerably higher than HIV-2, underscoring the need for tailored prevention and treatment strategies.

ARTICLE HIGHLIGHTS

Research background

An extensive literature review was carried out in various databases up until February 2023, using key terms such as Human immunodeficiency virus (HIV), pregnancy, and Africa. Through this literature search, we noted a significant body of evidence detailing HIV infection prevalence among pregnant women in Africa.

Research motivation

Given the continued high incidence and impact of HIV among pregnant women in Africa, there is a critical need to

enhance our understanding of the specific factors that contribute to this high prevalence and the variations in these proportions. There is also an urgent need to examine strategies that could effectively mitigate both horizontal (person-to-person) and vertical (mother-to-child) HIV transmission during pregnancy and breastfeeding.

Research objectives

This research aims to provide a comprehensive understanding of HIV prevalence among pregnant women in Africa by identifying and analyzing the regional and clinical characteristics that contribute to variations in study-specific estimates.

Research methods

This systematic review and meta-analysis, compliant with Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines and registered in PROSPERO, assessed the seroprevalence of HIV serological markers among pregnant women in Africa up to 2023. All types of study designs from any African region were eligible if the sample size was greater than 10 and published in English or French. A literature search was conducted in databases such as Pubmed, Web of Science, African Index Medicus, and African Journal online, with relevant search terms. The quality of the included studies was assessed using the appropriate tool. The DerSimonian and Laird random-effects model was used to determine pooled HIV seroprevalence.

Research results

This systematic review analyzed data from 248 studies investigating HIV seroprevalence in pregnant women across various African countries from 1984 to 2020. The overall HIV seroprevalence was estimated at 9.3% [95% confidence interval (CI): 8.3-10.3]. The highest seroprevalence was found in Southern Africa (29.4%, 95%CI: 26.5-32.4), while Northern Africa had the lowest (0.7%, 95%CI: 0.3-1.3). Among the different types of HIV, HIV-1 seroprevalence was significantly higher than HIV-2 ($P < 0.001$).

Research conclusions

This comprehensive analysis identified a high HIV seroprevalence among pregnant women in Africa at an estimated 9.3%, highlighting the significant burden of HIV in the region.

Research perspectives

Considering the substantial HIV seroprevalence among pregnant women in Africa, this analysis underlines the need for sustained efforts to prevent HIV transmission and provide effective care and treatment for HIV-positive pregnant women, especially in regions with high seroprevalence. Future research should aim to elucidate the factors contributing to high seroprevalence, especially in Southern Africa, and devise effective preventive and therapeutic strategies tailored to the region's needs.

FOOTNOTES

Author contributions: Ebogo-Belobo JT, Kenmoe S, and Njouom R were responsible for conception and design of the study as well as project administration; Ebogo-Belobo JT, Kenmoe S, Mbongue Mikangue CA, Tchatchouang S, Robertine LF, Takuissu GR, Ndzie Ondigui JL, Bowo-Ngandji A, Kenfack-Momo R, Kengne-Ndé C, Mbaga DS, Menkem EZ, Kame-Ngasse GI, Magoudjou-Pekam JN, Kenfack-Zanguim J, Esemu SN, Tagnouokam-Ngoupo PA, Ndip L, and Njouom R were responsible for the data curation and interpretation of results; Kengne-Nde C and Kenmoe S were responsible for statistical analysis; Kenmoe S and Njouom R were responsible for the project supervision; Ebogo-Belobo JT and Kenmoe S wrote the original draft; All authors critically reviewed the first draft and approved the final version of the paper for submission, and have read and approve the final manuscript.

Conflict-of-interest statement: The authors deny any conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Qu XL
L-Editor: A

P-Editor: Cai YX

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