

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2018 February 8; 7(1): 1-66



THERAPEUTICS ADVANCES

- 1 Best practices in supervising cognitive behavioral therapy with youth
Friedberg RD

REVIEW

- 9 Behavioural and emotional disorders in childhood: A brief overview for paediatricians
Ogundele MO
- 27 Controversies in diagnosis and management of Kawasaki disease
Pilania RK, Bhattarai D, Singh S

MINIREVIEWS

- 36 Review of the evidence for the management of co-morbid Tics disorders in children and adolescents with attention deficit hyperactivity disorder
Ogundele MO, Ayyash HF

ORIGINAL ARTICLE

Case Control Study

- 43 Abdominal obesity adversely affects bone mass in children
Krishnan S, Anderson MP, Fields DA, Misra M

Retrospective Cohort Study

- 49 Neither hereditary periodic fever nor periodic fever, aphthae, pharyngitis, adenitis: Undifferentiated periodic fever in a tertiary pediatric center
De Pauli S, Lega S, Pastore S, Grasso DL, Bianco AMR, Severini GM, Tommasini A, Taddio A

Retrospective Study

- 56 Pediatricians lack knowledge for the diagnosis and management of functional constipation in children over 6 mo of age
Widodo A, Hegar B, Vandenplas Y

Clinical Practice Study

- 62 Outcomes of transconjunctival sutureless 27-gauge vitrectomy for stage 4 retinopathy of prematurity
Shah PK, Prabhu V, Narendran V

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Pediatrics*, Joseph UE Onakewhor, MD, Associate Professor, Department of Obstetrics and Gynecology, University of Benin Teaching Hospital, Benin City 300001, Nigeria

AIM AND SCOPE

World Journal of Clinical Pediatrics (*World J Clin Pediatr*, *WJCP*, online ISSN 2219-2808, DOI: 10.5409) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCP covers a variety of clinical medical topics, including fetal diseases, inborn, newborn diseases, infant diseases, genetic diseases, diagnostic imaging, endoscopy, and evidence-based medicine and epidemiology. Priority publication will be given to articles concerning diagnosis and treatment of pediatric diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJCP*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Clinical Pediatrics is now indexed in PubMed, PubMed Central.

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Rui-Fang Li*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Li-Jun Cai*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Quarterly

EDITORS-IN-CHIEF
Seng H Quak, MD, Professor, Department of Paediatrics, NUS - YLL School of Medicine, NUHS Tower Block, Singapore 119228, Singapore

Consolato M Sergi, FRCP(C), MD, PhD, Professor, Department of Lab Medicine and Pathology, University of Alberta, Alberta T6G 2B7, Canada

Toru Watanabe, MD, PhD, Professor, Department of Pediatrics, Niigata City General Hospital, Niigata

950-1197, Japan

EDITORIAL BOARD MEMBERS
All editorial board members resources online at <http://www.wjnet.com/2219-2808/editorialboard.htm>

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Clinical Pediatrics
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjnet.com>

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjnet.com>

PUBLICATION DATE
February 8, 2018

COPYRIGHT
© 2018 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
<http://www.wjnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION
<http://www.f6publishing.com>

Best practices in supervising cognitive behavioral therapy with youth

Robert D Friedberg

Robert D Friedberg, Center for the Study and Treatment of Anxious Youth, Palo Alto University, Palo Alto, CA 94304, United States

ORCID number: Robert D Friedberg (0000-0001-8821-1723).

Author contributions: This manuscript was written completely by the stated author.

Conflict-of-interest statement: The author declares no conflict of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Robert D Friedberg, PhD, ABPP, ACT Professor, Director, Center for the Study and Treatment of Anxious Youth, Palo Alto University, 1791 Arastradero Rd, Palo Alto, CA 94304, United States. rfriedberg@paloaltou.edu
Telephone: +1-408-7754904

Received: November 8, 2017

Peer-review started: November 9, 2017

First decision: December 1, 2017

Revised: December 16, 2017

Accepted: January 7, 2018

Article in press: January 7, 2018

Published online: February 8, 2018

Abstract

Clinical supervision of cognitive behavioral therapy (CBT) with youth ensures better patient care and fosters trainees' professional development. However,

often insufficient attention is directed toward disseminating best practices in supervision of CBT with youth. This Therapeutic Advances contribution aims to communicate the core content of supervision. Additionally, the key supervisory practices associated with CBT with youth are described. Supervisory outcomes are summarized and recommendations for supervisory practices are made.

Key words: Cognitive behavioral therapy; Pediatric populations; Supervision

© **The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: There are several core tips in this therapeutic advances article. First, the pivotal content of supervision of cognitive behavioral therapy with youth include training in case conceptualization, ethics/laws, collaborative empiricism, guided discovery, session structure, embracing immediacy, measurement-based care, and cognitive-behavioral technique. Enactive supervision characterized by behavioral rehearsal is essential. Further, tracking trainee progress *via* objective rating scales and providing frequent, constructive feedback is indispensable.

Friedberg RD. Best practices in supervising cognitive behavioral therapy with youth. *World J Clin Pediatr* 2018; 7(1): 1-8 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i1/1.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i1.1>

INTRODUCTION

Fortunately, the state of the science of cognitive behavioral therapy (CBT) with youth is strong^[1-3]. CBT shows good results with patients diagnosed with multiple disorders including depression^[4], anxiety^[5] obsessive-compulsive disorder^[6], trauma^[7], and disruptive behavior

disorders^[8,9].

Equipping supervisees with state-of-the-practice cognitive behavioral therapy skills for youth is an important yet very challenging training imperative. Didactic training acquired in classes and workshops is not a powerful way to change professional practices^[10,11]. Ongoing consultation potentiates didactic training. More specifically, "consultation likely provides therapists with a venue for clarification and practice of concepts, learning concepts over time, case consultation, and using problem solving to overcome implementation barriers"^[10].

Clinical supervision of CBT with youth is a multi-pronged professional activity that targets various foci^[12,13]. Of course, assuring the emotional and psychological well-being of young patients is the pre-eminent goal. Additionally, building trainees skills, knowledge and attitudes is a second pivotal task. Finally, assisting supervisees with difficult patients and igniting their professional development are important undertakings. Achieving these meritorious goals is both a rewarding and challenging endeavor.

This therapeutic advances article highlights several issues. The paper begins with a discussion about the importance of supervision. Second, the common content of supervision is explicated. Next, core supervisory practices are explained. A consideration of supervisory outcomes follows. The article concludes with recommendations for proper supervision of CBT with youth.

IMPORTANCE OF SUPERVISION

In the United States, there is a growing call for evidence-based approaches for treating psychiatric disorders in youth^[14]. Lack of access to good supervision is commonly seen as an obstacle to effective implementation in community contexts^[15]. Many clinicians label themselves as cognitive behavioral therapists, but this self-identification does not reflect the actual behaviors demonstrated in sessions^[14]. In particular, a recent study found that 71% of clinicians who self-labeled as CBT therapists failed to display evidence of CBT competence^[14]. Further, there were equivalent levels of non-competence between those clinicians who did and did not identify themselves as CBT clinicians. Additionally, over 50% of community clinicians trained in CBT reported departing from the approach suggesting that CBT is not being implemented with sufficient fidelity^[16]. Truth in labeling is imperative. If clinicians inaccurately claim a CBT orientation, the treatment dose is diluted and the delivery method is compromised. Competent supervision enables essential quality control. Without this quality control, clinicians are free to go rogue and suffer sizeable theoretical/technical drift.

CONTENT OF SUPERVISION

CBT clinicians are made not born. There is much to learn when becoming a cognitive behavioral therapist with youth^[17]. Good CBT with youth involves numerous

competencies^[17-21]. Appreciating the state of the science supporting CBT and the theoretical foundations which underlie the approach is imperative. Fashioning flexible and robust case formulations is also expected. Employing guided discovery and collaborative empiricism throughout the clinical work is another vital component. Adhering to the prototypical cognitive therapy session structure is *de rigueur*. Of course, mastery of the variety of CBT procedures and processes such as Socratic questioning, self-instruction, problem solving, imagery, behavioral activation, social skills training, behavioral experiments, and exposure/response prevention is fundamental.

Supervision is portrayed as the "pedagogical engine" of clinical training in CBT^[22]. Attention to core content areas and allocating sufficient time for training are vital. Research has indicated that in community based clinics, there is little discussion of evidence based procedures in supervision^[23]. Insufficient training times are associated with trainees' overestimation of their competence^[24]. Indeed, there is much heavy lifting to do in CBT training. Therefore, supervisors must promote high level didactic, procedural, and self-reflective learning experiences in an efficient manner. Fortunately, CBT supervision is described as goal-directed, structured, time limited, and personalized to the trainee^[25,26].

Supervisors and trainees are wise to remember that "cognitive therapy is work not magic"^[27]. This section details the core elements embedded in good supervision of CBT with youth including training in case conceptualization, ethical and legal alertness, multicultural responsiveness, employing collaborative empiricism and guided discovery, measurement based care, technical proficiency, as well as addressing trainees' beliefs about the clinical work.

Case conceptualization^[13,17-21,28-32] is an indispensable task. In fact, case conceptualization is seen as the nucleus of good CBT practice^[19]. Case formulation obviates an eclectic approach and bag of tricks mentality. Authors^[33] recently argued, "We have no data to suggest that an 'a la carte' approach to CBT produces positive patient outcomes". The selection, timing, and targets of various interventions are launched by case conceptualization. However, the ability to formulate cases is an acquired skill set^[20,34]. Case conceptualization involves several component bits of knowledge^[19,20]. More specifically, fluency in operant, classical, and social learning theory paradigms is essential. Additionally, full comprehension of theoretical tenets such as the hierarchical organizational model^[35,36] and the content-specificity hypothesis^[37-41] is necessary. Appreciation of socio-cultural variables and developmental vicissitudes is also pivotal. Required reading lists are encouraged to bulk up trainees' knowledge bases. Fortunately, several excellent teaching and training resources exist^[42-46]. Additionally, completing written case formulations and receiving supervisory feedback on them is also recommended^[30].

Instruction in ethics and legal regulations is also

necessary when supervising CBT with youth^[13,17,47]. Attention to issues of confidentiality are especially important when working with young patients. Clinicians need to be ever mindful regarding WHO is their patient. Additionally, alertness to child abuse and maltreatment is a priority. Training supervisees in identifying and managing common hazardous issues such as self-injurious, suicidal, homicidal, risky sexual and substance abusing behaviors is also pivotal.

Training in collaborative empiricism^[32,48] is an indispensable pedagogical task. Collaboration is especially valuable since it promotes trust and fosters experimentation with techniques^[32]. The empiricism part of the equation refers to the transparent data based nature of CBT with youth. Moreover, the reliance on data coming directly from young patients and their families is linked to CBT's phenomenological roots^[49]. In particular, collaboration is a difficult practice to develop especially for supervisees who are more comfortable with either overly prescriptive or non-directive approaches.

Teaching trainees the rudiments of guided discovery is important yet quite challenging^[48]. Many supervisees perceive guided discovery as a common pitfall in clinical practice^[33]. Simply stated, guided discovery involves helping young patients form more adaptive conclusions and flexible attitudes based on their personal data base. Similar to collaborative empiricism, guided discovery is rooted in a hypothesis testing stance^[50]. Simply stated, guided discovery facilitates the art of the possible^[45]. Empathic listening, Socratic dialogues homework assignments and behavioral experiments are components of guided discovery.

Teaching trainees' to implement the trademark session structure is another crucial task. Mood check-ins, agenda setting, processing session content, assigning homework, and eliciting feedback are the requisite components^[51]. Applying a regular format to sessions is typically foreign to most beginning trainees. It is also helpful to teach them that these elements are both procedures and processes so they are less likely to apply a mechanical, stereotyped approach to session structure.

Embracing immediacy in CBT with is another core skill^[52-54]. Immediacy involves addressing emotionally evocative moments in the here and now. A contemporary article contended immediacy occurs when "psychotherapeutic moments are charged with the urgency and genuineness of emotional experience in present tense and real time^[53]." Immediacy in session avoids an intellectualized, emotionally sterile, and mechanical approach to CBT with young people.

Measurement based care (MBC) is another vital content element. MBC ensures accountability and collaborative monitoring of treatment progress. Simply, MBC involves regular periodic examination of patients' functioning through a combination of symptom scales, indices of functional improvement, and patient satisfaction measures^[55].

Instruction in the theory, empirical support and practice of traditional cognitive behavioral techniques

is standard fare in CBT supervision with youth^[56-67]. Teaching psychoeducational, behavioral tasks, cognitive restructuring techniques, and exposure procedures typically involves reading assignments, verbal discussion, modeling, and opportunities for trainees to rehearse the intervention. Of course, practice is accompanied by supervisory feedback.

Supervisees' experience various thoughts and feelings regarding clinical work with young patients. Accordingly, processing trainees' thoughts, feelings and actions^[13,21,25-27,30,45-47,57,67-69] is an integral supervisory responsibility. Trainees hold various dysfunctional beliefs about their competence and adhere to unrelenting performance standards. Moreover, trainees may be impatient and intolerant of ambiguity. Some supervisees may be reluctant to address patients' heightened negative affectivity. Others may fear their young patients' anger. Trainees may also worry about risking their supervisees' disapproval. It is not uncommon for students' to resent getting direction from their supervisors. Regardless of the particular beliefs about their clinical work that go through supervisees' minds, supervisors apply cognitive behavioral practices and processes such as collaboration, guided discovery, and socratic dialogues to straighten out crooked thinking during training.

SUPERVISORY PROCEDURES AND PROCESSES

Supervisees' skills are sharpened *via* audio/video taped review didactic instruction, Socratic methods, modeling, behavioral rehearsal, and feedback^[12,13]. The procedures and processes utilized in supervision of CBT for youth are embedded within a productive learning environment. This section discusses the deployment of audiotaped/review, enactive supervision, and structured rating scales during training.

Trainees appear to learn best from supervisory relationships that are characterized by supportiveness, authenticity, and are clinically relevant^[70]. Moreover, supervisors who are respectful, knowledgeable, and collaborative appear most effective^[62]. Supervisees appreciate sessions that address clinical practice^[70]. In short, supervisors are well advised to cultivate a productive learning environment^[30].

Audio and/or video-taped review of trainees sessions with young patients is widely recommended^[12,13,18,22,23,59,60,62,63,70,71]. However, the actual use in community settings is disappointing^[23,71-74]. Several studies in the United Kingdom found reviews of tapes to occur in 6%^[74] and 20% of cases^[72]. Further, only 18% of supervisors studied in the United Kingdom reported reviewing tapes^[72]. These low incidences also characterize supervision in the United States. Only 12% of supervisors studied employed video-tape review and 8% used audiotape^[23].

Enactive supervision is recommended a best training strategy^[12,13,20,30,31,69]. Behavioral rehearsal is a powerful

training tool^[26,63,75-78]. In a recent study^[78], the procedure was defined as “a simulated interaction between a trainee and another individual”. Essentially, behavioral rehearsal facilitates learning through repeated practice. Authors^[63] have argued that “providing an opportunity for trainees to experiment with nascent skills promotes greater self-efficacy and better conceptual understanding”.

Supervisors are advised to keep several guidelines for role-playing in mind^[20,78]. Role-plays need to be explicitly and systematically processed. The lessons learned through the role-play need to be reviewed with the supervisee. Second, role-plays need to be emotionally similar to real life clinical scenarios in order to facilitate transfer of learning. More specifically, “if role plays are too emotionally sanitized and dissimilar to genuine therapist-patient interactions they are merely abstract intellectualized activities rather than experiential learning exercises”^[20].

There is some evidence that BR is anxiety producing for trainees^[79]. For instance, in one study, fewer trainees were willing to participate in a study involving performance evaluations based on BR and there was a high attrition rate. There appears to be a dose effect for BR with a 2:1 passive to active learning ratio suggested^[70]. Supervisors should strike a balance between exhausting trainees with too much BR and electing to do too little practice. Additionally, behavioral rehearsal is shown to be most effective with supervisees who are most engaged in the learning process^[77].

Providing positive and negative feedback to supervisees is another critical task^[12,13,29,61,80]. More specifically, trainees who engaged in behavioral rehearsal tended to overestimate their performance following the role-play^[81]. Further, supervisors tend to be overly complimentary perhaps in a desire to please their trainees^[26]. When constructive feedback is given, the criticisms are generally vague and unstructured^[26]. Feedback is important so supervisees can identify and address their smart spots, dumb spots and blind spots^[20]. In particular, smart spots are strengths, dumb spots refer to gaps in knowledge, and blind spots are errors caused by lack of awareness and/or obliviousness to the patient^[20].

Recording trainee progress on rating scales is an essential practice for providing feedback^[12,13,21,22,57,80]. Various instruments for measuring trainee progress were recently summarized^[22]. Most of the available measurement methods are based on work with trainees treating adults. The instruments emphasize application of procedural knowledge. The Cognitive Therapy Rating Scale (CTRS)^[56] is a widely used gold standard. It includes 11 items evaluated on a 6 point Likert scale. The items include understanding, interpersonal effectiveness, pacing, agenda setting, feedback, homework, focus on key cognitions, strategy for change, collaboration, guided discovery, and proficiency in cognitive behavioral procedures.

The Cognitive Behavioural Therapy Scale for Children and Young People (CBTS-CYP)^[64] assesses supervisees’

performance on across various competency areas. These domains include general skills, investigating, partnership, empathy, cognitive techniques, behavioral techniques, emotional techniques, formulation, and discovery experiments. Initial data indicates very sound psychometric properties.

The Cognitive Therapy Rating Scale for Children and Adolescents^[65,81,82] is a promising new measure that is based on the original CTRS but is modified to fit the needs of clinicians working with young patients. It retains items addressing pacing, interpersonal effectiveness/empathy, agenda setting, feedback, homework, strategy for change, focus on key cognitions, guided discovery, collaboration, and technical proficiency. However, the CTRS-CA adds extra items evaluated clinicians’ playfulness, informality, and credibility. Initial reports indicate supervisors’ high levels of satisfaction with the instrument^[83].

The Self-evaluation learning form (SELF)^[83] was originally developed for supervision with psychiatric residents, but it is also applicable to work with trainees from other disciplines. The SELF tracks patient metrics and supervisees’ progress as well as summarizing content from each supervisory session. The worksheet also serves as a reminder for any homework tasks assigned to the supervisee.

Training professionals to become supervisors is an area gaining increased attention. Most recently, meta-supervision is being employed as a training procedure. Meta-supervision is defined as the circumstance where “a highly experienced clinician serves as a consultant to a clinical supervisor^[84].” Essentially, this is supervision of supervision. Meta-supervision works to improve supervision skills, operationalize progress through performance ratings, and offers case management tips^[84].

A useful rubric and accompanying rating scale for meta-supervision is recently available^[25]. The rating scale addresses the supervisory context, aims, session structure, use of educational principles, CBT competencies, feedback, theoretical faithfulness, intervention methods, supervisory relationship issues as well as pacing and timing. The items are scored on a 1 (incompetent)-6 (expert) scale with higher scores indicating greater skillfulness. Further, the Cognitive Therapy Supervision Checklist^[85] is a checklist for supervisors to rate trainees’ competence. The scale evaluates clinical proficiency on various CBT procedures and processes. It explicitly addresses competencies set for by the American Association of Directors of Psychiatric Residency Training (AADPRT).

SUPERVISION OUTCOMES

While clinical supervision is the primary way trainees learn to do psychotherapy, there is minimal literature evaluating its effectiveness^[23]. Effectiveness may be studied in a variety of ways. Outcomes could be operationalized as positive changes in supervisory performance or young patients’ clinical presentations. For instance,

effectiveness could be measured as increases in young people's adaptive functioning or improved symptom scores. Alternatively, good supervisory outcomes could be evaluated in terms of trainees' acquisition/application of skills, fidelity to a treatment approach, and/or self-reflection.

Clinical effectiveness or improved treatment outcome is defined as the "acid test" of good supervision^[86-88]. In a recent study, supervision was found to have a significant moderate effect on clinical outcomes^[88]. More specifically, supervision accounted for 18% of the variance in patient outcomes. This effect is approximately two times the effect size owned by the common factors research^[88]. In general, there is wide agreement that good CBT training on is associated with improved supervisee performance^[74,89,90]. Effective training improves staff performance and technical proficiency^[15].

There is a growing body of research examining the effectiveness of supervision emphasizing self-practice and self-reflection^[90-94]. Self-reflection and self-practice increased trainees understanding of the cognitive model^[91-93]. Additionally, this model of supervision enhanced supervisees' technical proficiency^[90-92]. Finally, supervisees' flexibility was improved via this practice^[91].

LIMITATIONS

The majority of work on supervision of cognitive behavioral therapy is characterized by anecdotal reports, case studies, surveys, and quasi-experimental designs rendering the results vulnerable to various threats to internal and external validity. Factors such differential history, maturity, selection bias, and attrition compromise scientific conclusions. Finally, there is significant ambiguity regarding the selection of proper outcome variables or measures. Some investigators propose patient improvement as the gold-standard or acid-test whereas others employ indices reflecting improved skills, knowledge, and attitudes. The unclarity of outcome measures truncates generalizability of results.

RECOMMENDATIONS

Delivering and receiving good clinical supervision in CBT with youth are necessary steps toward improving the care of young patients. Achieving these lofty goals requires deliberate action. Based on the literature reviewed, several recommendations for advancing the science and practice of CBT supervision follows.

Competent supervision for CBT with youth requires that trainers are skillful in both clinical practice with young patients and training inexperienced colleagues. Consequently, supervisors need to be properly credentialed in the approach. Fortunately, credentialing bodies exist (American Board of Professional Psychology, Academy of Cognitive Therapy, British Association of Behavioral and Cognitive Psychotherapy, Oxford University, etc.). In short, supervisees are well-advised to seek supervision from documented experts.

Focused attention should be directed to the core content in supervision of CBT with youth. Acquiring and applying didactic and procedural knowledge is essential for trainees. Enactive supervision is highly recommended. Consequently, the opportunity to engage in behavioral rehearsal is key. In an action-oriented approach, practicing procedures is a priority. Behavioral rehearsal seems especially important when training supervisees in exposure techniques. Gaining greater self-efficacy in this crucial intervention may increase more application in clinical settings.

In order to do their job well, supervisors need first-hand knowledge of their students' work and young patients' functioning. Audiotape, videotape, or direct observation of sessions is a preferred pedagogical strategy. Reviewing tapes is commonly anxiety producing to supervisees. Additionally, tape review is time-consuming for supervisors. Finally, taping requires the proper electronic equipment which translates to increased cost to agencies. Perhaps, these are some the reasons that tape reviews are relatively rare in treatment-as-usual settings.

Hiring competent supervisors and creating a training infra-structure that supports best practices in supervision are costly endeavors. Good training efforts should be scalable and reach as many practitioners as possible. In an environment where lean budgets are pervasive, scalability of training is clearly linked with economic considerations.

Administrators, clinical supervisors, and front-line staff should be on the same page regarding the value of good supervision. However, often these multiple stakeholders are at odds with each other. Administrators worry about the loss of revenue when staff are engaged in activities that do not involve reimbursable clinical encounters. Staff then become concerned about their ability to meet productivity benchmarks if they take time away for supervision. Advocates for better supervision and training must persuade stakeholders that these educational activities are good returns on their investment of time and money. The studies listed in the supervisory outcome section offers a nice launching pad for arguments regarding returns on investment.

This therapeutic advances article made the case for providing competent supervision to clinicians conducting CBT with youth. The value of supervision was delineated. The core elements of supervision of CBT with youth were outlined and the fundamental supervisory processes were discussed. Finally, a sample of supervisory outcome studies were summarized. Ideally, this contribution in therapeutic advances spurs academicians, clinicians, and behavioral health care administrators to fully invest in competent supervision of clinicians who provide CBT to young patients.

REFERENCES

- 1 Weisz JR, Kuppens S, Ng MY, Eckshtain D, Ugueto AM, Vaughn-Coaxum R, Jensen-Doss A, Hawley KM, Krumholz Marchette

- LS, Chu BC, Weersing VR, Fordwood SR. What five decades of research tells us about the effects of youth psychological therapy: A multilevel meta-analysis and implications for science and practice. *Am Psychol* 2017; **72**: 79-117 [PMID: 28221063 DOI: 10.1037/a0040360]
- 2 **Weisz JR**, Kazdin AE. Evidence-based psychotherapies for children and adolescents. 3rd ed. New York: Guilford Publications, 2017
- 3 **Flessner CA**, Piacentini JC. Clinical handbook of psychological disorders in children and adolescents. New York: Guilford Publications, 2017
- 4 **David-Ferdon C**, Kaslow NJ. Evidence-based psychosocial treatments for child and adolescent depression. *J Clin Child Adolesc Psychol* 2008; **37**: 62-104 [PMID: 18444054 DOI: 10.1080/15374410701817865]
- 5 **Kendall PC**, Peterman JS. CBT for Adolescents With Anxiety: Mature Yet Still Developing. *Am J Psychiatry* 2015; **172**: 519-530 [PMID: 26029805 DOI: 10.1176/appi.ajp.2015.14081061]
- 6 **Wu Y**, Lang Z, Zhang H. Efficacy of Cognitive-Behavioral Therapy in Pediatric Obsessive-Compulsive Disorder: A Meta-Analysis. *Med Sci Monit* 2016; **22**: 1646-1653 [PMID: 27182928 DOI: 10.12659/MSM.895481]
- 7 **Dorsey S**, McLaughlin KA, Kerns SEU, Harrison JP, Lambert HK, Briggs EC, Revillion Cox J, Amaya-Jackson L. Evidence Base Update for Psychosocial Treatments for Children and Adolescents Exposed to Traumatic Events. *J Clin Child Adolesc Psychol* 2017; **46**: 303-330 [PMID: 27759442 DOI: 10.1080/15374416.2016]
- 8 **Comer JS**, Chow C, Chan PT, Cooper-Vince C, Wilson LA. Psychosocial treatment efficacy for disruptive behavior problems in very young children: a meta-analytic examination. *J Am Acad Child Adolesc Psychiatry* 2013; **52**: 26-36 [PMID: 23265631 DOI: 10.1016/j.jaac.2012.10.001]
- 9 **McCart MR**, Sheidow AJ. Evidence-Based Psychosocial Treatments for Adolescents With Disruptive Behavior. *J Clin Child Adolesc Psychol* 2016; **45**: 529-563 [PMID: 27152911 DOI: 10.1080/15374416.2016.1146990]
- 10 **Beidas RS**, Edmunds JM, Marcus SC, Kendall PC. Training and consultation to promote implementation of an empirically supported treatment: A randomized trial. *Psychiatr Serv* 2012; **63**: 660-665 [PMID: 22549401 DOI: 10.1176/appi.ps.201100401]
- 11 **Edmunds JM**, Brodman DM, Ringle VA, Read KL, Kendall PC, Beidas RS. Examining adherence to components of cognitive-behavioral therapy for youth anxiety after training and consultation. *Prof Psychol Res Pr* 2017; **48**: 54-61 [PMID: 28603339 DOI: 10.1037/pro0000100]
- 12 **Newman CF**. Training cognitive behavioral supervisors: Didactics, simulated practice, and "meta-supervision." *J Cog Psychother* 2013; **27**: 5-16 [DOI: 10.1891/0889-8391.27.1.5]
- 13 **Newman C**, Kaplan D. Supervision essentials for cognitive-behavioral therapy. Washington, DC: American Psychological Association; 2016
- 14 **Creed TA**, Wolk CB, Feinberg B, Evans AC, Beck AT. Beyond the Label: Relationship Between Community Therapists' Self-Report of a Cognitive Behavioral Therapy Orientation and Observed Skills. *Adm Policy Ment Health* 2016; **43**: 36-43 [PMID: 25491201 DOI: 10.1007/s10488-014-0618-5]
- 15 **Herschell AD**, Kolko DJ, Baumann BL, Davis AC. The role of therapist training in the implementation of psychosocial treatments: a review and critique with recommendations. *Clin Psychol Rev* 2010; **30**: 448-466 [PMID: 20304542 DOI: 10.1016/j.cpr.2010.02.005]
- 16 **Wiltsey Stirman S**, Calloway A, Toder K, Miller CJ, Devito AK, Meisel SN, Xhezo R, Evans AC, Beck AT, Crits-Christoph P. Community mental health provider modifications to cognitive therapy: implications for sustainability. *Psychiatr Serv* 2013; **64**: 1056-1059 [PMID: 24081406 DOI: 10.1176/appi.ps.201200456]
- 17 **Sburlati ES**, Schniering CA, Lyneham HJ, Rapee RM. A model of therapist competencies for the empirically supported cognitive behavioral treatment of child and adolescent anxiety and depressive disorders. *Clin Child Fam Psychol Rev* 2011; **14**: 89-109 [PMID: 21267654 DOI: 10.1007/s10567-011-0083-6]
- 18 **Dobson KS**, Shaw BF. The training of cognitive therapists: What we have learned from treatment manuals? *Psychotherapy: Theory, Research, Practice, and Training* 1993; **30**: 573-577 [DOI: 10.1037/0033-3204.30.4.573]
- 19 **Friedberg RD**. Where's the Beef? Concrete Elements When Supervising Cognitive-Behavioral Therapy With Youth. *J Am Acad Child Adolesc Psychiatry* 2015; **54**: 527-531 [PMID: 26088653 DOI: 10.1016/j.jaac.2015.03.020]
- 20 **Friedberg RD**, Gorman AA, Beidel DC. Training psychologists for cognitive-behavioral therapy in the raw world: a rubric for supervisors. *Behav Modif* 2009; **33**: 104-123 [PMID: 18768930 DOI: 10.1177/0145445508322609]
- 21 **Sudak DM**, Beck JS, Wright J. Cognitive behavioral therapy: a blueprint for attaining and assessing psychiatry resident competency. *Acad Psychiatry* 2003; **27**: 154-159 [PMID: 12969838 DOI: 10.1176/appi.ap.27.3.154]
- 22 **Friedberg RD**, Mahr S, Mahr F. Training psychiatrists in cognitivebehavioral psychotherapy: Current status and horizons. *Curr Psychiatry Rev* 2010; **6**: 159-170 [DOI: 10.2174/157340010791792563]
- 23 **Accurso EC**, Taylor RM, Garland AF. Evidence-based Practices Addressed in Community-based Children's Mental Health Clinical Supervision. *Train Educ Prof Psychol* 2011; **5**: 88-96 [PMID: 24761163 DOI: 10.1037/a0023537]
- 24 **Kavanaugh DJ**. Issues in the multidisciplinary training of cognitive behavioural interventions. *Behaviour Change* 1994; **11**: 38-44 [DOI: 10.1017/S0813483900005222]
- 25 **Corrie S**, Lane DA. CBT supervision. Thousand Oaks, CA: Sage, 2015
- 26 **Milne D**, Aylott H, Fitzpatrick J, Ellis MV. How does clinical supervision work? Using a "best evidence synthesis" approach to construct a basic model of supervision. *Clin Superv* 2008; **27**: 170-190 [DOI: 10.1080/07325220802487915]
- 27 **Friedberg RD**, McClure JM, Garcia JH. Cognitive therapy techniques for children and adolescents. New York: Guilford Publications, 2009
- 28 **Newman CF**. Core competencies in cognitive behavior therapy: Becoming a highly effective and competent cognitive behavioral therapist. New York: Routledge, 2013
- 29 **Nadeem E**, Gleacher A, Beidas RS. Consultation as an implementation strategy for evidence-based practices across multiple contexts: unpacking the black box. *Adm Policy Ment Health* 2013; **40**: 439-450 [PMID: 23716145 DOI: 10.1007/s10488-013-0502-8]
- 30 **Friedberg RD**, Taylor LA. Perspectives on supervision in cognitive therapy. *J Ration Emot Cogn Behav Ther* 1994; **12**: 147-162 [DOI: 10.1007/BF02354593]
- 31 **Friedberg RD**, Clark CA. Supervision of cognitive therapy with youth. In Neill TK, editors. Helping others help children: Clinical supervision of child psychotherapy. Washington, DC: American Psychological Association, 2006: 109-122
- 32 **Pearl AM**, Mahr FM, Friedberg RD. Supervising child psychiatrists in cognitive behavioral therapy. *J Cogn Psychother* 2013; **27**: 61-70 [DOI: 10.1891/0889-8391.27.1.61]
- 33 **Waltman S**, Hall BC, McFarr LM, Beck AT, Creed TA. In session stuck points and pitfalls of community clinicians learning CBT: Qualitative Investigation. *Cogn Behav Pract* 2016 [DOI: 10.1016/j.cbpra.2016.04.002]
- 34 **Padesky CA**. The next frontier: Building positive qualities with cognitive behavior therapy. Invited address presented at the 5th World Congress of Behavioral and Cognitive Therapies; 2007 July; Barcelona, Spain
- 35 **Beck AT**, Clark, DA. Anxiety and depression: An information processing perspective. *Anx Res* 1988; **1**: 23-36 [DOI: 10.1080/10615808808248218]
- 36 **Ingram RE**, Kendall PC. Cognitive clinical psychology: Implications of an information-processing perspective. In: Ingram RE, editor. Information processing approaches to clinical psychology. Orlando, FLA: Academic Press, 1986: 3-21
- 37 **Beck AT**. Cognitive therapy and the emotional disorders. New

- York: International Universities Press, 1976
- 38 **Jolly JB**. A multimethod test of the content-specificity hypothesis in young adolescents. *J Anxiety Disord* 1993; **7**: 223-233 [DOI: 10.1016/0887-6185(93)90004-5]
- 39 **Jolly JB**, Dyckman RA. Using self-report data to differentiate anxious and depressive symptoms in adolescents: Cognitive content-specificity and global distress. *Cognit Ther Res* 1994; **18**: 25-27 [DOI: 10.1007/BF02359393]
- 40 **Jolly JB**, Kramer TA. The hierarchical arrangement of internalizing cognitions. *Cognit Ther Res* 1994; **18**: 1-14 [DOI: 10.1007/BF02359391]
- 41 **Kuyken W**, Padesky CA, Dudley R. Collaborative case conceptualization. New York: Guilford Publications, 2009
- 42 **Manassis K**. Case formulation with children and adolescents. New York: Guilford Publications, 2014
- 43 **Persons JB**. The case formulation approach to cognitive behavioral therapy. New York: Guilford Publications, 2012
- 44 **Friedberg RD**, Gorman AA, Hollar-Wilt L, Buickians A, Murray M. Cognitive behavior therapy for the busy child psychiatrist and other mental health professionals. New York: Routledge, 2011
- 45 **Friedberg RD**, McClure JM. Clinical practice of cognitive therapy with children and adolescents: The nuts and bolts, 2nd Ed. New York: Guilford Publications, 2002
- 46 **Beidas RS**, Ditty M, Downey MM, Edmunds J. Professional evidence based practice with children and adolescents. In: Sbrulati ES, Lyneham HJ, Schniering CA, Rapee RM, editors. Evidence based CBT for anxiety and depression in children and adolescents: A competencies based approach. New York: Wiley Blackwell; 2014: 36-48
- 47 **Padesky CA**. Staff and patient education. In: Wright JH, Thase ME, Beck AT, Ludgate JW, editors. Cognitive therapy with inpatients: Developing a cognitive milieu. New York: Guilford Publications, 1993: 393-413
- 48 **Alford BA**, Beck AT. The integrative power of cognitive therapy. New York: Guilford Publications, 1997
- 49 **Perris C**. Cognitive therapy with schizophrenic patients. New York: Guilford Publications, 1989
- 50 **Cummings JA**, Ballantyne EC, Scallion LM. Essential processes for cognitive behavioral clinical supervision: Agenda setting, problem-solving, and formative feedback. *Psychotherapy (Chic)* 2015; **52**: 158-163 [PMID: 25895121 DOI: 10.101037/a0038712]
- 51 **Gosch EA**, Flannery-Schroeder E, Mauro CF, Compton SN. Principles of cognitive-behavioral therapy for anxiety disorders in children. *J Cogn Psychother* 2006; **20**: 247-262 [DOI: 10.1891/jcop.20.3.247]
- 52 **Friedberg RD**, Gorman AA. Integrating psychotherapeutic processes with cognitive behavioral procedures. *J Contemp Psychother* 2007; **37**: 185-193 [DOI: 10.1007/s10879-007-9053-1]
- 53 **Friedberg RD**, Tabbarah S, Poggesi RM. Therapeutic presence, immediacy, and the transparency with youth: Carpe the moment. *Cogn Beh Therapist* 2013 [DOI: 10.1017/S1754470X130000159]
- 54 **Scott K**, Lewis CC. Using Measurement-Based Care to Enhance Any Treatment. *Cogn Behav Pract* 2015; **22**: 49-59 [PMID: 27330267 DOI: 10.1016/j.cbpra.2014.01.010]
- 55 **Young JE**, Beck AT. Cognitive therapy rating scale. University of Pennsylvania, 1980
- 56 **Sudak DM**. Training in cognitive behavioral therapy in psychiatry residency: An overview for educators. *Behav Modif* 2009; **33**: 124-137 [PMID: 18723836 DOI: 10.1177/1059601108322626]
- 57 **Trafalis S**, Friedberg RD, Sullivan PJ, Teague AM, Hoyman LC, Berlyant MJ. Training community clinicians in CBT for youth. *Curr Psychiatry Rev* 2016; **12**: 88-96 [DOI: 10.2174/1573400511666150930233042]
- 58 **Padesky CA**. Developing therapist competency: training and supervision models. In: Salkovskis PM, editor. Frontiers of cognitive therapy. New York: Guilford Publications, 266-292
- 59 **Liese BS**, Alford BA. Recent advances in cognitive therapy supervision. *J Cogn Psychother* 1998; **12**: 91-94
- 60 **Rahovshik SG**, McManus F. Establishing evidence-based training in cognitive behavioral therapy: a review of current empirical findings and theoretical guidance. *Clin Psychol Rev* 2010; **30**: 496-516 [DOI: 10.1016/j.cpr.2010.03.004]
- 61 **Newman CF**, Beck JS. Selecting, training, and supervising therapists. In: Nezu AM, Nezu CM, editors. Evidence based outcome research: A practical guide to conducting randomized controlled trials for psychosocial interventions. Oxford, UK: Oxford University Press, 2007: 245-263
- 62 **Friedberg RD**, Fidaleo RA. Training inpatient staff in cognitive therapy. *J Cogn Psychother* 1992; **6**: 105-112
- 63 **Stallard P**, Myles P, Branson A. The Cognitive Behaviour Therapy Scale for Children and Young People (CBTS-CYP): development and psychometric properties. *Behav Cogn Psychother* 2014; **42**: 269-282 [PMID: 24495357 DOI: 10.1017/S135246581300115X]
- 64 **Friedberg RD**, Thordarson MA. Cognitive Therapy Rating Scale for Children and Adolescents (CTRS-CA). Center for the Study and Anxious Youth
- 65 **Sudak DM**, Codd RT, Ludgate J, Sokol L, Fox MG, Reiser R, Milne DL. Teaching and supervising cognitive-behavioral therapy. Hoboken, NJ: Wiley, 2010
- 66 **Jones E**, Mannassis K. Effective training methods. In: Sbrulati ES, Lyneham HJ, Schniering CA, Rapee RM, editors. Evidence based CBT for anxiety and depression in children and adolescents: A competencies based approach. New York: Wiley Blackwell, 2014: 10-22 [DOI: 10.1002/9781118500576.ch2]
- 67 **Rosenbaum M**, Ronen T. Clinical supervision from the standpoint of cognitive-behavior therapy. *Psychotherapy* 1998; **35**: 220-230 [DOI: 10.1037/h0087705]
- 68 **Ronen T**, Rosenbaum M. Beyond direct verbal instructions in cognitive behavioral supervision. *Cogn Beh Pract* 1998; **5**: 7-23 [DOI: 10.1016/S1077-7229(98)80019-9]
- 69 **Beidas RS**, Edmunds JM, Cannuscio CC, Gallagher M, Downey MM, Kendall PC. Therapists perspectives on the effective elements of consultation following training. *Adm Policy Ment Health* 2013; **40**: 507-517 [PMID: 23435832 DOI: 10.1007/s10488-013-0475-7]
- 70 **Gordon PK**. Ten steps to cognitive behavioral supervision. *Cognitive Behavioural therapist* 2012; **5**: 71-82 [DOI: 10.1017/S1754470X12000050]
- 71 **Townsend M**, Iannetta L, Freeston M, Hayes J. Clinical supervision in practice: A survey of UK cognitive-behavioral psychotherapies accredited by BABCP. *Behav Cogn Psychother* 2002; **30**: 485-500 [DOI: 10.1017/S1352465802004095]
- 72 **Milne DL**, Westerman C. Evidence-based clinical supervision: Rationale and illustration. *Clin Psychol Psychother* 2001; **8**: 444-457 [DOI: 10.1002/cpp.297]
- 73 **Milne D**, James I. A systematic review of effective cognitive-behavioural supervision. *Br J Clin Psychol* 2000; **39** (Pt 2): 111-127 [PMID: 10895356 DOI: 10.1348/014466500163149]
- 74 **Tompkins MA**. Enhancing self-efficacy to achieve competence. *J Cogn Psychother* 2013; **27**: 71-80 [DOI: 10.1891/0889-8391.27.1.71]
- 75 **Bearman SK**, Weisz JR, Chorpita BF, Hoagwood K, Ward A, Ugueto AM, Bernstein A; Research Network on Youth Mental Health. More practice, less preach? the role of supervision processes and therapist characteristics in EBP implementation. *Adm Policy Ment Health* 2013; **40**: 518-529 [PMID: 23525895 DOI: 10.1007/s10488-013-0485-5]
- 76 **Bearman SK**, Schneiderman RL, Zoloth E. Building an evidence base for effective supervision practices: an analogue experiment of supervision to increase EBT Fidelity. *Adm Policy Ment Health* 2017; **44**: 293-307 [PMID: 26867545 DOI: 10.1007/s10488-016-0723-8]
- 77 **Friedberg RD**, Brelsford GM. Training methods in cognitive behavioral therapy. *J Cogn Psychother* 2013; **27**: 9-29 [DOI: 10.1891/0889-8391.27.1.19]
- 78 **Beidas RS**, Cross W, Dorsey S. Show Me, Don't Tell Me: Behavioral Rehearsal as a Training and Analogue Fidelity Tool. *Cogn Behav Pract* 2014; **21**: 1-11 [PMID: 25382963 DOI: 10.1016/j.cbpra.2013.04.002]
- 79 **Dorsey S**, Lyon AR, Pullmann MD, Jungbluth N, Berliner L, Beidas R. Behavioral Rehearsal for Analogue Fidelity: Feasibility

- in a State-Funded Children's Mental Health Initiative. *Adm Policy Ment Health* 2017; **44**: 395-404 [PMID: 26966103 DOI: 10.1007/s10488-016-0727-4]
- 80 **Nakamura BJ**, Selbo-Bruns A, Okamura K, Chang J, Slavin L, Shimabukuro S. Developing a systematic evaluation approach for training programs within a train-the-trainer model for youth cognitive behavior therapy. *Behav Res Ther* 2014; **53**: 10-19 [PMID: 24362360 DOI: 10.1016/j.brat.2013.12.001]
 - 81 **Friedberg RD**. Manual for the Cognitive Therapy Rating Scale for children and adolescents. Palo Alto, CA: Center for the Study and Treatment of Anxious Youth, 2014
 - 82 **Thordarson MA**, Friedberg RD, Fanniff A, Cordova M. The Cognitive Therapy Rating Scale for Children and Adolescents (CTRS-CA): A pilot study. Poster presentation delivered at the 50th annual meeting of the Association for Behavioral and Cognitive Therapies; New York; 2016
 - 83 **Ularntinon S**, Friedberg RD. The SELF: a Supervisory Tool for Enhancing Residents' Self-Reflective Learning in CBT with Youth. *Acad Psychiatry* 2016; **40**: 172-176 [PMID: 25648451]
 - 84 **Newman CF**. Training cognitive behavioral therapy supervisors: Didactics, simulated practice and "meta-supervision." *J Cogn Psychother* 2013; **27**: 5-18 [DOI: 10.1891/0889-8391.27.1.5]
 - 85 **Sudak DM**, Wright JH, Bienenfeld D, Beck JS. Cognitive therapy supervision checklist. Unpublished scale (Online), 2001
 - 86 **Ellis M**, Ladany N. Inferences concerning supervisees and clients in clinical supervision: An integrative review. In: Watkins CE, editor. Handbook of psychotherapy supervision. Chicester, UK: John Wiley, 1997: 447-507
 - 87 **Milne D**. Beyond the "acid test": a conceptual review and reformulation of outcome evaluation in clinical supervision. *Am J Psychother* 2014; **68**: 213-230 [PMID: 25122986]
 - 88 **Callahan JL**, Almstrom CM, Swift JK, Borja SE, Heath CJ. Exploring the contribution of supervisors to intervention outcomes. *Train Educ Prof Psychol* 2009; **3**: 72-77 [DOI: 10.1037/a0014294]
 - 89 **James IA**, Blackburn IM, Milne DL, Reichfelt FK. Moderators of trainee therapists' competence in cognitive therapy. *Br J Clin Psychol* 2001; **40**: 131-141 [PMID: 11446235]
 - 90 **Milne DL**, Baker C, Blackburn IM, James I, Reichelt K. Effectiveness of cognitive therapy training. *J Behav Ther Exp Psychiatry* 1999; **30**: 81-92 [PMID: 10489085]
 - 91 **Laireiter AR**, Willutski U. Self-reflection and self-practice in training of cognitive behavioural therapy: an overview. *Clin Psychol Psychother* 2003; **18**: 19-30 [DOI: 10.1002/cpp.348]
 - 92 **Bennett-Levy J**, Lee N, Travers K, Pohlman S, Hamernick H. Cognitive therapy from the inside: enhancing therapist skills through practicing what we preach. *Behav Cogn Psychother* 2003; **31**: 143-158
 - 93 **Bennett-Levy J**, Turner F, Beaty T, Smith M, Paterson B, Farmer S. The value of self-practice of cognitive therapy techniques and self-reflection in the training of cognitive therapists. *Behav Cogn Psychother* 2001; **29**: 203-220 [DOI: 10.1017/S135246580100207]
 - 94 **Haarhoff B**, Gibson K, Flett R. Improving the quality of cognitive behaviour therapy case conceptualization: the role of self-practice/self-reflection. *Behav Cogn Psychother* 2011; **39**: 323-339 [PMID: 21320361 DOI: 10.1017/S1352465810000871]
 - 95 **Thwaites R**, Bennett-Levy J, Davis M, Chaddock A. Using Self-practice and self-reflection to enhance CBT competence and meta-competence. In Whittington A, Grey N, editors. How to become a more effective CBT therapist: Mastering meta-competence in clinical practice. New York: John Wiley, 2014: 241-254

P- Reviewer: Kute VBB, Sergi CM, Watanabe T **S- Editor:** Kong JX
L- Editor: A **E- Editor:** Li RF



Behavioural and emotional disorders in childhood: A brief overview for paediatricians

Michael O Ogundele

Michael O Ogundele, Department of Community Paediatrics, NHS Fife, Glenwood Health Centre, Glenrothes KY6 1HK, United Kingdom

ORCID number: Michael O Ogundele (0000-0003-0744-1434).

Author contributions: Ogundele MO conceived the idea, collected and analysed the data and prepared the manuscript.

Conflict-of-interest statement: The author declares no conflict of interest for this article.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Dr. Michael O Ogundele, MBBS, MRCP, MSc, Consultant Paediatrician, Department of Community Paediatrics, NHS Fife, Glenwood Health Centre, Napier Road, Glenrothes KY6 1HK, United Kingdom. m.ogundele@nhs.net
Telephone: +44-1592-765096
Fax: +44-1592-765096

Received: October 27, 2017

Peer-review started: October 29, 2017

First decision: November 20, 2017

Revised: November 30, 2017

Accepted: December 5, 2017

Article in press: December 5, 2017

Published online: February 8, 2018

Abstract

Mental health problems in children and adolescents include several types of emotional and behavioural

disorders, including disruptive, depression, anxiety and pervasive developmental (autism) disorders, characterized as either internalizing or externalizing problems. Disruptive behavioural problems such as temper tantrums, attention deficit hyperactivity disorder, oppositional, defiant or conduct disorders are the commonest behavioural problems in preschool and school age children. The routine Paediatric clinic or Family Medicine/General Practitioner surgery presents with several desirable characteristics that make them ideal for providing effective mental health services to children and adolescents. DSM-5 and ICD-10 are the universally accepted standard criteria for the classification of mental and behaviour disorders in childhood and adults. The age and gender prevalence estimation of various childhood behavioural disorders are variable and difficult to compare worldwide. A review of relevant published literature was conducted, including published meta-analyses and national guidelines. We searched for articles indexed by Ovid, PubMed, PubMed Medical Central, CINAHL, EMBASE, Database of Abstracts and Reviews, and the Cochrane Database of Systematic reviews and other online sources. The searches were conducted using a combination of search expressions including "childhood", "behaviour", "disorders" or "problems". Childhood behaviour and emotional problems with their related disorders have significant negative impacts on the individual, the family and the society. They are commonly associated with poor academic, occupational, and psychosocial functioning. It is important for all healthcare professionals, especially the Paediatricians to be aware of the range of presentation, prevention and management of the common mental health problems in children and adolescents.

Key words: Childhood behavioural disorders; Disruptive behaviour disorder; Conduct disorder; Challenging behaviour; Emotional disorder; Anxiety; Depression; Autism; Pervasive developmental disorders

© The Author(s) 2018. Published by Baishideng Publishing

Group Inc. All rights reserved.

Core tip: Mental health problems in children and young people (CYP) include several types of emotional and behavioural disorders, including disruptive, depression, anxiety and pervasive developmental (autism) disorders, characterized as either “internalizing” or “externalizing”. The routine Paediatric or General Practitioner clinic present with several desirable characteristics that make them ideal for providing effective mental health services to CYP. Childhood mental health disorders have significant negative impacts on the individual, the family and the society. It is particularly important for all Paediatricians to be aware of the range of presentation, prevention and management of the common mental health problems in CYP.

Ogundele MO. Behavioural and emotional disorders in childhood: A brief overview for paediatricians. *World J Clin Pediatr* 2018; 7(1): 9-26 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i1/9.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i1.9>

INTRODUCTION

Mental health disorders (MHD) are very common in childhood and they include emotional-obsessive-compulsive disorder (OCD), anxiety, depression, disruptive (oppositional defiance disorder (ODD), conduct disorder (CD), attention deficit hyperactive disorder (ADHD) or developmental (speech/language delay, intellectual disability) disorders or pervasive (autistic spectrum) disorders^[1]. Emotional and behavioural problems (EBP) or disorders (EBD) can also be classified as either “internalizing” (emotional disorders such as depression and anxiety) or “externalizing” (disruptive behaviours such as ADHD and CD). The terminologies of “problems” and “disorders” are interchangeably used throughout this article.

While low-intensity naughty, defiant and impulsive behaviour from time to time, losing one’s temper, destruction of property, and deceitfulness/stealing in the preschool children are regarded as normal, extremely difficult and challenging behaviours outside the norm for the age and level of development, such as unpredictable, prolonged, and/or destructive tantrums and severe outbursts of temper loss are recognized as behaviour disorders. Community studies have identified that more than 80% of pre-schoolers have mild tantrums sometimes but a smaller proportion, less than 10% will have daily tantrums, regarded as normative misbehaviours at this age^[2,3]. Challenging behaviours and emotional difficulties are more likely to be recognized as “problems” rather than “disorders” during the first 2 years of life^[4].

Emotional problems, such as anxiety, depression and post-traumatic stress disorder (PTSD) tend to occur

in later childhood. They are often difficult to be recognised early by the parents or other carers as many children have not developed appropriate vocabulary and comprehension to express their emotions intelligibly^[5]. Many clinicians and carers also find it difficult to distinguish between developmentally normal emotions (e.g., fears, crying) from the severe and prolonged emotional distresses that should be regarded as disorders^[6]. Emotional problems including disordered eating behaviour and low self-image are often associated with chronic medical disorders such as atopic dermatitis, obesity, diabetes and asthma, which lead to poor quality of life^[7-9].

Identification and management of mental health problems in primary care settings such as routine Paediatric clinic or Family Medicine/General Practitioner surgery are cost-effective because of their several desirable characteristics that make it acceptable to children and young people (CYP) (e.g., no stigma, in local setting, and familiar providers). Several models to improve the delivery of mental health services in the Paediatric/Primary care settings have been recommended and evaluated recently, including coordination with external specialists, joint consultations, improved Mental Health training and more integrated on-site intervention with specialist collaboration^[10,11].

A review of relevant published literature was conducted, including published meta-analyses and national guidelines. We searched for articles indexed by Ovid, PubMed, PubMed Medical Central, CINAHL, the Cochrane Database of Systematic reviews and other online sources. The searches were conducted using a combination of search expressions including “childhood”, “behaviour”, “disorders” or “problems”.

CLINICAL PRESENTATIONS OF CHILDHOOD BEHAVIOURAL AND EMOTIONAL DISORDERS

Various definitions for a wide range of childhood behavioural disorders are being used. The DSM-5^[12] offers the commonest universally accepted standard criteria for the classification of mental and behaviour disorders. The ICD-10 is the alternative classification standard^[13].

Challenging behaviours

Any abnormal pattern of behaviour which is above the expected norm for age and level of development can be described as “challenging behaviour”. It has been defined as: “Culturally abnormal behaviour (s) of such an intensity, frequency or duration that the physical safety of the person or others is likely to be placed in serious jeopardy or behaviour which is likely to seriously limit or deny access to and use of ordinary community facilities”^[14]. They can include self-injury, physical or verbal aggression, non-compliance, disruption of the environment, inappropriate vocalizations, and various stereotypies. These behaviours can impede

Table 1 Subtypes of attention deficit hyperactivity disorder (based on DSM-5)

Subtypes	Predominantly inattentive (ADD)	Predominantly hyperactivity/ impulsivity	Combined ADHD
Criteria	6 of 9 inattentive symptoms	6 of 9 hyperactivity/ impulsivity symptoms	Both criteria for (1) and (2)
Details	Fails to pay close attention to details or makes careless mistakes Has difficulty sustaining attention Does not appear to listen Struggles to follow through on instructions Has difficulty with organization Avoids or dislikes tasks requiring a lot of thinking Loses things Is easily distracted	Squirms and fidgets Can't stay seated Runs/climbs excessively Can't play/work quietly "On the go"/"driven by a motor" Blurts out answers Is unable to wait for his turn Intrudes/interrupts others Talks excessively	
Other criteria	Onset before age of 12, lasting more than 6 mo, symptoms pervasive in 2 or more settings, causing significant impairment of daily functioning o development		

ADHD: Attention deficit hyperactivity disorder.

learning, restrict access to normal activities and social opportunities, and require a considerable amount of both manpower and financial resources to manage effectively.

Many instances of challenging behaviour can be interpreted as ineffective coping strategies for a young person, with or without learning disability (LD) or impaired social and communication skills, trying to control what is going on around them. Young people with various disabilities, including LD, Autism, and other acquired neuro-behavioural disorders such as brain damage and post-infectious phenomena, may also use challenging behaviour for specific purposes, for example, for sensory stimulation, gaining attention of carers, avoiding demands or to express their limited communication skills^[15]. People who have a diverse range of neurodevelopmental disorders are more likely to develop challenging behaviours^[16].

Some environmental factors have been identified which are likely to increase the risk of challenging behaviour, including places offering limited opportunities for making choices, social interaction or meaningful occupation. Other adverse environments are characterized by limited sensory input or excessive noise, unresponsive or unpredictable carers, predisposition to neglect and abuse, and where physical health needs and pain are not promptly identified. For example, the rates of challenging behaviour in teenagers and people in their early 20s is 30%-40% in hospital settings, compared to 5% to 15% among children attending schools for those with severe LD^[15].

Aggression is a common, yet complex, challenging behaviour, and a frequent indication for referral to child and adolescent Psychiatrists. It commonly begins in childhood, with more than 58% of preschool children demonstrating some aggressive behaviour^[17]. Aggression has been linked to several risk factors, including individual temperaments; the effects of disturbed family dynamics; poor parenting practices; exposure to violence and the influence of attachment disorders. No single factor is sufficient to explain the development of aggressive behaviour^[18]. Aggression is commonly diagnosed in association with other mental health problems including ADHD, CD, ODD, depression, head injury, mental

retardation, autism, bipolar disorder, PTSD, or dyslexia^[19].

Disruptive behaviour problems

Disruptive behaviour problems (DBP) include attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD) and conduct disorder (CD). They constitute the commonest EBPs among CYP. Recent evidence suggests that DBPs should be regarded as a multidimensional phenotype rather than comprising distinct subgroups^[20].

ADHD is the commonest neuro-behavioural disorder in children and adolescents, with prevalence ranging between 5% and 12% in the developed countries^[21]. ADHD is characterized by levels of hyperactivity, impulsivity and inattention that are disproportionately excessive for the child's age and development^[12]. The ICD-10^[13] does not use the term "ADHD" but "hyperkinetic disorder", which is equivalent to severe ADHD. DSM-5 distinguishes between three subtypes of the disorder: predominantly hyperactive/impulsive, predominantly inattentive and combined types (Table 1).

CD refers to severe behaviour problems (Table 2), characterized by repetitive and persistent manifestations of serious aggressive or non-aggressive behaviours against people, animals or property such as being defiant, belligerent, destructive, threatening, physically cruel, deceitful, disobedient or dishonest, excessive fighting or bullying, fire-setting, stealing, repeated lying, intentional injury, forced sexual activity and frequent school truancy^[13,22]. Children with CD often have trouble understanding how other people think, sometimes described as being callous-unemotional. They may falsely misinterpret the intentions of other people as being mean. They may have immature language skills, lack the appropriate social skills to establish and maintain friendships, which aggravates their feelings of sadness, frustration and anger^[12].

CD is the commonest reason for CYP referral for psychological and psychiatric treatment. Roughly 50% of all CYP with a MHD have a CD^[23]. About 30%-75% of children with CD also have ADHD and 50% of them will also meet criteria for at least one other disorder including

Table 2 DSM-5 definition of conduct disorder and oppositional defiant disorder

Oppositional defiant disorder	Conduct disorder
<p>A pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness lasting at least 6 mo as evidenced by at least four out of 8 symptoms from any of the following categories, and exhibited during interaction with at least one individual who is not a sibling</p> <p>Angry/irritable mood: (1) Often loses temper; (2) Is often touchy or easily annoyed; (3) Is often angry and resentful</p> <p>Argumentative/defiant behavior: (4) Often argues with authority figures or, for children and adolescents, with adults; (5) Often actively defies or refuses to comply with requests from authority figures or with rules; (6) Often deliberately annoys others; (7) Often blames others for his or her mistakes or misbehavior</p> <p>Vindictiveness: (8) Has been spiteful or vindictive at least twice within the past 6 mo</p> <p>Note: The persistence and frequency of these behaviors should be used to distinguish a behavior that is within normal limits from a behavior that is symptomatic and the behavior should occur at least once per week for at least 6 mo</p> <p>The disturbance in behavior is associated with distress in the individual or others in his or her immediate social context (e.g., family, peer group, work colleagues), or it impacts negatively on social, educational, occupational, or other important areas of functioning</p> <p>The behaviors do not occur exclusively during the course of a psychotic, substance use, depressive, or bipolar disorder. Also, the criteria are not met for disruptive mood dysregulation disorder</p> <p>Specify current severity: Mild; moderate or severe based on number of settings with symptoms shown</p>	<p>A repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated, as manifested by the presence of at least three of the following 15 criteria in the past 12 mo from any of the categories below, with at least one criterion present in the past 6 mo</p> <p>Aggression to people and animals: (1) Often bullies, threatens, or intimidates others; (2) Often initiates physical fights; (3) Has used a weapon that can cause serious physical harm to others (e.g., a bat, brick, broken bottle, knife, gun); (4) Has been physically cruel to people; (5) Has been physically cruel to animals; (6) Has stolen while confronting a victim (e.g., mugging, purse snatching, extortion, armed robbery); (7) Has forced someone into sexual activity</p> <p>Destruction of property: (8) Has deliberately engaged in fire setting with the intention of causing serious damage; (9) Has deliberately destroyed others' property (other than by fire setting)</p> <p>Deceitfulness or theft: (10) Has broken into someone else's house, building, or car; (11) Often lies to obtain goods or favors or to avoid obligations (i.e., "cons" others); (12) Has stolen items of nontrivial value without confronting a victim (e.g., shoplifting, but without breaking and entering; forgery)</p> <p>Serious violations of rules: (13) Often stays out at night despite parental prohibitions, beginning before age 13 yr; (14) Has run away from home overnight at least twice while living in the parental or parental surrogate home, or once without returning for a lengthy period; (15) Is often truant from school, beginning before age 13 yr</p> <p>The disturbance in behavior causes clinically significant impairment in social, academic, or occupational functioning</p> <p>If the individual is age 18 yr or older, criteria are not met for antisocial personality disorder</p> <p>Specify whether: Childhood-onset type (prior to age 10 yr); Adolescent-onset type or Unspecified onset</p> <p>Specify if: With limited prosocial emotions: Lack of remorse or guilt; Callous-lack of empathy; Unconcerned about performance or Shallow or deficient affect</p> <p>Specify current severity: Mild; Moderate or Severe</p> <p>ICD-10</p> <p>It also requires the presence of three symptoms from the list of 15 (above), and duration of at least 6 mo. There are four divisions of conduct disorder: Socialised conduct disorder, unsocialised conduct disorder, conduct disorders confined to the family context and oppositional defiant disorder</p>

Mood, Anxiety, PTSD, Substance abuse, ADHD, learning problems, or thought disorders^[24,25]. Majority of boys have an onset of CD before the age of 10 years, while girls tend to present mainly between 14 and 16 years of age^[26]. Most CYP with CD grow out of this disorder, but a minority become more dissocial or aggressive and develop antisocial personality disorder as adults.

ODD is considered to be the mildest and commonest of the DBPs, with prevalence estimates of 6%-9% for pre-schoolers and boys outnumbering girls by at least two to one^[27]. CYP with ODD are typically openly hostile, negativistic, defiant, uncooperative, and irritable. They lose their tempers easily and are mean and spiteful towards others (Table 2). They are mostly defiant towards authority figures, but they may also be hostile to their siblings or peers. This pattern of adversarial behaviour significantly negatively impact on their lives at home, school, and wider society, and seriously impairs all their relationships^[28].

Emotional problems

Emotional problems in later childhood include panic disorder, generalized anxiety disorder (GAD), separation anxiety, social phobia, specific phobias, OCD and depression. Mild to moderate anxiety is a normal emotional response to many stressful life situations. Anxiety is

regarded as a disorder when it is disproportionately excessive in severity in comparison to the gravity of the triggering circumstances, leading to abnormal disruption of daily routines. Panic disorder is characterized by panic attacks untriggered by external stimuli. GAD is characterized by generalized worry across multiple life domains. Separation anxiety disorder is characterized by fear related to actual or anticipated separation from a caregiver. Social anxiety disorder (also called social phobia), is characterized by fear of social situations where peers may negatively evaluate the person^[12].

Common manifestations of Anxiety disorders include physical symptoms such as increased heart rate, shortness of breath, sweating, trembling, shaking, chest pain, abdominal discomfort and nausea^[29]. Other symptoms include worries about things before they happen, constant concerns about family, school, friends, or activities, repetitive, unwanted thoughts (obsessions) or actions (compulsions), fears of embarrassment or making mistakes, low self-esteem and lack of self-confidence^[30].

Depression often occurs in children under stress, experiencing loss, or having attentional, learning, conduct or anxiety disorders and other chronic physical ailments. It also tends to run in families^[7-9,31]. Symptoms of depression are diverse and protean, often mimicking other physical and neurodevelopmental problems,

Table 3 DSM-5 criteria for autism spectrum disorders

Persistent deficits in social communication and social interaction across multiple contexts, as manifested by 3 out of 3 of the following, currently or by history
Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation; to reduced sharing of interests, emotions, or affect; to failure to initiate or respond to social interactions
Deficits in nonverbal communicative behaviours used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures; to a total lack of facial expressions and nonverbal communication
Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to absence of interest in peers
Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two out of 4 of the following, currently or by history
Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases)
Insistence on sameness, inflexible adherence to routines, or ritualized patterns or verbal nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day)
Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interest)
Hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement)
Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities, or may be masked by learned strategies in later life)
Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning
Specify if
With or without accompanying intellectual impairment
With or without accompanying language impairment
Associated with a known medical or genetic condition or environmental factor
Specify current severity based on social communication impairments and restricted, repetitive patterns of behavior

including low mood, frequent sadness, tearfulness, crying, decreased interest or pleasure in almost all activities; or inability to enjoy previously favourite activities, hopelessness, persistent boredom; low energy, social isolation, poor communication, low self-esteem and guilt, feelings of worthlessness, extreme sensitivity to rejection or failure, increased irritability, agitation, anger, or hostility, difficulty with relationships, frequent complaints of physical illnesses such as headaches and stomach aches, frequent absences from school or poor performance in school, poor concentration, a major change in eating and/or sleeping patterns, weight loss or gain when not dieting, talk of or efforts to run away from home, thoughts or expressions of suicide or self-destructive behaviour^[31].

Disruptive mood dysregulation disorder (DMDD) is a childhood disorder characterized by a pervasively irritable or angry mood recently added to DSM-5. The symptoms include frequent episodes of severe temper tantrums or aggression (more than three episodes a week) in combination with persistently negative mood between episodes, lasting for more than 12 mo in multiple settings, beginning after 6 years of age but before the child is 10 years old^[32].

Autistic spectrum and pervasive development disorder

The definition of Autism has evolved over the years and has been broadened over time. DSM-IV-TR^[33] and the ICD-10^[13] defined the diagnostic category of pervasive developmental disorders (PDD) as the umbrella terminology used for a group of five disorders characterized by pervasive "qualitative abnormalities in reciprocal social interactions and in patterns of communication, and by a

restricted, stereotyped, repetitive repertoire of interests and activities" affecting "the individual's functioning in all situations". These included autism, asperger syndrome, childhood disintegrative disorder (CDD), pervasive developmental disorder not otherwise specified (PDD-NOS) and Rett syndrome.

Autism and Asperger Syndrome are the most widely recognised and clinically diagnosed among this group of disorders. CDD is a term used to describe children who have had a period of normal development for the first 2-3 years before a relatively acute onset of regression and emergence of autistic symptoms. PDD-NOS was used, particularly in the United States, to describe individuals who have autistic symptoms, but do not meet the full criteria for Autism or Asperger's Syndrome, denote a milder version of Autism, or to describe atypical autism symptoms emerging after 30 mo of age, and autistic individuals with other co-morbid disorders^[34].

The category of PDD has been removed from DSM-5^[12] and replaced with Autism Spectrum disorders (ASD). ASD (Table 3) is diagnosed primarily from clinical judgment usually by a multidisciplinary team, with minimal support from diagnostic instruments. Most individuals who received diagnosis based on the DSM-IV should still maintain their diagnosis under DSM-5, with some studies confirming that 91% to 100% of children with PDD diagnoses from the DSM-IV retained their diagnosis under the ASD category using the new DSM-5^[35,36], while a systematic review has found a slight decrease in the rate of ASD with DSM-5^[37].

There are many intervention approaches and strategies, used alone or in combination, for supporting individuals with ASD. These interventions need to

Table 4 Summary of common social communication enhancement strategies

Method	Description	Ref.
Augmentative and alternative communication	Supplements/replaces natural speech and/or writing with aided [<i>e.g.</i> , Picture Exchange Communication System, line drawings, Blissymbols, speech generating devices, and tangible objects] and/or unaided (<i>e.g.</i> , manual signs, gestures, and finger spelling) symbols Effective in decreasing maladaptive or challenging behaviour such as aggression, self-injury and tantrums, promotes cognitive development and improves social communication	[39,129-131]
Activity schedules/visual supports	Using photographs, drawings, or written words that act as cues or prompts to help individuals complete a sequence of tasks/activities or behave appropriately in various settings	[132]
Computer-/video-based instruction	Scripts are often used to promote social interaction, initiate or sustain interaction Use of computer technology or video recordings for teaching language skills, social skills, social understanding, and social problem solving	[40]

Table 5 Summary of common behavioural modification strategies for management of childhood emotional and behavioural disorder

Method	Description	Ref.
ABA	Uses principles of learning theory to bring about meaningful and positive change in behaviour, to help individuals build a variety of skills (<i>e.g.</i> , communication, social skills, self-control, and self-monitoring) and help generalize these skills to other situations	[122,123]
Discrete trial training	A one-to-one instructional approach based on ABA to teach skills in small, incremental steps in a systematic, controlled fashion, documenting stepwise clearly identified antecedent and consequence (<i>e.g.</i> , reinforcement in the form of praise or tangible rewards) for desired behaviours	[40]
Functional communication training	Combines ABA procedures with communicative functions of maladaptive behaviour to teach alternative responses and eliminate problem behaviours	[124]
Pivotal response treatment	A play-based, child-initiated behavioural treatment, designed to teach language, decrease disruptive behaviours, and increase social, communication and academic skills, building on a child's initiative and interests	[125]
Positive behaviour support	Uses ABA principles with person-centred values to foster skills that replace challenging behaviours with positive reinforcement of appropriate words and actions. PBS can be used to support children and adults with autism and problem behaviours	[126]
Self-management	Uses interventions to help individuals learn to independently regulate, monitor and record their behaviours in a variety of contexts, and reward themselves for using appropriate behaviours. It's been found effective for ADHD and ASD children	[127]
Time delay	It gradually decreases the use of prompts during instruction over time. It can be used with individuals regardless of cognitive level or expressive communication abilities	[40]
Incidental teaching	Utilizes naturally occurring teaching opportunities to reinforce desirable communication behaviour	[128]
Anger management	Various strategies can be used to teach children how to recognise the signs of their growing frustration and learn a range of coping skills designed to defuse their anger and aggressive behaviour, teach them alternative ways to express anger, including relaxation techniques and stress management skills	

ABA: Applied behaviour analysis; ADHD: Attention deficit hyperactivity disorder; ASD: Autistic spectrum disorder.

individualized and be closely tailored to the level of social and linguistic abilities, cultural background, family resources, learning style and degree of communication skills^[38].

Various communication enhancement strategies have been designed to manage ASD^[39], including augmentative and alternative communication (AAC), Facilitated Communication, computer-based instruction and video-based instruction (Table 4). Several behavioural and psychological interventions (Table 5) have also been used successfully in managing ASD children, including applied behaviour analysis (ABA) and functional communication training (FCT)^[40].

Social (pragmatic) communication disorder

Social (pragmatic) communication disorder (SCD) is a new diagnosis included under Communication Disorders in the Neurodevelopmental Disorders section of the DSM-5^[12]. It is characterized by persistent difficulties

with using verbal and nonverbal communication for social purposes, which can interfere with interpersonal relationships, academic achievement and occupational performance, in the absence of restricted and repetitive interests and behaviours (Table 6). Some authors consider that CYP with SCD present with similar but less severe restricted and repetitive interests and behaviours (RRIBs) characteristic of children on the autistic spectrum^[41]. SCD is thought to occur more frequently in family members of individuals with autism^[42].

The term "pragmatic" has been used previously to describe the communication skills that are needed in normal social intercourse and the rules that govern routine interpersonal interactions, including ability to pay at least some attention to the other person in a conversation, take turns, not interrupting the other speaker unless there is a very good reason, match language and volume to the situation and the listener, etc^[43]. Social and pragmatic deficit are known to also occur in

Table 6 DSM-5 criteria for social (pragmatic) communication disorder

Persistent difficulties in the social use of verbal and nonverbal communication as manifested by all of the following
Deficits in using communication for social purposes, such as greeting and sharing information, in a manner that is appropriate for social context
Impairment in the ability to change communication to match context or the needs of the listener, such as speaking differently in a classroom than on a playground, talking differently to a child than to an adult, and avoiding use of overly formal language
Difficulties following rules for conversation and storytelling, such as taking turns in conversation, rephrasing when misunderstood, and knowing how to use verbal and nonverbal signals to regulate interaction
Difficulties understanding what is not explicitly stated (e.g., making inferences) and nonliteral or ambiguous meaning of language (e.g., idioms, humor, metaphors, multiple meanings that depend on the context for interpretation)
The deficits result in functional limitations in effective communication, social participation, social relationships, academic achievement, or occupational performance, individually or in combination
The onset of the symptoms is in the early developmental period (but deficits may not become fully manifest until social communication demands exceed limited capacities)
The symptoms are not attributable to another medical or neurological condition or to low abilities in the domains of word structure and grammar, and are not better explained by autism spectrum disorder, intellectual disability (intellectual developmental disorder), global developmental delay, or another mental disorder

diverse clinical populations, including ADHD, William's syndrome, CD, closed head injury and spina bifida/hydrocephalus^[44].

Treatment modalities that have been used for supporting children with SCD are similar to those that have been used for several years in children with ASD (Tables 4 and 5). The first randomized controlled trial of social communication interventions designed primarily for children with SCD was reported in 2012^[45]. The Social Communication Intervention Project (<http://www.psych-sci.manchester.ac.uk/scip/>) targets development in social understanding and interaction, verbal and non-verbal pragmatic skills and language processing among children with SCD.

Pathological demand avoidance or Newson's syndrome

Pathological demand avoidance (PDA) or Newson's Syndrome is increasingly being accepted as part of the autism spectrum. PDA was first used in 2003^[46] for describing some CYP with autistic symptoms who showed some challenging behaviours. It is characterized by exceptional levels of demand avoidance requested by others, due to high anxiety levels when the individuals feel that they are losing control. Avoidance strategies can range from simple refusal, distraction, giving excuses, delaying, arguing, suggesting alternatives and withdrawing into fantasy, to becoming physically incapacitated (with an explanation such as "my legs don't work") or selectively mute in many situations. If they feel threatened to comply, they may become verbally or physically aggressive, best described as a "panic attack", apparently intended to shock^[46]. They tend to resort to "socially manipulative" behaviours. The outrageous acts and lack of concern for their behaviour appears to draw parallels with conduct problems (CP) and callous-unemotional traits (CUT), but reward-based techniques, effective with CP and CUT, seem not to work in people with PDA^[47]. PDA is currently neither part of the DSM-5^[12] nor the ICD-10^[13].

Though demand avoidance is a common characteristic of CYP with ASD, it becomes pathological when the levels are disproportionately excessive, and normal daily

activities and relationships are negatively impaired. Unlike typically autistic children, people with PDA tend to have much better social communication and interaction skills, and are consequently able to use these abilities to their advantage. They often have highly developed social mimicry and role play, sometimes becoming different characters or personas. The people with PDA appear to retain a keen awareness of how to "push people's buttons", suggesting a level of social insight when compared to CYP with Autism. On the other hand, children with PDA exhibit higher levels of emotional symptoms compared to those with ASD or CD. They also often experience excessive mood swings and impulsivity. While the prevalence of ASD in boys is more than four times higher compared to that of girls, the risk of developing PDA appears to be the same for both boys and girls^[47].

O'Nions *et al*^[48] have recently reported on the development and preliminary validation of the "Extreme Demand Avoidance Questionnaire" (EDA-Q), designed to quantify PDA traits based on parent-reported information, with good sensitivity (0.80) and specificity (0.85). EDA-Q is available online (<https://www.pdasociety.org.uk/resources/extreme-demand-avoidance-questionnaire>).

PREVALENCE OF BEHAVIOURAL AND EMOTIONAL DISORDERS IN CHILDHOOD

Accurate estimation of various childhood EBPs is difficult due to the problems of research methodologies relying on subjective assessments and varying definitions used. According to most studies, between 10% and 20% of CYP are affected annually by MHDs, and the rates are very similar across different racial and ethnic groups after controlling for income, resident status, education, and neighbourhood support. However, poverty and low socioeconomic status are risk factors that appear to increase the rate of MHDs across populations^[49]. A 2001 WHO report^[50] indicated the 6-mo prevalence rate for any MHD in CYP, up to age 17 years, to be 20.9%, with disruptive behaviour disorders (DBD) at 10.3%, second

only to Anxiety disorders at 13%. About 5% of CYP in the general population suffer from Depression at any given point in time, which is more prevalent among girls (54%)^[31,51].

A previous British Child and Adolescent Mental Health (CAMH) survey carried out by the office of National Statistics (ONS) in 1999 and 2004, comprising 7977 interviews from parents, children and teachers, found the prevalence of MHD among CYP (aged 5-16 years) to be 6% for conduct problems, 4% for emotional problems (Depression or Anxiety) and 1.5% for Hyperkinetic disorders^[51]. A similar survey in the United States between 2005 and 2011, the National survey of children's health (NSCH) involving 78042 households, indicated that 4.6% of CYP aged 3-17 years had a history DBD, with prevalence twice as high among boys as among girls (6.2% vs 3.0%), Anxiety (4.7%), Depression (3.9%), and ASD (1.1%)^[24]. Reported prevalence rates for DMDD range from 0.8% to 3.3% with the highest rate in preschool children^[52].

AETIOLOGY AND RISK FACTORS FOR CHILDREN'S BEHAVIOURAL AND EMOTIONAL DISORDERS

The exact causes of various childhood EBPs are unknown. Several studies have identified various combinations of genetic predisposition and adverse environmental factors that increase the risk of developing any of these disorders. These include perinatal, maternal, family, parenting, socio-economic and personal risk factors^[53]. Table 7 summarizes the evidence for various risk factors associated with development of childhood EBPs.

There is ample evidence supporting the genetic inheritability of many EBDs in CYP from their parents. From a prospective study of 209 parents along with their 331 biological offsprings, moderate inheritability ($r = 0.23$, $P < 0.001$) between parental and offspring CD was found^[74]. Anxiety seems to be transmissible from mothers to their preschool children, through both genetic factors and also through behaviour modelling and an anxious style of parenting^[6].

A developmental taxonomy theory has been proposed by Patterson *et al*^[75] to help understand the mechanisms underlying early onset and course of CPs. They described the vicious cycle of non-contingent parental responses to both prosocial and antisocial child behaviour leading to the inadvertent reinforcement of child behaviour problems. Parents' engagement in "coercive cycles" lead to children learning the functional value of their aversive behaviours (e.g., physical aggression) for escape and avoidance from unwanted interactions, ultimately leading to the use of heightened aversive behaviours from both the child and parents to obtain social goals. This adverse child behavioural training combined with social rejection often lead to deviant peer affiliation and delinquency in adolescence^[76].

NEUROBIOLOGY OF CHILDHOOD BEHAVIOURAL AND EMOTIONAL DISORDERS

Conflicting findings have been reported in the brain structural variations among CYP with EBPs using magnetic resonance imaging (MRI) studies. The most consistently reported structural abnormalities associated with the DBD include reduced grey matter volume (GMV) in the amygdala, frontal cortex, temporal lobes, and the anterior insula, which is involved in part of a network related to empathic concern for others. Reduced GMV along the superior temporal sulcus has also been found, particularly in girls^[77]. A decreased overall mean cortical thickness, thinning of the cingulate and prefrontal cortices; and decreased grey matter density in different brain regions have been reported^[78].

Subtle neurobiological changes in different parts of the brain of CYP with EBPs have been reported from many research studies of functional scans. Peculiar brain changes have been found in the hypothalamus, inferior and superior parietal lobes, right amygdala and anterior insula^[79]. Functional MRI studies have demonstrated less activation in the temporal cortex in violent adult offenders^[80] and in antisocial and psychopathic individuals^[81] compared to non-aggressive offenders.

Reduced basal Hypothalamic-Pituitary-Adrenal (HPA) axis activity has been reported in relation to childhood DBDs and exposure to abuse and neglect^[82]. It has been hypothesized that high levels of prenatal testosterone exposure appears to be part of the complex aetiology of EBDs, providing possible explanation for the higher prevalence in males for DBDs, by increasing susceptibility to toxic perinatal environments such as exposure to maternal nicotine and alcohol in pregnancy^[83].

COMPLICATIONS OF CHILDHOOD BEHAVIOURAL AND EMOTIONAL DISORDERS

EBDs in childhood, if left untreated, may have negative short-term and long-term effects on an individual's personal, educational, family and later professional life. CD has been linked to failure to complete schooling, attaining poor school achievement, poor interpersonal relationships, particularly family breakup and divorce, and experience of long-term unemployment. DBPs in parents have been linked to the abuse of their offspring, thereby increasing their risk of developing CD^[84,85]. Children presenting with hyperactivity-inattention behaviours are more likely to have a more favourable educational outcome compared with those with aggression or oppositional behaviours^[86,87].

A high prevalence of sleep disturbances is associated with various childhood EBPs. Sleep problems in early childhood is associated with increased prevalence of

Table 7 Summary of common risk factors for development of childhood emotional and behavioural disorder

Domain	Characteristic examples	Ref.
Maternal psychopathology (mental health status)	Low maternal education, one or both parents with depression, antisocial behaviour, smoking, psychological distress, major depression or alcohol problems, an antisocial personality, substance misuse or criminal activities, teenage parental age, marital conflict, disruption or violence, previous abuse as a child and single (unmarried status)	[4,54]
Adverse perinatal factors	Maternal gestational moderate alcohol drinking, smoking and drug use, early labour onset, difficult pregnancies, premature birth, low birth weight, and infant breathing problems at birth	[55,56]
Poor child-parent relationships	Poor parental supervision, erratic harsh discipline, parental disharmony, rejection of the child, and low parental involvement in the child's activities, lack of parental limit setting	[57,58]
Adverse family life	Dysfunctional families where domestic violence, poor parenting skills or substance abuse are a problem, lead to compromised psychological parental functioning, increased parental conflict, greater harsh, physical, and inconsistent discipline, less responsiveness to children's needs, and less supportive and involved parenting	[59]
Household tobacco exposure	Several studies have shown a strong exposure-response association between second-hand smoke exposure and poor childhood mental health	[60,61]
Poverty and adverse socio-economic environment	Personal and community poverty signs including homelessness, low socio-economic status, overcrowding and social isolation, and exposure to toxic air, lead, and/or pesticides or early childhood malnutrition often lead to poor mental health development Chronic stressors associated with poverty such as single-parenthood, life stress, financial worries, and ever-present challenges cumulatively compromise parental psychological functioning, leading to higher levels of distress, anxiety, anger, depressive symptoms and substance use in disadvantaged parents. Chronic stressors in children also lead to abnormal behaviour pattern of 'reactive responding' characterized by chronic vigilance, emotional reacting and sense of powerlessness	[62-66]
Early age of onset	Early starters are likely to experience more persistent and chronic trajectory of antisocial behaviours	[67-69]
Child's temperament	Physically aggressive behaviour rarely starts after age 5 Children with difficult to manage temperaments or show aggressive behaviour from an early age are more likely to develop disruptive behavioural disorders later in life Chronic irritability, temperament and anxiety symptoms before the age of 3 yr are predictive of later childhood anxiety, depression, oppositional defiant disorder and functional impairment	[70-72]
Developmental delay and Intellectual disabilities	Up to 70% of preschool children with DBD are more than 4 times at risk of developmental delay in at least one domain than the general population Children with intellectual disabilities are twice as likely to have behavioural disorders as normally developing children Rate of challenging behaviour is 5% to 15% in schools for children with severe learning disabilities but is negligible in normal schools	[15,73]
Child's gender	Boys are much more likely than girls to suffer from several DBD while depression tends to predominantly affect more girls than boys Unlike the male dominance in childhood ADHD and ASD, PDA tends to affect boys and girls equally	[24,25,27,47,51]

ADHD: Attention deficit hyperactivity disorder; ASD: Autistic spectrum disorder; DBD: Disruptive behaviour disorder; PDA: Pathological demand avoidance.

later Anxiety disorders and ODD^[88,89].

Several studies have confirmed a strong relationship between early childhood EBPs and poor future long-term physical and mental health outcomes. Chronic irritability in preschool children, CD and ODD in older children each may be predictive of any current and lifetime Anxiety, Depression and DBDs in later childhood, Mania, Schizophrenia, OCD, major depressive disorder and panic disorder^[84,90-92]. Individuals on the adolescent-onset CP path often consume more tobacco and illegal drugs and engage more often in risky sexual behaviour, self-harm, and have increased risk of PTSD, than individuals without childhood conduct problems. They also frequently experience parenting difficulties, including over-reactivity, lax and inconsistent discipline, child physical

punishment and lower levels of parental warmth and sensitivity^[74,84,93,94]. Approximately 40%-50% of CYP with CD are at the risk of developing antisocial personality disorder in adulthood^[84]. Other potential complications include adverse mental and physical health outcomes, social justice system involvement including incarceration, substance use and abuse, alcoholism, homelessness, poverty and domestic abuse^[95,96].

An analysis of several Scandinavian studies up to the 1980s has shown higher rates of violent death, estimated to be almost five times higher than expected among young people with previous MHD, with common associated predictive factors including behavioural problems, school problems, and co-morbid alcohol or drug abuse and criminality^[97].

ASSESSMENT AND DIAGNOSIS OF CHILDHOOD BEHAVIOURAL AND EMOTIONAL DISORDERS

Assessment through detailed history taking as well as observation of a child's behaviour are indispensable sources of information required for clinical diagnosis of EBPs^[1]. This should include general medical, developmental, family, social, educational and emotional history. Physical and neurological examination should include assessment of vision, hearing, dysmorphic features, neuro-cutaneous stigmata, motor skills and cognitive assessment. Condition-specific and generic observer feedback on screening rating scales and questionnaires can be used to complement direct clinical observations.

There is no single gold-standard diagnostic tool available for the diagnosis of EBDs, which largely depends on the clinical skills of an integrated collaboration of multi-professional experts. Diagnosis relies on interpretation of subjective multi-source feedback from parents or carers, teachers, peers, professional or other observers provided through a number of psychometric questionnaires or screening tools^[98]. Significant discrepancies between various respondents are quite common and clinical diagnosis cannot rely on the psychometric tools alone. There is evidence from the literature suggesting that parents have a tendency to over-report symptoms of ODD and CD in children compared to the teachers^[99].

There are several screening tools that are used for assessing the risk of MHD among CYP. The tools help to identify which individuals would require more in-depth clinical interventions^[100]. Supplement material shows a list of common Mental Health screening and assessment tools, summarizing their psychometric testing properties, cultural considerations and costs. The commonest behaviour screening tools include the Behavioral and Emotional Screening System (BESS; ages 3-18 years), the Behavior Assessment System for Children-2nd edition, Pediatric Symptom Checklist (PSC), the Ages and Stages Questionnaire-Social Emotional (ASQ-SE, Ages 0 to 5 years) and the Achenbach System of Empirically Based Assessment (ASEBA), for children aged 1.5 years through adulthood.

MANAGEMENT OF BEHAVIOURAL AND EMOTIONAL DISORDERS IN CHILDREN

Identification of appropriate treatment strategies depend on careful assessment of the prevailing symptoms, the family and caregiver's influences, wider socio-economic environment, the child's developmental level and physical health. It requires multi-level and multi-disciplinarian approaches that include professionals such as Psychologists, Psychiatrists, Behavioural Analysts, Nurses, Social care staff, Speech and language Therapists, Educational staff, Occupational Therapists, Physiotherapists, Paediatricians and Pharmacists. Use of pharmacotherapy is usually considered only in

combination with psychological and other environmental interventions^[15].

Holistic management strategies will include various combinations of several interventions such as child- and family-focused psychological strategies including Cognitive Behavioural Therapy (CBT), behavioural modification and social communication enhancement techniques, parenting skills training and psychopharmacology. These strategies can play significant roles in the management of children with a wide range of emotional, behavioural and social communication disorders. Effective alternative educational procedures also need to be implemented for the school age children and adolescents.

In early childhood, similar parenting strategies have been found useful to manage several apparently dissimilar EBPs (e.g., infant feeding or sleeping problems, preschool tantrums, disruptive and various emotional problems). This may suggest there is a common maintaining mechanism, which is probably related to poor self-regulation skills, involving the ability to control impulses and expressions of emotion^[101].

Several studies have confirmed the effectiveness of various psychological and pharmacologic therapies in the management of childhood EBDs. A meta-analysis of thirty-six controlled trials, involving 3042 children (mean sample age, 4.7 years), evaluating the effect of psychosocial treatments including parenting programmes on early DBPs, demonstrated large and sustained effects (Hedges'g = 0.82), with the largest effects for general externalizing symptoms and problems of oppositionality and non-compliance, and were weakest, relatively speaking, for problems of impulsivity and hyperactivity^[102].

The treatment of CD among CYP with callous-unemotional traits is still at early stages of research. The mainstay of management for CDs includes individual behavioural or cognitive therapy, psychotherapy, family therapy and medications^[103].

Parental skills training

Any challenging behaviour from CYP is likely to elicit persistent negative reactions from many parents, using ineffective controlling strategies and a decrease in positive responses^[104]. There is evidence from published research that social-learning and behaviourally based parent training is capable of producing lasting improvement in children with callous-unemotional traits or CD, reducing externalizing problems for children with DBDs, leading to significant parent satisfaction, particularly when delivered early in childhood^[84,105-107]. These interventions are typically delivered in a group format, one 2-h session per week for 4-18 wk, by trained leaders, with the focus on improving parenting skills to manage child behaviour, where parents typically learn to identify, define and observe problem behaviours in new ways, as well as learn strategies to prevent and respond to oppositional behaviour^[108,109].

Pooled estimates from a review of 37 randomised controlled studies identified a statistically significant

improvement on several rating scales among children with CD up to the age of 18 years^[23]. A previous meta-analysis of 24 studies confirmed that Parent-Child Interaction Therapy (PCIT) demonstrated significantly larger effect sizes for reducing negative parent behaviours, negative child behaviours, and caregiver reports of child behaviour problems than did most or all forms of Positive Parenting Programme (Triple P)^[110]. A recent Cochrane review of 13 studies confirmed the efficacy and cost-effectiveness of group-based parenting interventions for alleviating child conduct problems, enhancing parental mental health and parenting skills, at least in the short term^[111].

Differentiated educational strategies

Research has focused on identifying alternative educational strategies that can be used to improve learning opportunities for children presenting with challenging behaviours from various causes. Supportive school strategies for children with EBDs have traditionally focused on classroom management, social skills and anger management, but many researchers have more recently argued that academically-focused interventions may be most effective^[112]. Traditional school policies of suspending or expelling children with EBD can be harmful to them. Researchers have developed "step-by-step" guidelines for teachers to guide them in the selection and implementation of evidence-based strategies that have been identified as effective in increasing levels of engagement and achievement by children with EBD, including peer-assisted learning procedures, class-wide peer tutoring, self-management interventions and tiered intervention systems - most notably Response to Intervention (RtI) and Positive Behavioural Interventions and Supports (PBIS)^[113,114].

There is increasing evidence to confirm that school-based interventions to address emerging DBPs produce significant reductions in both parent-, self- and teacher-reported internalizing and externalizing symptoms^[114,115].

Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) is an educational system designed for the management of children with Autism and related communication disorders^[116,117]. There is some evidence that TEACCH programmes also lead to some improvements in motor skills and cognitive measures^[117].

Best practice management strategies for children with PDA are known to differ from those with Autism. Specific guidelines for children with PDA^[118] have been published by the British institute for Learning Disabilities. Educational support for CYP with PDA relies on highly individualized strategies that allows them to feel in control. They would respond much better to more indirect and negotiative approaches. For example, "I wonder how we might..." is likely to be more effective than "Now let's get on with your work"^[118].

Child-focused psychological interventions

Cognitive behavioural therapy (CBT) is one of the most

widely used non-pharmacologic treatments for individuals with emotional disorders, especially depression, and with individuals with behavioural problems including ASD^[119]. CBT integrates a combination of both cognitive and behavioural learning principles to encourage desirable behaviour patterns. Research evidence from several trials^[120] provide strong support for the effectiveness of cognitive-behavioural interventions among CYP with Anxiety and Depression. A recent study of child-focused CBT programme introduced at schools has shown that it produces significant improvement in disruptive behaviours among children^[121].

Self-esteem building strategies can help many children with EBDs, who often experience repeated failures at school and in their interactions with others. These children could be encouraged to identify and excel in their particular talents (such as sports) to help build their self-esteem.

Behavioural modification and social communication enhancement strategies

Behavioural interventions and techniques are designed to reduce problem behaviours and teach functional alternative strategies using the basic principles of behaviour change. Most interventions are based on the principles of Applied Behaviour Analysis (ABA) which is grounded on behavioural learning theory. Table 5 summarizes the common behavioural modification strategies for management of childhood EBDs.

Several strategies have been designed to help children acquire important social skills, such as how to have a conversation or play cooperatively with others, using social group settings and other platforms to teach peer interaction skills and promote socially appropriate behaviours and communication. There is ongoing research in the development of social communication treatment approaches^[45]. Table 4 summarizes common social communication enhancement strategies.

PSYCHOPHARMACOLOGY OF CHILDHOOD BEHAVIOURAL AND EMOTIONAL DISORDERS

Medications are often prescribed as part of a comprehensive plan for the management of childhood EBDs that includes other therapies. The greatest level of evidence for pharmacotherapy of childhood EBDs is available for their use in the management of childhood and adolescent ADHD. There is less evidence of any efficacy for medications in the management of other DBPs including ODD and CD. Table 8 lists the common classes of medications used in the management of childhood EBD.

Psychostimulants (including different formulations of Methylphenidate and Dexamphetamines) remain the primary medication of choice for management of ADHD in CYP for more than 60 years. About 75% to 80% of children with ADHD will benefit from the

Table 8 Major classes of medications used in management of childhood emotional and behavioural disorders

	Common examples	Indications for use	Common Side-effects	Follow up monitoring
Traditional antipsychotics	Haloperidol, Chlorpromazine, Thiotixene, Perphenazine, Trifluoperazine	Schizophrenia, Bipolar disorder, Schizoaffective, Disorder, Obsessive-compulsive disorder,	Tremors, Muscle spasms, Abnormal movements, Stiffness, Blurred vision, Constipation	Frequent blood tests (Clozapine), Blood pressure checks, Cholesterol testing, Heart Rate checks, Blood Sugar testing,
Atypical antipsychotics	Aripiprazole, Clozapine, Olanzapine, Quetiapine, Risperidone, Ziprasidone	Depression, Aggression, Mood instability, Irritability in ASD	Low white blood cell count (Agranulocytosis - with Clozapine), Diabetes, Lipid abnormalities, Weight gain, Other medication-specific side effects	Electrocardiogram, Height, Weight and blood chemistry tests
Tricyclic antidepressants	Amytriptyline, Desipramine, Doxepin, Imipramine, Nortriptyline	Depression, Anxiety, Seasonal Affective, Disorder, OCD, Posttraumatic Stress Disorder,	Dry mouth, Constipation, Blurry vision, Urinary retention, Dizziness, Drowsiness	Watch for worsening of depression and thoughts about suicide, Watch for unusual bruises, bleeding from the gums when brushing teeth, especially if taking other medications,
Selective Serotonin Reuptake Inhibitors	Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Sertraline	Social Anxiety, Bed-wetting and pre-menstrual syndrome	Headache, Nervousness, Nausea Insomnia, Weight Loss	Blood tests and Blood pressure checks may be needed
Serotonin-norepinephrine reuptake inhibitor	Venlafaxine, Levomilnacipran, Duloxetine, Desvenlafaxine			
Other antidepressants	Bupropion, Mirtazepine, Trazodone			
Stimulants	Methylphenidate Immediate Release and Modified Release (e.g., Concerta XL, Equasym XL), Dexamfetamines Immediate Release and Modified Release (e.g., Lisdexamfetamine)	ADHD	Decreased appetite/ weight loss, Sleep problems, Jitteriness, restless, Headaches, Dry mouth, Dysphoria, feeling sad, Anxiety, Increased heart rate, Dizziness	Blood pressure and heart rate will be checked before treatment and periodically during treatment. Child's height and weight are monitored
Non-stimulants	Atomoxetine			
Alpha-2 agonists	Clonidine, Guanfacine		Drowsiness, Dizziness, Sleepiness	
Benzodiazepines	Lorazepam, Clonazepam, Diazepam, Alprazolam, Oxazepam, Chlordiazepoxide	Anxiety, Panic disorder, Alcohol withdrawal, PTSD, OCD	Drowsiness, Dizziness, Sleepiness, Confusion, Memory loss, Blurred vision, Balance problems, Worsening behaviour	Do not stop these medications suddenly without slowly reducing (tapering) the dose as directed by the clinician. While taking buspirone, avoid grapefruit juice,
Antihistamines	Hydroxyzine HCl, Hydroxyzine, Pamoate, Alimemazine		Sleepiness, Drowsiness, Dizziness, Dry mouth, Confusion, Blurred Vision, Balance problems, Heartburn	Avoid alcohol, Blood tests may be needed prior to the start of treatment and during treatment
Other anxiolytics	Buspirone		Dizziness, Nausea, Headache, Lightheadedness, Nervousness	
Sleep-enhancement	Zolpidem, Zaleplon, Diphenhydramine, Trazodone	Insomnia (short-term)	Headache, Dizziness, Weakness, Nausea, Memory loss, Daytime sleepiness, Hallucinations, Dry mouth, Confusion, Blurred Vision, Balance problems, Heartburn	Blood tests may be needed before the start of treatment. Avoid alcohol

Modified from "Medications used for behavioral and emotional disorders. A guide for parents, foster parents, families, youth, caregivers, guardians, and social workers." May 2010. Available Online: URL: http://www.ct.gov/dcf/lib/dcf/ccmu/pdf/ccmu_-_educational_booklet_5-7-2010.pdf. ADHD: Attention deficit hyperactivity disorder; ASD: Autistic spectrum disorder; PTSD: Post traumatic stress disorder; OCD: Obsessive-compulsive disorder.

use of psychostimulants. Non-stimulant therapy with Atomoxetine or alpha 2-adrenergic agonists (Clonidine

and Guanfacine) are also effective second-line alternative options^[133]. A recent analysis of 16 randomized trials

and one meta-analysis, involving 2668 participants with ADHD, showed that both stimulant and non-stimulant medications led to clinically significant reductions in core symptoms with consistently high effect sizes. The psychosocial treatments alone combining behavioural, cognitive behavioural and skills training techniques demonstrated small- to medium-sized improvements for parent-rated ADHD symptoms, co-occurring emotional or behavioural symptoms and interpersonal functioning^[134].

The use of pharmacological treatments for symptoms of ASD is common but challenging, as there are no medications that directly treat the social and language impairments present in individuals with ASD. The medications used most frequently include antipsychotics (e.g., Risperidone) and Selective Serotonin Reuptake Inhibitors (SSRI) to treat mood and repetitive behaviour problems, and stimulants and other medications used to treat ADHD-related symptoms. The evidence base is good for using atypical antipsychotics to treat challenging and repetitive behaviours, but they also have significant side effects^[119,135]. Naltrexone is an opioid antagonist that has been shown from a systematic review (involving 155 children from 10 studies) to significantly improve symptoms of self-injury, irritability, restlessness and hyperactivity in autistic children, with minimal side effects and generally good tolerance, although long-term data are lacking^[136].

Medication use in preschool children for control of ASD and ADHD symptoms is still largely controversial. Stimulant medications for treatment of ADHD are not uniformly licensed for pre-schoolers as there is limited available research evidence to confirm efficacy and safety. Moreover, the effectiveness of parenting interventions in this age group are comparable to the effects of using stimulant drugs among the older CYP^[137,138].

Research evidence from two systematic reviews and 20 randomized controlled trials has recently documented the efficacy of psychopharmacology in the management of childhood DBP. Psychostimulants have been shown to have a moderate-to-large effect on oppositional behaviour, conduct problems, and aggression in youths with ADHD, with and without ODD or CD, while Atomoxetine has only a small effect. There is very-low-quality evidence that Clonidine and Guanfacine have a small-to-moderate effect on oppositional behaviour and conduct problems in youths with ADHD^[139].

Other behavioural disorders in children could also be successfully treated by medications. Traditional and the newer atypical antipsychotics can be used for OCD, Depression, aggression and mood instability^[140].

The commonest antidepressants in used in children are the SSRI and Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) medications as they work well and usually have fewer side effects compared to the older Tricyclic Antidepressants. Antidepressants can be used in the management of Major Depression, Anxiety, Seasonal Affective Disorder (SAD), OCD, PTSD and Social Anxiety. They may also be used to treat enuresis and pre-menstrual syndrome^[141].

CONCLUSION

Childhood EBDs have significant negative impacts on the society, in the form of direct behavioural consequences and costs, and on the individual, in the form of poor academic, occupational and psychosocial functioning and on the family. The costs to society include the trauma, disruption and psychological problems caused to the victims of crime or aggression in homes, schools and communities, together with the financial costs of services to treat the affected individuals, including youth justice services, courts, prison services, social services, foster homes, psychiatric services, accident and emergency services, alcohol and drug misuse services, in addition to unemployment and other required state benefits^[23].

Prevention and management of EBD is not easy and it requires an integrated multidisciplinary effort by healthcare providers at different levels to be involved in the assessment, prevention and management of affected individuals, and also to provide social, economic and psycho-emotional support to the affected families.

There is increasing evidence base for several psychosocial interventions but less so for pharmacological treatment apart from the use of stimulants for ADHD. Preventive measures that have been researched for controlling the risk of childhood emotional and behaviour problems include breastfeeding^[142], avoiding second-hand smoke exposure in non-smoker youths^[143] and intensive parenting interventions.

REFERENCES

- 1 **Parry TS.** Assessment of developmental learning and behavioural problems in children and young people. *Med J Aust* 2005; **183**: 43-48 [PMID: 15992341]
- 2 **Hong JS, Tillman R, Luby JL.** Disruptive behavior in preschool children: distinguishing normal misbehavior from markers of current and later childhood conduct disorder. *J Pediatr* 2015; **166**: 723-730.e1 [PMID: 25598304 DOI: 10.1016/j.jpeds.2014.11.041]
- 3 **Wakschlag LS, Choi SW, Carter AS, Hullsiek H, Burns J, McCarthy K, Leibenluft E, Briggs-Gowan MJ.** Defining the developmental parameters of temper loss in early childhood: implications for developmental psychopathology. *J Child Psychol Psychiatry* 2012; **53**: 1099-1108 [PMID: 22928674 DOI: 10.1111/j.1469-7610.2012.02595.x]
- 4 **Bagner DM, Rodríguez GM, Blake CA, Linares D, Carter AS.** Assessment of behavioral and emotional problems in infancy: a systematic review. *Clin Child Fam Psychol Rev* 2012; **15**: 113-128 [PMID: 22262040 DOI: 10.1007/s10567-012-0110-2]
- 5 **El-Radhi AS.** Management of common behaviour and mental health problems. *Br J Nurs* 2015; **24**: 586, 588-590 [PMID: 26067793 DOI: 10.12968/bjon.2015.24.11.586]
- 6 **Gardner F, Shaw DS.** Behavioral Problems of Infancy and Preschool Children (0-5). Chapter 53 in Rutter's Child and Adolescent Psychiatry Fifth Edition, 2009 [DOI: 10.1002/9781444300895.ch53]
- 7 **Lu Y, Mak KK, van Bever HP, Ng TP, Mak A, Ho RC.** Prevalence of anxiety and depressive symptoms in adolescents with asthma: a meta-analysis and meta-regression. *Pediatr Allergy Immunol* 2012; **23**: 707-715 [PMID: 22957535 DOI: 10.1111/pai.12000]
- 8 **Chernyshov PV, Ho RC, Monti F, Jirakova A, Velitchko SS, Hercogova J, Neri E.** Gender Differences in Self-assessed Health-related Quality of Life in Children with Atopic Dermatitis. *J Clin Aesthet Dermatol* 2016; **9**: 19-24 [PMID: 27672414]

- 9 **Quek YH**, Tam WWS, Zhang MWB, Ho RCM. Exploring the association between childhood and adolescent obesity and depression: a meta-analysis. *Obes Rev* 2017; **18**: 742-754 [PMID: 28401646 DOI: 10.1111/obr.12535]
- 10 **Kolko DJ**, Perrin E. The integration of behavioral health interventions in children's health care: services, science, and suggestions. *J Clin Child Adolesc Psychol* 2014; **43**: 216-228 [PMID: 24588366 DOI: 10.1080/15374416.2013.862804]
- 11 **American Academy of Child and Adolescent Psychiatry (AACAP)**. A Guide to Building Collaborative Mental Health Care Partnerships. In: *Pediatric Primary Care*, 2010: 1-27 Available from: URL: https://www.aacap.org/App_Themes/AACAP/docs/clinical_practice_center/guide_to_building_collaborative_mental_health_care_partnerships.pdf
- 12 **American Psychiatric Association (APA)**. Diagnostic and Statistical Manual of Mental Disorders 5th Edition. Washington (DC): APA, 2013. Available from: URL: <https://tinyurl.com/y82f6kyj>
- 13 **World Health Organization (WHO)**. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) Geneva Switzerland: World Health Organization, 1990. Available from: URL: <https://tinyurl.com/neayazp>
- 14 **Emerson E**. Challenging Behaviour: Analysis and intervention in people with learning disabilities. 2nd edition. Cambridge University Press, 2001: 2-4 [DOI: 10.1017/CBO9780511543739]
- 15 **National Institute for Health and Clinical Excellence (NICE)**. Challenging behaviour and learning disabilities: Prevention and interventions for people with learning disabilities whose behaviour challenges. 2015. Available from: URL: <https://www.nice.org.uk/guidance/ng11>
- 16 **Langridge D**. Health and Challenging Behaviour information sheet. The Challenging Behaviour Foundation. 2007. Available from: URL: http://www.challengingbehaviour.org.uk/learning-disability-files/14_WHealth-and-Challenging-Behaviour.pdf
- 17 **Tremblay RE**, Nagin DS, Séguin JR, Zoccolillo M, Zelazo PD, Boivin M, Pérouse D, Japel C. Physical aggression during early childhood: trajectories and predictors. *Pediatrics* 2004; **114**: e43-e50 [PMID: 15231972 DOI: 10.1542/peds.114.1.e43]
- 18 **Reebye P**. Aggression during early years - infancy and preschool. *Can Child Adolesc Psychiatr Rev* 2005; **14**: 16-20 [PMID: 19030496]
- 19 **Gurnani T**, Ivanov I, Newcorn JH. Pharmacotherapy of Aggression in Child and Adolescent Psychiatric Disorders. *J Child Adolesc Psychopharmacol* 2016; **26**: 65-73 [PMID: 26881859 DOI: 10.1089/cap.2015.0167]
- 20 **Bolhuis K**, Lubke GH, van der Ende J, Bartels M, van Beijsterveldt CEM, Lichtenstein P, Larsson H, Jaddoe VWV, Kushner SA, Verhulst FC, Boomsma DI, Tiemeier H. Disentangling Heterogeneity of Childhood Disruptive Behavior Problems Into Dimensions and Subgroups. *J Am Acad Child Adolesc Psychiatry* 2017; **56**: 678-686 [PMID: 28735697 DOI: 10.1016/j.jaac.2017.05.019]
- 21 **National Institute for Health and Care Excellence (NICE)**. Attention deficit hyperactivity disorder: diagnosis and management. [updated 2008 Sept 24]. Available from: URL: <https://www.nice.org.uk/guidance/cg72>
- 22 **Campbell SB**, Shaw DS, Gilliom M. Early externalizing behavior problems: toddlers and preschoolers at risk for later maladjustment. *Dev Psychopathol* 2000; **12**: 467-488 [PMID: 11014748 DOI: 10.1017/S0954579400003114]
- 23 **Dretzke J**, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, Bayliss S, Raftery J, Hyde C, Taylor R. The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children. *Health Technol Assess* 2005; **9**: iii, ix-ix, 1-233 [PMID: 16336845]
- 24 **Centers for Disease Control and Prevention (CDC)**. Perou RH, Bitsko SJ, Blumberg P, Pastor RM, Ghandour JC, Gfoerer SL. Mental Health Surveillance among Children - United States 2005-2011. Morbidity and Mortality Weekly Report (MMWR), 2013; **62** (Suppl 2): 1-35. Available from: URL: <https://www.cdc.gov/mmwr/pdf/other/su6202.pdf>
- 25 **State of Victoria Australia Better Health Channel**. Conduct Disorder. 2014. Available from: URL: <https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/conduct-disorder>
- 26 **American Academy of Child and Adolescent Psychiatry (AACAP)**. Conduct Disorder. 2103c. Available from: URL: http://www.rpsych.com/docs/Conduct_Disorder.pdf
- 27 **Nock MK**, Kazdin AE, Hiripi E, Kessler RC. Lifetime prevalence, correlates, and persistence of oppositional defiant disorder: results from the National Comorbidity Survey Replication. *J Child Psychol Psychiatry* 2007; **48**: 703-713 [PMID: 17593151 DOI: 10.1111/j.1469-7610.2007.01733.x]
- 28 **Bradley MC**, Mandell D. Oppositional defiant disorder: a systematic review of evidence of intervention effectiveness. *J Exp Criminol* 2005; **1**: 343-365 [DOI: 10.1007/s11292-005-0062-3]
- 29 **Ramsawh HJ**, Chavira DA, Stein MB. Burden of anxiety disorders in pediatric medical settings: prevalence, phenomenology, and a research agenda. *Arch Pediatr Adolesc Med* 2010; **164**: 965-972 [PMID: 20921356 DOI: 10.1001/archpediatrics.2010.170]
- 30 **American Academy of Child and Adolescent Psychiatry (AACAP)**. The Anxious Child. 2013b. Available from: URL: https://www.aacap.org/App_Themes/AACAP/docs/facts_for_families/47_the_anxious_child.pdf
- 31 **American Academy of Child and Adolescent Psychiatry (AACAP)**. The Depressed Child. 2013. Available from: URL: https://www.aacap.org/App_Themes/AACAP/docs/facts_for_families/04_the_depressed_child.pdf
- 32 **Stringaris A**. Irritability in children and adolescents: a challenge for DSM-5. *Eur Child Adolesc Psychiatry* 2011; **20**: 61-66 [PMID: 21298306 DOI: 10.1007/s00787-010-0150-4]
- 33 **American Psychiatric Association (APA)**. Diagnostic and Statistical Manual of Mental Disorders 4th Edition. Washington (DC): APA, 2000: 866. [DOI: 10.1176/appi.books.9780890420249.dsm-iv-tr]
- 34 **McPartland J**, Volkmar FR. Autism and related disorders. *Handb Clin Neurol* 2012; **106**: 407-418 [PMID: 22608634 DOI: 10.1016/B978-0-444-52002-9.00023-1]
- 35 **Huerta M**, Bishop SL, Duncan A, Hus V, Lord C. Application of DSM-5 criteria for autism spectrum disorder to three samples of children with DSM-IV diagnoses of pervasive developmental disorders. *Am J Psychiatry* 2012; **169**: 1056-1064 [PMID: 23032385 DOI: 10.1176/appi.ajp.2012.12020276]
- 36 **Kim YS**, Fombonne E, Koh YJ, Kim SJ, Cheon KA, Leventhal BL. A comparison of DSM-IV pervasive developmental disorder and DSM-5 autism spectrum disorder prevalence in an epidemiologic sample. *J Am Acad Child Adolesc Psychiatry* 2014; **53**: 500-508 [PMID: 24745950 DOI: 10.1016/j.jaac.2013.12.021]
- 37 **Kulage KM**, Smaldone AM, Cohn EG. How will DSM-5 affect autism diagnosis? A systematic literature review and meta-analysis. *J Autism Dev Disord* 2014; **44**: 1918-1932 [PMID: 24531932 DOI: 10.1007/s10803-014-2065-2]
- 38 **Maggini DM**, Johnson AH, Chafouleas SM, Ruberto LM, Berggren M. A systematic evidence review of school-based group contingency interventions for students with challenging behavior. *J Sch Psychol* 2012; **50**: 625-654 [PMID: 23040760 DOI: 10.1016/j.jsp.2012.06.001]
- 39 **Iacono T**, Trembath D, Erickson S. The role of augmentative and alternative communication for children with autism: current status and future trends. *Neuropsychiatr Dis Treat* 2016; **12**: 2349-2361 [PMID: 27703354 DOI: 10.2147/NDT.S95967]
- 40 **American Speech-Language-Hearing Association (ASHA)**. Autism (Practice Portal). Available from: URL: <http://www.asha.org/Practice-Portal/Clinical-Topics/Autism/>
- 41 **Reisinger LM**, Cornish KM, Fombonne E. Diagnostic differentiation of autism spectrum disorders and pragmatic language impairment. *J Autism Dev Disord* 2011; **41**: 1694-1704 [PMID: 21416199 DOI: 10.1007/s10803-011-1196-y]
- 42 **Miller M**, Young GS, Hutman T, Johnson S, Schwichtenberg AJ, Ozonoff S. Early pragmatic language difficulties in

- siblings of children with autism: implications for DSM-5 social communication disorder? *J Child Psychol Psychiatry* 2015; **56**: 774-781 [PMID: 25315782 DOI: 10.1111/jcpp.12342]
- 43 **Rapin I**. Historical data. In Rapin I (Ed). *Preschool Children with Inadequate Communication: Developmental Language Disorder, Autism, Low IQ. Clinics in Developmental Medicine*. Cambridge University Press, New York, 1996; 139: 57-97
- 44 **Norbury CF**. Practitioner review: Social (pragmatic) communication disorder conceptualization, evidence and clinical implications. *J Child Psychol Psychiatry* 2014; **55**: 204-216 [PMID: 24117874 DOI: 10.1111/jcpp.12154]
- 45 **Adams C**, Lockton E, Freed J, Gaile J, Earl G, McBean K, Nash M, Green J, Vail A, Law J. The Social Communication Intervention Project: a randomized controlled trial of the effectiveness of speech and language therapy for school-age children who have pragmatic and social communication problems with or without autism spectrum disorder. *Int J Lang Commun Disord* 2012; **47**: 233-244 [PMID: 22512510 DOI: 10.1111/j.1460-6984.2011.00146.x]
- 46 **Newson E**, Le Maréchal K, David C. Pathological demand avoidance syndrome: a necessary distinction within the pervasive developmental disorders. *Arch Dis Child* 2003; **88**: 595-600 [PMID: 12818906 DOI: 10.1136/adc.88.7.595]
- 47 **O'Nions E**, Viding E, Greven CU, Ronald A, Happé F. Pathological demand avoidance: exploring the behavioural profile. *Autism* 2014; **18**: 538-544 [PMID: 24104509 DOI: 10.1177/1362361313481861]
- 48 **O'Nions E**, Christie P, Gould J, Viding E, Happé F. Development of the 'Extreme Demand Avoidance Questionnaire' (EDA-Q): preliminary observations on a trait measure for Pathological Demand Avoidance. *J Child Psychol Psychiatry* 2014; **55**: 758-768 [PMID: 24117718 DOI: 10.1111/jcpp.12149]
- 49 **National Research Council/ Institute of Medicine (NHRC/IOM)**. Adolescent Health Services: Highlights and Considerations for State Health Policymakers, 2009: 1-25. Available from: URL: <http://www.nashp.org/sites/default/files/AdolHealth.pdf>
- 50 **World Health Organization (WHO)**. Mental health: new understanding new hope [report] Geneva (CH): WHO, 2001. Available from: URL: http://www.who.int/whr/2001/en/whr01_en.pdf?ua=1
- 51 **Green H**, McGinnity A, Meltzer H, Ford T, Goodman R. Mental health of children and young people in Great Britain 2004. NY: Palgrave Macmillan, 2005. Available from: URL: <http://content.digital.nhs.uk/catalogue/PUB06116/ment-heal-chil-youn-peop-gb-2004-rep1.pdf>
- 52 **Copeland WE**, Angold A, Costello EJ, Egger H. Prevalence, comorbidity, and correlates of DSM-5 proposed disruptive mood dysregulation disorder. *Am J Psychiatry* 2013; **170**: 173-179 [PMID: 23377638 DOI: 10.1176/appi.ajp.2012.12010132]
- 53 **Boden JM**, Fergusson DM, Horwood LJ. Risk factors for conduct disorder and oppositional/defiant disorder: evidence from a New Zealand birth cohort. *J Am Acad Child Adolesc Psychiatry* 2010; **49**: 1125-1133 [PMID: 20970700 DOI: 10.1016/j.jaac.2010.08.005]
- 54 **Plant DT**, Barker ED, Waters CS, Pawlby S, Pariante CM. Intergenerational transmission of maltreatment and psychopathology: the role of antenatal depression. *Psychol Med* 2013; **43**: 519-528 [PMID: 22694795 DOI: 10.1017/S0033291712001298]
- 55 **Murray J**, Burgess S, Zuccolo L, Hickman M, Gray R, Lewis SJ. Moderate alcohol drinking in pregnancy increases risk for children's persistent conduct problems: causal effects in a Mendelian randomisation study. *J Child Psychol Psychiatry* 2016; **57**: 575-584 [PMID: 26588883 DOI: 10.1111/jcpp.12486]
- 56 **Owens EB**, Hinshaw SP. Perinatal problems and psychiatric comorbidity among children with ADHD. *J Clin Child Adolesc Psychol* 2013; **42**: 762-768 [PMID: 23581554 DOI: 10.1080/15374416.2013.785359 DOI: 10.1080/15374416.2013.785359]
- 57 **Webster-Stratton C**, Reid MJ, Hammond M. Treating children with early-onset conduct problems: intervention outcomes for parent, child, and teacher training. *J Clin Child Adolesc Psychol* 2004; **33**: 105-124 [PMID: 15028546 DOI: 10.1207/S15374424JCCP3301_11]
- 58 **Smeekens S**, Riksen-Walraven JM, van Bakel HJ. Multiple determinants of externalizing behavior in 5-year-olds: a longitudinal model. *J Abnorm Child Psychol* 2007; **35**: 347-361 [PMID: 17243016 DOI: 10.1007/s10802-006-9095-y]
- 59 **Brody GH**, Murry VM, Kim S, Brown AC. Longitudinal pathways to competence and psychological adjustment among African American children living in rural single-parent households. *Child Dev* 2002; **73**: 1505-1516 [PMID: 12361315 DOI: 10.1111/1467-8624.00486]
- 60 **Padrón A**, Galán I, García-Esquinas E, Fernández E, Ballbé M, Rodríguez-Artalejo F. Exposure to secondhand smoke in the home and mental health in children: a population-based study. *Tob Control* 2016; **25**: 307-312 [PMID: 25808665 DOI: 10.1136/tobaccocontrol-2014-052077]
- 61 **Royal College of Physicians Royal College of Psychiatrists (RCP/RCPsych)**. Smoking and mental health. London: RCP, 2013. Available from: URL: <http://www.ncscot.co.uk/usr/pub/Smoking%20and%20mental%20health.pdf>
- 62 **McLoyd V**. How money matters for children's socioemotional adjustment: Family processes and parental investment. In: Carlo G, Crockett L, Caranza M editors. In: *Motivation and health: Addressing youth health disparities in the twenty first century*. Based on 57th Annual Nebraska Symposium on motivation. Springer; New York, 2011: 33-72
- 63 **Odgers CL**, Caspi A, Russell MA, Sampson RJ, Arseneault L, Moffitt TE. Supportive parenting mediates neighborhood socioeconomic disparities in children's antisocial behavior from ages 5 to 12. *Dev Psychopathol* 2012; **24**: 705-721 [PMID: 22781850 DOI: 10.1017/S0954579412000326]
- 64 **Galler JR**, Bryce CP, Waber DP, Hock RS, Harrison R, Eaglesfield GD, Fitzmaurice G. Infant malnutrition predicts conduct problems in adolescents. *Nutr Neurosci* 2012; **15**: 186-192 [PMID: 22584048 DOI: 10.1179/1476830512Y.0000000012]
- 65 **Conger RD**, Donnellan MB. An interactionist perspective on the socioeconomic context of human development. *Annu Rev Psychol* 2007; **58**: 175-199 [PMID: 16903807 DOI: 10.1146/annurev.psych.58.110405.085551]
- 66 **Taylor SE**, Seeman TE. Psychosocial resources and the SES-health relationship. *Ann N Y Acad Sci* 1999; **896**: 210-225 [PMID: 10681899 DOI: 10.1111/j.1749-6632.1999.tb08117.x]
- 67 **Shaw DS**, Hyde LW, Brennan LM. Early predictors of boys' antisocial trajectories. *Dev Psychopathol* 2012; **24**: 871-888 [PMID: 22781860 DOI: 10.1017/S0954579412000429]
- 68 **Waller R**, Dishion TJ, Shaw DS, Gardner F, Wilson MN, Hyde LW. Does early childhood callous-unemotional behavior uniquely predict behavior problems or callous-unemotional behavior in late childhood? *Dev Psychol* 2016; **52**: 1805-1819 [PMID: 27598253 DOI: 10.1037/dev0000165]
- 69 **Shaw DS**, Bell RQ, Gilliom M. A truly early starter model of antisocial behavior revisited. *Clin Child Fam Psychol Rev* 2000; **3**: 155-172 [PMID: 11225751 DOI: 10.1023/A:1009599208790]
- 70 **Fischer M**, Rolf JE, Hasazi JE, Cummings L. Follow-up of a preschool epidemiological sample: cross-age continuities and predictions of later adjustment with internalizing and externalizing dimensions of behavior. *Child Dev* 1984; **55**: 137-150 [PMID: 6705616 DOI: 10.2307/1129840]
- 71 **Mian ND**, Wainwright L, Briggs-Gowan MJ, Carter AS. An ecological risk model for early childhood anxiety: the importance of early child symptoms and temperament. *J Abnorm Child Psychol* 2011; **39**: 501-512 [PMID: 21153696 DOI: 10.1007/s10802-010-9476-0]
- 72 **Dougherty LR**, Smith VC, Bufferd SJ, Stringaris A, Leibenluft E, Carlson GA, Klein DN. Preschool irritability: longitudinal associations with psychiatric disorders at age 6 and parental psychopathology. *J Am Acad Child Adolesc Psychiatry* 2013; **52**: 1304-1313 [PMID: 24290463 DOI: 10.1016/j.jaac.2013.09.007]
- 73 **Szczepaniak D**, McHenry MS, Nutakki K, Bauer NS, Downs SM. The prevalence of at-risk development in children 30 to 60 months old presenting with disruptive behaviors. *Clin Pediatr (Phila)* 2013; **52**: 942-949 [PMID: 23836809 DOI: 10.1177/0009922813493832]

- 74 **Raudino A**, Woodward LJ, Fergusson DM, Horwood LJ. Childhood conduct problems are associated with increased partnership and parenting difficulties in adulthood. *J Abnorm Child Psychol* 2012; **40**: 251-263 [PMID: 21904828 DOI: 10.1007/s10802-011-9565-8]
- 75 **Patterson GR**, DeBaryshe BD, Ramsey E. A developmental perspective on antisocial behavior. *Am Psychol* 1989; **44**: 329-335 [PMID: 2653143 DOI: 10.1037/0003-066X.44.2.329]
- 76 **Brennan LM**, Shaw DS. Revisiting data related to the age of onset and developmental course of female conduct problems. *Clin Child Fam Psychol Rev* 2013; **16**: 35-58 [PMID: 23076722 DOI: 10.1007/s10567-012-0125-8]
- 77 **Michalska KJ**, Decety J, Zeffiro TA, Lahey BB. Association of regional gray matter volumes in the brain with disruptive behavior disorders in male and female children. *Neuroimage Clin* 2014; **7**: 252-257 [PMID: 25610787 DOI: 10.1016/j.nicl.2014.12.012]
- 78 **Fahim C**, He Y, Yoon U, Chen J, Evans A, Pérusse D. Neuroanatomy of childhood disruptive behavior disorders. *Aggress Behav* 2011; **37**: 326-337 [PMID: 21538379 DOI: 10.1002/ab.20396]
- 79 **Sebastian CL**, McCrory EJ, Cecil CA, Lockwood PL, De Brito SA, Fontaine NM, Viding E. Neural responses to affective and cognitive theory of mind in children with conduct problems and varying levels of callous-unemotional traits. *Arch Gen Psychiatry* 2012; **69**: 814-822 [PMID: 22868935 DOI: 10.1001/archgenpsychiatry.2011.2070]
- 80 **Raine A**, Yang Y, Narr KL, Toga AW. Sex differences in orbitofrontal gray as a partial explanation for sex differences in antisocial personality. *Mol Psychiatry* 2011; **16**: 227-236 [PMID: 20029391 DOI: 10.1038/mp.2009.136]
- 81 **Kiehl KA**, Smith AM, Mendrek A, Forster BB, Hare RD, Liddle PF. Temporal lobe abnormalities in semantic processing by criminal psychopaths as revealed by functional magnetic resonance imaging. *Psychiatry Res* 2004; **130**: 27-42 [PMID: 14972366 DOI: 10.1016/S0925-4927(03)00106-9]
- 82 **Kohrt BA**, Hruschka DJ, Kohrt HE, Carrion VG, Waldman ID, Worthman CM. Child abuse, disruptive behavior disorders, depression, and salivary cortisol levels among institutionalized and community-residing boys in Mongolia. *Asia Pac Psychiatry* 2015; **7**: 7-19 [PMID: 24890783 DOI: 10.1111/appy.12141]
- 83 **Martel MM**, Roberts BA. Prenatal testosterone increases sensitivity to prenatal stressors in males with disruptive behavior disorders. *Neurotoxicol Teratol* 2014; **44**: 11-17 [PMID: 24819590 DOI: 10.1016/j.ntt.2014.05.001]
- 84 **National Institute for Health and Clinical Excellence (NICE)**. Parent-training/education programmes in the management of children with conduct disorders. 2006. Available from: URL: <http://www.nice.org.uk/nicemedia/pdf/TA102guidance.pdf>
- 85 **Smith JD**, Dishion TJ, Shaw DS, Wilson MN, Winter CC, Patterson GR. Coercive family process and early-onset conduct problems from age 2 to school entry. *Dev Psychopathol* 2014; **26**: 917-932 [PMID: 24690305 DOI: 10.1017/S0954579414000169]
- 86 **Lynch RJ**, Kistner JA, Allan NP. Distinguishing among disruptive behaviors to help predict high school graduation: does gender matter? *J Sch Psychol* 2014; **52**: 407-418 [PMID: 25107411 DOI: 10.1016/j.jsp.2014.05.001]
- 87 **Serra-Pinheiro MA**, Mattos P, Regalla MA, de Souza I, Paixão C. Inattention, hyperactivity, oppositional-defiant symptoms and school failure. *Arq Neuropsiquiatr* 2008; **66**: 828-831 [PMID: 19099120 DOI: 10.1590/S0004-282X2008000600010]
- 88 **Spruyt K**, Gozal D. Sleep disturbances in children with attention-deficit/hyperactivity disorder. *Expert Rev Neurother* 2011; **11**: 565-577 [PMID: 21469929 DOI: 10.1586/ern.11.7]
- 89 **Shanahan L**, Copeland WE, Angold A, Bondy CL, Costello EJ. Sleep problems predict and are predicted by generalized anxiety/depression and oppositional defiant disorder. *J Am Acad Child Adolesc Psychiatry* 2014; **53**: 550-558 [PMID: 24745954 DOI: 10.1016/j.jaac.2013.12.029]
- 90 **Dougherty LR**, Smith VC, Bufferd SJ, Kessel E, Carlson GA, Klein DN. Preschool irritability predicts child psychopathology, functional impairment, and service use at age nine. *J Child Psychol Psychiatry* 2015; **56**: 999-1007 [PMID: 26259142 DOI: 10.1111/jcpp.12403]
- 91 **Stringaris A**, Lewis G, Maughan B. Developmental pathways from childhood conduct problems to early adult depression: findings from the ALSPAC cohort. *Br J Psychiatry* 2014; **205**: 17-23 [PMID: 24764545 DOI: 10.1192/bjp.bp.113.134221]
- 92 **Luby JL**, Gaffrey MS, Tillman R, April LM, Belden AC. Trajectories of preschool disorders to full DSM depression at school age and early adolescence: continuity of preschool depression. *Am J Psychiatry* 2014; **171**: 768-776 [PMID: 24700355 DOI: 10.1176/appi.ajp.2014.13091198]
- 93 **Kretschmer T**, Hickman M, Doerner R, Emond A, Lewis G, Macleod J, Maughan B, Munafò MR, Heron J. Outcomes of childhood conduct problem trajectories in early adulthood: findings from the ALSPAC study. *Eur Child Adolesc Psychiatry* 2014; **23**: 539-549 [PMID: 24197169 DOI: 10.1007/s00787-013-0488-5]
- 94 **van der Molen E**, Blokland AA, Hipwell AE, Vermeiren RR, Doreleijers TA, Loeber R. Girls' childhood trajectories of disruptive behavior predict adjustment problems in early adolescence. *J Child Psychol Psychiatry* 2015; **56**: 766-773 [PMID: 25302849 DOI: 10.1111/jcpp.12339]
- 95 **Burke JD**, Waldman I, Lahey BB. Predictive validity of childhood oppositional defiant disorder and conduct disorder: implications for the DSM-V. *J Abnorm Psychol* 2010; **119**: 739-751 [PMID: 20853919 DOI: 10.1037/a0019708]
- 96 **Fergusson DM**, Horwood LJ, Ridder EM. Show me the child at seven: the consequences of conduct problems in childhood for psychosocial functioning in adulthood. *J Child Psychol Psychiatry* 2005; **46**: 837-849 [PMID: 16033632 DOI: 10.1111/j.1469-7610.2004.00387.x]
- 97 **Engqvist U**, Rydelius PA. Death and suicide among former child and adolescent psychiatric patients. *BMC Psychiatry* 2006; **6**: 51 [PMID: 17081290 DOI: 10.1186/1471-244X-6-51]
- 98 **Ogundele MO**. The Influence of Socio-Economic Status on the Prevalence of School-Age Childhood Behavioral Disorders in a Local District Clinic of North West England. *J Fam Med and Health Care* 2016; **2**: 98-107 [DOI: 10.11648/j.jfmhc.20160204.22]
- 99 **Strickland J**, Hopkins J, Keenan K. Mother-teacher agreement on preschoolers' symptoms of ODD and CD: does context matter? *J Abnorm Child Psychol* 2012; **40**: 933-943 [PMID: 22661105 DOI: 10.1007/s10802-012-9622-y]
- 100 **American Academy of Pediatrics (AAP)**. Mental Health Screening and Assessment Tools for Primary Care. 2012. Available from: URL: https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf
- 101 **Shaw DS**, Bell RQ. Developmental theories of parental contributors to antisocial behavior. *J Abnorm Child Psychol* 1993; **21**: 493-518 [PMID: 8294650 DOI: 10.1007/BF00916316]
- 102 **Comer JS**, Chow C, Chan PT, Cooper-Vince C, Wilson LA. Psychosocial treatment efficacy for disruptive behavior problems in very young children: a meta-analytic examination. *J Am Acad Child Adolesc Psychiatry* 2013; **52**: 26-36 [PMID: 23265631 DOI: 10.1016/j.jaac.2012.10.001]
- 103 **Hawes DJ**, Price MJ, Dadds MR. Callous-unemotional traits and the treatment of conduct problems in childhood and adolescence: a comprehensive review. *Clin Child Fam Psychol Rev* 2014; **17**: 248-267 [PMID: 24748077 DOI: 10.1007/s10567-014-0167-1]
- 104 **Cunningham CE**, Boyle MH. Preschoolers at risk for attention-deficit hyperactivity disorder and oppositional defiant disorder: family, parenting, and behavioral correlates. *J Abnorm Child Psychol* 2002; **30**: 555-569 [PMID: 12481971 DOI: 10.1023/A:1020855429085]
- 105 **Gardner F**, Burton J, Klimes I. Randomised controlled trial of a parenting intervention in the voluntary sector for reducing child conduct problems: outcomes and mechanisms of change. *J Child Psychol Psychiatry* 2006; **47**: 1123-1132 [PMID: 17076751 DOI: 10.1111/j.1469-7610.2006.01668.x]
- 106 **Hutchings J**, Gardner F, Bywater T, Daley D, Whitaker C, Jones K, Eames C, Edwards RT. Parenting intervention in Sure Start

- services for children at risk of developing conduct disorder: pragmatic randomised controlled trial. *BMJ* 2007; **334**: 678 [PMID: 17350966 DOI: 10.1136/bmj.39126.620799.55]
- 107 **Perrin EC**, Sheldrick RC, McMenamy JM, Henson BS, Carter AS. Improving parenting skills for families of young children in pediatric settings: a randomized clinical trial. *JAMA Pediatr* 2014; **168**: 16-24 [PMID: 24190691 DOI: 10.1001/jamapediatrics.2013.2919]
 - 108 **Shaw DS**, Dishion TJ, Supplee L, Gardner F, Arnds K. Randomized trial of a family-centered approach to the prevention of early conduct problems: 2-year effects of the family check-up in early childhood. *J Consult Clin Psychol* 2006; **74**: 1-9 [PMID: 16551138 DOI: 10.1037/0022-006X.74.1.1]
 - 109 **Funderburk BW**, Eyberg SM. Parent-Child Interaction Therapy. In: History of Psychotherapy: Continuity and Change. Norcross JC VandenBos GR Freedheim DK editors. 2nd ed. Washington DC: American Psychological Association, 2011: 415-420 [DOI: 10.1037/12353-021]
 - 110 **Thomas R**, Zimmer-Gembeck MJ. Behavioral outcomes of Parent-Child Interaction Therapy and Triple P-Positive Parenting Program: a review and meta-analysis. *J Abnorm Child Psychol* 2007; **35**: 475-495 [PMID: 17333363 DOI: 10.1007/s10802-007-9104-9]
 - 111 **Furlong M**, McGilloway S, Bywater T, Hutchings J, Smith SM, Donnelly M. Cochrane review: behavioural and cognitive-behavioural group-based parenting programmes for early-onset conduct problems in children aged 3 to 12 years (Review). *Evid Based Child Health* 2013; **8**: 318-692 [PMID: 23877886 DOI: 10.1002/ebch.1905]
 - 112 **Lane KL**. Identifying and Supporting Students at Risk for Emotional and Behavioral Disorders within Multi-level Models: Data Driven Approaches to Conducting Secondary Interventions with an Academic Emphasis. *Education & Treatment of Children* 2007; **30**: 135-164 [DOI: 10.1353/etc.2007.0026]
 - 113 **Farley C**, Torres C, Wailehua C-UT, Cook L. Evidence-Based Practices for Students with Emotional and Behavioral Disorders: Improving Academic Achievement. *Beyond Behavior* 2012; **21**: 37-43
 - 114 **Winther J**, Carlsson A, Vance A. A pilot study of a school-based prevention and early intervention program to reduce oppositional defiant disorder/conduct disorder. *Early Interv Psychiatry* 2014; **8**: 181-189 [PMID: 23734628 DOI: 10.1111/eip.12050]
 - 115 **Horner RG**, Sugai G, Vincent C. School-wide Positive Behavior Support: Investing in Student Success. *Impact* 2005; **18**: 4
 - 116 **Mesibov GB**, Shea V, Schopler E. The TEACCH approach to autism spectrum disorders. New York NY: Springer-Verlag, 2007: 211 Available from: URL: <http://www.springer.com/gb/book/9780306486463>
 - 117 **Warren Z**, Veenstra-VanderWeele J, Stone W, Bruzek JL, Nahmias AS, Foss-Feig JH, Jerome RN, Krishnaswami S, Sathe NA, Glasser AM, Surawicz T, McPheeters ML. Therapies for Children With Autism Spectrum Disorders, 2011
 - 118 **Christie P**. The Distinctive Clinical and Educational Needs of Children with Pathological Demand Avoidance Syndrome: Guidelines for Good Practice. *Good Autism Practice* 2007; **8**: 3-11
 - 119 **Lindgren S**, Doobay A. Evidence-Based Interventions for Autism Spectrum Disorders. 2011. Available from: URL: <http://www.interventionsunlimited.com/editoruploads/files/Iowa%20DHS%20Autism%20Interventions%206-10-11.pdf>
 - 120 **Ollendick TH**, King NJ. Empirically supported treatments for children with phobic and anxiety disorders: current status. *J Clin Child Psychol* 1998; **27**: 156-167 [PMID: 9648033 DOI: 10.1207/s15374424jccp2702_3]
 - 121 **Liber JM**, De Boo GM, Huizenga H, Prins PJ. School-based intervention for childhood disruptive behavior in disadvantaged settings: a randomized controlled trial with and without active teacher support. *J Consult Clin Psychol* 2013; **81**: 975-987 [PMID: 23834227 DOI: 10.1037/a0033577]
 - 122 **Wong C**, Odom SL, Hume K, Cox AW, Fettig A, Kucharczyk S. Evidence-based practices for children youth and young adults with Autism Spectrum Disorder. Chapel Hill: The University of North Carolina Frank Porter Graham Child Development Institute Autism Evidence-Based Practice Review Group. 2013. Available from: URL: <http://autismpdc.fpg.unc.edu/sites/autismpdc.fpg.unc.edu/files/2014-EBP-Report.pdf>
 - 123 **Reichow B**, Volkmar FR. Social skills interventions for individuals with autism: evaluation for evidence-based practices within a best evidence synthesis framework. *J Autism Dev Disord* 2010; **40**: 149-166 [PMID: 19655240 DOI: 10.1007/s10803-009-0842-0]
 - 124 **Carr EG**, Durand VM. Reducing behavior problems through functional communication training. *J Appl Behav Anal* 1985; **18**: 111-126 [PMID: 2410400 DOI: 10.1901/jaba.1985.18-111]
 - 125 **Koegel RL**, Koegel LK. Pivotal response treatments for autism: Communication social and academic development. Baltimore MD: Brookes, 2006: 312. Available from: URL: <http://products.brookespublishing.com/Pivotal-Response-Treatments-for-Autism-P63.aspx>
 - 126 **Carr EG**, Dunlap G, Horner RH, Koegel RL, Turnbull AP, Sailor W, Fox L. Positive behavior support: evolution of an applied science. *J Pos Beh Interv* 2002; **4**: 4-16 [DOI: 10.1177/109830070200400102]
 - 127 **Reid R**, Trout AL, Schartz M. Self-Regulation Interventions for Children with Attention Hyperactivity Disorder. *Exceptional Children* 2005; **71**: 361-377
 - 128 **Schepis MM**, Reid DH, Ownbey J, Parsons MB. Training support staff to embed teaching within natural routines of young children with disabilities in an inclusive preschool. *J Appl Behav Anal* 2001; **34**: 313-327 [PMID: 11678526 DOI: 10.1901/jaba.2001.34-313]
 - 129 **Beukelman DR**, Mirenda P. Augmentative and alternative communication: Supporting children and adults with complex communication needs. Baltimore MD: Brookes, 2013: 616. Available from: URL: <http://products.brookespublishing.com/Augmentative-and-Alternative-Communication-P626.aspx>
 - 130 **Drager K**, Light J, McNaughton D. Effects of AAC interventions on communication and language for young children with complex communication needs. *J Pediatr Rehabil Med* 2010; **3**: 303-310 [PMID: 21791864 DOI: 10.3233/PRM-2010-0141]
 - 131 **Mirenda P**. Supporting individuals with challenging behavior through functional communication training and AAC: Research review. *Augment Altern Commun* 1997; **13**: 207-225 [DOI: 10.1080/07344619712331278048]
 - 132 **Hart JE**, Whalon KJ. Promote academic engagement and communication of students with autism spectrum disorder in inclusive settings. *ISC* 2008; **44**: 116-120 [DOI: 10.1177/1053451207310346]
 - 133 **Briars L**, Todd T. A Review of Pharmacological Management of Attention-Deficit/Hyperactivity Disorder. *J Pediatr Pharmacol Ther* 2016; **21**: 192-206 [PMID: 27453697 DOI: 10.5863/1551-6776-21.3.192]
 - 134 **Chan E**, Fogler JM, Hammerness PG. Treatment of Attention-Deficit/Hyperactivity Disorder in Adolescents: A Systematic Review. *JAMA* 2016; **315**: 1997-2008 [PMID: 27163988 DOI: 10.1001/jama.2016.5453]
 - 135 **McPheeters ML**, Warren Z, Sathe N, Bruzek JL, Krishnaswami S, Jerome RN, Veenstra-Vanderweele J. A systematic review of medical treatments for children with autism spectrum disorders. *Pediatrics* 2011; **127**: e1312-e1321 [PMID: 21464191 DOI: 10.1542/peds.2011-0427]
 - 136 **Roy A**, Roy M, Deb S, Unwin G, Roy A. Are opioid antagonists effective in attenuating the core symptoms of autism spectrum conditions in children: a systematic review. *J Intellect Disabil Res* 2015; **59**: 293-306 [PMID: 24589346 DOI: 10.1111/jir.12122]
 - 137 **Sonuga-Barke EJ**, Daley D, Thompson M, Laver-Bradbury C, Weeks A. Parent-based therapies for preschool attention-deficit/hyperactivity disorder: a randomized, controlled trial with a community sample. *J Am Acad Child Adolesc Psychiatry* 2001; **40**: 402-408 [PMID: 11314565 DOI: 10.1097/00004583-200104000-00008]
 - 138 **Doyle CA**, McDougle CJ. Pharmacologic treatments for the behavioral symptoms associated with autism spectrum disorders across the lifespan. *Dialogues Clin Neurosci* 2012; **14**: 263-279 [PMID: 23226952]

- 139 **Pringsheim T**, Hirsch L, Gardner D, Gorman DA. The pharmacological management of oppositional behaviour, conduct problems, and aggression in children and adolescents with attention-deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder: a systematic review and meta-analysis. Part 1: psychostimulants, alpha-2 agonists, and atomoxetine. *Can J Psychiatry* 2015; **60**: 42-51 [PMID: 25886655 DOI: 10.1177/070674371506000202]
- 140 **Kodish I**, Rockhill C, Varley C. Pharmacotherapy for anxiety disorders in children and adolescents. *Dialogues Clin Neurosci* 2011; **13**: 439-452 [PMID: 22275849 DOI: 10.1016/j.pcl.2010.10.002]
- 141 **Gledhill J**, Hodes M. Management of depression in children and adolescents. *Prog Neurol Psychiatry* 2015; **19**: 28-33 [DOI: 10.1002/pnp.375]
- 142 **Shelton KH**, Collishaw S, Rice FJ, Harold GT, Thapar A. Using a genetically informative design to examine the relationship between breastfeeding and childhood conduct problems. *Eur Child Adolesc Psychiatry* 2011; **20**: 571-579 [PMID: 22028070 DOI: 10.1007/s00787-011-0224-y]
- 143 **Bandiera FC**, Richardson AK, Lee DJ, He JP, Merikangas KR. Secondhand smoke exposure and mental health among children and adolescents. *Arch Pediatr Adolesc Med* 2011; **165**: 332-338 [PMID: 21464381 DOI: 10.1001/archpediatrics.2011.30]

P- Reviewer: Ho RCM, Yellanthoor RB, Yucel O **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Li RF



Controversies in diagnosis and management of Kawasaki disease

Rakesh Kumar Pilia, Dharmagat Bhattarai, Surjit Singh

Rakesh Kumar Pilia, Dharmagat Bhattarai, Surjit Singh, Department of Pediatrics, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh 160012, India

ORCID number: Rakesh Kumar Pilia (0000-0002-9015-1704); Dharmagat Bhattarai (0000-0003-4838-5037); Surjit Singh (000-0002-8738-4582).

Author contributions: Pilia RK and Bhattarai D wrote the first draft of the manuscript; Singh S reviewed the draft, made changes and completed the final version; all authors approved the submitted version.

Conflict-of-interest statement: None.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Surjit Singh, FRCP (C), MBBS, MD, FAMS, Professor, Department of Pediatrics, Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research (PGIMER), Sector 12, Chandigarh 160012, India. surjitsinghpgi@rediffmail.com
Telephone: +91-987-2283832

Received: October 28, 2017

Peer-review started: October 29, 2017

First decision: December 8, 2017

Revised: December 13, 2017

Accepted: December 28, 2017

Article in press: December 28, 2017

Published online: February 8, 2018

Abstract

Kawasaki disease (KD) is a common medium vessel systemic vasculitis that usually occurs in small children. It has a predilection for the coronary arteries, but other medium sized arteries can also be involved. The etiology of this disorder remains a mystery. Though typical presentation of KD is quite characteristic, it may also present as incomplete or atypical disease in which case the diagnosis can be very challenging. As both incomplete and atypical forms of KD can be associated with serious coronary artery complications, the pediatrician can ill afford to miss these diagnoses. The American Heart Association has enunciated consensus guidelines to facilitate the clinical diagnosis and treatment of this condition. However, there are still several issues that remain controversial. Intravenous immunoglobulin remains the cornerstone of management but several other treatment modalities, especially glucocorticoids, are increasingly finding favour. We review here some of the contemporary issues, and the controversies thereon, pertaining to management of KD.

Key words: Kawasaki disease; Diagnosis; Intravenous immunoglobulin; Treatment; Controversies

© The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The diagnosis of Kawasaki disease poses several challenges for the treating pediatricians as it is based on a set of criteria that are entirely clinical. To further complicate matters, several children present with incomplete and atypical forms of the disease. It is known that children with incomplete and atypical Kawasaki disease do not have milder form of the disease, rather the rate of coronary and non-coronary complications may even be higher in these subgroups as the diagnosis often gets delayed. While intravenous immunoglobulin

remains the cornerstone of management, several children require additional form of therapy thereby further challenging the clinical skills and judgment of the pediatricians.

Pilania RK, Bhattarai D, Singh S. Controversies in diagnosis and management of Kawasaki disease. *World J Clin Pediatr* 2018; 7(1): 27-35 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i1/27.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i1.27>

WHAT IS KAWASAKI DISEASE?

Kawasaki disease (KD) is the most common medium vessel vasculitis and usually affects young children. It has a special predilection for coronary arteries^[1,2]. KD is now the leading cause of pediatric acquired heart disease in developed countries like Japan, Korea and Taiwan as also in countries in North America and Europe. In several resource poor countries (e.g., India, China) as well, KD is now being increasingly reported^[3]. However, anecdotal evidence suggests that many children still remain undiagnosed and untreated in such settings^[4]. The etiology of KD remains an enigma^[5,6].

This disease was first recognized in 1961 by Dr. Tomisaku Kawasaki based on a constellation of clinical signs and symptoms and he reported it in 1967 as "muco-cutaneous lymph node syndrome"^[7]. Since then it has been reported from all continents. Even though the initial description of KD was given more than 50 years ago, the diagnosis still remains clinical and there is no laboratory test that can confirm a clinical diagnosis of KD^[8].

DIAGNOSIS OF KD

Diagnosis of KD is essentially based on a constellation of clinical signs and symptoms and supported by laboratory investigations^[8-12]. It cannot be overemphasized that there is no pathognomonic laboratory test for diagnosis of KD. A careful and meticulous history from parents, or documented clinical findings by a physician who has seen the child previously, may be useful in facilitating a diagnosis of KD^[13].

The diagnostic criteria for KD have been modified from time to time. There are two sets of diagnostic criteria that have been used most frequently for diagnosis of KD. These included the Kawasaki Disease Research Committee guidelines [Japanese Ministry of Health (JMH) guidelines], 2002^[14] and the American Heart Association (AHA) guidelines^[1,13]. AHA guidelines were published in 2004 and have been widely used since then^[1]. McCrindle *et al.*^[13] have recently published the AHA 2017 revised guidelines for diagnosis and management of KD. These criteria are based on clinical findings and do not differ significantly from the original descriptions of cases of

KD given by Dr. Kawasaki himself in 1967^[7].

Complete KD

The AHA 2017 have proposed a set of diagnostic criteria for complete KD (Table 1)^[13]. Fever is the most common presenting clinical manifestation and is seen in nearly all patients. While fever is essential for the diagnosis of KD as per AHA criteria but according to the Japanese criteria, fever need not be present in all patients (Table 2)^[14]. The duration of fever in KD is variable and is usually less than 2 wk but may persist for much longer periods of time. Clinical manifestations of KD evolve over days and many signs and symptoms may have disappeared by the time the patient seeks medical attention. This issue has been clearly highlighted in the recent AHA 2017 guidelines (Table 3)^[13].

Incomplete KD and atypical KD

The diagnosis of KD can test the clinical acumen of even an astute physician. The signs and symptoms of KD are nonspecific and may overlap with those of infectious diseases seen in young children^[2]. Adding to this challenge are patients with KD who do not fulfill the diagnostic criteria. A diagnosis of incomplete KD is usually made when there is ongoing fever but less than four clinical features^[13]. In such cases the attending pediatrician has to do a thorough clinical assessment and look at supportive laboratory investigations. Incomplete KD is common in infants (especially in babies below 6 mo) and young children. On the other hand, atypical KD is said to be present when there are atypical manifestations, as for instance nephritis^[15,16], pneumonia^[17], arthritis^[18], myositis^[19,20], uveitis^[21], retinal vasculitis^[22,23] and CNS involvement^[24,25]. Incomplete or atypical forms of KD should by no means be considered as mild KD because the risk of coronary abnormalities in these patients is comparable with, if not higher than, classic KD. This fact cannot be overemphasized^[26-29].

Important clinical signs not included in the diagnostic criteria

There are several manifestations that are not included in the diagnostic criteria but may provide important clues towards diagnosis of KD. Perineal desquamation is one such clinical sign. It usually appears a few days prior to the appearance of periungual desquamation and may provide the initial clinical clue^[30-32]. Similarly, reactivation of the Bacillus Calmette-Guérin (BCG) injection site is a pathognomonic clinical sign of KD and is almost exclusively observed in infants^[33-36]. However, this has not been given enough consideration in the diagnostic criteria. Reason for this may be that many developed countries are not using BCG vaccine as a routine. Sterile pyuria^[37,38], peripheral arthritis^[18] and gall bladder hydrops^[39,40] are other important indicators of KD. Extreme irritability, out of proportion to the fever, is often observed in young children with KD and may be a prominent clinical finding-but this too does not find a mention in the diagnostic criteria^[41,42].

Table 1 American Heart Association guidelines for diagnosis of Kawasaki disease (2017)^[13]**Classic KD is diagnosed with fever persisting for least 5 d**

At least four of the five principal clinical features:

Changes in lips and oral cavity: Erythema, lips cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosae

Changes in extremities

Acute: Erythema of palms, soles; edema of hands, feet

Subacute: Periungual peeling of fingers and toes in weeks 2 and 3

Polymorphous exanthema (diffuse maculopapular, urticarial, erythroderma, erythema-multiforme like, not vesicular or bullous)

Bilateral bulbar conjunctival injection without exudates

Cervical lymphadenopathy (> 1.5 cm diameter), usually unilateral

A careful history may reveal that ≥ 1 principal clinical features were present during the illness but resolved by the time of presentation

Exclusion of other diseases with similar findings (*e.g.*, scarlet fever, viral infections like measles, adenovirus, enterovirus, Stevens-Johnson syndrome, toxic shock syndrome, drug hypersensitivity reactions, systemic juvenile idiopathic arthritis)

KD: Kawasaki disease.

Table 2 Kawasaki Disease Research Committee guidelines (Japanese Ministry of Health guidelines) for diagnosis of Kawasaki disease (2002)^[14]**Five of the following six criteria**

Fever persisting ≥ 5 d

Bilateral conjunctival congestion

Changes of lips and oral cavity

Polymorphous exanthema

Changes of peripheral extremities

Acute non-purulent cervical lymphadenopathy

CONTROVERSIES IN DIAGNOSIS OF KD**Infections and KD**

KD should be considered as a diagnostic possibility in all children with fever more than 5 d for which there is no discernable cause^[13]. KD is more common in young children and 80% of patients are under 5. This is the age group wherein viral infections are also common. Some of the clinical features of KD (*e.g.*, conjunctival injection, rash and cervical lymphadenopathy) are also a common feature of viral illnesses like measles^[43], rubella^[32], adenoviral^[44,45], and enteroviral infections^[13,44]. It is, therefore, not difficult to understand why KD can be confused with a viral illness. There are, however, some clinical features that can help in this differentiation. Children with KD usually do not have rhinorrhea or conjunctival discharge, in contrast to patients with viral infections^[46]. They are also often very irritable. Edema over dorsum of hands and feet and the characteristic desquamation (perianal in first few days and periungual after days 10-12) is typical of KD but these findings are not there in all patients and can be easily missed if not looked for carefully^[46,47]. However, the picture gets further complicated when KD occurs concomitantly with a viral infection as is sometimes the case^[13,44].

One of the closest mimics of KD is scarlet fever. However, involvement of the lips and presence of conjunctival injection are features that are seen in KD but not in scarlet fever. Further, the fever in children with scarlet fever responds briskly to antimicrobials^[48].

KD in infants

Diagnosis of KD in infants is a challenging exercise for physicians and delays in diagnosis in this age group are not uncommon. KD in infants often does not fulfil the standard diagnostic criteria. KD may be incomplete in a large proportion of patients in this age group^[13]. Morbidity and mortality in this age group is highest compared to any other age group^[13,49]. Fever and excessively irritability may be the only clinical manifestations of KD in babies below 6 mo and such presentations can pose several difficult questions for the attending pediatrician. Delays in diagnosis are common in such situations. Young infants are said to be at highest risk of developing coronary artery abnormalities. The presence of fever and pyuria in an infant can be mistakenly attributed to a urinary tract infection. This is not uncommon in our experience. Other clinical features of KD (*e.g.*, rash, red eyes, and red lips) may then be ascribed to an adverse drug reaction to antimicrobials that are often given in such situations. Salgado *et al.*^[50] have reiterated these facts in their recent publication on KD in infants below 6 mo. Our experience is also similar^[51]. It is easy to understand why the diagnosis (and consequently the treatment) of KD gets delayed in these circumstances. Unfortunately, such delays can have disastrous consequences in the baby.

As per the recent AHA 2017 guidelines, the diagnosis of KD in infants may be considered in the following situations^[13]: (1) Infants < 6 mo old with prolonged fever and irritability; (2) infants with prolonged fever and unexplained aseptic meningitis; (3) infants or children with prolonged fever and unexplained or culture-negative shock; (4) infants or children with prolonged fever and cervical lymphadenitis unresponsive to antibiotic therapy; (5) infants or children with prolonged fever and retropharyngeal or parapharyngeal phlegmon unresponsive to antibiotic therapy.

KD in older children and adolescents

Diagnosis in older children and adolescents is difficult because KD is rarely kept as differential diagnosis by adult physicians. As the diagnosis usually gets delayed

Table 3 Salient differences between American Heart Association 2004 and 2017 criteria^[1,13]

Duration of fever	In the presence of ≥ 4 principal clinical features, particularly when redness and swelling of the hands and feet are present, KD can be diagnosed even with 4 d of fever
History	Presence of one or more principal clinical manifestations of disease that can be revealed on history but have disappeared by the time of presentation, have been considered important for diagnosis
KD shock syndrome	KDSS has been given special consideration in the 2017 revised guidelines because in the presence of shock the diagnosis of KD is often not considered
KD in infants	Clinicians should have a lower threshold for diagnosis of KD in this age group
Incomplete KD	Algorithm for incomplete KD has been simplified
KD and infections	The issue of infections and KD has been detailed at length. Diagnosis of KD must not be excluded even in the presence of a documented infection when typical clinical features of KD are present
Bacterial lymphadenitis	Ultrasonography and computed tomography findings in differentiating the 2 conditions- bacterial lymphadenitis is often single and has a hypoechoic core on ultrasonography, while lymphadenopathy in KD is usually multiple and is associated with retropharyngeal edema or phlegmon
2D-echocardiography	The limitations of echocardiography and other diagnostic modalities have been highlighted. Z-score (by Manlihot <i>et al</i>) for severity classification of coronary artery abnormalities has been adapted

KD: Kawasaki disease; KDSS: Kawasaki disease shock syndrome.

in these children, there is higher risk of coronary artery abnormalities^[52,54]. Further, echocardiographic coronary artery assessment in this group of patients is difficult because of the thick chest wall^[55].

Clinical consequences of missed KD can present as coronary ischemia in early adulthood^[56,57]. Due to lack of adequate awareness amongst adult cardiologists, such patients may never get recognized as having had late complications due to missed childhood KD^[57].

KD shock syndrome

Myocarditis is nearly universal in acute phase of KD and, at times, it can be severe and symptomatic^[58,59]. These patients are usually admitted in intensive care units with cardiovascular collapse and may be mistakenly treated for bacterial sepsis and septic shock^[13,60,61]. As a result, the diagnosis of KD gets delayed and this can have serious consequences. Such patients are at high risk of developing coronary artery abnormalities, intravenous immunoglobulin (IVIg) resistance and myocardial dysfunction^[62]. It is, therefore, prudent to keep a differential diagnosis of KD in all children presenting with seemingly obscure myocardial dysfunction and shock. A presumptive diagnosis of viral myocarditis / septic shock in the intensive care setting should have a differential diagnosis of KD. It is for these, and many other, reasons that KD shock syndrome (KDSS) has been given special consideration in the AHA 2017 revised guidelines^[13].

Laboratory investigations may not always be corroborative

There is no single laboratory test for confirmation of diagnosis of KD. Laboratory markers rarely provide conclusive evidence for diagnosis of KD. Clinical laboratory investigation may be used to support the diagnosis of KD, especially in children with incomplete or atypical KD and to assess the intensity of inflammation. Thrombocytopenia in acute stage of KD can be a marker of macrophage activation syndrome^[13,63]. Low platelet count has also been found to correlate with development of coronary aneurysms and such patients often have severe forms of the disease^[62].

N terminal pro-B-type natriuretic peptide (NT-pro-BNP) is a cardiac biomarker and has been found to be significantly elevated during acute stage of KD when compared to febrile controls^[64]. There are age based Pro-BNP nomograms to help the treating physician in differentiating KD from other febrile illnesses^[65]. The values are higher in patients who develop coronary artery abnormalities as compared to those with normal coronaries. Thus it has both diagnostic and prognostic implications. Level of ProBNP is also correlated with myocardial dysfunction in acute stage of KD^[66].

CONTROVERSIES IN IMAGING STUDIES IN KD

Role of 2D-echocardiography in KD

2D-echocardiography is an essential component of the diagnostic work-up in children with KD. It is a useful tool to assess the status of coronary arteries and other cardiac structures during acute stage as well as on follow-up^[13,55,67]. It is important to bear in mind, however, that a negative echocardiographic examination does not rule out KD. However, from the perspective of a developing country, there are several issues with regard to this investigation. It cannot be overemphasized that the quality of scans obtained on echocardiography is operator dependent. This investigation has significant inter-observer variability and needs expertise and patience, especially in infants and young children^[10]. Artifacts pose an important problem and these can make the examination exceptionally difficult, especially when the left circumflex or right coronary artery is being scanned^[55]. In developing countries like India there is a dearth of trained pediatric cardiologists. As a result, the investigation may be carried out by an adult cardiologist, who may not have the requisite expertise to assess the coronary arteries especially in young infants. It comes as no surprise that echocardiography reports are often incomplete and inaccurate in clinical practice, especially in developing countries^[10].

Table 4 Coronary artery abnormalities severity classification in different guidelines

Criteria	Description
JMH criteria ^[14]	Aneurysm definition < 5 yr - ID > 3 mm ≥ 5 yr - ID > 4 mm
Updated JMH (2008) ^[93]	Small aneurysm (dilatation with ID < 4 mm or if child is ≥ 5 yr of age, ID ≤ 1.5 times that of an adjacent segment) Medium aneurysm (dilatation with ID > 4 mm but ≤ 8 mm or if child is ≥ 5 yr of age, ID 1.5 to 4 times that of an adjacent segment) Large aneurysm (dilatation with ID > 8 mm or if child is ≥ 5 yr of age, ID > 4 times that of an adjacent segment)
AHA 2004 criteria ^[1]	Aneurysm ID z score > 2.5 (as per body surface area adjusted z scores) Small: < 5 mm Medium: 5 to 8 mm Giant aneurysm: > 8 mm based on absolute diameter
AHA 2017 criteria (Manlhiot <i>et al</i>) ^[13,68]	No involvement (Z score < 2) Dilation only (Z score 2 to < 2.5; or if initially < 2, a decrease in Z score during follow-up ≥ 1 thereby suggesting that coronary artery was dilated during acute stage though diameter was within normal standards and the diameter has regressed on follow-up) Small aneurysm (Z score ≥ 2.5 to < 5) Medium aneurysm (Z score ≥ 5 to < 10, and absolute dimension < 8 mm) Large or giant aneurysm (≥ 10, or absolute dimension ≥ 8 mm)

ID: Internal diameter; AHA: American Heart Association; JMH: Japanese Ministry of Health.

The Japanese Ministry of Health has enunciated criteria for defining coronary involvement in KD on the basis of absolute dimension of internal diameter of coronary artery^[14]. McCrindle *et al*^[13] and Manlhiot *et al*^[68] have proposed the classification scheme based on z score for severity of coronary artery abnormalities, which has been adapted and recommended by AHA 2017 guidelines (Table 4). It is mandatory that body surface area-adjusted 'Z' scores be used to grade the severity of coronary artery involvement so that objectivity can be maintained and results can be compared with other studies^[13]. Echocardiography findings in KD other than coronary artery ectasia, dilatation and aneurysm, include lack of tapering of coronary arteries, myocardial dysfunction, pericardial effusion, aortic root dilatation and valvular regurgitation^[13,55,59]. As myocarditis is almost universal, functional abnormalities are likely to be more in acute stage of KD^[58]. An echocardiography examination should be done at diagnosis and, if normal, should be repeated on a daily basis for the next few days. Repeat echocardiography should be carried out 1-2 wk later and then at 4-6 wk. A normal echocardiography examination during the first week of illness does not rule out the development of coronary artery aneurysms later. Echocardiography should be repeated more frequently in children who have coronary artery z-scores > 2^[13]. Recent literature suggests that follow-up echocardiography examination should include assessment of myocardial functions in addition to assessment of coronary arteries^[69].

Computerized tomography coronary angiography in KD

While 2-dimensional echocardiography remains the imaging modality of choice to identify coronary artery abnormalities, it is subject to several fallacies and is operator dependent. Computerized tomography

(CT) coronary angiography is rapidly emerging as a useful imaging modality for better characterization of dilatations, ectasia and aneurysms especially in the mid- and distal segments of coronary arteries. It provides precise details in terms of aneurysm size and morphology^[70]. The limiting factor in more widespread use of this investigation hitherto was the high radiation exposure and therefore its application in children was rather limited. Over the last 5 years, with the advent of higher detector and dual-source CT scanners (DSCT), it is possible to delineate the coronary artery anatomy with higher temporal resolution and motion-free images at all heart rates with acceptable radiation risk^[70]. CT coronary angiography can detect dilatations, ectasia and aneurysms in the mid and distal segments of coronary arteries with precise details in terms of aneurysm size and morphology. In the convalescent phase, it also can be used to delineate complications like segmental stenosis, intra-aneurysmal thrombus and mural calcifications.

Magnetic resonance coronary angiography

Magnetic resonance (MR) is useful in evaluation of coronary artery lesions and myocardial involvement in all stages of KD. The main advantage of MR is that there is no radiation exposure. However, young children would often need to be sedated and the procedure is time consuming. Interpretation of MR images requires a lot of expertise and skill^[71,72].

CONTROVERSIES IN MANAGEMENT OF KD

Treatment of KD is yet another challenging and controversial issue. Prompt treatment of KD is absolutely

essential if one is to avoid the chances of development of CAA^[11,13]. Intravenous immunoglobulin (IVIG) remains the standard of care based on objective evidence collated from prospective studies and meta-analyses^[13]. However, there are still several controversies regarding management of children with KD.

Acute phase management

IVIG: For IVIG to be most effective, it should be given in the first few days of the illness^[73]. However, if the child presents after day 10 of fever, IVIG should still be given if the acute inflammatory parameters are high^[73]. Though there are recent meta-analyses stating similar outcomes of KD treatment at different doses of IVIG, a dose of 2 gm/kg administered intravenously is the preferred option^[13,74]. It has also been suggested that administration of IVIG before day 5 of fever may inadvertently increase the need for further IVIG therapy and also increase the chances of developing a refractory state^[75].

Aspirin: Though aspirin is a widely used anti-inflammatory agent in KD and is given along with IVIG, its efficacy remains questionable as there is no proof that addition of aspirin in the acute phase significantly decreases the chances of development of coronary artery abnormalities^[76].

Most clinicians prefer to use aspirin in doses of 30-50 mg/kg during the acute phase of KD. Duration of aspirin therapy is another controversial issue^[77,78]. Some centres prefer to continue it for 2 wk irrespective of fever status but consensus is rapidly evolving over continuing it only for febrile phase and then to change to a low dose (3 to 5 mg/kg per day) for its anti-platelet effect^[79]. This low dose is then continued for 6-8 wk and is stopped if follow-up echocardiographic examination is normal. Aspirin is continued indefinitely if there is persistence of CAA^[13].

Corticosteroid therapy in acute phase: Kato *et al*^[80] reported that administration of steroids during the acute phase of KD resulted in increased incidence of CAA. But it is now argued that these results were due to the confounding factor of steroids having been given to children who were sicker than the other group^[81]. Kobayashi *et al*^[82] have recently published their study on use of steroids with IVIG and found that steroids may be useful in acute phase of KD.

Recent AHA guidelines do not support for administration of methylprednisolone pulses simultaneously with IVIG therapy but suggest possible benefit of 2-3 wk tapering steroid therapy along with IVIG and aspirin doses^[13]. Upfront steroid therapy may be considered only for patients with KD who are proven to be IVIG resistant or presenting with significant CAA^[10,46]. The choice of steroid is usually intravenous methylprednisolone pulse followed by tapering dose of oral prednisolone^[13].

Refractory KD

Almost one-tenth patients with KD may be refractory

to primary IVIG therapy. In such conditions, fever will continue to appear even after more than 36 to 48 h of IVIG therapy. There is no consensus on management protocols to be followed in such patients. AHA guidelines emphasize use of a repeat dose of IVIG (2 mg/kg) in this subgroup. Alternatively, the guidelines reiterate the role of 3 doses of methylprednisolone with tapering prednisolone^[13]. Infliximab, given as a single dose of 5-6 mg/kg intravenously, is also very useful in treatment of refractory KD and appears to decrease the chances of developing CAA^[83]. Administration of infliximab often results in prompt reduction of fever^[84,85]. Tremoulet *et al*^[86] have shown that addition of infliximab in the primary treatment regimen did not reduce the incidence of IVIG resistant KD. However, fever duration, inflammatory markers and reaction rate were less in the infliximab group. There are various ongoing randomized trials to assess the efficacy of anti-TNF drugs. Plasma exchange has also been found to be helpful in patients with intractable KD^[87,88]. Other therapeutic options that are being considered includes interleukin-1 antagonist (*e.g.*, anakinra), cyclosporine, and tacrolimus, *etc*^[89-91].

For the preventing of thrombosis, low dose aspirin remains the first choice of therapy. If the patients show evidence of rapidly expanding CAA, heparin or warfarin anticoagulation along with aspirin can be given^[13]. Aspirin with another antiplatelet agent along with systemic anticoagulant agent like heparin or warfarin may be considered for patients with history of coronary thrombosis or giant aneurysm^[79]. Thrombolytic treatment or coronary recanalization procedures may be required for the minority of patients who develop coronary thrombosis in the context of KD. Abciximab is also useful in such patients^[13].

Management after acute phase

Risk stratification of coronary artery abnormalities is of primary importance for the long term follow-up and management of patients with KD. It is our practice to keep all children with KD on long term follow-up, because there is some concern regarding development of premature atherosclerosis even in children who do not have overt CAA during the acute phases^[92,93]. Healthy lifestyle and an active physical regimen should be emphasized upon.

Patients with coronary dilatation that persists beyond 6 wk need to be kept on low dose aspirin for longer periods of time. For patients with large and giant aneurysms, frequent echocardiographic assessment should be continued. Such patients may also require CT coronary angiography at periodic (say 3-5 yearly) intervals. Statins have also been recommended in these situations. Thromboprophylaxis can be maintained with antiplatelet drugs (*e.g.*, aspirin/dipyridamol used singly or in combination) and anticoagulants (*e.g.*, heparin/warfarin)^[13].

To conclude KD is now one of the most common causes for acquired heart disease in children and all pediatricians need to be familiar with its varied clinical

presentations. With some experience it is not difficult to pick up children with classic KD. However, the diagnosis of children with incomplete and atypical KD can pose significant issues for the attending pediatrician. The recent AHA 2017 guidelines have suggested a simplified management protocol for children with KD. Therapies other than IVIG are now being increasingly used in these patients.

REFERENCES

- 1 Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, Shulman ST, Bolger AF, Ferrieri P, Baltimore RS, Wilson WR, Baddour LM, Levison ME, Pallasch TJ, Falace DA, Taubert KA; Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease; Council on Cardiovascular Disease in the Young; American Heart Association; American Academy of Pediatrics. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004; **110**: 2747-2771 [PMID: 15505111 DOI: 10.1161/01.CIR.0000145143.19711.78]
- 2 Rowley AH. The Complexities of the Diagnosis and Management of Kawasaki Disease. *Infect Dis Clin North Am* 2015; **29**: 525-537 [PMID: 26154665 DOI: 10.1016/j.idc.2015.05.006]
- 3 Singh S, Aulakh R, Kawasaki T. Kawasaki disease and the emerging coronary artery disease epidemic in India: is there a correlation? *Indian J Pediatr* 2014; **81**: 328-332 [PMID: 24072580 DOI: 10.1007/s12098-013-1229-y]
- 4 Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. *Arch Dis Child* 2015; **100**: 1084-1088 [PMID: 26111818 DOI: 10.1136/archdischild-2014-307536]
- 5 Burgner D, Harnden A. Kawasaki disease: what is the epidemiology telling us about the etiology? *Int J Infect Dis* 2005; **9**: 185-194 [PMID: 15936970 DOI: 10.1016/j.ijid.2005.03.002]
- 6 Rowley AH. Kawasaki disease: novel insights into etiology and genetic susceptibility. *Annu Rev Med* 2011; **62**: 69-77 [PMID: 20690826 DOI: 10.1146/annurev-med-042409-151944]
- 7 Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. *Aterugi* 1967; **16**: 178-222 [PMID: 6062087]
- 8 Singh S, Kawasaki T. Kawasaki Disease in India, Lessons Learnt Over the Last 20 Years. *Indian Pediatr* 2016; **53**: 119-124 [PMID: 26897142 DOI: 10.1007/s13312-016-0804-5]
- 9 Gupta A, Singh S. Kawasaki disease for dermatologists. *Indian Dermatol Online J* 2016; **7**: 461-470 [PMID: 27990380 DOI: 10.4103/2229-5178.193903]
- 10 Singh S, Sharma A, Jiao F. Kawasaki Disease: Issues in Diagnosis and Treatment--A Developing Country Perspective. *Indian J Pediatr* 2016; **83**: 140-145 [PMID: 26400032 DOI: 10.1007/s12098-015-1890-4]
- 11 Newburger JW, Takahashi M, Burns JC. Kawasaki Disease. *J Am Coll Cardiol* 2016; **67**: 1738-1749 [PMID: 27056781 DOI: 10.1016/j.jacc.2015.12.073]
- 12 Scuccimarri R. Kawasaki disease. *Pediatr Clin North Am* 2012; **59**: 425-445 [PMID: 22560578 DOI: 10.1016/j.pcl.2012.03.009]
- 13 McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, Kobayashi T, Wu MH, Saji TT, Pahl E; American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention. Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. *Circulation* 2017; **135**: e927-e999 [PMID: 28356445 DOI: 10.1161/CIR.0000000000000484]
- 14 Ayusawa M, Sonobe T, Uemura S, Ogawa S, Nakamura Y, Kiyosawa N, Ishii M, Harada K; Kawasaki Disease Research Committee. Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). *Pediatr Int* 2005; **47**: 232-234 [PMID: 15771703 DOI: 10.1111/j.1442-200x.2005.02033.x]
- 15 Veiga PA, Pieroni D, Baier W, Feld LG. Association of Kawasaki disease and interstitial nephritis. *Pediatr Nephrol* 1992; **6**: 421-423 [PMID: 1457322 DOI: 10.1007/BF00873999]
- 16 Chuang GT, Tsai IJ, Lin MT, Chang LY. Acute kidney injury in patients with Kawasaki disease. *Pediatr Res* 2016; **80**: 224-227 [PMID: 27064240 DOI: 10.1038/pr.2016.81]
- 17 Singh S, Gupta A, Jindal AK, Gupta A, Suri D, Rawat A, Vaidya PC, Singh M. Pulmonary presentation of Kawasaki disease-A diagnostic challenge. *Pediatr Pulmonol* 2018; **53**: 103-107 [PMID: 28950425 DOI: 10.1002/ppul.23885]
- 18 Gong GW, McCrindle BW, Ching JC, Yeung RS. Arthritis presenting during the acute phase of Kawasaki disease. *J Pediatr* 2006; **148**: 800-805 [PMID: 16769390 DOI: 10.1016/j.jpeds.2006.01.039]
- 19 Agarwal S, Gupta A, Suri D, Rawat A, Singh S. Proximal Muscle Weakness in a Child with Kawasaki Disease. *Indian J Pediatr* 2015; **82**: 866 [PMID: 25680785 DOI: 10.1007/s12098-015-1709-3]
- 20 Lee EY, Oh JY, Chong CY, Choo JT, Mahadev A, Tan NW. A Case of Atypical Kawasaki Disease With Myositis. *Glob Pediatr Health* 2015; **2**: 2333794X15599649 [PMID: 27335976 DOI: 10.1177/233794X15599649]
- 21 Madhusudan S, Singh S, Suri D, Gupta A, Gupta A. Acute anterior uveitis as the presenting feature of Kawasaki disease. *Indian J Pediatr* 2014; **81**: 415 [PMID: 24562721 DOI: 10.1007/s12098-014-1367-x]
- 22 Agarwal S, Mulkutkar S, Suri D, Singh S, Gupta A. Retinal Vasculitis in Kawasaki Disease. *Indian J Pediatr* 2015; **82**: 1183-1184 [PMID: 25990595 DOI: 10.1007/s12098-015-1763-x]
- 23 Font RL, Mehta RS, Streusand SB, O'Boyle TE, Kretzer FL. Bilateral retinal ischemia in Kawasaki disease. Postmortem findings and electron microscopic observations. *Ophthalmology* 1983; **90**: 569-577 [PMID: 6877786 DOI: 10.1016/S0161-6420(83)34522-X]
- 24 Wright H, Waddington C, Geddes J, Newburger JW, Burgner D. Facial nerve palsy complicating Kawasaki disease. *Pediatrics* 2008; **122**: e783-e785 [PMID: 18678602 DOI: 10.1542/peds.2007-3238]
- 25 Martínez-Guzmán E, Gámez-González LB, Rivas-Larrauri F, Sorcia-Ramírez G, Yamazaki-Nakashimada M. Neurological manifestations in atypical Kawasaki disease. *Rev Alerg Mex* 2017; **64**: 376-380 [PMID: 29046034]
- 26 Vignesh P, Bhattad S, Singhal M, Singh S. A 5-year-old boy with only fever and giant coronary aneurysms: the enigma of Kawasaki disease? *Rheumatol Int* 2016; **36**: 1191-1193 [PMID: 27154559 DOI: 10.1007/s00296-016-3490-7]
- 27 Maric LS, Knezovic I, Papic N, Mise B, Roglic S, Markovinovic L, Tesovic G. Risk factors for coronary artery abnormalities in children with Kawasaki disease: a 10-year experience. *Rheumatol Int* 2015; **35**: 1053-1058 [PMID: 25429794 DOI: 10.1007/s00296-014-3186-9]
- 28 Perrin L, Letierce A, Guittion C, Tran TA, Lambert V, Koné-Paut I. Comparative study of complete versus incomplete Kawasaki disease in 59 pediatric patients. *Joint Bone Spine* 2009; **76**: 481-485 [PMID: 19811939 DOI: 10.1016/j.jbspin.2008.11.015]
- 29 Sonobe T, Kiyosawa N, Tsuchiya K, Aso S, Imada Y, Imai Y, Yashiro M, Nakamura Y, Yanagawa H. Prevalence of coronary artery abnormality in incomplete Kawasaki disease. *Pediatr Int* 2007; **49**: 421-426 [PMID: 17587261 DOI: 10.1111/j.1442-200X.2007.02396.x]
- 30 Chao SM, Phua KB. Perineal eruption as an early sign of Kawasaki disease. *Ann Acad Med Singapore* 1991; **20**: 244-247 [PMID: 1883184]
- 31 Isidori C, Sebastiani L, Cardellini MC, Di Cara G, Rigante D,

- Esposito S. Early Desquamating Perineal Erythema in a Febrile Infant: A Characteristic Clinical Feature of Kawasaki Disease. *Int J Environ Res Public Health* 2017; **14**: E710 [PMID: 28665334 DOI: 10.3390/ijerph14070710]
- 32 **Falcini F**, Ozen S, Magni-Manzoni S, Candelli M, Ricci L, Martini G, Cuttica RJ, Oliveira S, Calabri GB, Zulian F, Pistorio A, La Torre F, Rigante D. Discrimination between incomplete and atypical Kawasaki syndrome versus other febrile diseases in childhood: results from an international registry-based study. *Clin Exp Rheumatol* 2012; **30**: 799-804 [PMID: 23020938]
- 33 **Gamez-Gonzalez LB**, Hamada H, Llamas-Guillen BA, Ruiz-Fernandez M, Yamazaki-Nakashimada M. BCG and Kawasaki disease in Mexico and Japan. *Hum Vaccin Immunother* 2017; **13**: 1091-1093 [PMID: 28281896 DOI: 10.1080/21645515.2016.1267083]
- 34 **Garrido-García LM**, Castillo-Moguel A, Vázquez-Rivera M, Cravioto P, Fernando G. Reaction of the BCG Scar in the Acute Phase of Kawasaki Disease in Mexican Children. *Pediatr Infect Dis J* 2017; **36**: e237-e241 [PMID: 28498302 DOI: 10.1097/INF.0000000000001633]
- 35 **Rezai MS**, Shahmohammadi S. Erythema at BCG Inoculation Site in Kawasaki Disease Patients. *Mater Sociomed* 2014; **26**: 256-260 [PMID: 25395889 DOI: 10.5455/msm.2014.26.256-260]
- 36 **Kumar A**, Singh S. BCG Site Reactivation in Kawasaki Disease. *Arthritis Rheumatol* 2016; **68**: 2026 [PMID: 27059401 DOI: 10.1002/art.39708]
- 37 **Watanabe T**. Pyuria in patients with Kawasaki disease. *World J Clin Pediatr* 2015; **4**: 25-29 [DOI: 10.5409/wjcp.v4.i2.25]
- 38 **Choi JY**, Park SY, Choi KH, Park YH, Lee YH. Clinical characteristics of Kawasaki disease with sterile pyuria. *Korean J Pediatr* 2013; **56**: 13-18 [PMID: 23390440 DOI: 10.3345/kjp.2013.56.1.13]
- 39 **Sun Q**, Zhang J, Yang Y. Gallbladder Hydrops Associated With Kawasaki Disease: A Case Report and Literature Review. *Clin Pediatr (Phila)* 2017; 9922817696468 [PMID: 28952362 DOI: 10.1177/0009922817696468.]
- 40 **Mathai SS**, Kulkarni VB, Harsh P. Gall bladder hydrops - a rare initial presentation of Kawasaki disease. *Indian J Pediatr* 2013; **80**: 616-617 [PMID: 23180399 DOI: 10.1007/s12098-012-0890-x]
- 41 **Thapa R**, Chakrabartty S. Atypical Kawasaki disease with remarkable paucity of signs and symptoms. *Rheumatol Int* 2009; **29**: 1095-1096 [PMID: 19381640 DOI: 10.1007/s00296-009-0899-2]
- 42 **Golshevsky D**, Cheung M, Burgner D. Kawasaki disease--the importance of prompt recognition and early referral. *Aust Fam Physician* 2013; **42**: 473-476 [PMID: 23826599]
- 43 **Hu P**, Guan Y, Fan XC, Lu FY, Song LM. Incomplete Kawasaki disease induced by measles in a 6-month-old male infant. *Int J Dermatol* 2016; **55**: e34-e36 [PMID: 26518488 DOI: 10.1111/ijd.13122]
- 44 **Chang LY**, Lu CY, Shao PL, Lee PI, Lin MT, Fan TY, Cheng AL, Lee WL, Hu JJ, Yeh SJ, Chang CC, Chiang BL, Wu MH, Huang LM. Viral infections associated with Kawasaki disease. *J Formos Med Assoc* 2014; **113**: 148-154 [PMID: 24495555 DOI: 10.1016/j.jfma.2013.12.008]
- 45 **Fukuda S**, Ito S, Fujiwara M, Abe J, Hanaoka N, Fujimoto T, Katsumori H. Simultaneous development of Kawasaki disease following acute human adenovirus infection in monozygotic twins: A case report. *Pediatr Rheumatol Online J* 2017; **15**: 39 [PMID: 28511718 DOI: 10.1186/s12969-017-0169-x]
- 46 **Singh S**, Newburger JW, Kuijpers T, Burgner D. Management of Kawasaki disease in resource-limited settings. *Pediatr Infect Dis J* 2015; **34**: 94-96 [PMID: 25741801 DOI: 10.1097/INF.0000000000000600]
- 47 **Jindal AK**, Singh S. Dryness at Fingertips: Is It a Premonitory Sign of Skin Peeling in Kawasaki Disease? *J Clin Rheumatol* 2017; **23**: 286 [PMID: 28661924 DOI: 10.1097/RHU.0000000000000519]
- 48 **Cox JR**, Sallis RE. Recognition of kawasaki disease. *Perm J* 2009; **13**: 57-61 [PMID: 21373247 DOI: 10.7812/TPP/08-042]
- 49 **Singh S**, Bhattad S, Gupta A, Suri D, Rawat A, Rohit M. Mortality in children with Kawasaki disease: 20 years of experience from a tertiary care centre in North India. *Clin Exp Rheumatol* 2016; **34**: S129-S133 [PMID: 26633295]
- 50 **Salgado AP**, Ashouri N, Berry EK, Sun X, Jain S, Burns JC, Tremoulet AH. High Risk of Coronary Artery Aneurysms in Infants Younger than 6 Months of Age with Kawasaki Disease. *J Pediatr* 2017; **185**: 112-116.e1 [PMID: 28408126 DOI: 10.1016/j.jpeds.2017.03.025]
- 51 **Singh S**, Agarwal S, Bhattad S, Gupta A, Suri D, Rawat A, Singhal M, Rohit M. Kawasaki disease in infants below 6 months: a clinical conundrum? *Int J Rheum Dis* 2016; **19**: 924-928 [PMID: 26990891 DOI: 10.1111/1756-185X.12854]
- 52 **Kontopoulou T**, Kontopoulos DG, Vaidakis E, Mousoulis GP. Adult Kawasaki disease in a European patient: a case report and review of the literature. *J Med Case Rep* 2015; **9**: 75 [PMID: 25890055 DOI: 10.1186/s13256-015-0516-9]
- 53 **Gupta K**, Rohit M, Sharma A, Nada R, Jain S, Varma S. An Adolescent with Kawasaki Disease. *Indian Pediatr* 2016; **53**: 51-56 [PMID: 26840674 DOI: 10.1007/s13312-016-0791-6]
- 54 **Chen J**, Li Y. Acute Complete Adult-onset Kawasaki Disease in a Middle-Aged Woman. *J Coll Physicians Surg Pak* 2017; **27**: 517-519 [PMID: 28903849]
- 55 **Altman CA**. Clinical assessment of coronary arteries in Kawasaki disease: Focus on echocardiographic assessment. *Congenit Heart Dis* 2017; **12**: 636-640 [PMID: 28921836 DOI: 10.1111/chd.12496]
- 56 **Vijayvergiya R**, Bhattad S, Varma S, Singhal M, Gordon J, Singh S. Presentation of missed childhood Kawasaki disease in adults: Experience from a tertiary care center in north India. *Int J Rheum Dis* 2017; **20**: 1023-1027 [PMID: 28378434 DOI: 10.1111/1756-185X.13073]
- 57 **Waterhouse BR**, Tulloh RMR, Kim Y, Creasy W, Adlam D, Johnson TW. Retrospective study of the impact of unrecognised Kawasaki disease, coronary aneurysm and ectasia. *Int J Cardiol* 2017; **248**: 308-313 [PMID: 28818354 DOI: 10.1016/j.ijcard.2017.08.018]
- 58 **Dahdah N**. Not just coronary arteritis, Kawasaki disease is a myocarditis, too. *J Am Coll Cardiol* 2010; **55**: 1507; author reply 1507-1507; author reply 1508 [PMID: 20359606 DOI: 10.1016/j.jacc.2009.11.067]
- 59 **Hashimoto I**, Saitou Y, Sakata N, Shibata K. Evaluation of longitudinal and radial left ventricular functions using two- and three-dimensional echocardiography before and after intravenous immunoglobulin administration in patients with acute Kawasaki disease. *Pediatr Int* 2017 [PMID: 28892213 DOI: 10.1111/ped.13423]
- 60 **Seaton KK**, Kharbanda A. Evidence-based management of Kawasaki disease in the emergency department. *Pediatr Emerg Med Pract* 2015; **12**: 1-20; quiz 21 [PMID: 25693305]
- 61 **Çakan M**, Gemici H, Aktay-Ayaz N, Keskindemirci G, Bornaun H, İkizoglu T, Çeliker A. Kawasaki disease shock syndrome: a rare and severe complication of Kawasaki disease. *Turk J Pediatr* 2016; **58**: 415-418 [PMID: 28276216 DOI: 10.24953/turkjped.2016.04.012]
- 62 **Xie T**, Wang Y, Fu S, Wang W, Xie C, Zhang Y, Gong F. Predictors for intravenous immunoglobulin resistance and coronary artery lesions in Kawasaki disease. *Pediatr Rheumatol Online J* 2017; **15**: 17 [PMID: 28320400 DOI: 10.1186/s12969-017-0149-1]
- 63 **Dumont B**, Jeannoel P, Trape L, Rolland E, Gay C, Stephan JL. Macrophage activation syndrome and Kawasaki disease: Four new cases. *Arch Pediatr* 2017; **24**: 640-646 [PMID: 28583781 DOI: 10.1016/j.arcped.2017.04.017]
- 64 **Rawat A**, Singh S. Biomarkers for Diagnosis of Kawasaki Disease. *Indian Pediatr* 2015; **52**: 473-474 [PMID: 26121719 DOI: 10.1007/s13312-015-0658-2]
- 65 **Reddy M**, Singh S, Rawat A, Sharma A, Suri D, Rohit MK. Pro-brain natriuretic peptide (ProBNP) levels in North Indian children with Kawasaki disease. *Rheumatol Int* 2016; **36**: 551-559 [PMID: 26849890 DOI: 10.1007/s00296-016-3430-6]
- 66 **Lin K-H**, Chang S-S, Yu C-W, Lin S-C, Liu S-C, Chao H -y.

- Usefulness of natriuretic peptide for the diagnosis of Kawasaki disease: a systematic review and meta-analysis. *BMJ Open* 2015; **5**: e006703-e006703 [PMID: 25872939 DOI: 10.1136/bmjopen-2014-006703]
- 67 **Kothur K**, Singh S, Sharma Y, Mittal BR. Prospective follow-up cardiac evaluation of children with Kawasaki disease in Northern India using the Japanese echocardiography criteria. *J Cardiol* 2007; **50**: 299-307 [PMID: 18044459]
 - 68 **Manlhiot C**, Millar K, Golding F, McCrindle BW. Improved classification of coronary artery abnormalities based only on coronary artery z-scores after Kawasaki disease. *Pediatr Cardiol* 2010; **31**: 242-249 [PMID: 20024653 DOI: 10.1007/s00246-009-9599-7]
 - 69 **Lee H**, Shin J, Eun L. Myocardial Assessment in School-Aged Children with Past Kawasaki Disease. *J Korean Med Sci* 2017; **32**: 1835-1839 [PMID: 28960037 DOI: 10.3346/jkms.2017.32.11.1835]
 - 70 **Singhal M**, Singh S, Gupta P, Sharma A, Khandelwal N, Burns JC. Computed Tomography Coronary Angiography for Evaluation of Children With Kawasaki Disease. *Curr Probl Diagn Radiol* 2017 [PMID: 29203262 DOI: 10.1067/j.cpradiol.2017.09.013]
 - 71 **Takemura A**, Suzuki A, Inaba R, Sonobe T, Tsuchiya K, Omuro M, Korenaga T. Utility of coronary MR angiography in children with Kawasaki disease. *AJR Am J Roentgenol* 2007; **188**: W534-W539 [PMID: 17515343 DOI: 10.2214/AJR.05.1414]
 - 72 **Tacke CE**, Romeih S, Kuipers IM, Spijkerboer AM, Groenink M, Kuijpers TW. Evaluation of cardiac function by magnetic resonance imaging during the follow-up of patients with Kawasaki disease. *Circ Cardiovasc Imaging* 2013; **6**: 67-73 [PMID: 23197079 DOI: 10.1161/CIRCIMAGING.112.976969]
 - 73 **Rowley AH**, Shulman ST. Pathogenesis and management of Kawasaki disease. *Expert Rev Anti Infect Ther* 2010; **8**: 197-203 [PMID: 20109049 DOI: 10.1586/eri.09.109]
 - 74 **Chen J**, Ma B, Lin L-X, Xue Y-M. Treatment of Kawasaki disease by different doses of immunoglobulin: a meta analysis of efficacy and safety. *Transl Pediatr* 2012; **1**: 99-107 [PMID: 4728885 DOI: 10.3978/j.issn.2224-4336.2012.04.05]
 - 75 **Muta H**, Ishii M, Egami K, Furui J, Sugahara Y, Akagi T, Nakamura Y, Yanagawa H, Matsuishi T. Early intravenous gamma-globulin treatment for Kawasaki disease: the nationwide surveys in Japan. *J Pediatr* 2004; **144**: 496-499 [PMID: 15069399 DOI: 10.1016/j.jpeds.2003.12.033]
 - 76 **Terai M**, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. *J Pediatr* 1997; **131**: 888-893 [PMID: 9427895 DOI: 10.1016/S0022-3476(97)70038-6]
 - 77 **Dallaire F**, Fortier-Morissette Z, Blais S, Dhanrajani A, Basodan D, Renaud C, Mathew M, De Souza AM, Dionne A, Blanchard J, Saulnier H, Kaspary K, Rached-d'Astous S, Dahdah N, McCrindle BW, Human DG, Scuccimarri R. Aspirin Dose and Prevention of Coronary Abnormalities in Kawasaki Disease. *Pediatrics* 2017; **139** [PMID: 28562282 DOI: 10.1542/peds.2017-0098]
 - 78 **Ho LGY**, Curtis N. What dose of aspirin should be used in the initial treatment of Kawasaki disease? *Arch Dis Child* 2017; **102**: 1180-1182 [PMID: 29066520 DOI: 10.1136/archdischild-2017-313538]
 - 79 **Zhu FH**, Ang JY. The Clinical Diagnosis and Management of Kawasaki Disease: a Review and Update. *Curr Infect Dis Rep* 2016; **18**: 32 [PMID: 27681743 DOI: 10.1007/s11908-016-0538-5]
 - 80 **Kato H**, Koike S, Yokoyama T. Kawasaki disease: effect of treatment on coronary artery involvement. *Pediatrics* 1979; **63**: 175-179 [PMID: 440805]
 - 81 **Eleftheriou D**, Levin M, Shingadia D, Tulloh R, Klein NJ, Brogan PA. Management of Kawasaki disease. *Arch Dis Child* 2014; **99**: 74-83 [PMID: 24162006 DOI: 10.1136/archdischild-2012-302841]
 - 82 **Kobayashi T**, Saji T, Otani T, Takeuchi K, Nakamura T, Arakawa H, Kato T, Hara T, Hamaoka K, Ogawa S, Miura M, Nomura Y, Fuse S, Ichida F, Seki M, Fukazawa R, Ogawa C, Furuno K, Tokunaga H, Takatsuki S, Hara S, Morikawa A; RAISE study group investigators. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. *Lancet* 2012; **379**: 1613-1620 [PMID: 22405251 DOI: 10.1016/S0140-6736(11)61930-2]
 - 83 **Matsubara T**, Furukawa S, Yabuta K. Serum levels of tumor necrosis factor, interleukin 2 receptor, and interferon-gamma in Kawasaki disease involved coronary-artery lesions. *Clin Immunol Immunopathol* 1990; **56**: 29-36 [PMID: 2113446 DOI: 10.1016/0090-1229(90)90166-N]
 - 84 **Singh S**, Sharma D, Suri D, Gupta A, Rawat A, Rohit MK. Infliximab is the new kid on the block in Kawasaki disease: a single-centre study over 8 years from North India. *Clin Exp Rheumatol* 2016; **34**: S134-S138 [PMID: 27086575]
 - 85 **Burns JC**, Mason WH, Hauger SB, Janai H, Bastian JF, Wofhrley JD, Balfour I, Shen CA, Michel ED, Shulman ST, Melish ME. Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr* 2005; **146**: 662-667 [PMID: 15870671 DOI: 10.1016/j.jpeds.2004.12.022]
 - 86 **Tremoulet AH**, Jain S, Jaggi P, Jimenez-Fernandez S, Pancheri JM, Sun X, Kanegaye JT, Kovalchin JP, Printz BF, Ramilo O, Burns JC. Infliximab for intensification of primary therapy for Kawasaki disease: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet* 2014; **383**: 1731-1738 [PMID: 24572997 DOI: 10.1016/S0140-6736(13)62298-9]
 - 87 **Sonoda K**, Mori M, Hokusaki T, Yokota S. Infliximab plus plasma exchange rescue therapy in Kawasaki disease. *J Pediatr* 2014; **164**: 1128-1132.e1 [PMID: 24560183 DOI: 10.1016/j.jpeds.2014.01.020]
 - 88 **Ebato T**, Ogata S, Ogihara Y, Fujimoto M, Kitagawa A, Takanashi M, Ishii M. The Clinical Utility and Safety of a New Strategy for the Treatment of Refractory Kawasaki Disease. *J Pediatr* 2017; **191**: 140-144 [PMID: 29173297 DOI: 10.1016/j.jpeds.2017.08.076]
 - 89 **Shafferman A**, Birmingham JD, Cron RQ. High dose Anakinra for treatment of severe neonatal Kawasaki disease: a case report. *Pediatr Rheumatol Online J* 2014; **12**: 26 [PMID: 25045337 DOI: 10.1186/1546-0096-12-26]
 - 90 **Sánchez-Manubens J**, Gelman A, Franch N, Teodoro S, Palacios JR, Rudi N, Rivera J, Antón J. A child with resistant Kawasaki disease successfully treated with anakinra: a case report. *BMC Pediatr* 2017; **17**: 102 [PMID: 28390409 DOI: 10.1186/s12887-017-0852-6]
 - 91 **Dusser P**, Koné-Paut I. IL-1 Inhibition May Have an Important Role in Treating Refractory Kawasaki Disease. *Front Pharmacol* 2017; **8**: 163 [PMID: 28400731 DOI: 10.3389/fphar.2017.00163]
 - 92 **JCS Joint Working Group**. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2008)--digest version. *Circ J* 2010; **74**: 1989-2020 [PMID: 20724794 DOI: 10.1253/circj.CJ-10-74-0903]
 - 93 **JCS Joint Working Group**. Guidelines for diagnosis and management of cardiovascular sequelae in Kawasaki disease (JCS 2013). Digest version. *Circ J* 2014; **78**: 2521-2562 [PMID: 25241888 DOI: 10.1253/circj.CJ-66-0096]

P- Reviewer: Al-Haggag L, Gonzalez-Granado L **S- Editor:** Cui LJ
L- Editor: A **E- Editor:** Li RF



Review of the evidence for the management of co-morbid Tic disorders in children and adolescents with attention deficit hyperactivity disorder

Michael O Ogundele, Hani F Ayyash

Michael O Ogundele, Department of Community Paediatrics, NHS Fife, Glenwood Health Centre, Glenrothes KY6 1HK, United Kingdom

Hani F Ayyash, Cambridgeshire and Peterborough NHS Foundation Trust, Peterborough Integrated Neurodevelopmental Service, University of Cambridge Health Partners, Cambridge CB21 5EF, United Kingdom

ORCID number: Michael O Ogundele (0000-0003-0744-1434); Hani F Ayyash (0000-0002-1005-1667).

Author contributions: Ogundele MO conceived the idea; Ogundele MO and Ayyash HA prepared the manuscript.

Conflict-of-interest statement: There is no conflict of interest associated with any of the authors who contributed their efforts in this manuscript.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Dr. Michael O Ogundele, MBBS, MRCP, MSc, Consultant Paediatrician, Department of Community Paediatrics, NHS Fife, Glenwood Health Centre, Napier Road, Glenrothes KY6 1HK, United Kingdom. m.ogundele@nhs.net Telephone: +44-1592-765096

Received: October 27, 2017

Peer-review started: October 29, 2017

First decision: November 20, 2017

Revised: November 30, 2017

Accepted: December 5, 2017

Article in press: December 5, 2017

Published online: February 8, 2018

Abstract

Attention deficit hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in children and adolescents, with prevalence ranging between 5% and 12% in the developed countries. Tic disorders (TD) are common co-morbidities in paediatric ADHD patients with or without pharmacotherapy treatment. There has been conflicting evidence of the role of psychostimulants in either precipitating or exacerbating TDs in ADHD patients. We carried out a literature review relating to the management of TDs in children and adolescents with ADHD through a comprehensive search of MEDLINE, EMBASE, CINAHL and Cochrane databases. No quantitative synthesis (meta-analysis) was deemed appropriate. Meta-analysis of controlled trials does not support an association between new onset or worsening of tics and normal doses of psychostimulant use. Supratherapeutic doses of dextroamphetamine have been shown to exacerbate TD. Most tics are mild or moderate and respond to psychoeducation and behavioural management. Level A evidence support the use of alpha adrenergic agonists, including Clonidine and Guanfacine, reuptake noradrenalin inhibitors (Atomoxetine) and stimulants (Methylphenidate and Dexamphetamines) for the treatment of Tics and comorbid ADHD. Priority should be given to the management of co-morbid Tourette's syndrome (TS) or severely disabling tics in children and adolescents with ADHD. Severe TDs may require antipsychotic treatment. Antipsychotics, especially Aripiprazole, are safe and effective treatment for TS or severe Tics, but they only moderately control the co-occurring ADHD symptomatology. Short vignettes of different common clinical scenarios are presented to help clinicians determine the most appropriate treatment to consider in each patient presenting with ADHD and co-morbid TDs.

Key words: Tics disorders; Childhood; Attention deficit hyperactivity disorder; Adolescence; Tourette's syndrome

© The Author(s) 2018. Published by Baishideng Publishing

Group Inc. All rights reserved.

Core tip: Attention deficit hyperactivity disorder (ADHD) and Tic disorders (TD) are common co-morbidities in children and adolescents, with 60% of children with Tourette's syndrome having ADHD. This review covers the classification, prevalence, aetiology, diagnosis and treatment of childhood TD and co-morbid ADHD. Most tics are mild or moderate, responding to psychoeducation and behavioural management. Level A evidence supports the use of alpha adrenergic agonists, Atomoxetine and stimulants for the treatment of Tics and co-morbid ADHD. Severe TDs may require antipsychotic treatment. Short clinical vignettes are presented to help guide the selection of the most appropriate treatment in each patient presenting with ADHD and co-morbid TDs.

Ogundele MO, Ayyash HF. Review of the evidence for the management of co-morbid Tic disorders in children and adolescents with attention deficit hyperactivity disorder. *World J Clin Pediatr* 2018; 7(1): 36-42 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i1/36.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i1.36>

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is the commonest neurobehavioural disorder in children and adolescents, with prevalence ranging between 5% and 12% in the developed countries^[1]. Up to 80% of ADHD patients have one or more co-morbid conditions which include Tic disorders (TD). There is a complex interplay between TD and ADHD in children and young people. TDs are common comorbidities in paediatric ADHD patients with or without treatment with pharmacotherapy. ADHD and other co-morbid disorders like Tics/Tourette's syndrome (TS), especially if left untreated, can have lasting impairing effects on several aspects of daily functioning.

Tics naturally wax and wane in clinical severity and are exacerbated by stress, including consequences of untreated ADHD. There has been conflicting evidence of the role of psychostimulants in either precipitating or exacerbating TDs in ADHD patients. Some anecdotal evidence also suggests that tics may improve with ADHD treatment.

SYMPTOMS AND NATURAL HISTORY OF TD

Tics have been defined as sudden, rapid, recurrent, non-rhythmic, stereotyped, involuntary movements or vocalizations. Motor tic can be either simple or complex, depending on whether one or several muscle groups are simultaneously or concurrently affected. Motor tics commonly include behaviours such as eye-

blinking, lip-licking, or mouth opening. It can also involve more complex movements like facial grimacing, head movements, shoulder shrugging or combinations of these^[2].

Vocal or phonic tics are involuntary sounds that include throat clearing, coughing, barking, sniffing, unnecessary belching or more complex vocalizations such as repeating parts of words or phrases^[3].

TS (also known as Gilles de la Tourette's syndrome) is a complex neurodevelopmental disorder characterized by combination of motor and vocal tics. Motor tics often precede the onset of phonic tics of TS by many years. The phonic tics may commence from about the age of 3 years. Severe TS may manifest as forceful bouts of self-harming motor tics, including hitting or biting, as well as socially unacceptable utterances (coprolalia) and gestures^[3].

The Tourette's Syndrome Study Group definition from 1993 requires the concurrent presence of motor and vocal tics occurring almost daily for at least one year, beginning before the 21st birthday^[4]. The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) requires both multiple motor and one or more vocal tics have been present at some time during the illness, although not necessarily concurrently for the diagnosis of TS. It also describes TD/TS as waxing and waning in frequency and symptoms must have lasted for more than one year since the first onset^[5]. The average age of developing TS is 7 years, with a range from three to eight years. Most patients with childhood TD show remarkable symptoms improvement by the age of 19 years. Adult-onset cases of TS are usually the most severe forms of presentation^[3].

Motor or phonic tics often begin with the patient experiencing some psycho-sensory phenomena known as the "premonitory urge" which may be localized to an area of the tics or a generalised inner tension. Most individuals with Tics/TS also experience feelings of momentary relief after the tic has occurred. TD are typically exacerbated by stressful life-events associated with high levels of emotional excitements and fatigue, and can include normally routine activities such as the start of school, birthdays, arrival of a new sibling, changes in the social or physical environment like moving house or going on holidays.

The symptoms of childhood TD/TS are usually mild and they are almost invariably co-morbid with other mental health and behavioural problems including ADHD, Obsessive-compulsive behaviour or disorder (OCD), learning disabilities (LD) and mood disorders. Tics/TS can significantly impair the patient's self-esteem, peer and or family relationships^[3]. Although tics often improve after adolescence, recent studies suggest that comorbid OCD and ADHD often persist^[6]. Other common comorbidities in children with Tics/TS include anxiety disorders, depression, autistic spectrum disorder (ASD), conduct disorder (CD), oppositional defiant disorder (ODD), self-injurious behaviours, sleep disorders, rage attacks and personality disorders^[2,7].

CLASSIFICATION OF TD

DSM-5^[5] classifies TD into four categories, according to the duration and age of symptoms onset: (1) TS: Both multiple motor and one or more vocal tics (not necessarily concurrently) that have been present for more than a year; (2) Chronic TD: Presence of a single or multiple motor or vocal tics (not both), appearing before age 18, present for more than a year; (3) Transient TD: Single or multiple motor or vocal tics (not both), occurring nearly daily for at least 4 wk but not longer than 12 consecutive months; and (4) TD not otherwise specified: Tics that do not meet the conditions for definition of any other TD. This includes adult-onset tics.

PREVALENCE OF TD AND CO-MORBID CHILDHOOD ADHD

Transient TD affect between 5% and 25% of school children at any given time^[8]. The reported prevalence of TD/TS is variable according to different sample sources, definitions or diagnostic methods used. It is also influenced by the age and sex of the study cohorts. A published meta-analysis including 13 studies reported that the prevalence of childhood TS varied between 0.4% and 3.8% and average 1% among school children (higher in boys, 1.06% vs 0.25% in girls)^[9].

ADHD is the commonest neurodevelopmental comorbidity reported among children with TS. While only seven percent of children and adolescents with ADHD are diagnosed with TS, up to 60% of patients with TS have ADHD. ADHD diagnosis is generally known to antedate the occurrence of motor or vocal tics among children with TS, but their concurrent emergence is also possible^[2]. The Yale Global Tic Severity Scale (YGTSS) scores in children with ADHD are reported not to be significantly different from those without ADHD, but children with obsessive compulsive behaviours tend to have significantly higher YGTSS scores^[10].

AETIOLOGY OF TD

Several genetic studies among twins and families have contributed significantly to our knowledge about the important roles of genetic risk factors in predicting vertical transmission of TS and related TD. The exact nature and mechanism of the genetic inheritance are however unknown. The genetic vulnerability of TS has been associated with some extensively studied candidate genes, including the dopamine receptors (*DRD1*, *DRD2*, *DRD4*, and *DRD5*), the dopamine transporter, some noradrenergic genes (*ADRA2a*, *ADRA2C*, and *DBH*), and serotonergic genes (*5HTT*)^[3]. Abnormalities in any one or more of these genes could potentially act together with unfavourable environmental factors, to increase the risk of individuals having TD/TS.

POSSIBLE COMMON PATHOGENESIS OF CHILDHOOD TD AND ADHD

The risk for developing ADHD as well as TD is associated with early exposure to certain adverse perinatal conditions. The extensive co-occurrence of the two disorders also suggests a shared genetic background^[11,12]. Prenatal maternal smoking is associated with increased risk for TS/TD as well as its comorbidity with other psychiatric conditions^[13].

Abnormalities in noradrenergic and dopaminergic chemoreceptors and neurotransmission within corticostriatal circuits have been implicated in the development of both TS/Tics and ADHD. These alterations are thought to be responsible for clinical symptoms arising from failure to inhibit intrusive thoughts, sensory input, and motor output^[14]. Iron deficiency has also been commonly associated with ADHD and recently with Tics/TS^[15,16].

DIAGNOSTIC CHALLENGES OF TD

The Diagnostic and Statistical Manual, 5th edition (DSM-5)^[5] and the International Classification of Disease and related Health Problems, 10th revision (ICD-10)^[17] are the most universally accepted diagnostic criteria for TS/TD. The clinical nature and progression of TS/TD present the clinician with some peculiar challenges. The intermittent symptoms may delay recognition in the early stages of the disorder. Assessment of childhood and adolescent TD/TS requires multi-source feedback from several familiar carers to document the frequency and severity of the symptoms, specific triggers, and ascertain the level of any functional impairment, including effect on self-esteem and the associated mental health co-morbidities.

SCREENING AND ASSESSMENT TOOLS FOR TD

At least 5 severity scales have been recommended for use in children and young people with TS/Tics, including the Yale Global Tic Severity Scale (YGTSS), Tourette Syndrome Clinical Global Impression, Tourette's Disorder Scale, Shapiro Tourette Syndrome Severity Scale, and Premonitory Urges for Tics Scale. Six others have been suggested, including the Hopkins Motor and Vocal Tic Scale, Rush Video-Based Tic Rating Scale, Parent Tic Questionnaire and Tourette Syndrome Symptom List. The YGTSS is the commonest screening tool employed worldwide for both clinical and research purposes, and it is the most favoured tool recommended by TS international guidelines^[18].

A further two screening instruments in common use, have also been recommended by an International Movement Disorders Society subcommittee; Motor tic, Obsession and compulsions, Vocal tic Evaluation Survey

Table 1 Common differential diagnosis of Tics

Stereotypy (in developmental disorders such as autism spectrum disorders and stereotypic movement disorder)
Functional movement disorders in children
Neurological: Stroke, head trauma
Primary movement disorders: Dystonia
Post-infectious: PANDAS, Sydenham's chorea
Infectious: Encephalitis
Epileptic seizures
Toxic: Carbon monoxide poisoning
Chromosomal disorders: Down syndrome and Fragile X syndrome
Genetic conditions: Huntington's disease, Wilson's disease and Tuberous sclerosis
Medication-induced tics: Neuroleptics, Stimulants, Antiepileptics, Lithium

Modified from Oluwabusi *et al*^[19] 2016. PANDAS: Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

(MOVES) and Autism-Tics, Attention Deficit/Hyperactivity Disorder and Other Co-morbidities Inventory (A-TAC)^[18].

DIFFERENTIAL DIAGNOSIS OF TD

The diagnosis TS/TD is based on clinical history and examination, supplemented by various screening and diagnostic feedback tools. Both DSM-5^[5] and ICD-10^[17] preclude the presence of any direct physiologic causes such as a substance (*e.g.*, stimulants) or a general medical condition (*e.g.*, Huntington disease or post-viral encephalitis) to make a firm diagnosis of TS/TD. TS/TD need to be differentiated from any voluntary coordinated stereotyped movements or vocalisations, which may not always be easy to achieve clinically in younger children. TS/TD diagnosis must also exclude other specific dyskinetic disorders such as akathisia, tardive dyskinesia, or other hyperkinetic movement disorders (Table 1). Routine laboratory and radiological investigations may be required to exclude other organic causes of tics^[19]. Tics may be differentiated from other common movement disorders by its tendency to occur in a milder form during sleep^[3].

MANAGEMENT OF TICS/TOURETTE SYNDROME (ALONE OR CO-MORBID WITH ADHD)

Tics/TS are best managed in multidisciplinary teams with multifaceted expertise in Neurology, Psychiatry, Psychology, and Paediatrics, with supportive services from Education and Social welfare services. The primary choice of management strategies depends on the severity of the symptoms and their associated impairments.

Mild to moderate symptoms

First line of management for mild to moderate TD/TS involves comprehensive psychoeducation of patients and families, addressing the aetiology, triggering factors and management strategies of tics and associated behaviours, personal coping mechanisms, prognosis, and symptomatic natural progression^[14]. Counselling interventions for dealing with peer rejection, academic and family problems or employment difficulties are also recommended^[2].

Comprehensive Behavioural Intervention for Tics (CBIT) is a combination of several psychological support interventions including Psychoeducation, Functional analysis, Relaxation Training, Habit Reversal Therapy (HRT), social support and reward systems^[20]. Exposure and Response Prevention (ERP) is another type of therapy that enables the patient to effectively overcome and deal with the premonitory urges. For example, an alternative learnt movement is carried out for a brief moment after each pre-monitory feeling. These strategies are particularly helpful in older children^[2].

Growing evidence confirm effectiveness of various elements of the CBIT including self-monitoring (counting tics), relaxation techniques, and Habit reversal therapy involving awareness and competing response training^[21,22]. However, these comprehensive multidisciplinary support services are not readily available in many centres, mainly due to the paucity of well-trained therapists^[23]. These counselling and behavioural modification interventions may be sufficient to successfully manage many children with uncomplicated Tics/TS, who do not need Pharmacotherapy.

Moderate to severe Tics/TS symptoms

In more complicated cases causing interference with peer or family relationships, social interactions, academic or job performance, or with other functional activities, Pharmacotherapy for TD/TS may be recommended in addition to the first line counselling and behavioural interventions^[2].

First line pharmacotherapy

Alpha adrenergic agonists: Clonidine or Guanfacine (as single agent or combined with ADHD stimulants/non-stimulants) are the first line recommended treatment for tics/TS. These drugs were initially developed for the management of hypertension and have sedation or tiredness as major side effects. They can also cause possible rebound hypertension if stopped abruptly. There is a need to closely monitor blood pressure in patients on Clonidine or Guanfacine.

ADHD stimulants/non-stimulants: Apparent worsening or new onset of tics during ADHD treatment is oftentimes due to the coincidental waxing and waning

natural history of tics. It is best to persevere for a few weeks with normal doses of stimulant treatment (various formulations of Methylphenidate and or Dexamphetamines) if it is effectively controlling the ADHD symptoms. In most cases the tics will gradually subside spontaneously. If stimulants have to be stopped due to emerging or worsening tics, clinicians may consider re-challenging children with psychostimulants after a watchful period when the tics seem to have subsided. An alternative approach would involve treatment of ADHD and the co-morbid TD with alpha agonists either as replacement or additional therapy to psychostimulants.

Non-stimulant Atomoxetine should be considered as alternatives if alpha agonists are not tolerated. Atomoxetine can also be effective for treatment of ADHD with comorbid anxiety, and less effectively for co-morbid Tics/TS^[24].

Second line pharmacotherapy

Antipsychotics: Various generations of antipsychotics are the recommended second line management for more complicated cases of TS/Tics. Recent studies about the atypical antipsychotics such as Risperidone, and Aripiprazole, suggest that their efficacy in the control of severe TD/TS symptoms is related to their ability to selectively block dopamine D2 postsynaptic receptors. Reviews of the atypical psychotropics have shown demonstrable effective treatment for tics, but they do not affect premonitory urges, and they are only moderately effective in controlling the co-occurring ADHD symptomatology^[25].

The older generation of antipsychotics, such as Haloperidol and Pimozide, which were the preferred treatment options in the past due to their greater effectiveness, are now rarely used in the treatment of childhood TD/TS because of their significant adverse effects including extrapyramidal side-effects and tardive dyskinesia for Haloperidol, and cardiotoxicity for Pimozide^[26].

Adjuvant therapy

Deep brain stimulation (DBS) has recently become a viable therapeutic option for TS in refractory cases^[27]. A recent study suggests that iron deficiency may be associated with more severe tics and therapeutic iron supplements lead to alleviation of symptoms. The relationship between TD and iron deficiency appears to be independent of any co-morbidities such as OCD, ADHD, or anxiety^[15].

SUMMARY OF TREATMENT FOR ADHD AND CO-MORBID TD USING COMMON CLINICAL SCENARIOS

Clinical guidelines have been published for the management of TD in Europe^[28], Canada^[29], and the United States^[30]. We shall consider recommendations for ma-

nagement of ADHD co-morbid with TD/TS using three common clinical scenarios.

Scenario 1

In a patient with ADHD and co-morbid mild to moderate TD: Consider giving priority to the treatment of ADHD as it will likely be having the greater impact on the child's functioning and education. Furthermore, ADHD medications are more effective and have less potential side effects^[2]. Tics reduction (and not tics exacerbation) has been reported with acute immediate release Dexamethylphenidate (IR dMPH) challenge in children and adolescents with ADHD and co-morbid Tics disorder^[31]. However, supra-therapeutic doses of Dextroamphetamine should be avoided, as they may worsen tics severity in some individuals^[32].

Treatment of tics may be considered in these patients only if the symptoms are associated with significant functional impairments. Various clinical options for the management of the tics include temporary withdrawal of stimulant treatment, addition or replacement of the stimulants with alpha adrenergic agents (Clonidine or Guanfacine) and or non-stimulant Atomoxetine.

Scenario 2

In a patient with ADHD and co-morbid TS or severe tics: Greater benefit and satisfaction to the patient may be achieved by treating the Tourette's symptoms first^[2]. The treatment of TS/severe tics will follow the standard strategies of progressing from psychological and behavioural interventions to the first and or second line Pharmacotherapy, in that order. Treating the TS first offers the added advantage of minimizing the risk of worsening tics with the introduction of psychostimulants as the most effective treatment for ADHD.

Scenario 3

In a child already diagnosed with ADHD and treated with stimulants developing significant Tics disorder: New research evidence does not contraindicate continuing use of the stimulants. Conservative "watchful" approach may be adopted to check if the tics will abate spontaneously (following the natural course). In most cases the tics will gradually subside.

The next step would be to consider modification of treatment (add new drug or replace medication as in scenario 2). Studies have confirmed that combination of alpha 2 agonist like Clonidine with psychostimulant Methylphenidate is effective and safe for the management of ADHD and co-morbid TD^[2]. An earlier meta-analysis of 9 studies involving 477 subjects has confirmed that alpha-2 agonists offer the best combined improvement in both tics and ADHD symptoms. It also showed that Methylphenidate offers the greatest and most immediate improvement of ADHD symptoms without aggravating the tic symptoms. Atomoxetine and Desipramine also offer additional evidence-based treatments of ADHD in children with comorbid TD^[32].

CONCLUSION

Recent published evidence suggests that the incidence and severity of tics and TS are not increased by the use of psychostimulants, using the usual recommended dosing, except in a small number of individual cases. A more recent meta-analysis of 22 controlled trials among 2385 ADHD children has failed to demonstrate any significant relationship between treatment with stimulants and new tics or increasing severity of existing ones. Apparent symptom worsening or new tics appearing during ADHD treatment can often be attributed to the coincidental "waxing and waning" natural history of tics^[33].

Most tics respond to psychoeducation and behavioural management. Level A of evidence support the use of alpha adrenergic agonists, including Clonidine and Guanfacine, reuptake noradrenalin inhibitors (Atomoxetine) and stimulants (Methylphenidate and Dexamphetamines) for the treatment of Tics/TS and comorbid ADHD^[14]. Priority should be given to the management of co-morbid TS or severely disabling tics in children and adolescents with ADHD.

Severe TD may require antipsychotic treatment (such as Aripiprazole or Risperidone). The newer atypical antipsychotics, especially Aripiprazole, are safe and effective treatment for TS or severe tics, but they only moderately control the co-occurring ADHD symptomatology. Consideration of different common clinical scenarios could help to determine the most appropriate treatment to consider in each patient presenting with ADHD and co-morbid TD.

REFERENCES

- 1 **National Institute for Health and Care Excellence (NICE).** Attention deficit hyperactivity disorder: diagnosis and management. [published 2008 Sept 24; accessed 2017 Oct]. Available from: URL: <http://nice.org.uk/guidance/cg72>
- 2 **Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD).** ADHD and coexisting conditions: Tics and Tourette Syndrome. 2005. [accessed 2017 November]. Available from: URL: http://naceonline.com/MyADHDCareTeam.com/links/ADHD_and_Coexisting_Conditions_Tics_and_Tourette_Syndrom_e.pdf
- 3 **Leckman JF.** Tourette's syndrome. *Lancet* 2002; **360**: 1577-1586 [PMID: 12443611 DOI: 10.1016/S0140-6736(02)11526-1]
- 4 **The Tourette Syndrome Classification Study Group.** Definitions and classification of tic disorders. *Arch Neurol* 1993; **50**: 1013-1016 [PMID: 8215958 DOI: 10.1001/archneur.1993.00540100012008]
- 5 **American Psychiatric Association (APA).** Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington (DC): American Psychiatric Association; 2013. [accessed 2017 Nov]. Available from: URL: <https://tinyurl.com/y82f6kyj>
- 6 **Groth C, Mol Debes N, Rask CU, Lange T, Skov L.** Course of Tourette Syndrome and Comorbidities in a Large Prospective Clinical Study. *J Am Acad Child Adolesc Psychiatry* 2017; **56**: 304-312 [PMID: 28335874 DOI: 10.1016/j.jaac.2017.01.010]
- 7 **Hirschtritt ME, Lee PC, Pauls DL, Dion Y, Grados MA, Illmann C, King RA, Sander P, McMahon WM, Lyon GJ, Cath DC, Kurlan R, Robertson MM, Osiecki L, Scharf JM, Mathews CA; Tourette Syndrome Association International Consortium for Genetics.** Lifetime prevalence, age of risk, and genetic relationships of comorbid psychiatric disorders in Tourette syndrome. *JAMA Psychiatry* 2015; **72**: 325-333 [PMID: 25671412 DOI: 10.1001/jamapsychiatry.2014.2650]
- 8 **Tallur K, Minns RA.** Tourette's syndrome. *Paediatr Child Health* 2010; **20**: 88-93 [DOI: 10.1016/j.paed.2009.10.010]
- 9 **Knight T, Steeves T, Day L, Lowerison M, Jette N, Pringsheim T.** Prevalence of tic disorders: a systematic review and meta-analysis. *Pediatr Neurol* 2012; **47**: 77-90 [PMID: 22759682 DOI: 10.1016/j.pediatrneurol.2012.05.002]
- 10 **Pringsheim T.** Tic Severity and Treatment in Children: The Effect of Comorbid Attention Deficit Hyperactivity Disorder and Obsessive Compulsive Behaviors. *Child Psychiatry Hum Dev* 2017; **48**: 960-966 [PMID: 28289952 DOI: 10.1007/s10578-017-0718-z]
- 11 **Tsetsos F, Padmanabhuni SS, Alexander J, Karagiannidis I, Tsifintaris M, Topaloudi A, Mantzaris D, Georgitsi M, Drineas P, Paschou P.** Meta-Analysis of Tourette Syndrome and Attention Deficit Hyperactivity Disorder Provides Support for a Shared Genetic Basis. *Front Neurosci* 2016; **10**: 340 [PMID: 27499730 DOI: 10.3389/fnins.2016.00340]
- 12 **Abdulkadir M, Tischfield JA, King RA, Fernandez TV, Brown LW, Cheon KA, Coffey BJ, de Bruijn SF, Elzerman L, Garcia-Delgar B, Gilbert DL, Grice DE, Hagström J, Hedderly T, Heyman I, Hong HJ, Huyser C, Ibanez-Gomez L, Kim YK, Kim YS, Koh YJ, Kook S, Kuperman S, Lamerz A, Leventhal B, Ludolph AG, Madruga-Garrido M, Maras A, Messchendorp MD, Mir P, Morer A, Münchau A, Murphy TL, Openner TJ, Plessen KJ, Rath JJ, Roessner V, Fründt O, Shin EY, Sival DA, Song DH, Song J, Stolte AM, Tübing J, van den Ban E, Visscher F, Wanderer S, Woods M, Zinner SH, State MW, Heiman GA, Hoekstra PJ, Dietrich A.** Pre- and perinatal complications in relation to Tourette syndrome and co-occurring obsessive-compulsive disorder and attention-deficit/hyperactivity disorder. *J Psychiatr Res* 2016; **82**: 126-135 [PMID: 27494079 DOI: 10.1016/j.jpsychires.2016.07.017]
- 13 **Browne HA, Modabbernia A, Buxbaum JD, Hansen SN, Schendel DE, Parner ET, Reichenberg A, Grice DE.** Prenatal Maternal Smoking and Increased Risk for Tourette Syndrome and Chronic Tic Disorders. *J Am Acad Child Adolesc Psychiatry* 2016; **55**: 784-791 [PMID: 27566119 DOI: 10.1016/j.jaac.2016.06.010]
- 14 **Ganos C, Martino D, Pringsheim T.** Tics in the Pediatric Population: Pragmatic Management. *Mov Disord Clin Pract* 2017; **4**: 160-172 [PMID: 28451624 DOI: 10.1002/mdc3.12428]
- 15 **Ghosh D, Burkman E.** Relationship of serum ferritin level and tic severity in children with Tourette syndrome. *Childs Nerv Syst* 2017; **33**: 1373-1378 [PMID: 28470381 DOI: 10.1007/s00381-017-3424-z]
- 16 **Wang Y, Huang L, Zhang L, Qu Y, Mu D.** Iron Status in Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis. *PLoS One* 2017; **12**: e0169145 [PMID: 28046016 DOI: 10.1371/journal.pone.0169145]
- 17 **World Health Organization (WHO).** Multiaxial classification of child and adolescent psychiatric disorders: international classification of disease and related health problems, 10th revision (ICD-10). Cambridge: Cambridge University Press, 1998: 43-45
- 18 **Martino D, Pringsheim TM, Cavanna AE, Colosimo C, Hartmann A, Leckman JF, Luo S, Münchau A, Goetz CG, Stebbins GT, Martinez-Martin P; Members of the MDS Committee on Rating Scales Development.** Systematic review of severity scales and screening instruments for tics: Critique and recommendations. *Mov Disord* 2017; **32**: 467-473 [PMID: 28071825 DOI: 10.1002/mds.26891]
- 19 **Oluwabusi OO, Parke S, Ambrosini PJ.** Tourette syndrome associated with attention deficit hyperactivity disorder: The impact of tics and psychopharmacological treatment options. *World J Clin Pediatr* 2016; **5**: 128-135 [PMID: 26862512 DOI: 10.5409/wjcp.v5.i1.128]
- 20 **McGuire JF, Piacentini J, Scahill L, Woods DW, Villarreal R, Wilhelm S, Walkup JT, Peterson AL.** Bothering tics in patients with chronic tic disorders: Characteristics and individualized treatment response to behavior therapy. *Behav Res Ther* 2015; **70**: 56-63 [PMID: 25988365 DOI: 10.1016/j.brat.2015.05.006]
- 21 **Seragni G, Chiappedi M, Bettinardi B, Zibordi F, Colombo T,**

- Reina C, Angelini L. Habit Reversal Training in children and adolescents with chronic tic disorders: an Italian randomized, single blind, pilot study. *Minerva Pediatr* 2018; **70**: 5-11 [PMID: 26583455]
- 22 **McGuire JF**, Ricketts EJ, Piacentini J, Murphy TK, Storch EA, Lewin AB. Behavior Therapy for Tic Disorders: An Evidence-based Review and New Directions for Treatment Research. *Curr Dev Disord Rep* 2015; **2**: 309-317 [PMID: 26543797 DOI: 10.1007/s40474-015-0063-5]
- 23 **Sukhodolsky DG**, Woods DW, Piacentini J, Wilhelm S, Peterson AL, Katsovich L, Dziura J, Walkup JT, Scahill L. Moderators and predictors of response to behavior therapy for tics in Tourette syndrome. *Neurology* 2017; **88**: 1029-1036 [PMID: 28202705 DOI: 10.1212/WNL.0000000000003710]
- 24 **Hutchison SL**, Ghuman JK, Ghuman HS, Karpov I, Schuster JM. Efficacy of atomoxetine in the treatment of attention-deficit hyperactivity disorder in patients with common comorbidities in children, adolescents and adults: a review. *Ther Adv Psychopharmacol* 2016; **6**: 317-334 [PMID: 27721971 DOI: 10.1177/2045125316647686]
- 25 **Gerasch S**, Kanaan AS, Jakubowski E, Müller-Vahl KR. Aripiprazole Improves Associated Comorbid Conditions in Addition to Tics in Adult Patients with Gilles de la Tourette Syndrome. *Front Neurosci* 2016; **10**: 416 [PMID: 27672358 DOI: 10.3389/fnins.2016.00416]
- 26 **Eddy CM**, Rickards HE, Cavanna AE. Treatment strategies for tics in Tourette syndrome. *Ther Adv Neurol Disord* 2011; **4**: 25-45 [PMID: 21339906 DOI: 10.1177/1756285610390261]
- 27 **Testini P**, Min HK, Bashir A, Lee KH. Deep Brain Stimulation for Tourette's Syndrome: The Case for Targeting the Thalamic Centromedian-Parafascicular Complex. *Front Neurol* 2016; **7**: 193 [PMID: 27891112 DOI: 10.3389/fneur.2016.00193]
- 28 **Roessner V**, Plessen KJ, Rothenberger A, Ludolph AG, Rizzo R, Skov L, Strand G, Stern JS, Termine C, Hoekstra PJ; ESSTS Guidelines Group. European clinical guidelines for Tourette syndrome and other tic disorders. Part II: pharmacological treatment. *Eur Child Adolesc Psychiatry* 2011; **20**: 173-196 [PMID: 21445724 DOI: 10.1007/s00787-011-0163-7]
- 29 **Pringsheim T**, Doja A, Gorman D, McKinlay D, Day L, Billingshurst L, Carroll A, Dion Y, Luscombe S, Steeves T, Sandor P. Canadian guidelines for the evidence-based treatment of tic disorders: pharmacotherapy. *Can J Psychiatry* 2012; **57**: 133-143 [PMID: 22397999 DOI: 10.1177/070674371205700302]
- 30 **Murphy TK**, Lewin AB, Storch EA, Stock S; American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter for the assessment and treatment of children and adolescents with tic disorders. *J Am Acad Child Adolesc Psychiatry* 2013; **52**: 1341-1359 [PMID: 24290467 DOI: 10.1016/j.jaac.2013.09.015]
- 31 **Lyon GJ**, Samar SM, Conelea C, Trujillo MR, Lipinski CM, Bauer CC, Brandt BC, Kemp JJ, Lawrence ZE, Howard J, Castellanos FX, Woods D, Coffey BJ. Testing tic suppression: comparing the effects of dexamethylphenidate to no medication in children and adolescents with attention-deficit/hyperactivity disorder and Tourette's disorder. *J Child Adolesc Psychopharmacol* 2010; **20**: 283-289 [PMID: 20807066 DOI: 10.1089/cap.2010.0032]
- 32 **Bloch MH**, Panza KE, Landeros-Weisenberger A, Leckman JF. Meta-analysis: treatment of attention-deficit/hyperactivity disorder in children with comorbid tic disorders. *J Am Acad Child Adolesc Psychiatry* 2009; **48**: 884-893 [PMID: 19625978 DOI: 10.1097/CHI.0b013e3181b26e9f]
- 33 **Cohen SC**, Mulqueen JM, Ferracioli-Oda E, Stuckelman ZD, Coughlin CG, Leckman JF, Bloch MH. Meta-Analysis: Risk of Tics Associated With Psychostimulant Use in Randomized, Placebo-Controlled Trials. *J Am Acad Child Adolesc Psychiatry* 2015; **54**: 728-736 [PMID: 26299294 DOI: 10.1016/j.jaac.2015.06.011]

P- Reviewer: Govindarajan GK, Wang YZ **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Li RF



Case Control Study

Abdominal obesity adversely affects bone mass in children

Sowmya Krishnan, Michael P Anderson, David A Fields, Madhusmita Misra

Sowmya Krishnan, David A Fields, Department of Pediatrics, University of Oklahoma Health Sciences Center, Harold Hamm Diabetes Center, Oklahoma City, OK 73104, United States

Michael P Anderson, College of Public Health, University of Oklahoma Health Science Center, Oklahoma City, OK 73104, United States

Madhusmita Misra, Massachusetts General Hospital for Children and Harvard Medical School, Boston, MA 02114, United States

ORCID number: Sowmya Krishnan (0000-0001-5600-0753); Michael P Anderson (0000-0002-2319-2282); David A Fields (0000-0002-6845-1196); Madhusmita Misra (0000-0002-9405-2981).

Author contributions: Krishnan S collected data; Anderson MP helped in statistical analysis; Fields DA and Misra M helped in writing the paper.

Supported by Novo-Nordisk, No. C7042301.

Institutional review board statement: The study has been approved by the University of Oklahoma Health sciences Center Institutional review board research ethics committee and has been performed in accordance with the ethical standards as laid down in the 1964 declaration of Helsinki and its later amendments.

Informed consent statement: All study participants or their legal guardians provided informed consent prior to enrollment in the study.

Conflict-of-interest statement: David A Fields has received grant funding from Nestle and Mead Johnson.

Data sharing statement: Consent was not obtained from participants for sharing data but presented data is anonymized and risk of identification is low.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and

the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Sowmya Krishnan, MD, Associate Professor, Department of Pediatrics, University of Oklahoma Health Sciences Center, Harold Hamm Diabetes Center, 1200, N Children's Avenue, Suite 4500, Oklahoma City, OK 73104, United States. sowmya-krishnan@ouhsc.edu
Telephone: +1-405-2718000-43091
Fax: +1-405-2713093

Received: August 25, 2017

Peer-review started: September 17, 2017

First decision: October 23, 2017

Revised: November 8, 2017

Accepted: November 27, 2017

Article in press: November 27, 2017

Published online: February 8, 2018

Abstract**AIM**

To determine the effect of childhood obesity and insulin resistance on bone health.

METHODS

We conducted a cross sectional study in pubertal adolescents and young adults 13-20 years old who were either overweight/obese or normal weight. Participants were Tanner 3 or above for pubertal stage, and had fasting blood work done to measure glucose, insulin, C-reactive protein and lipid levels. Homeostatic model of insulin resistance (HOMA-IR) was calculated using the formula (Fasting Blood Glucose *Insulin/405). Body composition and bone mineral density were measured using dual energy X-ray absorptiometry (DXA; Hologic QDR 4500, Waltham, MA, United Kingdom).

RESULTS

Percent trunk fat was associated inversely with whole

body bone mineral content (BMC), whereas HOMA-IR was associated positively with whole body BMC.

CONCLUSION

Our results suggest that abdominal adiposity may have an adverse effect on whole body bone parameters and that this effect is not mediated by insulin resistance.

Key words: Obesity; Bone mineral density; Insulin resistance

© **The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Abdominal adiposity has an adverse impact on whole body bone mineral content in adolescents. This effect does not seem to be mediated by the increased insulin resistance associated with increased abdominal adiposity. Attention to body composition rather than just body weight is needed to counsel adolescents regarding optimal bone health.

Krishnan S, Anderson MP, Fields DA, Misra M. Abdominal obesity adversely affects bone mass in children. *World J Clin Pediatr* 2018; 7(1): 43-48 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i1/43.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i1.43>

INTRODUCTION

The antecedents of adult onset osteoporosis start in childhood, and while the effect of several childhood systemic diseases on bone health^[1] has been recognized, the effect of childhood obesity on bone health remains unclear. Historically in adults, higher body mass index (BMI) was believed to be bone protective with increased bone mineral density (BMD) reported with higher BMI^[2]. Further studies have revealed this to be proportional to total lean mass rather than total fat mass. However, the relative distribution of fat in the body may also play a role, and visceral adiposity in particular has been demonstrated to have an adverse impact on bone^[3,4]. Visceral adiposity is directly associated with insulin resistance, and the link between obesity and bone health may be mediated by the underlying insulin resistance. Insulin is a bone anabolic hormone^[5] and higher insulin levels may result in increased bone formation. However, a state of insulin resistance may negate the beneficial effects of insulin on bone. This in fact has been suggested in recent studies in adults^[6,7]. However, data in children remain inconclusive.

Data regarding the relationship between insulin resistance, BMD and fracture risk are conflicting. While adults with long standing type 2 diabetes tend to have more fractures^[8-10], their BMD has been reported to be high or normal in various studies. Potential conflicting factors include the duration of type 2 diabetes (as type 2 diabetes can go unrecognized for a long time), and

degree of hyperglycemia. While obese boys tend to have more fractures than their lean counterparts^[11], the pathophysiology behind this association remains to be delineated, and the effect of insulin resistance without overt type 2 diabetes on bone health in adolescents remains unclear. In this study, we examined the association of body composition and insulin resistance with whole body BMD and bone mineral content (BMC) in a group of overweight and normal weight pubertal adolescents, none of whom had type 2 diabetes. We hypothesized that overweight children with greater visceral adiposity (as assessed by percent trunk fat) would have lower BMD and BMC compared to their normal weight counterparts, which would be associated with the degree of insulin resistance.

MATERIALS AND METHODS

This was a cross-sectional study of children 13-20 years who were either normal weight or overweight. Subjects were recruited from our clinics and through recruitment fliers and campus wide e-mail notifications between 2006-2008. A total of 37 children were enrolled. Study subjects were defined as being overweight if their BMI was above the 85th percentile for age and gender (Group 1) and normal weight if their BMI was between the 3rd to 85th percentiles for age and gender (Group 2). The research protocol was approved by the Institutional Review Board at the University of Oklahoma Health Sciences Center. All subjects < 18 years old provided assent for study participation. Participants 18 years or older and parents of participants < 18 years old provided consent for study participation.

Children were excluded from the study if: (1) They had any coexisting endocrine, genetic or metabolic disease that may affect bone metabolism; or (2) if they were on any medications that may affect bone, including those that could affect substrate metabolism, psychotropic medications, weight loss medications, and oral contraceptives for female subjects. To control for the well-described increase in bone mineral acquisition during early stages of puberty, children who were prepubertal or early pubertal (Tanner 1 and 2) were excluded. Children were also excluded if they had impaired fasting glucose or diabetes based on fasting glucose values^[12].

After obtaining appropriate consent and assent, each child underwent a history and physical examination by a board certified pediatrician. Height and weight were used to calculate BMI, waist and hip circumference were obtained on each subject, and the presence and degree of acanthosis nigricans noted if present. Study participants then underwent a fasting blood draw for glucose and insulin levels, lipid profile and apolipoprotein C-III levels. Homeostatic model of insulin resistance (HOMA-IR) was calculated using the formula: (Fasting Blood Glucose *Insulin)/405. Studies have shown that HOMA-IR correlates well with insulin resistance as measured by insulin clamp studies^[13]. All testing was

Table 1 Descriptive data of the overweight and normal weight groups

Covariates	Overweight <i>n</i> = 23	Normal weight <i>n</i> = 14	<i>P</i> value
	mean (SD)	mean (SD)	
Age (mo)	187 (25.4)	198 (31.1)	0.40 ^b
Gender (% age females)	43.48%	57.14%	0.42
Birth weight (g)	3385 (644)	3179 (908)	0.42 ^b
Weight (kg)	93.7 (19.9)	57.4 (7.51)	< 0.0001 ^a
Weight %ile	95.1 (6.35)	52.5 (20.8)	< 0.0001 ^b
Height (cm)	168 (9.90)	167 (6.92)	0.72 ^a
Height %ile	59.3 (30.5)	60.1 (31.2)	0.88 ^b
BMI kg/m ²	32.9 (5.60)	20.5 (1.51)	< 0.0001 ^a
BMI %ile	96.6 (3.17)	47.3 (17.1)	< 0.0001 ^b
Total activity time/d (min)	303 (125)	307 (109)	0.93
Apolipoprotein C III (mg/dL)	6.71 (1.53)	6.56 (140)	0.75 ^a
C-reactive protein	2.81 (2.85) ^c	2.61(2.41) ^d	0.86
HOMA-IR	3.23 (1.78)	2.49 (3.49)	0.02
Waist circumference (cm)	98.5 (13.7)	69.2 (5.79)	< 0.0001 ^a
Hip circumference (cm)	118 (11.4)	94.8 (5.72)	< 0.0001 ^a
Waist to hip ratio	0.84 (0.06)	0.73 (0.05)	< 0.0001 ^a
Total lean mass (kg) (DXA)	50.58 (10.78)	55.40 (12.68)	0.23 ^a
Percent trunk fat (DXA)	36.4 (9.3)	17.1 (6.49)	< 0.0001
Spine BMD (g/cm ³)	1.06 (0.14)	1.06 (0.13)	0.95 ^a
BMD L-spine Z-score	1.32 (1.24)	1.36 (1.00)	0.92
Whole body BMD (g/cm ³)	1.10 (0.09)	1.06 (0.07)	0.21 ^a
Whole body BMC (g)	2417 (408)	2116 (281)	0.02 ^a

^aStudent's *t*-test; ^bWilcoxon-Mann-Whitney test; ^c*n* = 16; ^d*n* = 9. SD: Standard deviation; HOMA-IR: Homeostatic model assessment-estimated insulin resistance; BMD: Bone mineral density; BMC: Bone mineral content; BMI: Body mass index.

done by an experienced nurse assigned to the study at the General Clinical Research Center at the University of Oklahoma.

Whole body (WB) BMC and BMD, lumbar spine BMD, and body composition were measured using dual energy X-ray absorptiometry (DXA; Hologic QDR 4500, Waltham, MA, United Kingdom). Percent trunk fat [(trunk fat/total fat) × 100] was used as a surrogate for visceral fat^[14]. Similarly, the waist to hip ratio was used as a surrogate for visceral fat^[14]. Daily physical activity was assessed using a step activity monitor (Step Watch 3, Orthocare Innovations, Oklahoma City, OK, United States)^[15]. Subjects were asked to wear the step activity monitor on their right ankle during the day time when they were awake for 5 to 7 consecutive days. The monitor records the number of strides taken on a minute to minute basis. Data from the monitor is downloaded to a computer software program which calculates the activity time in a day (any minute in which a stride was taken is considered an active time) and the total amount of strides taken each day averaged over the days the monitor was worn. The accuracy of the step activity monitor exceeds 99% ± 1% in older adults^[15], as well as in children^[16]. Test-retest intraclass reliability coefficient for the measurement of total daily strides and total daily minutes of activity are *R* = 0.94 and *R* = 0.91, respectively^[15].

Statistical analysis

Statistical analysis for this study was performed and reviewed by Michael A Anderson (co-author), a bio-statistician at Department of public health, University of Oklahoma Health Sciences Center. Descriptive statistics

were computed for age, gender, smoking, birth weight, current weight, height, BMI, waist circumference, hip circumference, waist to hip ratio, BMC and BMD, trunk % fat, and HOMA-IR. All continuous variables were assessed for normality using the Shapiro-Wilk test for normality and comparisons between overweight and normal weight groups were made using the Student *t*-test or the Wilcoxon-Mann-Whitney test, as appropriate. One outlier was identified (HOMA-IR > 13) and after checking for data entry error, this subject was excluded from data analysis. Pearson's correlation coefficient was used to test the strength of the linear association. Robust regression was used to fit a multiple linear regression model to test the effect of HOMA-IR and percent trunk fat on WB-BMC and all BMD variables while controlling for gender and physical activity (total activity time % of day), which are potential confounders of the association. The effect of percent trunk fat on HOMA-IR while controlling for gender and physical activity was similarly tested.

RESULTS

Demographic data revealed no significant difference in age, gender, birth weight or current height between the two groups (Table 1). Per study design, group 1 consisting of overweight participants had a significantly higher mean body weight, BMI, waist circumference, hip circumference, waist to hip ratio and percent trunk fat (Table 1). Total activity time per day and sedentary time per day did not differ between the two groups.

WB-BMC was significantly higher in the overweight

Table 2 Robust regression with whole body bone mineral content or spine bone mineral density as the dependent variable after

Variable	Whole body BMC		Spine BMD	
	β	P value	β	P value
Gender	-704.28	< 0.0001	0.0876	0.18
Activity time % of day	-0.55	0.79	-0.0003	0.86
Waist to hip ratio	-111.619	0.86	0.4707	0.27
Percent trunk fat	-2112.67	< 0.0001	-0.3706	0.18
Total lean mass	-0.0022	0.59	0.00	0.98
HOMA IR	123.3	< 0.0001	-0.1295	0.29

Other covariates in the model include waist to hip ratio, trunk to total fat ratio, total lean mass, CRP, total activity time, apo CIII ratio, gender, HOMA-IR. BMC: Bone mineral content; BMD: Bone mineral density; HOMA-IR: Homeostatic model assessment-estimated insulin resistance.

group as was HOMA-IR (Table 1). BMD in both lower extremities was also significantly higher in the overweight group compared to the normal weight group (Table 1). In contrast, WB BMD, and spine BMD did not differ across groups. Similarly Lumbar spine BMD Z-score and total body less head (TBLH) BMD Z-score did not significantly differ between the two groups.

Robust regression with HOMA-IR as the dependent variable revealed that waist to hip ratio [$\beta = 12.72$ (3.88); $P < 0.01$], and activity time % of day [$\beta = -0.03$ (0.04); $P = 0.05$], but not percent trunk fat, were significantly related to HOMA-IR. Robust regression with WB-BMC as the dependent variable revealed a significant inverse association with percent trunk fat [$\beta = -2112.67$ (338.13); $P < 0.01$] (Table 2), and a positive association with HOMA-IR ($P = 0.03$) (Table 2) after controlling for potential confounders, gender and physical activity. BMD variables (WB BMD, and spine BMD) had inverse associations with percent trunk fat, but did not reach statistical significance. Apolipoprotein C-III which is considered to be a marker of insulin resistance^[17] did not differ significantly between the two groups and had no significant association with any BMD/BMC variables. Insulin values did not have a significant correlation with either WB-BMC (-0.12 , $P = 0.46$) or subtotal BMC (-0.16 , $P = 0.36$).

DISCUSSION

In this cross sectional study of bone parameters in normal-weight and overweight adolescents in the later stages of puberty, we show that higher trunk fat is associated with lower WB-BMC, whereas higher HOMA-IR is associated with higher WB-BMC after controlling for potential confounders. Both our groups were well matched for age and gender.

As expected, overweight subjects (Group 1) had a higher waist to hip ratio, percent trunk fat and HOMA-IR than normal-weight participants (Group 2). Waist to hip ratio is a reasonable surrogate for visceral adiposity, as is percent trunk fat^[14]. The positive relationship between HOMA-IR and waist to hip ratio observed in our study has been documented by others^[18,19]. Similarly higher BMC in obese and overweight subjects as observed in our study has been reported by others^[20,21].

However, data are lacking regarding associations of insulin resistance parameters with bone variables in adolescents. Overweight subjects had higher BMD than normal-weight subjects in the lower extremities, consistent with the impact of greater loading (from greater body size) in overweight adolescents at this weight bearing region. This has been previously shown in the Framingham study in adults^[22].

In our study, WB BMC was positively associated with HOMA-IR and negatively with the percent trunk fat, a good surrogate measure of visceral fat^[14]. In adults, insulin resistance has been shown to have an adverse impact on bone mass^[23]. In the MIDUS 11 study by Srikanthan *et al*^[6] with approximately 717 adult participants, higher HOMA-IR levels were associated with higher BMD in the femoral neck but with decreased femoral neck strength. The femoral neck is not a site recommended for measurement of BMD in adolescents as landmarks are not well defined at this age making repeat measurements difficult. While the study by Srikanthan *et al*^[6] included subjects with impaired glucose tolerance and diabetes, we excluded subjects with either of these conditions. Thus a higher HOMA IR value in our study would primarily be driven by higher insulin levels. A very elegant review by Fulzele *et al*^[24] details the effects of insulin on bone acquisition, acting *via* insulin receptors expressed on osteoblasts. Given the multitude of anabolic actions of insulin on bone, it is not surprising that higher insulin levels would be associated with higher bone mass, despite associated insulin resistance. Also, HOMA-IR is a very crude measure of insulin resistance, and additionally, in any particular individual, there can be differential/partial insulin resistance in different organ/tissues^[25,26]. Higher bone mass associated with higher HOMA-IR in overweight adolescents may mean that their osteoblasts are still sensitive to insulin signaling and its bone anabolic effects.

In contrast, recent literature suggests that visceral adiposity affects bone health adversely^[3,27]. In our study, there was no association between WB BMC and waist to hip ratio, however, there was a significant inverse association between WB BMC and percent trunk fat, a good indicator of abdominal adiposity relative to total fat mass and visceral adiposity^[14], consistent with other studies^[3,28]. While it is not surprising that we

observed this inverse relationship of percent trunk fat with WB BMC, the pathogenic mechanism underlying this relationship remains unclear. Our initial postulate that the adverse effect of abdominal adiposity on bone mass in overweight children may be mediated by insulin resistance secondary to higher abdominal adiposity did not hold true. Another possible pathogenic mechanism in overweight adults may be an atherogenic lipid profile^[29]. An elegant review by Tintut *et al.*^[29] discusses the relationship of poor bone mineralization with an adverse lipid profile, which may be mediated by vascular ischemia secondary to atherosclerosis. However, this is unlikely to be the mechanism linking low bone mass and abdominal adiposity in adolescents, in whom frank atherosclerosis is unusual despite an adverse lipid profile. In addition, we found no associations of lipids including apolipoprotein C III with bone variables. The possibility that certain adipokines secreted preferentially by visceral fat may mediate this effect needs to be further explored.

Higher cortisol and decreased growth hormone secretion is well reported in obese subjects. A higher fracture rate has been reported in obese adolescents^[11], however, our sample size was not large enough to draw any conclusions regarding fracture prevalence. It is interesting that physical activity did not differ significantly between our two groups, and may reflect low levels of activity in both groups. We do not have vitamin D levels on the subjects, however, the impact of vitamin D supplementation on bone mass in subjects who are vitamin D sufficient remains controversial^[30]. Finally, this is a cross sectional study and thus the results do not imply causation.

In conclusion, our data add to existing literature that suggests that abdominal adiposity has an adverse impact on WB BMC in adolescents. In addition, our study shows that this effect is not mediated by the increased insulin resistance associated with increased abdominal adiposity. Attention to body composition rather than just body weight is needed to counsel adolescents regarding optimal bone health. Further studies are needed to delineate the mechanisms by which visceral adiposity adversely affects bone health.

ARTICLE HIGHLIGHTS

Research background

Adult onset osteoporosis has its antecedent in childhood. With the rise in obesity epidemic, the effect of childhood obesity on bone health needs to be delineated. Historically in adults, higher body mass index (BMI) was believed to be bone protective with increased bone mineral density reported with higher BMI. Further studies have revealed this to be proportional to total lean mass rather than total fat mass. However, the relative distribution of fat in the body may also play a role, and visceral adiposity in particular has been demonstrated to have an adverse impact on bone. Visceral adiposity is directly associated with insulin resistance, and the link between obesity and bone health may be mediated by the underlying insulin resistance. Insulin is a bone anabolic hormone and higher insulin levels may result in increased bone formation. However, a state of insulin resistance may negate the beneficial effects of insulin on bone. This in fact has been suggested in recent studies in adults. However, data in children remain inconclusive.

Research motivation

The main motivation for this research study was to understand the effect of body composition and insulin resistance on bone health in children.

Research methods

The study showed that percent trunk fat was associated inversely with whole body bone mineral content (BMC), whereas homeostatic model of insulin resistance was associated positively with whole body BMC.

Research results

These results suggest that abdominal adiposity may have an adverse effect on whole body bone parameters and that this effect is not mediated by insulin resistance.

Research perspectives

Future research should look at other possible connection between adipose tissue and bone health.

REFERENCES

- 1 **Baim S**, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Lewiecki EM, Silverman S. Official Positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Position Development Conference. *J Clin Densitom* 2008; **11**: 75-91 [PMID: 18442754 DOI: 10.1016/j.jocd.2007.12.007]
- 2 **Beck TJ**, Petit MA, Wu G, LeBoff MS, Cauley JA, Chen Z. Does obesity really make the femur stronger? BMD, geometry, and fracture incidence in the women's health initiative-observational study. *J Bone Miner Res* 2009; **24**: 1369-1379 [PMID: 19292617 DOI: 10.1359/jbmr.090307]
- 3 **Gilsanz V**, Chalfant J, Mo AO, Lee DC, Dorey FJ, Mittelman SD. Reciprocal relations of subcutaneous and visceral fat to bone structure and strength. *J Clin Endocrinol Metab* 2009; **94**: 3387-3393 [PMID: 19531595 DOI: 10.1210/jc.2008-2422]
- 4 **Cohen A**, Dempster DW, Recker RR, Lappe JM, Zhou H, Zwahlen A, Müller R, Zhao B, Guo X, Lang T, Saeed I, Liu XS, Guo XE, Cremers S, Rosen CJ, Stein EM, Nickolas TL, McMahon DJ, Young P, Shane E. Abdominal fat is associated with lower bone formation and inferior bone quality in healthy premenopausal women: a transiliac bone biopsy study. *J Clin Endocrinol Metab* 2013; **98**: 2562-2572 [PMID: 23515452 DOI: 10.1210/jc.2013-1047]
- 5 **Fulzele K**, Riddle RC, DiGirolamo DJ, Cao X, Wan C, Chen D, Faugere MC, Aja S, Hussain MA, Brüning JC, Clemens TL. Insulin receptor signaling in osteoblasts regulates postnatal bone acquisition and body composition. *Cell* 2010; **142**: 309-319 [PMID: 20655471 DOI: 10.1016/j.cell.2010.06.002]
- 6 **Srikanthan P**, Crandall CJ, Miller-Martinez D, Seeman TE, Greendale GA, Binkley N, Karlamangla AS. Insulin resistance and bone strength: findings from the study of midlife in the United States. *J Bone Miner Res* 2014; **29**: 796-803 [PMID: 23983216 DOI: 10.1002/jbmr.2083]
- 7 **Shin D**, Kim S, Kim KH, Lee K, Park SM. Association between insulin resistance and bone mass in men. *J Clin Endocrinol Metab* 2014; **99**: 988-995 [PMID: 24423302 DOI: 10.1210/jc.2013-3338]
- 8 **de Liefde II**, van der Klift M, de Laet CE, van Daele PL, Hofman A, Pols HA. Bone mineral density and fracture risk in type-2 diabetes mellitus: the Rotterdam Study. *Osteoporos Int* 2005; **16**: 1713-1720 [PMID: 15940395 DOI: 10.1007/s00198-005-1909-1]
- 9 **Schwartz AV**, Sellmeyer DE, Ensrud KE, Cauley JA, Tabor HK, Schreiner PJ, Jamal SA, Black DM, Cummings SR; Study of Osteoporotic Features Research Group. Older women with diabetes have an increased risk of fracture: a prospective study. *J Clin Endocrinol Metab* 2001; **86**: 32-38 [PMID: 11231974 DOI: 10.1210/jcem.86.1.7139]
- 10 **Janghorbani M**, Feskanich D, Willett WC, Hu F. Prospective study of diabetes and risk of hip fracture: the Nurses' Health Study. *Diabetes Care* 2006; **29**: 1573-1578 [PMID: 16801581 DOI: 10.2337/dc06-0440]

- 11 **Goulding A**, Jones IE, Taylor RW, Williams SM, Manning PJ. Bone mineral density and body composition in boys with distal forearm fractures: a dual-energy x-ray absorptiometry study. *J Pediatr* 2001; **139**: 509-515 [PMID: 11598596 DOI: 10.1067/mpd.2001.116297]
- 12 **American Diabetes Association.** (2) Classification and diagnosis of diabetes. *Diabetes Care* 2015; **38** Suppl: S8-S16 [PMID: 25537714 DOI: 10.2337/dc15-S005]
- 13 **Matthews DR**, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412-419 [PMID: 3899825 DOI: 10.1007/BF00280883]
- 14 **Savgan-Gurol E**, Bredella M, Russell M, Mendes N, Klibanski A, Misra M. Waist to hip ratio and trunk to extremity fat (DXA) are better surrogates for IMCL and for visceral fat respectively than for subcutaneous fat in adolescent girls. *Nutr Metab (Lond)* 2010; **7**: 86 [PMID: 21143876 DOI: 10.1186/1743-7075-7-86]
- 15 **Gardner AW**, Montgomery PS, Scott KJ, Afaq A, Blevins SM. Patterns of ambulatory activity in subjects with and without intermittent claudication. *J Vasc Surg* 2007; **46**: 1208-1214 [PMID: 17919876 DOI: 10.1016/j.jvs.2007.07.038]
- 16 **McDonald CM**, Widman L, Abresch RT, Walsh SA, Walsh DD. Utility of a step activity monitor for the measurement of daily ambulatory activity in children. *Arch Phys Med Rehabil* 2005; **86**: 793-801 [PMID: 15827934 DOI: 10.1016/j.apmr.2004.10.011]
- 17 **Lee HY**, Birkenfeld AL, Jornayvaz FR, Jurczak MJ, Kanda S, Popov V, Frederick DW, Zhang D, Guigni B, Bharadwaj KG, Choi CS, Goldberg IJ, Park JH, Petersen KF, Samuel VT, Shulman GI. Apolipoprotein CIII overexpressing mice are predisposed to diet-induced hepatic steatosis and hepatic insulin resistance. *Hepatology* 2011; **54**: 1650-1660 [PMID: 21793029 DOI: 10.1002/hep.24571]
- 18 **Stepien M**, Stepien A, Wlazel RN, Paradowski M, Rizzo M, Banach M, Rysz J. Predictors of insulin resistance in patients with obesity: a pilot study. *Angiology* 2014; **65**: 22-30 [PMID: 23267236 DOI: 10.1177/0003319712468291]
- 19 **Du T**, Yuan G, Zhang M, Zhou X, Sun X, Yu X. Clinical usefulness of lipid ratios, visceral adiposity indicators, and the triglycerides and glucose index as risk markers of insulin resistance. *Cardiovasc Diabetol* 2014; **13**: 146 [PMID: 25326814 DOI: 10.1186/s12933-014-0146-3]
- 20 **Maggio AB**, Belli DC, Puigdefabregas JW, Rizzoli R, Farpour-Lambert NJ, Beghetti M, McLin VA. High bone density in adolescents with obesity is related to fat mass and serum leptin concentrations. *J Pediatr Gastroenterol Nutr* 2014; **58**: 723-728 [PMID: 24399210 DOI: 10.1097/MPG.0000000000000297]
- 21 **Leonard MB**, Shults J, Wilson BA, Tershakovec AM, Zemel BS. Obesity during childhood and adolescence augments bone mass and bone dimensions. *Am J Clin Nutr* 2004; **80**: 514-523 [PMID: 15277178]
- 22 **Felson DT**, Zhang Y, Hannan MT, Anderson JJ. Effects of weight and body mass index on bone mineral density in men and women: the Framingham study. *J Bone Miner Res* 1993; **8**: 567-573 [PMID: 8511983 DOI: 10.1002/jbmr.5650080507]
- 23 **Shin D**. Association between metabolic syndrome, radiographic knee osteoarthritis, and intensity of knee pain: results of a national survey. *J Clin Endocrinol Metab* 2014; **99**: 3177-3183 [PMID: 24780047 DOI: 10.1210/jc.2014-1043]
- 24 **Fulzele K**, Clemens TL. Novel functions for insulin in bone. *Bone* 2012; **50**: 452-456 [PMID: 21723973 DOI: 10.1016/j.bone.2011.06.018]
- 25 **Parker VE**, Savage DB, O'Rahilly S, Semple RK. Mechanistic insights into insulin resistance in the genetic era. *Diabet Med* 2011; **28**: 1476-1486 [PMID: 21992440 DOI: 10.1111/j.1464-5491.2011.03463.x]
- 26 **Brown MS**, Goldstein JL. Selective versus total insulin resistance: a pathogenic paradox. *Cell Metab* 2008; **7**: 95-96 [PMID: 18249166 DOI: 10.1016/j.cmet.2007.12.009]
- 27 **Júnior IF**, Cardoso JR, Christofaro DG, Codogno JS, de Moraes AC, Fernandes RA. The relationship between visceral fat thickness and bone mineral density in sedentary obese children and adolescents. *BMC Pediatr* 2013; **13**: 37 [PMID: 23510224 DOI: 10.1186/1471-2431-13-37]
- 28 **Russell M**, Mendes N, Miller KK, Rosen CJ, Lee H, Klibanski A, Misra M. Visceral fat is a negative predictor of bone density measures in obese adolescent girls. *J Clin Endocrinol Metab* 2010; **95**: 1247-1255 [PMID: 20080853 DOI: 10.1210/jc.2009-1475]
- 29 **Tintut Y**, Demer LL. Effects of bioactive lipids and lipoproteins on bone. *Trends Endocrinol Metab* 2014; **25**: 53-59 [PMID: 24183940 DOI: 10.1016/j.tem.2013.10.001]
- 30 **Winzenberg T**, Powell S, Shaw KA, Jones G. Effects of vitamin D supplementation on bone density in healthy children: systematic review and meta-analysis. *BMJ* 2011; **342**: c7254 [PMID: 21266418 DOI: 10.1136/bmj.c7254]

P- Reviewer: Arslan N, Urganci N, Wang R, Watanabe T

S- Editor: Ji FF **L- Editor:** A **E- Editor:** Li RF



Retrospective Cohort Study

Neither hereditary periodic fever nor periodic fever, aphthae, pharyngitis, adenitis: Undifferentiated periodic fever in a tertiary pediatric center

Silvia De Pauli, Sara Lega, Serena Pastore, Domenico Leonardo Grasso, Anna Monica Rosaria Bianco, Giovanni Maria Severini, Alberto Tommasini, Andrea Taddio

Silvia De Pauli, Sara Lega, Andrea Taddio, Department of Medicine, Surgery and Health, University of Trieste, Trieste 34142, Italy

Sara Lega, Serena Pastore, Domenico Leonardo Grasso, Anna Monica Rosaria Bianco, Giovanni Maria Severini, Alberto Tommasini, Andrea Taddio, Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste 34137, Italy

ORCID number: Silvia De Pauli (0000-0002-0486-0441); Sara Lega (0000-0003-4028-4194); Serena Pastore (0000-0003-4697-0777); Domenico Leonardo Grasso (0000-0002-0617-8630); Anna Monica Rosaria Bianco (0000-0001-8101-9659); Giovanni Maria Severini (0000-0002-5790-2000); Alberto Tommasini (0000-0002-6943-7927); Andrea Taddio (0000-0001-6817-4953).

Author contributions: De Pauli S wrote the manuscript and cared for patients; Lega S discussed and revised critically the manuscript; Pastore S discussed and corrected the draft; Grasso DL performed ENT evaluation and revised the manuscript; Bianco AM performed genetic analyses and revised the manuscript; Severini GM reviewed the genetic content and discussed results; Tommasini A cared for patients and discussed the work; Taddio A cared for patients and critically discussed the manuscript; De Pauli S and Lega S contributed equally to the work.

Supported by the Institute for Maternal and Child Health IRCCS Burlo Garofolo, No. RC36/11.

Institutional review board statement: The study was approved by the IRB at the IRCCS Burlo Garofolo.

Informed consent statement: The written informed consent was obtained by all the subjects recruited in the study or by their parents/guardians.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Alberto Tommasini, MD, PhD, Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Via dell'Istria 65/1, Trieste 34137, Italy. alberto.tommasini@burlo.trieste.it
Telephone: +39-40-3785422
Fax: +39-40-3785452

Received: September 23, 2017

Peer-review started: September 24, 2017

First decision: November 27, 2017

Revised: December 3, 2017

Accepted: December 14, 2017

Article in press: December 14, 2017

Published online: February 8, 2018

Abstract

AIM

To describe the frequency and clinical characteristics of patients with undifferentiated periodic fever (UPF) and to investigate whether a clinical classification of UPF based on the PRINTO-Eurofever score can help predicting the response to treatment and the outcome at follow-up.

METHODS

Clinical and therapeutic information of patients with

recurrent fever who presented at a single pediatric rheumatology center from January 2006 through April 2016 were retrospectively collected. Patients with a clinical suspicion of hereditary periodic fever (HPF) syndrome and patients with clinical picture of periodic fever, aphthae, pharyngitis, adenitis (PFAPA) who were refractory to tonsillectomy underwent molecular analysis of five HPF-related genes: *MEFV* (NM_000243.2), *MVK* (NM_000431.3), *TNFRSF1A* (NM_001065.3), *NLRP3* (NM_001079821.2), *NLRP12* (NM_001277126.1). All patients who had a negative genetic result were defined as UPF and further investigated. PRINTO-Eurofever score for clinical diagnosis of HPF was calculated in all cases.

RESULTS

Of the 221 patients evaluated for periodic fever, twelve subjects with a clinical picture of PFAPA who were refractory to tonsillectomy and 22 subjects with a clinical suspicion of HPF underwent genetic analysis. Twenty-three patients (10.4%) resulted negative and were classified as UPF. The median age at presentation of patients with UPF was 9.5 mo (IQR 4-24). Patients with UPF had a higher frequency of aphthae (52.2% *vs* 0%, $P = 0.0026$) and musculoskeletal pain (65.2% *vs* 18.2%, $P = 0.0255$) than patients with genetic confirmed HPF. Also, patients with UPF had a higher frequency of aphthous stomatitis (52.2% *vs* 10.7%, $P < 0.0001$), musculoskeletal pain (65.2% *vs* 8.0%, $P < 0.0001$), and abdominal pain (52.2% *vs* 4.8%, $P < 0.0001$) and a lower frequency of pharyngitis (56.6% *vs* 81.3%, $P = 0.0127$) compared with typical PFAPA in the same cohort. Twenty-one of 23 patients with UPF (91.3%) received steroids, being effective in 16; 13 (56.2%) were given colchicine, which was effective in 6. Symptoms resolution occurred in 2 patients with UPF at last follow-up. Classification according to the PRINTO-Eurofever score did not correlate with treatment response and prognosis.

CONCLUSION

UPF is not a rare diagnosis among patients with periodic fever. Clinical presentation place UPF half way on a clinical spectrum between PFAPA and HPF. The PRINTO-Eurofever score is not useful to predict clinical outcome and treatment response in these patients.

Key words: Hereditary periodic fever syndromes; Therapy; Genetics; Autoinflammatory diseases; Undifferentiated periodic fever

© The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Children with non-infectious recurrent fever more often fall into two diagnostic categories. The first and most common is periodic fever, aphthae, pharyngitis, adenitis (PFAPA), the second, far more rare, are hereditary periodic fevers. Very recently a third category has been increasingly recognized, and is that of undifferentiated periodic fevers or undifferentiated

periodic fever (UPF). UPF include patients who do not meet the diagnostic criteria for PFAPA or for a monogenic disease. The clinical presentation and management of patients with UPF are poorly defined. In this study, the authors describe a cohort of patients with UPF showing that: (1) The clinical manifestations are on a half way of clinical spectrum between PFAPA and hereditary periodic fever; (2) PRINTO-Eurofever score is not useful to guide treatment choices and does not predict disease course; and (3) Both steroids and colchicine are useful to control symptoms in most cases. The authors conclude that further studies are needed to better define UPF and guide their management in clinical practice.

De Pauli S, Lega S, Pastore S, Grasso DL, Bianco AMR, Severini GM, Tommasini A, Taddio A. Neither hereditary periodic fever nor periodic fever, aphthae, pharyngitis, adenitis: Undifferentiated periodic fever in a tertiary pediatric center. *World J Clin Pediatr* 2018; 7(1): 49-55 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i1/49.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i1.49>

INTRODUCTION

Periodic fever is defined as recurrences of seemingly unprovoked episodes of fever that last from a few days to a few weeks, separated by symptom-free intervals of variable duration^[1].

The most common cause of periodic fever syndrome in children is PFAPA (periodic fever, aphthae, pharyngitis, adenitis), an autoinflammatory condition^[2] characterized by recurrence of fever associated with aphthous stomatitis, pharyngitis, and/or cervical adenopathy. The diagnosis of PFAPA is based on Thomas criteria: recurring fevers that begin before age 5 and are accompanied by at least one of the clinical signs aphthous stomatitis, pharyngitis or adenitis, without upper respiratory infection^[3]. The pathogenesis of PFAPA is likely multifactorial, but evidence of familial recurrence of this syndrome may support a genetic predisposition. Patient with PFAPA respond to steroids^[2] and heal spontaneously, usually in few years, or after tonsillectomy without sequelae^[4,5]. Lack of response to tonsillectomy in PFAPA is uncommon and should raise the suspicion of a monogenic condition^[6,7].

Other rarer periodic fever syndromes are due to definite monogenic defects involving mechanisms of inflammation (hereditary periodic fevers - HPF). The first described was familial mediterranean fever (FMF) which has been linked to *MEFV* gene in late nighties. Afterwards, a number of HPF syndromes have been described, and their genetic bases has been provided. This is the case for example of: tumor necrosis factor receptor-associated periodic syndrome (TRAPS), associated with *TNFRSF1A* gene defects, hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), related to *MVK* gene, and cryopyrin-associated periodic syndromes (CAPS) for which defects on either *NLRP3* or *NLRP12* have been

identified^[8,9].

Timely diagnosis of HPF is essential since effective therapies are now available, and complications, such as amyloidosis and sensor neural impairment, can be avoided^[10].

The term undifferentiated periodic fever (UPF) has been increasingly used to define those patients presenting with a complaint of periodic fever in whom the diagnostic criteria for PFAPA are not satisfied and genetic work-up for periodic fever gives a negative result.

On a practical ground, subjects with PFAPA who are refractory to tonsillectomy and/or to steroids may be as well included in the group of UPF.

Even though patients with UPF are increasingly recognized in clinical practice, the only epidemiologic data available comes from the Eurofever Registry were, in 2014, patients with an "undefined periodic fever" accounted for almost 9% of cases^[11].

The management of such patients is challenging, as clinical manifestations are poorly described and the prognosis and response to treatment are unknown. Federici *et al.*^[12] recently validated a score for clinical classification of patients with periodic fever into the main four phenotypes of HPF (PRINTO-Eurofever score), and proposed that it could be used to classify patients with periodic fever in daily practice. The score considers age at disease onset, ethnicity and the presence or absence of specific clinical symptoms.

With the present study, we aimed to describe the frequency and clinical characteristics of patients with a diagnosis of UPF. Moreover, we calculated the PRINTO-Eurofever score in subjects with UPF to investigate if a clinical classification in HPF-like phenotypes (clinical score of HPF in the absence of genetic confirmation) could help predicting the response to treatment and prognosis.

MATERIALS AND METHODS

Patients

This was a retrospective cohort study conducted at a single Rheumatology Center caring for pediatric patients with rheumatologic and autoinflammatory conditions. The Study was approved by the local Ethics Committee. Clinical charts of patients who received a diagnosis of periodic fever during a ten-year period, from January 2006 through April 2016, were reviewed. Patients older than 18 years at the time of data collection were not included as they were no more referred to our Institute.

Criteria

All the patients with periodic fever were included in the study. Subjects with a clinical suspicion of HPF and subjects with a suspicion of PFAPA (Thomas's criteria) who didn't respond to steroid treatment or had a recurrence of symptoms after tonsillectomy underwent genetic analysis for five genes mostly involved in HPF, namely: *MEFV* (NM_000243.2) for familial mediterranean fever (FMF), *MVK* (NM_000431.3) for mevalonate kinase

deficiency (MKD), *TNFRSF1A* (NM_001065.3) for TNF α receptor associated periodic syndrome (TRAPS), *NLRP3* (NM_001079821.2) and *NLRP12* (NM_001277126.1) for familial cold urticaria syndrome. Patients with known causative mutation were diagnosed with the corresponding disorder.

Subjects with negative results or polymorphisms of unknown significance were considered as UPF^[13], irrespective of whether they came from the group of PFAPA who were refractory to tonsillectomy or patients suspected with HPF. This choice was based on the consideration that both subjects with a clinical suspicion of HPF and subjects with a suspicion of PFAPA, refractory to tonsillectomy or to steroids, share the same problems as concerns the lack of a definite prognosis and of a therapeutic approach.

Thus, three groups of subjects were finally identified based on clinical and genetical features: Typical PFAPA, genetically confirmed HPF, UPF.

Data collection

Data collected included information on: gender, family history, ethnicity, duration of fever episodes, presence of pharyngitis, adenitis or aphthae, presence of musculoskeletal, chest or abdominal pain, diarrhea, vomiting, skin rash, conjunctivitis, and sensory neural hearing loss. Data were collected at disease onset and during follow-up. PRINTO-Eurofever score was calculated retrospectively at last follow-up^[12]. Based on PRINTO-Eurofever score, patients who scored positive were assigned to a specific HPF phenotype according to the same scoring system. A possible relationship between the clinical diagnosis based on PRINTO-Eurofever criteria and response to treatment at follow up was assessed.

Statistical analysis

Statistical analysis were made using GraphPad Prism 5 software. Categorical variables were summarized as frequency and percentage and were compared across independent groups by the Fisher's exact test (two tailed, confidence interval 95%). Numerical variables with asymmetrical distribution were summarized by median and interquartile range (IQR) and were compared by the Kruskal-Wallis test. A *P* value < 0.05 was considered for significance.

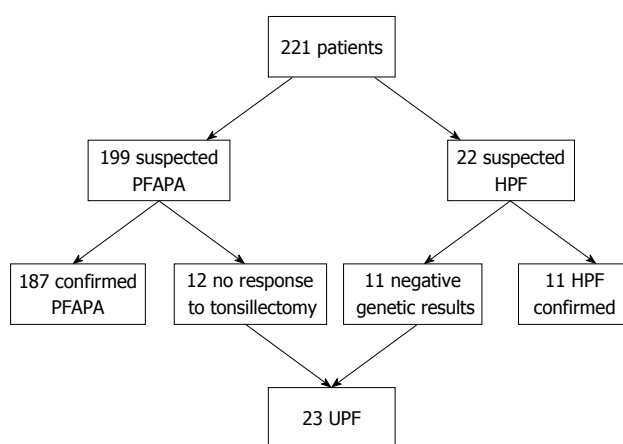
RESULTS

During a ten-year period, 221 patients were evaluated for periodic fever. Twenty-two patients had a suspicion of HPF and a definite diagnosis could be genetically confirmed in 11 of them (5 MKD, 3 TRAPS, 2 FMF, 1 FCU). The other 11 subjects resulted negative and were considered as UPF.

PFAPA was suspected in 199 subjects, 12 of whom did not respond to steroids or persisted after tonsillectomy and underwent genetic analysis. None of these

Table 1 Baseline characteristics and symptoms distribution of patients with periodic fever in our cohort

	Undifferentiated periodic fever (<i>n</i> = 23)	PFAPA (<i>n</i> = 187)	HPF (<i>n</i> = 11)
Females, <i>n</i> (%)	18 (70%)	74 (38%)	7 (63%)
Ethnicity, <i>n</i>			
EU	20	183	11
Arabian	2	2	0
Mix	1	2	0
Median age at onset, mo (IQR)	9.5 (4-24)	12.5 (2.5-96)	9 (1-174)
Median age at first visit, mo (IQR)	51 (33-113)	42.15 (8-120)	48 (12-216)
Symptoms, <i>n</i> (%)			
Pharyngitis	13 (56.6%)	152 (81.3%)	4 (36.3%)
Aphthae	12 (52.2%)	20 (10.7%)	0 (0%)
Chest pain	0 (0%)	0 (0%)	1 (9%)
Abdominal pain	12 (52.2%)	9 (4.8%)	6 (54.5%)
Musculoskeletal pain	15 (65.2%)	15 (8.0%)	2 (18.2%)

**Figure 1** Selection of undifferentiated periodic fever cohort. PFAPA: Periodic fever, aphthae, pharyngitis, adenitis; HPF: Hereditary periodic fever; UPF: Undifferentiated periodic fever.

subjects had causative mutations of HPF genes. In 6 patients, variants of unknown significance were found. Four patients had heterozygous mutations of which two were in the *MEFV* gene (P369S-R408Q and V726A), one in the *MVK* gene (V377I) and one in *NLRP12* (variation H304Y). Two patients had a homozygous R202Q variant in *MEFV*. Thus, all 12 subjects were considered as UPF.

Overall, a total of 23 patients (10%) met the diagnosis of UPF and were thus included in the analysis. UPF Cohort selection is reported in Figure 1.

Baseline characteristics of patients with UPF and comparison with HPF and PFAPA

Baseline demographic and clinical characteristics of patients are described in Table 1.

The most frequent complaints at first visit in UPF were exudative pharyngitis (13 patients, 56.6%), musculoskeletal pain (15 pt, 65.2%), aphthous stomatitis (12 pt, 52.2%) and abdominal pain (12 pt, 52.2%). No patient suffered from chest pain. Abdominal pain in the UPF group was reported as mild to moderate and never led to an evaluation for acute abdomen.

Median duration of disease at last follow-up was 6.3 years (IQR 0.9-17.8 year). Median follow-up since inclusion in the study was 3.3 years (IQR 0.3-9.4 year).

Subjects with UPF had a similar age at disease onset compared with HPF ($P = 0.9$), while they had an earlier onset compared with PFAPA ($P = 0.008$).

Compared with HPF, patients with UPF were more likely to have aphthae (52.2% vs 0%, $P = 0.0026$) and musculoskeletal pain (65.2% vs 18.2%, $P = 0.0255$), while compared with PFAPA they were more likely to have aphthous stomatitis (52.2% vs 10.7%, $P < 0.0001$), musculoskeletal pain (65.2% vs 8.0%, $P < 0.0001$), abdominal pain (52.2% vs 4.8%, $P < 0.0001$) but were less likely to have pharyngitis (56.6% vs 81.3%, $P = 0.0127$).

Therapeutic strategies received at any time and response to therapy in UPF

An oral glucocorticoid (betamethasone) was the first therapeutic choice in 21/23 patients. In 16 patients (69.5%), oral administration of betamethasone determined immediate resolution of the acute episode; in 11 patients, a standard dose of 0.1 mg/kg of betamethasone was effective, in 5 higher doses of 0.2-0.3 mg/kg were required. In 8 patients, who came from the group with initial suspicion of PFAPA, acute episodes became more frequent after glucocorticoid treatment. Tonsillectomy was performed in 12 patients being ineffective in all of them.

Thirteen patients were treated with daily oral colchicine (0.5-1.5 mg/die), which reduced or abated symptoms recurrence in 6 patients (46%). All patients receiving colchicine had been previously treated with steroids. The reason for switching to colchicine was steroids being ineffective in 3 patients, and need for too high or too frequent corticosteroid doses in 10 patients.

At last follow-up, 21/23 (91%) were still receiving medical treatment for the management of acute symptoms: 10 patients received corticosteroids during acute episodes; 7 patients were on daily colchicine and 4 patients were receiving non-steroidal antiinflammatory drugs (NSAID); 2 patients healed spontaneously.

Classification of patients based on PRINTO-Eurofever score at baseline and response to therapy

At baseline, 11 subjects could be classified as HPF-like: 3 patients had a positive score for FMF, 5 for MKD, 3 for

Table 2 Treatment response in undifferentiated periodic fever cohort as a whole and in undifferentiated periodic fever subgroups according to PRINTO-Eurofever classification at baseline¹

	Undifferentiated periodic fever (n = 23)	Positive score (n = 11)	Negative score (n = 12)
Glucocorticoids			
Total	21	11	12
Responsive	16	9	10
Not responsive	5	2	2
Colchicine			
Total	13	6	7
Responsive	6	4	2
Not responsive	7	2	5
Tonsillectomy			
Total	12	5	7
Responsive	0	0	0
Not responsive	12	5	7

¹Statistical significance could not be calculated, due to the small size of the sample.

TRAPS, 1 for CAPS (1 patient was positive for FMF and MKD). Twelve patients had negative scores for HPF.

We didn't observe a clear relationship between PRINTO-Eurofever score at baseline and response to treatment received at any time. In particular, no patient who responded to colchicine had a clinical score supportive of FMF. As opposite, 2 out of 7 patients who did not respond to colchicine had a positive score for FMF.

DISCUSSION

In a single pediatric rheumatology center, 10% of patients presenting with a complaint of periodic fever could be classified as UPF. Even if PFAPA was by far the most frequent diagnosis, UPF was a more common diagnosis compared to HPF.

Age at symptoms presentation patients with UPF was quite varied, ranging from 2 to 111 mo. Interestingly, the median age at disease onset in of UPF was closer to that of HPF than that of PFAPA, similarly to what has been reported in the literature^[11], suggesting the possibility of a stronger contribution of genetic factors in UPF compared with PFAPA.

Musculoskeletal pain and recurrent pharyngitis were the most frequent complaints followed by recurrence of aphthous stomatitis and abdominal pain. The high frequency of pharyngitis and stomatitis reflects the fact that the majority of patients classified as UPF had been initially diagnosed as PFAPA. It should be noted, however, that all these patients had a more complex phenotype compared to patients with a definitive diagnosis of PFAPA, as most of them complained of musculoskeletal or abdominal pain, in addition to pharyngitis.

The frequency of abdominal pain alone was similar in UPF and HPF, and in both cases it was significantly higher than in PFAPA. Notably, chest pain was never reported in patients with UPF.

According to these observations, UPF seem to be half way on a clinical spectrum of disease severity ranging from PFAPA to HPF. Patients with UPF in fact had more frequent "extrapharyngeal" symptoms, namely

musculoskeletal and abdominal pain, compared to PFAPA but despite their frequency, these symptoms were never as severe as those reported in HPF.

Overall, steroids were an effective strategy to control symptoms in a high proportion of patients.

For patients who needed steroids at high doses or frequency, daily oral colchicine was a useful alternative strategy to control symptom recurrence.

Tonsillectomy did not resolve fever recurrence in UPF patients, but this observation is biased, as this was one of the criteria that we chose for patients' inclusion in the UPF group.

We evaluated if a clinical classification of our cases could have been used to predict the response to therapy. So far, the only suitable classification proposed for subjects with periodic fever syndromes is the PRINTO-Eurofever score, which was developed to help experts classifying patients with suspected autoinflammatory fever syndromes without relying on genetic analyses. The score was calculated based on clinical features selected on a multivariate analysis on a large group of patients with different periodic fevers^[12].

We showed that PRINTO-Eurofever classification at baseline could not predict response to any treatment.

Thus, even though the short time to last follow up for some patients, PRINTO-Eurofever score at baseline seems not to be predictive of symptoms persistence over time.

Several limitations of the study are acknowledged. Due to its retrospective design, clinical data were not systematically collected. The sample size is small, and recruitment occurred at one Tertiary-referral Clinic thus limiting the generalizability of our observation. Moreover, the median time to follow-up was too short to estimate long-term prognosis. In fact, considering that a significant proportion of UPF showed both recurrent aphthous ulcers and abdominal or musculoskeletal pain, it is still possible that part of them will develop a Behcet disease (BD) on a longer follow-up. Indeed, Cantarini *et al.*^[14] recently showed that many subjects with adult BD complained of periodic fever and aphthae during

childhood. Moreover, we cannot exclude that some patient with UPF could have a different monogenic disorder, but this seem unlikely at present, given that increasing the number of candidate genes in genetic panels did not result in increased diagnoses^[15].

In conclusion, according to our observation patients with UPF seem not to be rare in clinical practice. Clinical presentation places them half way on a clinical spectrum between PFAPA and HPF. Classification of patients with UPF into a specific HPF phenotype according PRINTO-Eurofever criteria is not useful to guide treatment choice and does not predict disease prognosis. Given the above-mentioned limitation, what we observed represent and initial attempt to describe a poorly defined subset of patients with periodic fever commonly encountered in clinical practice. Further studies are needed to better define patients with UPF and guide their management in clinical practice.

ARTICLE HIGHLIGHTS

Research background

Undifferentiated periodic fevers (UPF) include periodic fever not meeting the diagnostic criteria for typical PFAPA or for hereditary periodic fever syndromes. Even if UPF are increasingly recognized, there is currently no recommendation to guide the management of children with this condition.

Research motivation

Clinical criteria to classify periodic fever without the help of genetic analyses have been proposed by PRINTO-Eurofever, and might be particularly useful for subjects with UPF. Thus, we studied the clinical features of our patients in relation with their scores in the PRINTO-Eurofever classification.

Research objectives

Our study aims at improving knowledge on UPF and at evaluating if the application of the PRINTO-Eurofever classification can help the clinical management of these patients.

Research methods

A data base was filled in by retrospective review of clinical records, follow-up visits and phone calls. A structured questionnaire was used to classify all the subjects with the PRINTO-Eurofever score. The response to therapies and the prognosis at follow-up was compared with the clinical diagnosis obtained with the PRINTO-Eurofever score.

Research results

The clinical manifestations are on a half way of clinical spectrum between PFAPA and hereditary periodic fever. PRINTO-Eurofever score is not useful to guide treatment choices and does not predict disease course. Both steroids and colchicine are useful to control symptoms in most cases.

Research conclusions

UPF are as common as hereditary periodic fever, however knowledge on prognosis and response to therapies in these patients is lacking.

Research perspectives

Multicenter studies and experts' agreement are needed to develop recommendations for the management of UPF.

REFERENCES

- 1 McDermott MF, Frenkel J. Hereditary periodic fever syndromes. *Neth J Med* 2001; **59**: 118-125 [PMID: 11583827 DOI: 10.1016/

- 50300-2977(01)00149-8]
- 2 Stojanov S, Lapidus S, Chitkara P, Feder H, Salazar JC, Fleisher TA, Brown MR, Edwards KM, Ward MM, Colbert RA, Sun HW, Wood GM, Barham BK, Jones A, Aksentijevich I, Goldbach-Mansky R, Athreya B, Barron KS, Kastner DL. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is a disorder of innate immunity and Th1 activation responsive to IL-1 blockade. *Proc Natl Acad Sci U S A* 2011; **108**: 7148-7153 [PMID: 21478439 DOI: 10.1073/pnas.1103681108]
- 3 Thomas KT, Feder HM Jr, Lawton AR, Edwards KM. Periodic fever syndrome in children. *J Pediatr* 1999; **135**: 15-21 [PMID: 10393598 DOI: 10.1016/S0022-3476(99)70321-5]
- 4 Manthiram K, Nesbitt E, Morgan T, Edwards KM. Family History in Periodic Fever, Aphthous Stomatitis, Pharyngitis, Adenitis (PFAPA) Syndrome. *Pediatrics* 2016; **138**: pii e20154572 [PMID: 27565549 DOI: 10.1542/peds.2015-4572]
- 5 Peridis S, Koudounakis E, Theodoridis A, Stefanaki K, Helmig G, Houlakis M. Surgical outcomes and histology findings after tonsillectomy in children with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. *Am J Otolaryngol* 2010; **31**: 472-475 [PMID: 20015793 DOI: 10.1016/j.amjoto.2009.06.005]
- 6 Lantto U, Koivunen P, Tapiainen T, Renko M. Long-Term Outcome of Classic and Incomplete PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis) Syndrome after Tonsillectomy. *J Pediatr* 2016; **179**: 172-177.e1 [PMID: 27692464 DOI: 10.1016/j.jpeds.2016.08.097]
- 7 Pehlivan E, Adrovic A, Sahin S, Barut K, Kul Cinar O, Kasapcopur O. PFAPA Syndrome in a Population with Endemic Familial Mediterranean Fever. *J Pediatr* 2017; **192**: 253-255 [PMID: 29031862 DOI: 10.1016/j.jpeds.2017.08.078]
- 8 Aksentijevich I, Nowak M, Mallah M, Chae JJ, Watford WT, Hofmann SR, Stein L, Russo R, Goldsmith D, Dent P, Rosenberg HF, Austin F, Remmers EF, Balow JE Jr, Rosenzweig S, Komarow H, Shoham NG, Wood G, Jones J, Mangra N, Carrero H, Adams BS, Moore TL, Schikler K, Hoffman H, Lovell DJ, Lipnick R, Barron K, O'Shea JJ, Kastner DL, Goldbach-Mansky R. De novo CIAS1 mutations, cytokine activation, and evidence for genetic heterogeneity in patients with neonatal-onset multisystem inflammatory disease (NOMID): a new member of the expanding family of pyrin-associated autoinflammatory diseases. *Arthritis Rheum* 2002; **46**: 3340-3348 [PMID: 12483741 DOI: 10.1002/art.10688]
- 9 Martinon F, Aksentijevich I. New players driving inflammation in monogenic autoinflammatory diseases. *Nat Rev Rheumatol* 2015; **11**: 11-20 [PMID: 25247411 DOI: 10.1038/nrrheum.2014.158]
- 10 Touitou I, Galeotti C, Rossi-Semerano L, Hentgen V, Piram M, Koné-Paut I, CeRéMAI, French reference center for autoinflammatory diseases. The expanding spectrum of rare monogenic autoinflammatory diseases. *Orphanet J Rare Dis* 2013; **8**: 162 [PMID: 24131530 DOI: 10.1186/1750-1172-8-162]
- 11 Toplak N, Frenkel J, Ozen S, Lachmann HJ, Woo P, Koné-Paut I, De Benedetti F, Neven B, Hofer M, Dolezalova P, Kümmerle-Deschner J, Touitou I, Hentgen V, Simon A, Girschick H, Rose C, Wouters C, Vesely R, Arostegui J, Stojanov S, Ozdogan H, Martini A, Ruperto N, Gattorno M; Paediatric Rheumatology International Trials Organisation (PRINTO), Eurotraps and Eurofever Projects. An international registry on autoinflammatory diseases: the Eurofever experience. *Ann Rheum Dis* 2012; **71**: 1177-1182 [PMID: 22377804 DOI: 10.1136/annrheumdis-2011-200549]
- 12 Federici S, Sormani MP, Ozen S, Lachmann HJ, Amarian G, Woo P, Koné-Paut I, Dewarrat N, Cantarini L, Insalaco A, Uziel Y, Rigante D, Quartier P, Demirkaya E, Herlin T, Meini A, Fabio G, Kallinich T, Martino S, Butbul AY, Olivieri A, Kuemmerle-Deschner J, Neven B, Simon A, Ozdogan H, Touitou I, Frenkel J, Hofer M, Martini A, Ruperto N, Gattorno M; Paediatric Rheumatology International Trials Organisation (PRINTO) and Eurofever Project. Evidence-based provisional clinical classification criteria for autoinflammatory periodic fevers. *Ann Rheum Dis* 2015; **74**: 799-805 [PMID: 25637003 DOI: 10.1136/annrheumdis-2014-206580]

- 13 **Shinar Y**, Obici L, Aksentijevich I, Bennetts B, Austrup F, Ceccherini I, Costa JM, De Leener A, Gattorno M, Kania U, Kone-Paut I, Lezer S, Livneh A, Moix I, Nishikomori R, Ozen S, Phylactou L, Risom L, Rowczenio D, Sarkisian T, van Gijn ME, Witsch-Baumgartner M, Morris M, Hoffman HM, Touitou I; European Molecular Genetics Quality Network. Guidelines for the genetic diagnosis of hereditary recurrent fevers. *Ann Rheum Dis* 2012; **71**: 1599-1605 [PMID: 22661645 DOI: 10.1136/annrheumdis-2011-201271]
 - 14 **Cantarini L**, Vitale A, Bersani G, Nieves LM, Cattalini M, Lopalco G, Caso F, Costa L, Iannone F, Lapadula G, Galeazzi M, Ceribelli A, Brunetta E, Selmi C, Rigante D. PFAPA syndrome and Behçet's disease: a comparison of two medical entities based on the clinical interviews performed by three different specialists. *Clin Rheumatol* 2016; **35**: 501-505 [PMID: 25665824 DOI: 10.1007/s10067-015-2890-5]
 - 15 **Rusmini M**, Federici S, Caroli F, Grossi A, Baldi M, Obici L, Insalaco A, Tommasini A, Caorsi R, Gallo E, Olivieri AN, Marzano A, Coviello D, Ravazzolo R, Martini A, Gattorno M, Ceccherini I. Next-generation sequencing and its initial applications for molecular diagnosis of systemic auto-inflammatory diseases. *Ann Rheum Dis* 2016; **75**: 1550-1557 [PMID: 26386126 DOI: 10.1136/annrheumdis-2015-207701]
- P- Reviewer:** Al-Biltagi M, Fretzayas A, Kute VBB, Sergi C, Watanabe T, Wang R, Yellanthoor RB **S- Editor:** Kong JX **L- Editor:** A **E- Editor:** Li RF



Retrospective Study

Pediatricians lack knowledge for the diagnosis and management of functional constipation in children over 6 mo of age

Ariani Widodo, Badriul Hegar, Yvan Vandenplas

Ariani Widodo, Badriul Hegar, Department of Child Health, Universitas Indonesia, Jakarta 10430, Indonesia

Yvan Vandenplas, Department of Pediatrics, UZ Brussel, Vrije Universiteit Brussel, Laarbeeklaan, Brussels 1090, Belgium

Author contributions: Widodo A and Hegar B developed the questionnaire and collected and analysed the data of the research; Widodo A and Vandenplas Y wrote the manuscript, which was corrected and approved by Hegar B.

Institutional review board statement: The Universitas Indonesia in Jakarta approved the study protocol.

Conflict-of-interest statement: The authors report no potential conflict of interest related to this manuscript.

Data sharing statement: No additional data are available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Unsolicited manuscript

Correspondence to: Yvan Vandenplas, MD, PhD, Department of Pediatrics, UZ Brussels, Vrije Universiteit Brussel, Laarbeeklaan 101, Brussels 1090, Belgium. yvan.vandenplas@uzbrussel.be
Telephone: +32-2-4775794
Fax: +32-2-4775783

Received: December 30, 2016

Peer-review started: January 4, 2017

First decision: March 13, 2017

Revised: August 3, 2017

Accepted: December 4, 2017

Article in press: December 4, 2017

Published online: February 8, 2018

Abstract

AIM

To assess the knowledge of general pediatricians throughout Indonesia about the diagnosis and treatment of childhood constipation.

METHODS

A comprehensive questionnaire was distributed to general pediatricians from several teaching hospitals and government hospitals all over Indonesia.

RESULTS

Data were obtained from 100 pediatricians, with a mean of 78.34 ± 18.00 mo clinical practice, from 20 cities throughout Indonesia. Suspicion of constipation in a child over 6 mo of age arises when the child presents with a decreased frequency of bowel movements (according to 87% of participants) with a mean of one bowel movement per 3.59 ± 1.0 d, hard stools (83%), blood in the stools (36%), fecal incontinence (33%), and/or difficulty in defecating (47%). Only 26 pediatricians prescribe pharmacologic treatment as first therapeutic approach, while the vast majority prefers nonpharmacologic treatment, mostly (according to 68%) The preferred nonpharmacologic treatment are high-fiber diet (96%), increased fluid intake (90%), toilet training (74%), and abdominal massage (49%). Duration of non-pharmacological treatment was limited to 1 to 2 wk. Seventy percent of the pediatricians recommending toilet training could only mention some elements of the technique, and only 15% was able to explain it fully and correctly. Lactulose is the most

frequent pharmacologic intervention used (87% of the participants), and rectal treatment with sodium citrate, sodium lauryl sulfo acetate, and sorbitol is the most frequent rectal treatment (85%). Only 51% will prescribe rectal treatment for fecal impaction. The majority of the pediatricians (69%) expect a positive response during the first week with a mean ($\pm$ SD) of 4.1 ($\pm$ 2.56) d. Most participants (86%) treat during one month or even less. And the majority (67%) stops treatment when the frequency and/or consistency of the stools have become normal, or if the patient had no longer complaints.

CONCLUSION

These data provide an insight on the diagnosis and management of constipation in childhood in Indonesia. Although general pediatricians are aware of some important aspects of the diagnosis and management of constipation, overall knowledge is limited. Efforts should be made to improve the distribution of existing guidelines. These findings highlight and confirm the difficulties in spreading existing information from guidelines to general pediatricians.

Key words: Functional constipation; Guideline lactulose; Rectal treatment; Polyethylene glycol

© The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Diagnosis and management of functional constipation in children by general paediatricians is sub-optimal because of a lack of knowledge of published guidelines. Our data confirm that efforts should be made to improve distribution of existing guidelines to primary health care.

Widodo A, Hegar B, Vandenplas Y. Pediatricians lack knowledge for the diagnosis and management of functional constipation in children over 6 mo of age. *World J Clin Pediatr* 2018; 7(1): 56-61 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i1/56.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i1.56>

INTRODUCTION

Constipation is worldwide a common problem in children. Three to five percent of all clinic consultations to pediatricians are due to constipation, and the number keeps increasing^[1]. Primary care physicians such as pediatricians or family physicians are frequently consulted by parents because of constipation^[2]. Scientific societies develop clinical practice guidelines with the goal to improve diagnosis and management and result in a better quality of care. However, these recommendations from scientific societies are not easily picked up by primary health care level^[3]. Guidelines for the diagnosis and management of constipation,

both for adults and children, have been published by professional associations such as the North American and European Societies of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN and ESPGHAN)^[4]. Not many studies were conducted in Indonesia, but it has been estimated that the prevalence of constipation ranges between 12% and 48%, depending on multiple variables^[5,6]. Although constipation is rarely an emergency, when it is not managed properly it can cause serious complications in the long term such as significant abdominal pain, lowered self-esteem, depression, and decreased quality of life^[4,7]. Functional constipation has been identified as an important health problem during childhood and contrary to common belief, has a significant impact on quality of life of children and their families^[8]. There is currently no Indonesian guideline. This study aims to evaluate the diagnosis and quality of management of constipation in children among pediatricians in Indonesia, in order to include our findings in National Guidelines.

MATERIALS AND METHODS

We developed a comprehensive anonymous questionnaire consisting of both multiple-choice and open questions (Table 1: Questionnaire). The questionnaires were distributed to 103 general pediatricians during a national meeting of the Indonesian Society of Pediatrics, both from academic and non-academic centers, working in 20 different cities in Indonesia. They were asked to fill in the questionnaire on the spot and returned the document as soon as it was completed to the research staff.

The first series of question asks about the symptoms making the pediatrician suspicious of the possible diagnosis constipation as cause for the symptoms. Participants could indicate more than one symptom out of a proposed list: Number of bowel movements, consistency of the stools, difficulties in defecation, blood in the stools, encopresis... The second series of questions regarded treatment, duration of treatment, and outcome. Specific information about recommendations regarding toilet training was asked for as an open question.

RESULTS

The response rate was 97%; 3 out of 103 general pediatricians returned the questionnaire with incomplete answers. The participants worked as general pediatricians for a mean duration of 78.34 ± 18.00 mo in hospitals distributed over the Western, Middle, and Eastern parts of Indonesia.

The pediatricians suspected constipation when a child over 6 mo of age presents with a decrease in frequency of bowel movement (87% of the participants) with a mean of 3.59 ± 1.0 d between two defecations (Question 1), hard stools (83%), presence of blood in the stools (36%), encopresis (33%), and/or difficulty in defecating (47%) (Table 2).

Table 1 Questionnaire about constipation in children older than 6 mo

We are studying the diagnostic criteria and management of constipation in children over 6 months of age. This questionnaire will be handled anonymously. Please tell us more about your experience in dealing with children with constipation. Many aspects in the diagnosis and management of constipation are debated. Therefore, there is no right or wrong answer. We look forward to your participation in completing this short questionnaire, which will take you around 5 to 10 min.

1 Please specify your profession: General Pediatrician Yes / No

How long are you working as General Pediatrician? ____ year(s) and ____ month(s)

In which city do you work? _____

2 Which criteria do you use to diagnose constipation in children older than 6 months? (more than one answer is possible):

- ☐ Infrequent defecation, less than once in every ____ day(s)
- ☐ Hard consistency of stool
- ☐ Bleeding when passing stools
- ☐ Fecal incontinence
- ☐ Difficulties in defecation
- ☐ Crying before passing stool with normal consistency
- ☐ Other (please specify) _____

3 Which treatment do you recommend as first approach? (more than one answer is possible):

- ☐ Take a high-fiber diet
- ☐ Increase fluid intake
- ☐ Apply abdominal massage for babies
- ☐ Start appropriate toilet training
- ☐ Other (please specify) _____

4 If you answered "toilet training" in question 3, please explain briefly the method of toilet training which you suggested :

5 When do you start pharmacological therapy in a constipated child > 6 months old?

- ☐ Immediately when the diagnosis of constipation is established
- ☐ If non-pharmacological treatment does not respond after ____ day(s)/ week(s)/ month(s)
- ☐ I do not recommend any pharmacological therapy
- ☐ Other (please specify) _____

6 The pharmacological treatment that I recommend is :

- ☐ Lactulose
- ☐ Sorbitol
- ☐ Magnesium salt
- ☐ Laxative suppository
- ☐ Other (please specify) _____

7 The rectal pharmacological treatment that you mostly recommend is:

- ☐ Enema with a combination of sodium citrate, sodium lauryl sulfoacetate, and sorbitol (Microlax®)
- ☐ Trifenylnmethaan (Dulcolax®)
- ☐ Docusate Sodium, Sorbitol (Yal®)
- ☐ Glycerin suppository
- ☐ I do not recommend such treatment
- ☐ Other (please specify) _____

8 When do you recommend rectal treatment?

- ☐ When impacted feces are diagnosed on physical examination
- ☐ When patient had no bowel movement during ____ days
- ☐ When stool is too hard to pass
- ☐ When patient has too much difficulties to produce stools
- ☐ Other (please specify) _____

9 Is there any other information/ education that you provide to the patients/parents?

10 In average, how long does it take for your patients to show a positive response to your first therapeutic approach? ____ days/ week(s)/ month(s)

11 In average, how long do you treat your patients for constipation? ____ week(s)/ month(s)/ year(s)

12 When do you stop treatment?

Thank you so much for your participation

Seventeen participants (17%) did choose a combination of symptoms: Decreased frequency, hard stool and difficulties in defecation. Another 17 pediatricians chose only decreased frequency and hard stools. Eleven percent indicated only decreased frequency, while 14% answered they considered any of the symptoms or any combination as possibly indicating the diagnosis of constipation. Other participants combined any other variation of symptoms (Figure 1).

Regarding treatment, only 26% of the general pediatricians prescribed pharmacologic treatment as a first option. Non-pharmacologic treatment was recom-

mended for a period of one to two weeks by 68% of the participants: high-fiber diet (96% of the participants), increased fluid intake (90%), toilet training (74%) and abdominal massage (46%) (Figure 2). However, seventy percents of the pediatricians indicating toilet training as therapeutic intervention could mention only some elements of the toilet training recommendations for constipated children. Only 15% were able to explain it fully and correctly, which includes age-appropriate technique and timing for toilet training according to the guidelines published by NASPGHAN and ESPGHAN^[4]. Lactulose was the most frequent (87% of participants)

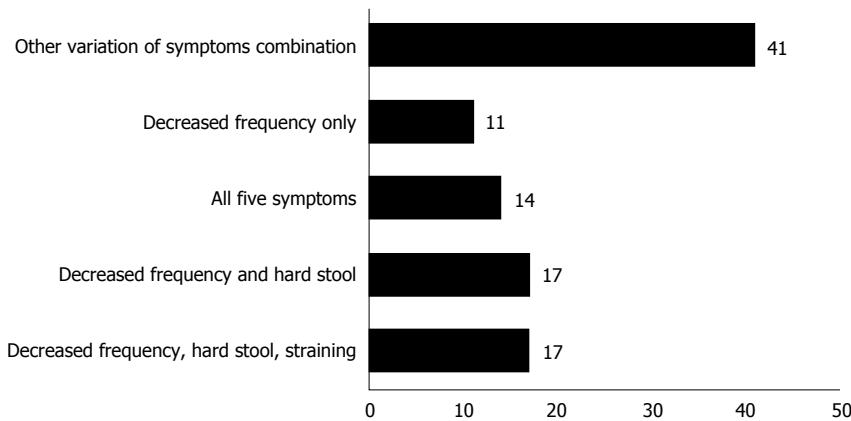


Figure 1 Constipation symptoms according to the participants.

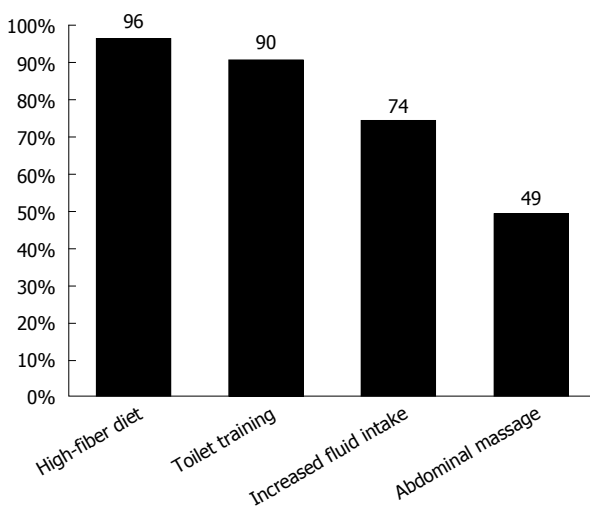


Figure 2 Preferred non-pharmacological treatment by the general pediatricians.

Table 2 Symptom that raise the suspicion of constipation

Symptom at presentation	Frequency
Decreased bowel movement	87%
Hard stool	83%
Difficulties in defecation	47%
Blood in stool	36%
Encopresis	33%

pharmacologic intervention used and a micro-enema with a combination of sodium citrate, sodium lauryl sulfoacetate and sorbitol was the most frequent rectal treatment (85%) prescribed. Only 51 of the pediatricians did recommend rectal treatment for fecal impaction. Some would only recommend rectal treatment after failure of lactulose.

The majority of the pediatricians (69%) answered to expect a positive response during the first week after starting therapy, with a mean ($\pm$ SD) of 4.1 ($\pm$ 2.56) d. Most participants (86%) recommend treatment during one month or even less. And the majority (67%)

also stops the treatment when the frequency and/or consistency of the stools have become normal, or if the patient had no longer complaints.

DISCUSSION

Constipation is common during childhood and has an important impact on quality of life with a negative impact on psychological wellbeing. Functional constipation in young individuals influences quiet substantially familial stress^[8]. The NASPGHAN and ESPGHAN Joint Guideline recommends the use of Rome III diagnostic criteria for functional constipation, based on history and physical examination^[4]. The number of physician visits due to childhood constipation has doubled between 1958 and 1986^[9]. About 3% of the visits to a general pediatric practice and as many as 30% of consultations to a pediatric gastroenterologists are because of symptoms suggestive for constipation^[2]. Many authors have hypothesized that this important increase in childhood constipation might be due to changing patterns in toilet training, imbalanced diet, or that parents nowadays are more likely to consult because of symptoms of constipation.

Little is known about the knowledge of pediatricians (and general practitioners) on the diagnosis and management of childhood constipation or the management. In most children, constipation is usually associated with stool retention, incomplete evacuation of stool, and fecal incontinence^[4]. Fecal incontinence is involuntary or voluntary passage of feces into the underwear or in socially inappropriate places^[10]. Fecal incontinence is also known as encopresis and fecal soiling. In our study, only 33% of the respondents suspected childhood constipation in the presence of fecal incontinence. This is a major lack of knowledge as fecal incontinence is reported to occur in up to 29.6% of the children with of constipation^[11]. According to other data, about 2% of an unslected population suffers fecal incontinence, albeit relate dto constipation is as much as 82%^[12]. According to data from a tertiary care center, as many as 85% of the children diagnosed with fecal impaction presented

with fecal incontinence^[13]. Thus, not recognizing this symptom fecal incontinence as a symptom of constipation will lead to underdiagnosis of constipation.

Treatment success corresponds to how aggressively the child was treated. The Indonesian pediatricians expect a positive response to fast and treat over a to short period^[4]. Any form of colonic evacuation followed by daily laxative therapy results in a better outcome than less aggressive management^[2]. The long term efficacy of treatment remains an issue. After treatment during two months, more than one third (37%) is still considered as constipated^[2]. Laxatives or stool softeners are the most used approach, in up to 87% of children. Frequent used laxatives are magnesium hydroxide (77%), senna syrup (23%), mineral oil (8%) and lactulose (8%)^[2]. About 68% of the participants preferred non-pharmacological treatment as first intervention, before giving any medication. The rise in prevalence of constipation in the past decade may lead to speculations about the role of decreased fiber intake in constipation. We found a discrepancy in diet management between recommendations by the ESPGHAN/NASPGHAN guideline and the answers provided by the participants in our study. The guideline states that evidence does not support the use of extra fiber above the recommended intake in the treatment of functional constipation^[4], while the majority of the Indonesian pediatricians recommended families a high-fiber diet (96%). However, at least in the Western world, most of the children do have a low fibre intake, resulting in a recommendation to increase the fibre intake up to the normal, recommended level. The efficacy of extra fibre has not been shown, mainly because it was poorly studied^[4]. Therefore this dietary intervention cannot be recommended. However, data have never suggested that constipation worsened with a high fibre diet. As a consequence, the advice to have a high fibre diet should be considered as "not recommended", but it does not mean that this recommendation is erroneous. The NASPGHAN/ESPGHAN guideline also mentions that extra fluid intake above the recommended intake has not been shown to be beneficial in the treatment of constipation, while most Indonesian participants recommended an increase in fluid intake (90%)^[4]. The comment that was made regarding fibre can be repeated regarding water. Dietary modifications should only be done to ensure a balanced diet and so that sufficient fibers and fluid are consumed^[4]. However, other authors had described the benefits of consuming a high dietary fiber^[14].

Toilet training is a frequent non-pharmacologic treatment recommended by the pediatricians. Seventy percent of participants choosing toilet training could mention some elements of toilet training technique, but only 15% of them were able to explain it thoroughly and correctly. This is extremely detrimental as toilet training is proven to be beneficial to increase bowel movement^[4,14]. Therefore, pediatricians should further enhance their knowledge on toilet training in order to give proper education to parents.

The management of constipation with fecal impaction should be conducted more aggressively. Literature suggests to use enemas or oral medication with polyethylene glycol to obtain fecal disimpaction^[4,15]. Most of the participants (87%) recommended lactulose for disimpaction. As much as 26% of the pediatricians prefer rectal treatment as first option in the therapy. Impaction, if left untreated, may lead to involuntary overflow soiling and pain in passing stools. Therefore, general pediatricians should give a more intrusive approach in order to resolve fecal impaction. An electronic questionnaire which was developed to test the diagnostic and management approaches for functional constipation without or with fecal incontinence was sent out to over 8000 persons^[16]. Almost 1000 answered (80% trainees and 20% physicians). A large majority (84%) of the respondents acknowledged to not or insufficiently know about the NASPGHAN guidelines that were published in 2006^[16]. A questionnaire testing the awareness of pediatric Rome criteria for the diagnosis of functional gastrointestinal disorders showed comparable results: Less than 30% of the general pediatricians knew about the Rome criteria, in contrast to almost all pediatric gastroenterologists^[17]. Adequate dissemination of recommendations and guidelines is to be a major problem. These recommendations may be perceived as difficult and even inappropriate to implement. Physicians may simply also just not agree with some of the recommendations because of missing evidence. As a consequence, physicians may refuse to include recommendations from guidelines in their daily practice^[18]. Functional constipation and functional gastrointestinal disorders are common problems. Childhood constipation does have a major impact on health care budgets: the management of childhood constipation is estimated to be cost about \$2500/year^[19].

A shortcoming of this research is that the questionnaire was not validated. In another weakness of the design of this study is that no information was collected regarding the fibre and fluid intake at baseline. However, considering that the questionnaire collects information on the theoretical criteria used by pediatricians for the diagnosis and management of constipation, it was not possible to collect information on the daily fibre and fluid intake of Indonesian children (with constipation).

This study provides an insight of the pattern and quality of diagnosis and management of constipation in Indonesian children. Although constipation is a frequent condition, knowledge about appropriate diagnosis and treatment is weak among young general pediatricians. Non-evidence based advices are often given to patients and their family, resulting in less effective treatment. Especially fecal incontinence is insufficiently recognized as a symptom of constipation. The appropriate management of fecal impaction still needs to be stressed among pediatricians. Pediatricians need more comprehensive knowledge on proper toilet training advices to be able to teach patients. Therefore, the knowledge of general should be improved as well as the implementation

regarding available constipation guidelines is important to be assessed to ensure early diagnosis and prompt treatment. Data from this research confirm that training regarding diagnosis and management of functional constipation is needed. A better knowledge of medication to obtain rapid solution of the problem, the need for effective disimpaction and erroneous considerations regarding adverse effects will improve the outcome^[16]. Awareness campaigns informing the population about the magnitude and impact of childhood constipation have to be considered considering its social and economic impact^[8]. A better dissemination of recommendations is a priority^[18].

ARTICLE HIGHLIGHTS

Background

Criteria for the diagnosis and management of functional constipation are not well known by general pediatricians and primary health care, despite published guidelines.

Research frontiers

Our research was limited to one country.

Innovations and breakthrough

This research confirms the frequency of childhood constipation. Knowledge of primary health care physicians on the diagnosis and management is limited. Published guidelines are insufficiently disseminated.

Applications

It is likely that these findings can be extrapolated to the rest of the world, since similar data are reported for the United States and Indonesia.

Terminology

Childhood constipation, electronic questionnaire, primary healthcare, guidelines, laxative.

REFERENCES

- 1 **Biggs WS**, Dery WH. Evaluation and treatment of constipation in infants and children. *Am Fam Physician* 2006; **73**: 469-477 [PMID: 16477894]
- 2 **Borowitz SM**, Cox DJ, Kovatchev B, Ritterband LM, Sheen J, Sutphen J. Treatment of childhood constipation by primary care physicians: efficacy and predictors of outcome. *Pediatrics* 2005; **115**: 873-877 [PMID: 15805358 DOI: 10.1542/peds.2004-0537]
- 3 **Ebben RH**, Vloet LC, Verhofstad MH, Meijer S, Mintjes-de Groot JA, van Achterberg T. Adherence to guidelines and protocols in the prehospital and emergency care setting: a systematic review. *Scand J Trauma Resusc Emerg Med* 2013; **21**: 9 [PMID: 23422062 DOI: 10.1186/1757-7241-21-9]
- 4 **Tabbers MM**, Di Lorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, Staiano A, Vandenplas Y, Benninga MA; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; North American Society for Pediatric Gastroenterology. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr* 2014; **58**: 258-274 [PMID: 24345831 DOI: 10.1097/MPG.0000000000000266]
- 5 **Bardosono S**, Sunardi D. Functional Constipation and its related factors among female workers. *Maj Kedokt Indon* 2011; **61**: 126-129
- 6 **Prawono LA**, Fauzi A, Syam AF, Makmun D. Paradigm on chronic constipation: pathophysiology, diagnostic, and recent therapy. *Indonesian J Gastroenterol Hepatol Dig Endosc* 2012; **13**: 174-180
- 7 **Rowan-Legg A**; Canadian Paediatric Society, Community Paediatrics Committee. Managing functional constipation in children. *Paediatr Child Health* 2011; **16**: 661-670 [PMID: 23204909]
- 8 **Rajindrajith S**, Devanarayana NM, Crispus Perera BJ, Benninga MA. Childhood constipation as an emerging public health problem. *World J Gastroenterol* 2016; **22**: 6864-6875 [PMID: 27570423 DOI: 10.3748/wjg.v22.i30.6864]
- 9 **Sonnenberg A**, Koch TR. Physician visits in the United States for constipation: 1958 to 1986. *Dig Dis Sci* 1989; **34**: 606-611 [PMID: 2784759 DOI: 10.1007/BF01536339]
- 10 **Rasquin A**, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, Walker LS. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology* 2006; **130**: 1527-1537 [PMID: 16678566 DOI: 10.1053/j.gastro.2005.08.063]
- 11 **Nurko S**, Scott SM. Coexistence of constipation and incontinence in children and adults. *Best Pract Res Clin Gastroenterol* 2011; **25**: 29-41 [PMID: 21382577 DOI: 10.1016/j.bpg.2010.12.002]
- 12 **Rajindrajith S**, Devanarayana NM, Benninga MA. Constipation-associated and nonretentive fecal incontinence in children and adolescents: an epidemiological survey in Sri Lanka. *J Pediatr Gastroenterol Nutr* 2010; **51**: 472-476 [PMID: 20562725 DOI: 10.1097/MPG.0b013e3181d33b7d]
- 13 **Loening-Baucke V**. Functional fecal retention with encopresis in childhood. *J Pediatr Gastroenterol Nutr* 2004; **38**: 79-84 [PMID: 14676600 DOI: 10.1097/00005176-200401000-00018]
- 14 **Catto-Smith AG**. 5. Constipation and toileting issues in children. *Med J Aust* 2005; **182**: 242-246 [PMID: 15748137]
- 15 **Bekkali NL**, van den Berg MM, Dijkgraaf MG, van Wijk MP, Bongers ME, Liem O, Benninga MA. Rectal fecal impaction treatment in childhood constipation: enemas versus high doses oral PEG. *Pediatrics* 2009; **124**: e1108-e1115 [PMID: 19948614 DOI: 10.1542/peds.2009-0022]
- 16 **Yang CH**, Punati J. Practice patterns of pediatricians and trainees for the management of functional constipation compared with 2006 NASPGHAN guidelines. *J Pediatr Gastroenterol Nutr* 2015; **60**: 308-311 [PMID: 25714574 DOI: 10.1097/MPG.0000000000000591]
- 17 **Sood MR**, Di Lorenzo C, Hyams J, Miranda A, Simpson P, Mousa H, Nurko S. Beliefs and attitudes of general pediatricians and pediatric gastroenterologists regarding functional gastrointestinal disorders: a survey study. *Clin Pediatr (Phila)* 2011; **50**: 891-896 [PMID: 21464079 DOI: 10.1177/0009922811398041]
- 18 **Sood MR**. Evidence-based diagnosis and treatment of functional constipation: "are we there yet?". *J Pediatr Gastroenterol Nutr* 2015; **60**: 288-289 [PMID: 25564822 DOI: 10.1097/MPG.0000000000000687]
- 19 **Liem O**, Harman J, Benninga M, Kelleher K, Mousa H, Di Lorenzo C. Health utilization and cost impact of childhood constipation in the United States. *J Pediatr* 2009; **154**: 258-262 [PMID: 18822430 DOI: 10.1016/j.jpeds.2008.07.060]

P- Reviewer: Maffei HVL, Malowitz S, Soylu OB **S- Editor:** Gong ZM
L- Editor: A **E- Editor:** Li RF



Clinical Practice Study

Outcomes of transconjunctival sutureless 27-gauge vitrectomy for stage 4 retinopathy of prematurity

Parag K Shah, Vishma Prabhu, Venkatapathy Narendran

Parag K Shah, Vishma Prabhu, Venkatapathy Narendran, Department of Pediatric Retina and Ocular Oncology, Aravind Eye Hospital, Coimbatore, Tamil Nadu 641014, India

ORCID number: Parag K Shah (0000-0002-5014-6599); Vishma Prabhu (0000-0001-6845-0209); Venkatapathy Narendran (0000-0003-1201-9801).

Author contributions: All authors equally contributed to this paper with regard to study conception and design, literature review and analysis, manuscript drafting, critical revision, and editing, and final approval of the final version.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Aravind Eye Hospital.

Informed consent statement: The participating patients provided informed consent and gave permission for publication.

Conflict-of-interest statement: We have no financial relationships to disclose.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited Manuscript

Correspondence to: Dr. Parag K Shah, DNB, Department of Pediatric Retina and Ocular Oncology, Aravind Eye Hospital, Avinashi Road and Postgraduate Institute of Ophthalmology, Coimbatore, Tamil Nadu 641014, India. parag@cbe.aravind.org
Telephone: +91-422-4360400
Fax: +91-422-2593030

Received: November 2, 2017

Peer-review started: November 2, 2017

First decision: November 30, 2017

Revised: December 3, 2017

Accepted: December 14, 2017

Article in press: December 14, 2017

Published online: February 8, 2018

Abstract

AIM

To report our initial experience with lens-sparing vitrectomy for stage 4 retinopathy of prematurity using the 27-gauge (G) system.

METHODS

This retrospective case series involved nine eyes of five babies with active stage 4 ROP, who underwent 27-G lens-sparing vitrectomy. Surgery was done using 27-G valved cannulas and sclerotomies were made 1.5 mm from the limbus. Bilateral sequential vitrectomy was done in eight eyes.

RESULTS

At one-year follow-up, anatomical outcome was favourable in all nine (100%) eyes. High-speed cutting and smaller sclerotomies were helpful in reducing the intra and post-operative complications.

CONCLUSION

27-G vitrectomy is well suited for stage 4 ROP surgeries.

Key words: Vitrectomy; Retinopathy of prematurity; 27-gauge

© The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This is a retrospective study of nine eyes of five children with active stage 4 retinopathy of prematurity, who underwent 27-gauge microincision vitrectomy surgeries with excellent outcomes.

Shah PK, Prabhu V, Narendran V. Outcomes of transconjunctival sutureless 27-gauge vitrectomy for stage 4 retinopathy of prematurity. *World J Clin Pediatr* 2018; 7(1): 62-66 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i1/62.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i1.62>

INTRODUCTION

Pars plana vitrectomy was first described by Machemer *et al*^[1] in 1971 when he used the 17-gauge (G) system, where the incisions were > 1 mm in size. Later, O'Malley and Heintz^[2] introduced the 20-G system where the incisions became 0.9 mm in size. Although this remained the standard of care for almost three decades, the disadvantage was that apart from relatively bulky instruments, it needed conjunctival dissection followed by applications of sutures. A big change was seen when small-gauge (23 and 25 G) instrumentation was introduced^[3,4]. With thinner instrumentation, the incision became smaller to 0.5 mm and transconjunctival entry with sutureless closure became a possibility. This is extremely beneficial in the small eyes of premature neonates^[5]. The advent of 27-G vitrectomy with only 0.4 mm incisions has led to a new beginning of transconjunctival microincision vitrectomy surgery (MIVS) in retinopathy of prematurity (ROP). Oshima *et al*^[6] in 2010 were the first to describe the safety and feasibility of the 27-gauge MIVS system with excellent visual and anatomical outcomes in adults. However, its use in ROP is still not established, although Yonekawa *et al*^[7] have reported 25 and 27-G hybrid vitrectomy in complex surgeries including ROP.

The purpose of this study was to describe our initial experience in using the 27-G trocar and cannula system in pediatric eyes with stage 4 ROP.

MATERIALS AND METHODS

This is a retrospective non-comparative case series of nine eyes of five babies. All eyes had stage 4 ROP. Four babies had bilateral disease and both eyes were operated sequentially under same general anesthesia^[8]. Care was taken to rescrub and re-prepare the surgical field of the second eye as done for any new case. The entire team rescrubbed and a new set of surgical instruments were used for each eye. Written informed consent was obtained from their parents for the procedure. Ethics committee approval was obtained for this study. The study was conducted from January 2015 to December 2015. Patient records were reviewed and the data collected were date of birth, gestational age, birth weight, postconceptional age, postnatal age, and intra and post-operative status of each eye.

All surgeries were performed under general anesthesia by a single surgeon, using the Constellation Vision System with Vitrectomy 27-G Total Plus Vitrectomy Pak system (Alcon Laboratories, Texas, United States).

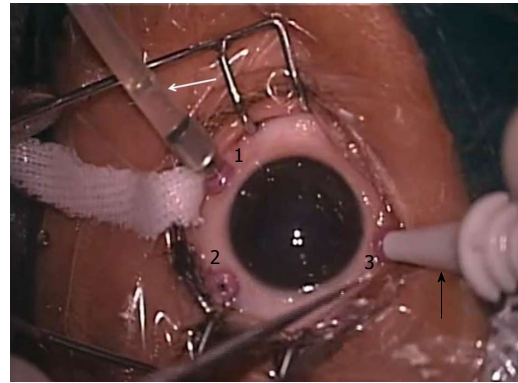


Figure 1 Intraoperative picture of a left eye. The three sclerotomies 1.5 mm from the limbus are labeled as 1 (inferotemporal port), 2 (superotemporal port) and 3 (superonasal port) of the 27-gauge vitrectomy system (silicon band pieces are not shown in this representative photograph). The white arrow shows the infusion tube through which balanced salt solution flows and maintains intraocular pressure. The black arrow shows the trocar handle inserting the last superonasal port.

Valved 27-G cannulas were used. The intraocular portions of the 27-G cannula, which are designed for adult eyes, were shortened for these small pediatric eyes, similar to what has been described by Babu *et al*^[9]. We took a 42 silicon band, which has a width of 4 mm and a thickness of 1.25 mm. The band was divided at 2 mm and again cut in the center to get two small pieces of 2 mm x 2 mm each. The trocar and cannula were passed through these pieces till the hub with the help of a toothed forceps. Cannulas were inserted at inferotemporal, superotemporal, and superonasal quadrants, 1.5 mm away from the limbus (Figure 1). The conjunctiva and Tenon's capsule were displaced over the sclera to avoid communication between conjunctival and scleral entry sites.

Trocar cannulas were inserted *via* a "straight in" (perpendicular to the sclera) or angled (less than 90 degrees to the sclera) approach in a 1-step procedure. First, a core vitrectomy was performed using a cutting speed of 5000 cuts per minute and a suction of 150 mmHg in core mode. Peripheral vitrectomy was done using 7500 cuts per minute with the same suction in shave mode of the machine. After the vitrectomy, partial fluid air exchange was done, the cannulas were removed, and sclerotomies were left sutureless after thorough examination for any leakage. Babies were examined on postoperative days 1, 14, and after one month.

RESULTS

Nine eyes of five babies were operated during the study period. Mean gestational age of these babies was 29.2 wk (range, 28-31 wk). Mean birth weight was 1177 g (range, 950-1850 g). Mean postconceptional age at the time of surgery was 39 wk (range, 36-43 wk), and mean postnatal age was 9.6 wk (range, 6-12 wk). Out of nine eyes, seven had stage 4a and two had 4b disease. Two eyes of case 1 had ROP in zone 1, while the rest of the

Table 1 Baseline characteristics and final outcome of the cases

Case No	GA (wk)	BW (gm)	PCA (wk)	Eye	Zone	Stage	Preoperative laser	Intraoperative anti-VEGF	Final outcome
1	30	1100	36	RE	1	4a	Y	Y	F
				LE	1	4a	Y	Y	F
2	31	950	43	RE	2	4a	Y	N	F
				LE	2	4a	Y	N	F
3	28	1000	37	RE	2	4b	Y	N	F
				LE	2	4a	Y	N	F
4	28	1850	38	RE	2	4a	Y	N	F
				LE	2	4a	Y	N	F
5	29	985	41	RE	2	4b	N	N	F

GA: Gestational age; BW: Birth weight; PCA: Postconceptional age; RE: Right eye; LE: Left eye; F: Favourable.

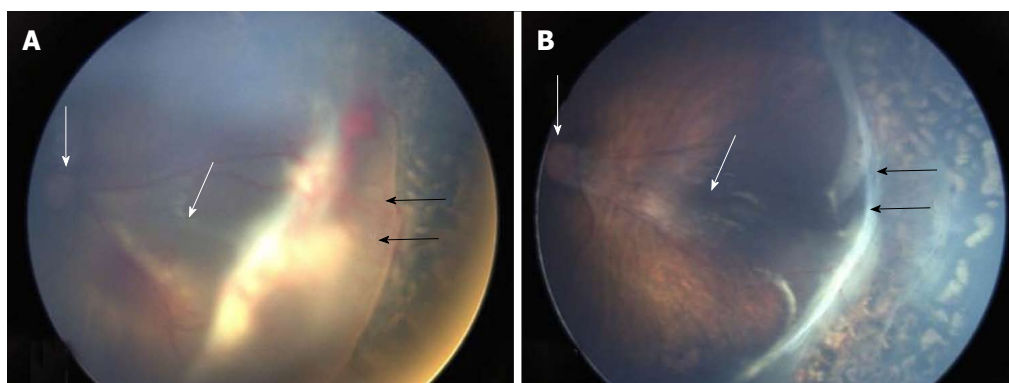


Figure 2 Anatomical success was achieved in all ten eyes at 4-mo follow-up. A: Preoperative picture of left eyes showing stage 4A ROP with partial retinal detachment (black arrows), and the optic disc is shown by the thin white arrow; B: Postoperative picture of the same eye showing settled retinal detachment with residual fibrous tissue (black arrows). The optic disc and fovea are shown by the white arrows, respectively.

eyes had ROP in zone 2. Eight eyes of four cases had undergone laser therapy prior to vitrectomy (Table 1). Two eyes of case 1 underwent vitrectomy along with intravitreal injection of ranibizumab as this case had excessive vascularity. At 4-mo follow-up, anatomical success was seen in all ten (100%) eyes (Figure 2). We did not encounter any postoperative hypotony in any of our cases. No other complications were noted in the follow-up period. At an average follow-up of 12 mo, all eyes showed stable regressed ROP.

DISCUSSION

The introduction of 27-G vitrectomy had major concerns like reduced endoillumination, instrument fragility, and reduced flow rate during surgery^[10]. Oshima *et al*^[6] in their study describe the various steps taken to improve the MIVS. This study done in 2010 with 31 adult eyes undergoing vitreoretinal surgeries for epiretinal membrane, macular hole, vitreous hemorrhage, focal tractional retinal detachment, and vitreomacular traction also analyzed the duty cycles of cutter, infusion and aspiration rates, and clinical outcome of 27-G MIVS. Brighter light sources such as xenon and mercury vapour bulb were used to increase the endoillumination. The smaller gauge did increase the fragility of the cutter during vitrectomy and to avoid this, the shaft of the cutter was reduced from 32 mm to 25 mm, which gives a good

rigidity similar to that of a conventional 25-G vitrectomy.

High cutting rates of 27-G vitrectomy was proved to be a major advantage as it reduced the risk of iatrogenic damage to the retinal surface and intraoperative retinal tears by preventing uncut vitreous fibers entering the cutter port. Clinically and experimentally it has been proved that high cutting rates reduce retinal traction and thereby retinal breaks^[11,12].

Postoperative complications seen with 23 and 25-gauge surgery like poor wound sealing causing leakage, hypotony, and endophthalmitis^[13-15] were serious concerns, but one-step insertion technique in 27-G vitrectomy surgeries avoided these problems. Opening and closing procedures are simplified with the one-step insertion technique, consequently shortening the total operative time. Similarly, Rizzo and colleagues^[16] in 2012 described 27-G vitrectomy in 16 patients and achieved a good clinical outcome. Additional surgical indications included were rhegmatogenous retinal detachment and tractional retinal detachment. No intraoperative and postoperative complications were encountered and no cases were converted to the 23 or 25-G system.

A retrospective case series of 95 adult eyes by Khan *et al*^[17] has been extremely valuable as it includes a large sample size of 27-G MIVS operated till date. This study evaluated the change in visual acuity, postoperative intraocular pressure (IOP), and the mean operative time by diagnosis. They reported an initial fall in IOP over

the first week, which started to increase after day 30. A recently published study of cases with 20, 23, and 25-G surgeries showed a decrease in baseline IOP over a period of 3 mo and then gradual regain^[18]. Thus, they concluded that IOP regains faster to the baseline value in MIVS.

In our study, 27-G MIVS performed in pediatric eyes is the first of its kind and has not been reported till date. The problem of bending of the shaft is minimal as the plus system has a small cuff of metal supporting the base and ROP vitrectomy just needs a good core vitrectomy with keeping the instruments more perpendicular compared to adults in whom base shaving may be required. None of our case had hypotony in the postoperative period as compared to 5% in a study by Khan *et al.*^[17]. However, our sample size is much smaller compared to their study. Singh *et al.*^[19] showed that the different gauge vitrectomy systems are equally effective and safe. All of our cases were sutureless and at the end of the surgery none developed any wound leak, which was seen in about 0%-7.1% of cases of 23 and 25-G vitrectomy^[20-22]. No sclerotomy-related retinal tears were noted while with 23 and 25-gauge vitrectomy 0%-3.1% have been reported^[22-25].

In one case during vitrectomy, the cannula came out along with the vitrectomy cutter, and this could have been avoided by carefully removing the cutter. This could be more common in the 27-G system compared to the 25-G system, as Alcon 27-G cannulas are valved and hence get snugly attached to the instruments. In four babies, bilateral simultaneous vitrectomy was performed as all these babies had bilateral acute disease. The anatomical outcome was 100% in our study, which is better than previously reported ROP vitrectomies with larger gauges^[8,26-28].

Limitation of our study is small sample size. Thus to summarize, the 27-G system could be favourable for pediatric cases, since this technique has a favorable wound sealing structure with fewer postoperative complications and better surgical outcomes. However, studies with a larger sample size are needed to substantiate this.

ARTICLE HIGHLIGHTS

Research background

Retinopathy of prematurity (ROP) vitrectomy is challenging due to the altered and more compact structures in a pediatric eye. Hence, there is a need to invent smaller vitrectomy instruments to make the outcome of this surgery better. 27-gauge vitrectomy being the smallest gauge available commercially could have the most benefit in the pediatric age group.

Research motivation

27-gauge instruments are smaller in size and have capability of high speed cutting, which is ideal for pediatric eyes. Hence, this study was conducted to examine the feasibility of this instrument in ROP surgery.

Research objectives

The main research objective was to assess the feasibility of 27-gauge vitrectomy for ROP and to examine if the ease of surgery and surgical

outcomes could be bettered.

Research methods

27-gauge vitrectomy has been reported mainly in adult eyes. Very few studies have explored its use in the pediatric age group and especially in ROP. This is one of the few studies which tried 27-gauge vitrectomy exclusively in stage 4 ROP.

Research results

The results of this study show that sutureless transconjunctival 27-gauge vitrectomy has good anatomical outcome in stage 4 ROP.

Research conclusions

27-gauge vitrectomy is beneficial for pediatric eyes. It is safe and effective. This study shows that smaller gauge instruments are most suitable for lens-sparing vitrectomy in ROP where the surgical space is very limited with the ever looming danger of damaging the lens anteriorly and the retinal posteriorly. Even with the limited surgical space, it become easier to maneuver with 27-gauge instruments without damaging the critical structures.

Research perspectives

In the future, 27-gauge vitrectomy has the potential to become the standard of care for all ROP-related lens-sparing vitrectomies.

REFERENCES

- 1 **Machemer R**, Buettner H, Norton EW, Parel JM. Vitrectomy: a pars plana approach. *Trans Am Acad Ophthalmol Otolaryngol* 1971; **75**: 813-820 [PMID: 5566980]
- 2 **O'Malley C**, Heintz RM Sr. Vitrectomy with an alternative instrument system. *Ann Ophthalmol* 1975; **7**: 585-588, 591-594 [PMID: 1147502]
- 3 **Eckardt C**. Transconjunctival sutureless 23-gauge vitrectomy. *Retina* 2005; **25**: 208-211 [PMID: 15689813 DOI: 10.1097/00006982-200502000-00015]
- 4 **Fujii GY**, De Juan E Jr, Humayun MS, Chang TS, Pieramici DJ, Barnes A, Kent D. Initial experience using the transconjunctival sutureless vitrectomy system for vitreoretinal surgery. *Ophthalmology* 2002; **109**: 1814-1820 [PMID: 12359600 DOI: 10.1016/S0161-6420(02)01119-3]
- 5 **Gonzales CR**, Boshra J, Schwartz SD. 25-Gauge pars plicata vitrectomy for stage 4 and 5 retinopathy of prematurity. *Retina* 2006; **26**: S42-S46 [PMID: 16946678 DOI: 10.1097/01.iae.0000244288.63757.be]
- 6 **Oshima Y**, Wakabayashi T, Sato T, Ohji M, Tano Y. A 27-gauge instrument system for transconjunctival sutureless microincision vitrectomy surgery. *Ophthalmology* 2010; **117**: 93-102 [PMID: 19880185 DOI: 10.1016/j.ophtha.2009.06.043]
- 7 **Yonekawa Y**, Thanos A, Abbey AM, Thomas BJ, Todorich B, Faia LJ, Williams GA, Capone A Jr, Wolfe JD, Hassan TS. Hybrid 25- and 27-Gauge Vitrectomy for Complex Vitreoretinal Surgery. *Ophthalmic Surg Lasers Imaging Retina* 2016; **47**: 352-355 [PMID: 27065375 DOI: 10.3928/23258160-20160324-08]
- 8 **Shah PK**, Narendran V, Kalpana N. Safety and efficacy of simultaneous bilateral 25-gauge lens-sparing vitrectomy for vascularly active stage 4 retinopathy of prematurity. *Eye (Lond)* 2015; **29**: 1046-1050 [PMID: 25998945 DOI: 10.1038/eye.2015.78]
- 9 **Babu N**, Shah PK, Narendran V, Kalpana N, Kim R. An easy method to raise the 25-gauge trocar and cannula system for retinopathy of prematurity-related lens-sparing vitrectomy. *Retina* 2014; **34**: 1014-1015 [PMID: 24695066 DOI: 10.1097/IAE.0000000000000128]
- 10 **Thompson JT**. Advantages and limitations of small gauge vitrectomy. *Surv Ophthalmol* 2011; **56**: 162-172 [PMID: 21236459 DOI: 10.1016/j.survophthal.2010.08.003]
- 11 **Rizzo S**, Genovesi-Ebert F, Belting C. Comparative study between a standard 25-gauge vitrectomy system and a new ultrahigh-speed 25-gauge system with duty cycle control in the treatment of

- various vitreoretinal diseases. *Retina* 2011; **31**: 2007-2013 [PMID: 21685823 DOI: 10.1097/IAE.0b013e318213623a]
- 12 **Teixeira A**, Chong LP, Matsuoka N, Arana L, Kerns R, Bhadri P, Humayun M. Vitreoretinal traction created by conventional cutters during vitrectomy. *Ophthalmology* 2010; **117**: 1387-1392 [PMID: 20176400 DOI: 10.1016/j.ophtha.2009.11.004]
 - 13 **Woo SJ**, Park KH, Hwang JM, Kim JH, Yu YS, Chung H. Risk factors associated with sclerotomy leakage and postoperative hypotony after 23-gauge transconjunctival sutureless vitrectomy. *Retina* 2009; **29**: 456-463 [PMID: 19174725 DOI: 10.1097/IAE.0b013e318195cb28]
 - 14 **Shimada H**, Nakashizuka H, Hattori T, Mori R, Mizutani Y, Yuzawa M. Incidence of endophthalmitis after 20- and 25-gauge vitrectomy causes and prevention. *Ophthalmology* 2008; **115**: 2215-2220 [PMID: 18930557 DOI: 10.1016/j.ophtha.2008.07.015]
 - 15 **Byeon SH**, Lew YJ, Kim M, Kwon OW. Wound leakage and hypotony after 25-gauge sutureless vitrectomy: factors affecting postoperative intraocular pressure. *Ophthalmic Surg Lasers Imaging* 2008; **39**: 94-99 [PMID: 18435331 DOI: 10.3928/15428877-20080301-04]
 - 16 **Rizzo S**, Barca F, Caporossi T, Mariotti C. Twenty-seven-gauge vitrectomy for various vitreoretinal diseases. *Retina* 2015; **35**: 1273-1278 [PMID: 25946694 DOI: 10.1097/IAE.0000000000000545]
 - 17 **Khan MA**, Shahlaee A, Toussaint B, Hsu J, Sivalingam A, Dugel PU, Lakhanpal RR, Riemann CD, Berrocal MH, Regillo CD, Ho AC. Outcomes of 27 Gauge Microincision Vitrectomy Surgery for Posterior Segment Disease. *Am J Ophthalmol* 2016; **161**: 36-43 [PMID: 26429584 DOI: 10.1016/j.ajo.2015.09.024]
 - 18 **Mi CW**, Thompson JT. Long-term follow-up of intraocular pressure after vitrectomy in eyes without preexisting glaucoma. *Retina* 2015; **35**: 2543-2551 [PMID: 26035511 DOI: 10.1097/IAE.0000000000000641]
 - 19 **Singh RP**, Bando H, Brasil OF, Williams DR, Kaiser PK. Evaluation of wound closure using different incision techniques with 23-gauge and 25-gauge microincision vitrectomy systems. *Retina* 2008; **28**: 242-248 [PMID: 18301029 DOI: 10.1097/IAE.0b013e318156dea3]
 - 20 **Lakhanpal RR**, Humayun MS, de Juan E Jr, Lim JI, Chong LP, Chang TS, Javaheri M, Fujii GY, Barnes AC, Alexandrou TJ. Outcomes of 140 consecutive cases of 25-gauge transconjunctival surgery for posterior segment disease. *Ophthalmology* 2005; **112**: 817-824 [PMID: 15878061 DOI: 10.1016/j.ophtha.2004.11.053]
 - 21 **Ibarra MS**, Hermel M, Prenner JL, Hassan TS. Longer-term outcomes of transconjunctival sutureless 25-gauge vitrectomy. *Am J Ophthalmol* 2005; **139**: 831-836 [PMID: 15860288 DOI: 10.1016/j.ajo.2004.12.002]
 - 22 **Fine HF**, Iranmanesh R, Iturralde D, Spaide RF. Outcomes of 77 consecutive cases of 23-gauge transconjunctival vitrectomy surgery for posterior segment disease. *Ophthalmology* 2007; **114**: 1197-1200 [PMID: 17544779 DOI: 10.1016/j.ophtha.2007.02.020]
 - 23 **Gupta OP**, Ho AC, Kaiser PK, Regillo CD, Chen S, Dyer DS, Dugel PU, Gupta S, Pollack JS. Short-term outcomes of 23-gauge pars plana vitrectomy. *Am J Ophthalmol* 2008; **146**: 193-197 [PMID: 18547538 DOI: 10.1016/j.ajo.2008.04.010]
 - 24 **Jalil A**, Ho WO, Charles S, Dhawahir-Scala F, Patton N. Iatrogenic retinal breaks in 20-G versus 23-G pars plana vitrectomy. *Graefes Arch Clin Exp Ophthalmol* 2013; **251**: 1463-1467 [PMID: 23504085 DOI: 10.1007/s00417-013-2299-2]
 - 25 **Scartozzi R**, Bessa AS, Gupta OP, Regillo CD. Intraoperative sclerotomy-related retinal breaks for macular surgery, 20- vs 25-gauge vitrectomy systems. *Am J Ophthalmol* 2007; **143**: 155-156 [PMID: 17188054 DOI: 10.1016/j.ajo.2006.07.038]
 - 26 **Bhende P**, Gopal L, Sharma T, Verma A, Biswas RK. Functional and anatomical outcomes after primary lens-sparing pars plana vitrectomy for Stage 4 retinopathy of prematurity. *Indian J Ophthalmol* 2009; **57**: 267-271 [PMID: 19574693 DOI: 10.4103/0301-4738.53050]
 - 27 **Kychenthal A**, Dorta P. 25-gauge lens-sparing vitrectomy for stage 4A retinopathy of prematurity. *Retina* 2008; **28**: S65-S68 [PMID: 18317348 DOI: 10.1097/IAE.0b013e318159ec49]
 - 28 **El Rayes EN**, Vinekar A, Capone A Jr. Three-year anatomic and visual outcomes after vitrectomy for stage 4B retinopathy of prematurity. *Retina* 2008; **28**: 568-572 [PMID: 18398359 DOI: 10.1097/IAE.0b013e3181610f97]

P- Reviewer: Stewart MW S- Editor: Cui LJ L- Editor: Wang TQ
E- Editor: Li RF





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>



World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2018 May 8; 7(2): 67-74





MINIREVIEWS

- 67 Is obesity related to the lung function of non-asthmatic children?

Fretzayas A, Moustaki M, Loukou I, Douros K

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Pediatrics*, Shraga Aviner, MD, PhD, Doctor, Pediatric Day-Care Center, the Barzilai Medical Center, Ashkelon 78278, Israel

AIM AND SCOPE

World Journal of Clinical Pediatrics (*World J Clin Pediatr*, *WJCP*, online ISSN 2219-2808, DOI: 10.5409) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCP covers a variety of clinical medical topics, including fetal diseases, inborn, newborn diseases, infant diseases, genetic diseases, diagnostic imaging, endoscopy, and evidence-based medicine and epidemiology. Priority publication will be given to articles concerning diagnosis and treatment of pediatric diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJCP*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Clinical Pediatrics is now indexed in PubMed, PubMed Central.

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Wen-Wen Tan*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Fang-Fang Ji*
Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Quarterly

EDITORS-IN-CHIEF
Seng H Quak, MD, Professor, Department of Pediatrics, NUS - YLL School of Medicine, NUHS Tower Block, Singapore 119228, Singapore

Consolato M Sergi, FRCP(C), MD, PhD, Professor, Department of Lab Medicine and Pathology, University of Alberta, Alberta T6G 2B7, Canada

Toru Watanabe, MD, PhD, Professor, Department of Pediatrics, Niigata City General Hospital, Niigata

950-1197, Japan

EDITORIAL BOARD MEMBERS
All editorial board members resources online at <http://www.wjnet.com/2219-2808/editorialboard.htm>

EDITORIAL OFFICE
Jin-Lei Wang, Director
World Journal of Clinical Pediatrics
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjnet.com>

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8243
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjnet.com>

PUBLICATION DATE
May 8, 2018

COPYRIGHT
© 2018 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
<http://www.wjnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION
<http://www.f6publishing.com>

Is obesity related to the lung function of non-asthmatic children?

Andrew Fretzayas, Maria Moustaki, Ioanna Loukou, Konstantinos Douros

Andrew Fretzayas, School of Medicine, University of Athens, Athens 11527, Greece

Andrew Fretzayas, Department of Pediatrics, Athens Medical Center, Athens University Medical School, Maroussi 15125, Greece

Maria Moustaki, Ioanna Loukou, Department of Cystic Fibrosis, "Agia Sofia", Children's Hospital, Athens 11527, Greece

Konstantinos Douros, Respiratory Unit, Third Department of Pediatrics, Athens University Medical School, "Attikon" University Hospital, Haidari 15125, Greece

ORCID number: Andrew Fretzayas (0000-0003-0964-8594); Maria Moustaki (0000-0001-6818-4350); Ioanna Loukou (0000-0002-3617-4526); Konstantinos Douros (0000-0001-7632-1159).

Author contributions: All authors contributed equally to this paper.

Conflict-of-interest statement: Dr. Moustaki has nothing to disclose.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Andrew Fretzayas, MD, PhD, Professor of Pediatrics, Department of Pediatrics, Athens Medical Center, Athens University Medical School, 5-7 Distomou Str, Maroussi 15125, Greece. afretz@med.uoa.gr
Telephone: +30-210-6157269
Fax: +30-210-6862376

Received: February 12, 2018

Peer-review started: February 12, 2018

First decision: March 2, 2018

Revised: March 12, 2018

Accepted: April 11, 2018

Article in press: April 11, 2018

Published online: May 8, 2018

Abstract

Overweight and obesity are highly prevalent in developed and developing countries among children and adolescents. During the last two decades, it became evident that excess weight is adversely related to respiratory health in childhood and adolescence mainly in terms of asthma occurrence. Additionally, there is a mounting body of evidence that overweight/obesity may also affect lung function in non-asthmatic subjects. The aim of this review was to present and discuss the studies that investigated this issue in non-asthmatic children and adolescents. Only a few studies have evaluated the impact of excess weight on static volumes and their results point towards an inverse relationship between overweight/obesity and functional residual capacity. More studies have been conducted on the impact of excess weight on dynamic lung volumes with inconsistent, however, results. Nevertheless, a relatively consistent finding was that the ratio of forced expiratory volume in 1 s/forced vital capacity was significantly lower among overweight/obese children compared to their counterparts with normal weight. The underlying mechanisms of these observations have not been adequately elucidated but it is believed to result from complex interaction of mechanical, developmental, and metabolic causes. There is a need for more well-designed studies in order to clarify the impact of excess weight on lung function in non-asthmatic subjects, as well as to explore the contribution of factors such as duration and degree of obesity, and fat distribution. Despite the absence of conclusive data, there are still

convincing evidence to be communicated to the children and their families as part of the arguments to encourage them to adopt a healthier lifestyle.

Key words: Obesity; Lung function; Spirometry; Lung volumes; Plethysmography

© **The Author(s)** 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We herein present an overview of the existing studies regarding the influence of excess weight on static and dynamic volumes of lung function in otherwise healthy children and adolescents. Although the existing data, are to some extent, conflicting, it seems that in this age group, obesity is correlated to a significant, though not necessarily clinically important, decrease of forced expiratory volume in 1 s/forced vital capacity ratio and a reduction of functional residual capacity. These observations are of clinical relevance, as they may be the origin of respiratory problems in adulthood, especially if obesity persists till then.

Fretzayas A, Moustaki M, Loukou I, Douros K. Is obesity related to the lung function of non-asthmatic children? *World J Clin Pediatr* 2018; 7(2): 67-74 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i2/67.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i2.67>

INTRODUCTION

There is sufficient data indicating that the prevalence of overweight and obesity among children and adolescents is substantial, particularly in industrialized countries. In a recent global pooled analysis, it was found that the mean body mass index (BMI) and the prevalence of obesity have increased worldwide in children and adolescents over the last four decades^[1]. This rising trend has attenuated or even plateaued-albeit at high levels-in high income countries, since the end of the previous century. On the contrary, the rising still continues in middle and low income countries^[2]. The high prevalence of overweight and obesity is of utmost importance for public health; the increased BMI in childhood and adolescence enhances substantially the likelihood of overweight or obesity persistence in adulthood^[3] and so, the adverse health effects are not restricted to children. The most extensively studied health effects of overweight and obesity in adulthood involve cardiovascular diseases and cancer^[4]. However, it has become more than obvious that obesity is also associated with respiratory health through various pathophysiologic pathways^[5] and can affect lung function even in otherwise healthy subjects^[5].

The aim of this review is to present the existing data on the impact of obesity in plethysmographic and spirometric indices of pulmonary function of otherwise

healthy children. The implications of the relevant observations would also be discussed.

DEFINITION OF OBESITY

Different expert committees have advocated the use of BMI as a convenient tool with acceptable reliability for the screening of obesity in children aged 2-18 years^[6]. In particular, BMI $\geq 95^{\text{th}}$ percentile for age has been defined as obesity whereas BMI $\geq 85^{\text{th}}$ and $< 95^{\text{th}}$ percentile for age as overweight^[7]. The majority of studies that investigated the association of obesity with lung function in childhood and adolescence used BMI as an indicator of obesity. However, in some studies researchers preferred to use waist circumference percentiles (WCP) because this index is believed to reflect more accurately the amount of visceral adipose tissue^[6]. The results of all relevant studies will be presented here, irrespective of the tool that was used for the definition of obesity.

IMPACT OF OVERWEIGHT-OBESITY ON PLETHYSMOGRAPHIC INDICES OF LUNG FUNCTION (STATIC LUNG VOLUMES)

PubMed was searched from January 1997 till the end of October 2017. Only articles in English language were eligible. Five studies were identified that had investigated the impact of overweight/obesity on the plethysmographic indices of lung function in children and adolescents. A summary of these studies is presented in Table 1, in chronological order. The relationship of BMI with total lung capacity (TLC) was investigated by all researchers without finding any significant association. The only exception was the study of van de Griendt *et al*^[8] who did not simply assessed the relationship of BMI with TLC but rather tried to explore the effect of BMI reduction on lung volumes after an intervention program of weight reduction. The % predicted TLC increased by 2.27% (0.86%-3.86%) after weight loss and this increase was statistically significant. Nevertheless, the population of this study was consisted of extremely obese children with either a BMI equivalent $\geq 35 \text{ kg/m}^2$, or a BMI equivalent to at least 30 kg/m^2 plus a comorbidity related to obesity; as a consequence, it is questionable whether generalization of the study findings is proper or not. Quite similarly, however, in the study of Li *et al*^[9], and despite the absence of any association between BMI and TLC, there was a significant inverse correlation between trunk and subtotal body fat with TLC. Kongkiattikul *et al*^[10], who also explored the association of trunk or body fat percentage with lung volumes, presented only data regarding functional residual capacity (FRC), and no information was given for TLC.

Four studies presented data for FRC and showed either significantly lower FRC levels in subjects with

Table 1 Summary of studies that investigated the impact of overweight/obesity on the plethysmographic indices of lung function

No.	Ref.	No. of children, age range (yr)	Exclusion criteria for the study population	Obesity indices	Plethysmographic variables
1	Li <i>et al</i> ^[9] , 2003	64, 7-18	Children with chronic cardiorespiratory problems	BMI, Trunk Body Fat, and Subtotal Body Fat (total-head). The last 2 indices were calculated as a percentage of body mass	TLC, RV, FRC
2	van de Griendt <i>et al</i> ^[8] , 2012	112, 8.5-18.9	Children diagnosed as asthmatics	BMI, WC	TLC, ERV
3	Davidson <i>et al</i> ^[12] , 2014	327, 6-17	Children diagnosed as asthmatics	BMI	TLC, RV, FRC, ERV, VC
4	Rastogi <i>et al</i> ^[11] , 2014	168, 13-18	History of smoking or chronic inflammatory conditions	BMI, WC, Waist-hip ratio	TLC, RV, FRC, RV/TLC, ERV, IC
5	Kongkiattikul <i>et al</i> ^[10] , 2015	45, 8.6-17.3	Children with an underlying pulmonary disease	BMI, WC, WHR Hip circumference Body fat percentage Truncal fat percentage Fat mass index Fat free mass index	TLC, RV, FRC, RV/TLC (only results for FRC were presented)

BMI: Body mass index; TLC: Total lung capacity; RV: Residual volume; FRC: Functional residual capacity; IC: Inspiratory capacity; WC: Waist circumference; WHR: Waist-hip ratio; ERV: Expiratory reserve volume.

adiposity or, similarly, a statistically significant inverse association between FRC and adiposity. BMI was the index of adiposity in three of these studies whereas Li *et al*^[9] found an inverse association between FRC and trunk or subtotal body fat but not with BMI. From the studies that presented data for expiratory reserve volume (ERV) and residual volume (RV)^[11,12], it seems that both ERV and RV decreased with increased adiposity. ERV also increased on an average of 15% in severely obese individuals who lost weight following an intervention program^[8].

IMPACT OF OVERWEIGHT-OBESITY ON SPIROMETRIC INDICES OF LUNG FUNCTION

Table 2 depicts the summary of the studies that investigated the relationship of overweight/obesity in children and/or adolescents with the spirometric variables of lung function. Twenty-three relevant studies were identified by searching PubMed from January 1997 till October 2017. Only articles in English language were eligible.

As a general remark, the findings of these 23 studies are, to some extent, inconsistent. In 3 of the studies^[9], which are discussed in the rest of the present paragraph, no difference was found in forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), FV1/FVC and FEF_{25%-75%} between obese and/or overweight and normal-weight children. Li *et al* did not find an association between BMI and other adiposity indices with spirometric variables within a group of obese subjects. The study, however, did not include either overweight or normal weight individuals to serve as controls. Taking, therefore,

into consideration the small sample size and the limited variation of BMI, as all subjects had BMI > 95th centile, it is likely that this study may have not had the power to detect significant associations between BMI and spirometric parameters. Liyanage *et al*^[13] also did not find any difference when they compared overweight and obese with normal weight children. However, because the former two categories constituted one group the effect of more severe obesity on dynamic lung volumes may have been missed. Similarly, Rastogi *et al*^[11] did not find any association between BMI or waist circumference and spirometric variables. However, asthma was neither an exclusion criterion for participants recruitment nor was taken into account in the final analysis. Accordingly, definitive conclusions cannot be drawn from this study for non-asthmatic adolescents. Kongkiattikul *et al*^[10], who measured static as well as dynamic volumes, mentioned only the statistical significance that observed for FRC. It could therefore be hypothesized that no difference of spirometric variables was identified among the studied subjects in relation to the degree of their adiposity.

Twenty out of 23 studies revealed statistical association between the degree of adiposity and at least one of the spirometric variables. In general, the results depict a trend of significantly decreased spirometric values in the individuals at higher BMI centiles. Interestingly, however, a number of these studies revealed results that were not so clear-cut and implied a more complex association between obesity and lung function; these particular studies are discussed in some details in the following lines^[14,15]. Yao *et al*^[15] recruited obese children irrespective of asthma status. Nevertheless, in their analysis they controlled for physician-diagnosed asthma and found that excess weight was positively

Table 2 Summary of studies that investigated the impact of overweight/obesity on spirometric indices of lung function

No.	Ref.	Obesity indices	Study population	Main findings
1	Lazarus <i>et al</i> ^[34] , 1997	Total body fat calculated from equations based on skinfold thickness	Representative sample of 2464 Australian school children aged 9, 12, and 15 yo	Total body fat was inversely associated with FVC and FEV1 after adjusting for height and weight
2	Li <i>et al</i> ^[9] , 2003	Trunk and subtotal (total-head) body fat mass	Sixty-four obese children, 7-18 yo without cardiorespiratory problems.	No significant associations between the obesity and the spirometric indices
3	Perez-Padilla <i>et al</i> ^[35] , 2006	Trunk body fat	A cross-sectional study of 6784 students 6-20 yo	In children < 11 yr FEV1 and FVC increased with BMI. In subjects > 12 yr lung function increased with BMI, reached a plateau (at a BMI Z score of 1SD) and then decreased among those with highest BMI
4	Nageswari <i>et al</i> ^[36] , 2007	% body mass	Twenty obese/overweight children and 20 normal-weight (controls), 12-16 yo	FEV1, FVC, FEF _{25%-75%} were significantly lower in the obese group compared to the controls
5	Chen <i>et al</i> ^[18] , 2009	Subtotal body fat (total-head)	A cross-sectional study of 718 children 6-17 yo	WC, but not BMI, was positively associated with FEV1 and FVC, and negatively associated with FEV1/FVC
6	Spathopoulos <i>et al</i> ^[37] , 2009	% body mass	Three hundred fifty-seven overweight, 300 obese, and 196 normal-weight children. Not well-controlled asthma cases were excluded	All spirometric parameters were significantly different across the three groups. BMI > 85 th centile was a significant independent predictor of reduced spirometric parameters after controlling for confounders
7	Cibella <i>et al</i> ^[16] , 2011	BMI	Cross-sectional study carried out in a sample of 708 children 10-16 yo	FEV1 and FVC were lower in children with BMI > 85 th centile compared to those with normal BMI. No difference was found for FEF _{25%-75%} , FEV1/FVC
8	Feng <i>et al</i> ^[19] , 2012	BMI	A cross-sectional performed on 1572 healthy children 9-18 yo. Children with asthma were excluded	WC was inversely associated with FEV1, FVC and FEV1/FVC. BMI was positively related with FEV1 and FVC and negatively associated with FEV1/FVC
9	van de Griendt <i>et al</i> ^[8] , 2012	BMI	One hundred twelve obese children 8.5-18.9 yo, taking part in a multidisciplinary treatment programme.	FEV1 and FVC increased by 2.91% and 3.08% after weight reduction following a 6 mo intervention program and this increase was significant. No significant change was observed in MEF ₅₀
10	Paralikar <i>et al</i> ^[38] , 2012	WC	Thirty obese boys 12-17 yo and 30 age-matched normal-weight boys	FEV1, FEV1/FVC and MVV were significantly decreased in the obese group
11	Bekkers <i>et al</i> ^[20] , 2013	BMI, WC	Children from a birth cohort (<i>n</i> = 1058) examined at the age of 8 yo	Large WC in girls was associated with lower FEV1 /FVC ratio
12	Davidson <i>et al</i> ^[12] , 2013	BMI	Three hundred twenty-seven children 6-17 yo referred for lung testing due to various respiratory problems. Individuals with cardiopulmonary, chest wall disease, or asthma, were excluded	Positive relationship between BMI z-score and percent predicted FVC, and VC. Negative relationship between BMI z-score and FRC, ERV, RV, and FEV1/FVC
13	Han <i>et al</i> ^[17] , 2014	BMI, PBF, WC	Cross-sectional study in 2681 children 6-17 yo	Among children without asthma, BMI, PBF, and WC were associated with higher FEV1 and FVC, and lower FEV1/FVC
14	Khan <i>et al</i> ^[39] , 2014	BMI, WC, WHR, skinfold measurements	A sample of 1583 children, < 18 yo. No data on asthma diagnosis was provided	Overweight/obese boys, had WC and WHR inversely associated with residual FVC, FEV _{0.75} , and FEV1
15	Rastogi <i>et al</i> ^[11] , 2014	BMI	A sample of 168 adolescents, 13-18 yo, irrespective of asthma status	Obese adolescents had lower RV, RV/TLC ratio, ERV, and FRC, and higher IC adolescents; the 2 groups did not differ in measures of lower airway obstruction, namely FEV1/FVC, and MEF
16	Torun <i>et al</i> ^[40] , 2014	BMI	A cross-sectional study of 30 overweight, 34 obese and 64 morbidly obese children, 9-17 yo, referred to a paediatric endocrinology dept. Asthmatic patients were excluded from the study	PEF and FEV ₂₅₋₇₅ were significantly reduced in in the overweight, obese and morbidly obese children

17	Bekkers <i>et al</i> ^[41] , 2015	BMI, WC	Children from a birth cohort examined at the ages of 8 yo (<i>n</i> = 1090) and 12 yo (<i>n</i> = 1288)	At 8 yo, large WC was associated with lower FEV1/FVC after adjusting for BMI (only in girls)
18	Kongkiattikul <i>et al</i> ^[10] , 2015	BMI, FMI, body fat percentage, truncal fat percentage, mean fat free mass index	Forty-five obese children, 8-18 yo	Negative correlation between FRC and almost all obesity indices
19	Cibella <i>et al</i> ^[14] , 2015	BMI	A cross-sectional study of 2393 healthy children 10-17 yo. Children with asthma were excluded	FVC and FEV1 were positively but disproportionately correlated to weight. FEV1/FVC and FEF _{25-75%} /FVC ratios were negatively correlated to weight
20	Costa Junior <i>et al</i> ^[42] , 2016	BMI, WC, body composition (tetrapolar bioimpedance)	A cross-sectional study of 40 obese and 35 normal-weight children, 6-10 yo. Children with respiratory problems were excluded	Obese children had lower FEV1 and FEV1/FVC
21	Liyanage <i>et al</i> ^[13] , 2016	BMI	A cross-sectional study of 55 obese and 220 normal-weight children, 9-15 yo. Children with asthma were excluded	No significant difference in spirometric values
22	Akin <i>et al</i> ^[43] , 2017	BMI, WC, neck circumference	A cross-sectional study of 178 children, 5 to 15 yo. Children with asthma were excluded	Negative correlation between FEV1, FEV1/FVC, and obesity indices
23	Yao <i>et al</i> ^[15] , 2017	BMI	1717 children, 5 to 18 yo, irrespective of asthma status	BMI is associated positively with FVC, FEV1, and PEF, and FEF _{25-75%} , but negatively with FEV1/FVC

yo: Years old; PBF: Percent body fat; WHR: Waist-to-hip ratio; MVV: Maximum voluntary ventilation; BMI: Body mass index; WC: Waist circumference; WHR: Waist-hip ratio; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity.

and significantly associated with FEV1, FVC, and FEF_{25%-75%}, but negatively and significantly associated with FEV1/FVC. In order to interpret these findings they commented that the lower FEV1/FVC ratio in relation to higher FEV1 and FVC indicated that the lung volumes were larger in obese subjects but the airways size has not grown proportionately. Quite similar results were found in another recent study by Cibella *et al*^[14] who also analyzed their data after controlling for age, and showed that the effect of excess weight on spirometric values was independent of age. It is worth mentioning that the results of a precedent study from the same research group in 2011^[16] did not point to the same direction. However, the results of these two studies are not comparable since the population of the 2011 study included both asthmatic and non-asthmatic subjects without taking into account for asthma status. The study that first described this distinct trend of associations between adiposity indices and spirometric variables was that of Han *et al*^[17] in 2014 which was, however, designed to explore the association of obesity indices and asthma. It is very interesting that the finding of significantly lower FEV1/FVC ratio in obese/overweight subjects has not been exclusively observed in the aforementioned studies; it is almost universally present among the rest of the presented studies.

The results quite often varied in studies^[18,19] that used different surrogates of obesity (BMI or WC). This discrepancy indicates that adiposity markers are not necessarily interchangeable at least as far it concerns studies exploring the variations of lung function variables. Furthermore, it seems that the population age span may have affected the results of the studies to

some extent. As it was shown in the PIAMA birth cohort study^[20], significantly lower FEV1/FVC was observed in the whole study population, regardless of gender, at the age of 12 years but not at the age of 8 years. Therefore cross sectional studies that included children between 6-18 years may have resulted in different findings depending on the number of subjects in each specific age sub-group.

DISCUSSION

The above presented findings, despite a degree of inconsistency, indicate that the excess weight in childhood and adolescence has an adverse influence on the lung function of otherwise healthy subjects. A recent meta-analysis^[21] that evaluated the effects of overweight/obesity in both children and adults found that lung function is detrimentally affected but its pattern differs between adults and children. Based on the data of the included studies, authors showed that the FEV1/FVC ratio was lower in obese/overweight children with a decrement of 2.4%. They did not find a significant difference for FEV1 or FVC. However, these conclusions were reached through a pooled analysis in asthmatic and non-asthmatic children and without having controlled for asthma status within the childhood population.

There are several factors that could have attributed to the relatively diverse findings of the studies we included in the present systematic review. The sample size employed was small in some of them; in others, the age range of the recruited participants was fairly wide and no age groups for sub-analysis were specified; not all studies excluded children with asthma diagnosis;

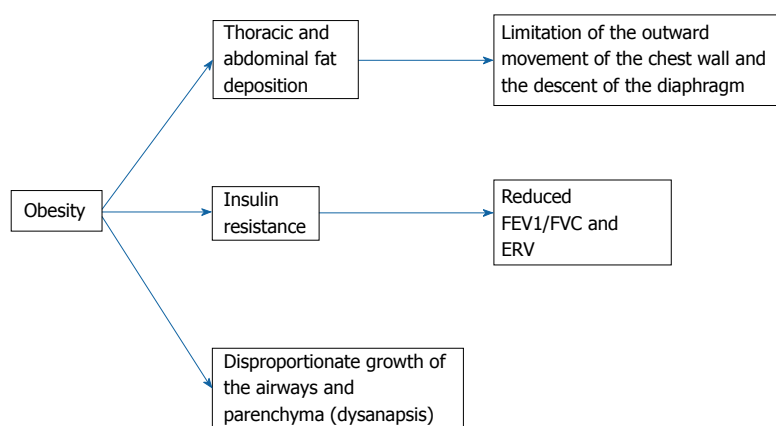


Figure 1 Mechanisms underlying reduced lung function in obese children. ERV: Expiratory reserve volume; FEV1: Forced expiratory volume in 1 s; FVC: Forced vital capacity.

there was not available information on the duration of the overweight/obesity, a variable that may also have an impact on lung function^[22]. The variation of obesity prevalence among the different populations, as well as the type of fat deposition which was not taken into account in the majority of the studies, may also have contributed to the observed discordance of the results among some of the studies. A factor not to be overlooked is that studied populations were of different ethnicity, and it is known that the amount of visceral adiposity tissue is dependent on ethnic origin^[23]. Lastly, data for maturity stage (Tanner stage) were not provided in any of the studies and therefore no adjustment was made for this parameter.

The physiologic mechanisms that underlie the impact of obesity on lung function are not entirely understood. It seems that the thoracic and abdominal fat deposition limit the outward movement of the chest wall and the descent of the diaphragm^[24]. Additionally, obesity is associated with reduced compliance of the respiratory system although it is not clarified whether both lung and chest wall compliance are reduced or not^[24,25]. It is also of note that obesity may coexist with obstructive sleep apnea syndrome (OSAS). Obese children have a 4.5 fold increased risk for OSAS^[26] a syndrome that may further contribute to hypoventilation in obesity^[27]. More recent studies suggest that the adverse effects of obesity on lung function are due not only to mechanical reasons but also to the metabolic abnormalities encountered in obesity. Rastogi *et al.*^[11] found that insulin resistance was a significant determinant of FEV1/FVC ratio and ERV in adolescents, even after adjusting for general and truncal adiposity. The above are supported from the results of a recent study conducted in obese women^[28]. Additionally hepatic steatosis is more prevalent in obese children and as it was recently shown in adult population hepatic steatosis was associated with poor pulmonary function^[29]. The main proposed mechanisms underlying reduced lung function in obese children are depicted in Figure 1.

Another interesting aspect on this issue was proposed by Forno *et al.*^[30] who have shown in a recent study that obesity was related to dysanapsis. The notion of dysanaptic growth of the lung was first introduced by Green *et al.*^[31] in 1974 and it indicates a normal but disproportionate growth of the airways and parenchyma so as large lungs to be accompanied by airways with incommensurate small proportions^[31,32]. In spirometry airway dysanapsis is indicated by normal FEV1 (above the 5th centile), normal high FVC (above the 75th centile), and low FEV1/FVC ratio (< 0.8)^[38]. Forno *et al.*^[30] used the data of six different cohorts and analyzed them cross-sectionally - or longitudinally if that was feasible - and found that obesity was associated with dysanapsis in childhood and adolescence.

In the majority of studies the lung function values of overweight/obese children were within normal limits, and so, it could be argued that the impairment of lung function is of no clinical relevance. This may seem plausible while the subjects are at rest but it would not be likely in the case of exercise tolerance. It should be kept in mind that obesity is not only a consequence of sedentary life style but also that the physical performance of obese subjects may be lower. The latter may be due in part to the altered lung function that leads to a vicious cycle of inadequate physical activity and obesity persistence. Additionally, the persistence of overweight/obesity to adulthood may also adversely affect their lung function as adults^[22,33].

As obesity is a worldwide public health problem, its adverse impact on lung function of non-asthmatic children and adolescents is of utmost importance since it may contribute to the increased morbidity of obese subjects. The physicians should be aware of this aspect of obesity and communicate this information to children and their families.

REFERENCES

- 1 NCD Risk Factor Collaboration (NCD-RisC). Worldwide

- trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* 2017; **390**: 2627-2642 [PMID: 29029897 DOI: 10.1016/S0140-6736(17)32129-3]
- 2 **Ng M**, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, Mullany EC, Biryukov S, Abbafati C, Abera SF, Abraham JP, Abu-Rmeileh NM, Achoki T, AlBuhairan FS, Alemu ZA, Alfonso R, Ali MK, Ali R, Guzman NA, Ammar W, Anwar P, Banerjee A, Barquera S, Basu S, Bennett DA, Bhutta Z, Blore J, Cabral N, Nonato IC, Chang JC, Chowdhury R, Courville KJ, Criqui MH, Cundiff DK, Dabhadkar KC, Dandona L, Davis A, Dayama A, Dharmaratne SD, Ding EL, Durrani AM, Esteghamati A, Farzadfar F, Fay DF, Feigin VL, Flaxman A, Forouzanfar MH, Goto A, Green MA, Gupta R, Hafezi-Nejad N, Hankey GJ, Harewood HC, Havmoeller R, Hay S, Hernandez L, Husseini A, Idrisov BT, Ikeda N, Islami F, Jahangir E, Jassal SK, Jee SH, Jeffreys M, Jonas JB, Kabagambe EK, Khalifa SE, Kengne AP, Khader YS, Khang YH, Kim D, Kimokoti RW, Kinge JM, Kokubo Y, Kosen S, Kwan G, Lai T, Leinsalu M, Li Y, Liang X, Liu S, Logroscino G, Lotufo PA, Lu Y, Ma J, Mainoo NK, Mensah GA, Merriman TR, Mokdad AH, Moschandreas J, Naghavi M, Naheed A, Nand D, Narayan KM, Nelson EL, Neuhouser ML, Nisar MI, Ohkubo T, Oti SO, Pedroza A, Prabhakaran D, Roy N, Sampson U, Seo H, Sepanlou SG, Shibuya K, Shiri R, Shiue I, Singh GM, Singh JA, Skirbekk V, Stapelberg NJ, Sturua L, Sykes BL, Tobias M, Tran BX, Trasande L, Toyoshima H, van de Vijver S, Vasankari TJ, Veerman JL, Velasquez-Melendez G, Vlassov VV, Vollset SE, Vos T, Wang C, Wang X, Weiderpass E, Werdecker A, Wright JL, Yang YC, Yatsuya H, Yoon J, Yoon SJ, Zhao Y, Zhou M, Zhu S, Lopez AD, Murray CJ, Gakidou E. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**: 766-781 [PMID: 24880830 DOI: 10.1016/S0140-6736(14)60460-8]
 - 3 **Singh AS**, Mulder C, Twisk JW, van Mechelen W, Chinapaw MJ. Tracking of childhood overweight into adulthood: a systematic review of the literature. *Obes Rev* 2008; **9**: 474-488 [PMID: 18331423 DOI: 10.1111/j.1467-789X.2008.00475.x]
 - 4 **GBD 2015 Obesity Collaborators**, Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, Marczak L, Mokdad AH, Moradi-Lakeh M, Naghavi M, Salama JS, Vos T, Abate KH, Abbafati C, Ahmed MB, Al-Aly Z, Alkerwi A, Al-Raddadi R, Amare AT, Amberbir A, Amegah AK, Amini E, Amrock SM, Anjana RM, Ärnlöv J, Asayesh H, Banerjee A, Barac A, Baye E, Bennett DA, Beyene AS, Biadgilign S, Biryukov S, Bjertness E, Boneya DJ, Campos-Nonato I, Carrero JJ, Cecilio P, Cercy K, Ciobanu LG, Cornaby L, Damtew SA, Dandona L, Dandona R, Dharmaratne SD, Duncan BB, Eshrati B, Esteghamati A, Feigin VL, Fernandes JC, Fürst T, Gebrehiwot TT, Gold A, Gona PN, Goto A, Habtewold TD, Hadush KT, Hafezi-Nejad N, Hay SI, Horino M, Islami F, Kamal R, Kasaeian A, Katikireddi SV, Kengne AP, Kesavachandran CN, Khader YS, Khang YH, Khubchandani J, Kim D, Kim YJ, Kinfu Y, Kosen S, Ku T, Defo BK, Kumar GA, Larson HJ, Leinsalu M, Liang X, Lim SS, Liu P, Lopez AD, Lozano R, Majeed A, Malekzadeh R, Malta DC, Mazidi M, McAlinden C, McGarvey ST, Mengistu DT, Mensah GA, Mensink GBM, Mezgebe HB, Mirakhorimov EM, Mueller UO, Noubiap JJ, Obermeyer CM, Ogbo FA, Owolabi MO, Patton GC, Pourmalek F, Qorbani M, Rafay A, Rai RK, Ranabhat CL, Reinig N, Safiri S, Salomon JA, Sanabria JR, Santos IS, Sartorius B, Sawhney M, Schmidhuber J, Schutte AE, Schmidt MI, Sepanlou SG, Shamsizadeh M, Sheikhbahaei S, Shin MJ, Shiri R, Shiue I, Roba HS, Silva DAS, Silverberg JJ, Singh JA, Stranges S, Swaminathan S, Tabarés-Seisdedos R, Tadese F, Tedla BA, Tegegne BS, Terkawi AS, Thakur JS, Tonelli M, Topor-Madry R, Tyrovolas S, Ukwaja KN, Uthman OA, Vaezghasemi M, Vasankari T, Vlassov VV, Vollset SE, Weiderpass E, Werdecker A, Wesana J, Westerman R, Yano Y, Yonemoto N, Yonga G, Zaidi Z, Zenebe ZM, Zipkin B, Murray CJL. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med* 2017; **377**: 13-27 [PMID: 28604169 DOI: 10.1056/NEJMoa1614362]
 - 5 **Peters U**, Suratt BT, Bates JHT, Dixon AE. Beyond BMI: Obesity and Lung Disease. *Chest* 2018; **153**: 702-709 [PMID: 28728934 DOI: 10.1016/j.chest.2017.07.010]
 - 6 **Krebs NF**, Himes JH, Jacobson D, Nicklas TA, Guilday P, Styne D. Assessment of child and adolescent overweight and obesity. *Pediatrics* 2007; **120** Suppl 4: S193-S228 [PMID: 18055652 DOI: 10.1542/peds.2007-2329D]
 - 7 **Ogden CL**, Flegal KM. Changes in terminology for childhood overweight and obesity. *Natl Health Stat Report* 2010; **(25)**: 1-5 [PMID: 20939253]
 - 8 **van de Griendt EJ**, van der Baan-Slootweg OH, van Essen-Zandvliet EE, van der Palen J, Tammenga-Smeulders CL, Benninga MA, van Aalderen WM. Gain in lung function after weight reduction in severely obese children. *Arch Dis Child* 2012; **97**: 1039-1042 [PMID: 23076338 DOI: 10.1136/archdischild-2011-301304]
 - 9 **Li AM**, Chan D, Wong E, Yin J, Nelson EA, Fok TF. The effects of obesity on pulmonary function. *Arch Dis Child* 2003; **88**: 361-363 [PMID: 12651773 DOI: 10.1136/adc.88.4.361]
 - 10 **Kongkiattikul L**, Sritippayawan S, Chomtho S, Deerojanawong J, Prapphal N. Relationship between Obesity Indices and Pulmonary Function Parameters in Obese Thai Children and Adolescents. *Indian J Pediatr* 2015; **82**: 1112-1116 [PMID: 25947270 DOI: 10.1007/s12098-015-1777-4]
 - 11 **Rastogi D**, Bhalani K, Hall CB, Isasi CR. Association of pulmonary function with adiposity and metabolic abnormalities in urban minority adolescents. *Ann Am Thorac Soc* 2014; **11**: 744-752 [PMID: 24785169 DOI: 10.1513/AnnalsATS.201311-403OC]
 - 12 **Davidson WJ**, Mackenzie-Rife KA, Witmans MB, Montgomery MD, Ball GD, Egbogah S, Eves ND. Obesity negatively impacts lung function in children and adolescents. *Pediatr Pulmonol* 2014; **49**: 1003-1010 [PMID: 24167154 DOI: 10.1002/ppul.22915]
 - 13 **Liyanage G**, Jayamanne B D, Aaqiff M, Sriwardhana D. Effect of body mass index on pulmonary function in children *Ceylon Med J* 2016; **61**: 163-166 [PMID: 28076945 DOI: 10.4038/cmj.v61i4.8382]
 - 14 **Cibella F**, Bruno A, Cuttitta G, Bucchieri S, Melis MR, De Cantis S, La Grutta S, Viegi G. An elevated body mass index increases lung volume but reduces airflow in Italian schoolchildren. *PLoS One* 2015; **10**: e0127154 [PMID: 25970463 DOI: 10.1371/journal.pone.0127154]
 - 15 **Yao TC**, Tsai HJ, Chang SW, Chung RH, Hsu JY, Tsai MH, Liao SL, Hua MC, Lai SH, Chen LC, Yeh KW, Tseng YL, Lin WC, Chang SC, Huang JL; Prediction of Allergies in Taiwanese Children (PATCH) Study Group. Obesity disproportionately impacts lung volumes, airflow and exhaled nitric oxide in children. *PLoS One* 2017; **12**: e0174691 [PMID: 28376119 DOI: 10.1371/journal.pone.0174691]
 - 16 **Cibella F**, Cuttitta G, La Grutta S, Melis MR, Bucchieri S, Viegi G. A cross-sectional study assessing the relationship between BMI, asthma, atopy, and eNO among schoolchildren. *Ann Allergy Asthma Immunol* 2011; **107**: 330-336 [PMID: 21962093 DOI: 10.1016/j.anai.2011.08.001]
 - 17 **Han YY**, Forno E, Celedón JC. Adiposity, fractional exhaled nitric oxide, and asthma in U.S. children. *Am J Respir Crit Care Med* 2014; **190**: 32-39 [PMID: 24922361 DOI: 10.1164/rccm.201403-0565OC]
 - 18 **Chen Y**, Rennie D, Cormier Y, Dosman JA. Waist circumference associated with pulmonary function in children. *Pediatr Pulmonol* 2009; **44**: 216-221 [PMID: 19205050 DOI: 10.1002/ppul.20854]
 - 19 **Feng K**, Chen L, Han SM, Zhu GJ. Ratio of waist circumference to chest circumference is inversely associated with lung function in Chinese children and adolescents. *Respirology* 2012; **17**: 1114-1118 [PMID: 22758916 DOI: 10.1111/j.1440-1843.2012.02219.x]
 - 20 **Bekkers MB**, Wijga AH, de Jongste JC, Kerkhof MC, Postma D, Gehring U, Smit HA, Brunekreef B. Waist circumference, BMI, and lung function in 8-year-old children: the PIAMA birth cohort study. *Pediatr Pulmonol* 2013; **48**: 674-682 [PMID: 23143885]

- DOI: 10.1002/ppul.22722]
- 21 **Forno E**, Han YY, Mullen J, Celedón JC. Overweight, Obesity, and Lung Function in Children and Adults-A Meta-analysis. *J Allergy Clin Immunol Pract* 2018; **6**: 570-581.e10 [PMID: 28967546 DOI: 10.1016/j.jaip.2017.07.010]
 - 22 **Santamaria F**, Montella S, Greco L, Valerio G, Franzese A, Maniscalco M, Fiorentino G, Peroni D, Pietrobelli A, De Stefano S, Sperli F, Boner AL. Obesity duration is associated to pulmonary function impairment in obese subjects. *Obesity* (Silver Spring) 2011; **19**: 1623-1628 [PMID: 21311508 DOI: 10.1038/oby.2011.1]
 - 23 **Lear SA**, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). *Am J Clin Nutr* 2007; **86**: 353-359 [PMID: 17684205 DOI: 10.1093/ajcn/86.2.353]
 - 24 **Robinson PD**. Obesity and its impact on the respiratory system. *Paediatr Respir Rev* 2014; **15**: 219-226 [PMID: 25092493 DOI: 10.1016/j.prrv.2014.06.003]
 - 25 **Parameswaran K**, Todd DC, Soth M. Altered respiratory physiology in obesity. *Can Respir J* 2006; **13**: 203-210 [PMID: 16779465 DOI: 10.1155/2006/834786]
 - 26 **Redline S**, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory problems. *Am J Respir Crit Care Med* 1999; **159**: 1527-1532 [PMID: 10228121 DOI: 10.1164/ajrccm.159.5.9809079]
 - 27 **Arens R**, Muzumdar H. Childhood obesity and obstructive sleep apnea syndrome. *J Appl Physiol* (1985) 2010; **108**: 436-444 [PMID: 19875714 DOI: 10.1152/japplphysiol.00689.2009]
 - 28 **Lecube A**, Sampol G, Muñoz X, Lloberes P, Hernández C, Simó R. Insulin resistance is related to impaired lung function in morbidly obese women: a case-control study. *Diabetes Metab Res Rev* 2010; **26**: 639-645 [PMID: 20882512 DOI: 10.1002/dmrr.1131]
 - 29 **Mann JP**, Valenti L, Scorletti E, Byrne CD, Nobili V. Nonalcoholic Fatty Liver Disease in Children. *Semin Liver Dis* 2018; **38**: 1-13 [PMID: 29471561 DOI: 10.1055/s-0038-1627456]
 - 30 **Forno E**, Weiner DJ, Mullen J, Sawicki G, Kurland G, Han YY, Cloutier MM, Canino G, Weiss ST, Litonjua AA, Celedón JC. Obesity and Airway Dysanapsis in Children with and without Asthma. *Am J Respir Crit Care Med* 2017; **195**: 314-323 [PMID: 27552676 DOI: 10.1164/rccm.201605-1039OC]
 - 31 **Green M**, Mead J, Turner JM. Variability of maximum expiratory flow-volume curves. *J Appl Physiol* 1974; **37**: 67-74 [PMID: 4836570 DOI: 10.1152/jappl.1974.37.1.67]
 - 32 **Mead J**. Dysanapsis in normal lungs assessed by the relationship between maximal flow, static recoil, and vital capacity. *Am Rev Respir Dis* 1980; **121**: 339-342 [PMID: 7362140 DOI: 10.1164/arrd.1980.121.2.339]
 - 33 **Suresh S**, O'Callaghan M, Sly PD, Mamun AA. Impact of childhood anthropometry trends on adult lung function. *Chest* 2015; **147**: 1118-1126 [PMID: 25340561 DOI: 10.1378/chest.14-0698]
 - 34 **Lazarus R**, Colditz G, Berkey CS, Speizer FE. Effects of body fat on ventilatory function in children and adolescents: cross-sectional findings from a random population sample of school children. *Pediatr Pulmonol* 1997; **24**: 187-194 [PMID: 9330415 DOI: 10.1002/(SICI)1099-0496(199709)24:3<187::AID-PPUL4>3.0.CO;2-K]
 - 35 **Pérez-Padilla R**, Rojas R, Torres V, Borja-Aburto V, Olaiz G, The Empece Working Group. Obesity among children residing in Mexico City and its impact on lung function: a comparison with Mexican-Americans. *Arch Med Res* 2006; **37**: 165-171 [PMID: 16314204 DOI: 10.1016/j.arcmed.2005.05.009]
 - 36 **Nageswari KS**, Sharma R, Kohli DR. Assessment of respiratory and sympathetic cardiovascular parameters in obese school children. *Indian J Physiol Pharmacol* 2007; **51**: 235-243 [PMID: 18341219]
 - 37 **Spathopoulos D**, Paraskakis E, Trypsianis G, Tsalkidis A, Arvanitidou V, Emporiadou M, Bouras D, Chatzimichael A. The effect of obesity on pulmonary lung function of school aged children in Greece. *Pediatr Pulmonol* 2009; **44**: 273-280 [PMID: 19208374 DOI: 10.1002/ppul.20995]
 - 38 **Paralikar SJ**, Kathrotia RG, Pathak NR, Jani MB. Assessment of pulmonary functions in obese adolescent boys. *Lung India* 2012; **29**: 236-240 [PMID: 22919162 DOI: 10.4103/0970-2113.99106]
 - 39 **Khan S**, Little J, Chen Y. Relationship Between Adiposity and Pulmonary Function in School-Aged Canadian Children. *Pediatr Allergy Immunol Pulmonol* 2014; **27**: 126-132 [PMID: 25276486 DOI: 10.1089/ped.2014.0349]
 - 40 **Torun E**, Cakir E, Ozguc F, Ozgen IT. The effect of obesity degree on childhood pulmonary function tests. *Balkan Med J* 2014; **31**: 235-238 [PMID: 25337419 DOI: 10.5152/balkanmedj.2014.13101]
 - 41 **Bekkers MB**, Wijga AH, Gehring U, Koppelman GH, de Jongste JC, Smit HA, Brunekreef B. BMI, waist circumference at 8 and 12 years of age and FVC and FEV1 at 12 years of age; the PIAMA birth cohort study. *BMC Pulm Med* 2015; **15**: 39 [PMID: 25896340 DOI: 10.1186/s12890-015-0032-0]
 - 42 **Costa Junior D**, Peixoto-Souza FS, Araujo PN, Barbalho-Moulin MC, Alves VC, Gomes EL, Costa D. Influence of Body Composition on Lung Function and Respiratory Muscle Strength in Children With Obesity. *J Clin Med Res* 2016; **8**: 105-110 [PMID: 26767078 DOI: 10.14740/jocmr2382w]
 - 43 **Akın O**, Arslan M, Haymana C, Karabulut E, Hacıhamdioglu B, Yavuz ST. Association of neck circumference and pulmonary function in children. *Ann Allergy Asthma Immunol* 2017; **119**: 27-30 [PMID: 28527867 DOI: 10.1016/j.anai.2017.04.018]

P- Reviewer: Arslan N, Tarantino G **S- Editor:** Ji FF

L- Editor: Filipodia **E- Editor:** Tan WW



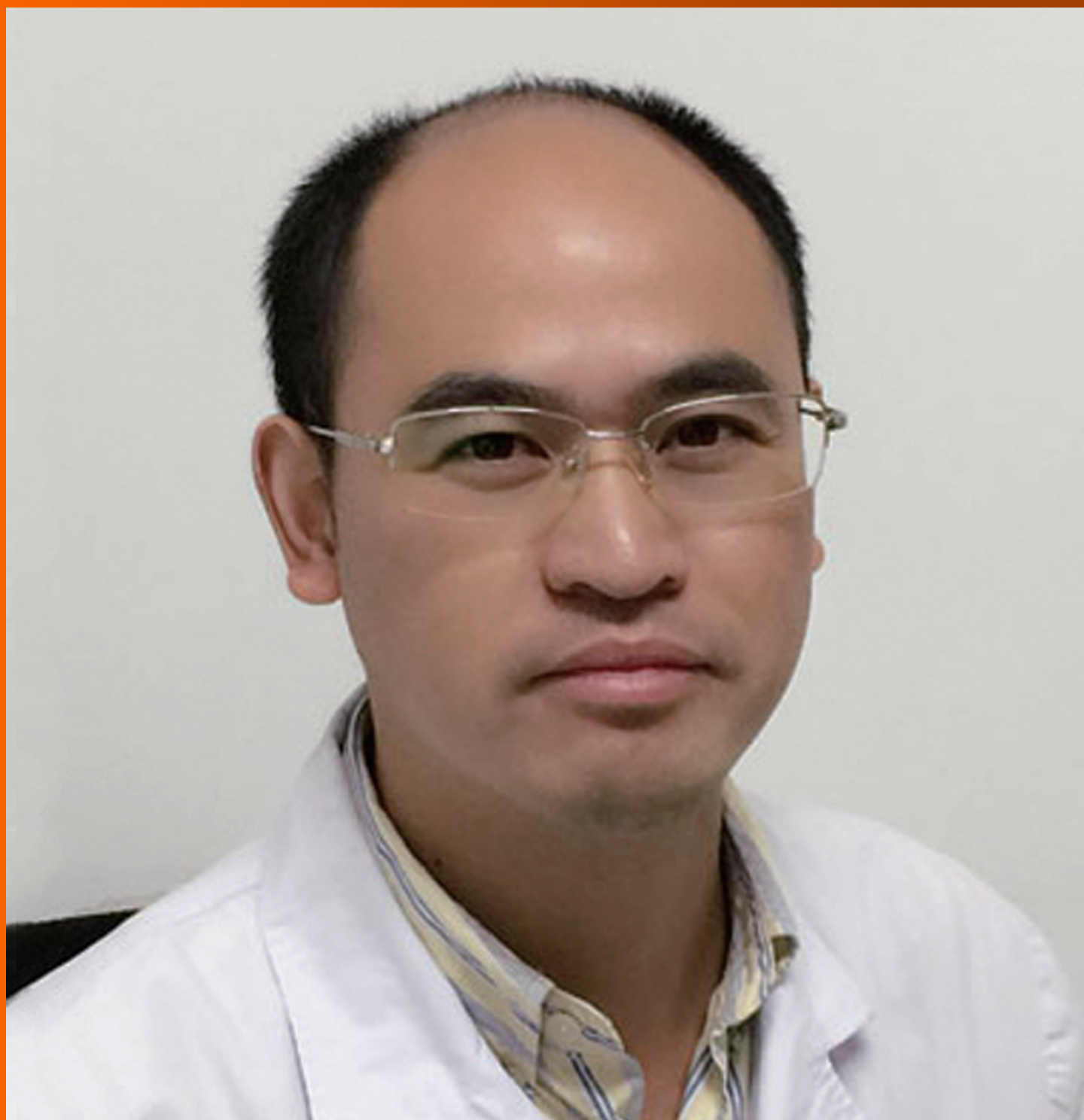


Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>



World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2018 August 30; 7(3): 75-88





EDITORIAL

- 75 Innovation for rare diseases and bioethical concerns: A thin thread between medical progress and suffering

Tommasini A, Magnolato A, Bruno I

MINIREVIEWS

- 83 Clinical features of acute kidney injury in patients with Kawasaki disease

Watanabe T

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Pediatrics*, Yi-Zhong Wang, PhD, Assistant Professor, Department of Infectious Diseases/Department of Gastroenterology, Hepatology, and Nutrition, Shanghai Children's Hospital, Shanghai Jiao Tong University, Shanghai 200040, China

AIM AND SCOPE

World Journal of Clinical Pediatrics (*World J Clin Pediatr*, *WJCP*, online ISSN 2219-2808, DOI: 10.5409) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCP covers a variety of clinical medical topics, including fetal diseases, inborn, newborn diseases, infant diseases, genetic diseases, diagnostic imaging, endoscopy, and evidence-based medicine and epidemiology. Priority publication will be given to articles concerning diagnosis and treatment of pediatric diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJCP*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Clinical Pediatrics is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

EDITORS FOR
THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Han Song*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Fang-Fang Ji*
Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL

World Journal of Clinical Pediatrics

ISSN

ISSN 2219-2808 (online)

LAUNCH DATE

June 8, 2012

EDITORS-IN-CHIEF

Consolato M Sergi, FRCP(C), MD, PhD, Professor,
Department of Lab Medicine and Pathology, University
of Alberta, Alberta T6G 2B7, Canada

Toru Watanabe, MD, PhD, Professor, Department
of Pediatrics, Niigata City General Hospital, Niigata
950-1197, Japan

EDITORIAL BOARD MEMBERS

All editorial board members resources online at <http://www.wjnet.com/2219-2808/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director
World Journal of Clinical Pediatrics
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjnet.com>

PUBLISHER

Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjnet.com>

PUBLICATION DATE

August 30, 2018

COPYRIGHT

© 2018 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

<http://www.wjnet.com/bpg/gcinfo/204>

ONLINE SUBMISSION

<http://www.f6publishing.com>

Innovation for rare diseases and bioethical concerns: A thin thread between medical progress and suffering

Alberto Tommasini, Andrea Magnolato, Irene Bruno

Alberto Tommasini, Andrea Magnolato, Irene Bruno, Department of Pediatrics, Institute of Maternal and Child Health, IRCCS Burlo Garofolo, Trieste 34137, Italy

ORCID number: Alberto Tommasini (0000-0002-6943-7927); Andrea Magnolato (0000-0002-5099-6526); Irene Bruno (0000-0002-2437-6198).

Author contributions: Tommasini A conceived the idea and wrote the manuscript draft; Magnolato A described and discussed the third clinical case and corrected the manuscript; Bruno I supervised and approved the work.

Supported by the IRCCS Burlo Garofolo, grant No. RC24/17.

Conflict-of-interest statement: The authors declare that they have no conflict of interest concerning the present article.

Open-Access: This article is an open-access article, which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Alberto Tommasini, MD, PhD, Adjunct Professor, Medical Assistant, Senior Scientist, Department of Pediatrics, Institute of Maternal and Child Health, IRCCS Burlo Garofolo, via dell'Istria 65/1, Trieste 34137, Italy. alberto.tommasini@burlo.trieste.it
Telephone: +39-40-3785422

Received: June 27, 2018

Peer-review started: June 30, 2018

First decision: July 9, 2018

Revised: August 6, 2018

Accepted: August 12, 2018

Article in press: August 13, 2018

Published online: August 30, 2018

Abstract

With the development of precision medicines based on small molecules, antibodies, RNAs and gene therapy, technological innovation is providing some exciting possibilities to treat the most severe genetic diseases. However, these treatments do not always lead to a cure for the disease, and there are several factors that may hinder their overall success. Patients living during a period of great medical change and innovation may benefit from these technological advances but may also just face failures, both in terms of frustrated hopes as well as suffering. In this article, we are telling the stories of three children with rare and severe disorders, who live in an age of significant medical changes, bearing the burden of difficult scientific and ethical choices. The first two cases that are suffering respectively from severe immunodeficiency and beta thalassemia have already been described in scientific journals, as well as in popular magazines. Although similar when considering the medical challenges, the two cases had opposite outcomes, which resulted in distinct ethical implications. The third case is a baby with spinal muscular atrophy, living at a time of continued innovation in the treatment of the disease. With these cases, we discuss the challenges of providing correct information and proper counseling to families and patients that are making the bumpy journey on the road of medical innovation.

Key words: X-severe combined immunodeficiency; Primary immunodeficiency; Beta thalassemia; Spinal muscular atrophy; Bioethics; History of medicine; Precision medicine; Genetics

© **The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Precision therapies are heralded to change the prognosis of rare and severe genetic disorders. However, the new treatments are not always curative and what can be viewed on one hand as a partial improvement,

on the other may result, at least for some patients, in prolonged suffering. During this period of change, great hopes but unpredictable outcomes can mark the lives of patients. Recalling and considering the ethical debates on historical cases can help doctors in giving the right advice to the families of patients with rare and severe disorders.

Tommasini A, Magnolato A, Bruno I. Innovation for rare diseases and bioethical concerns: A thin thread between medical progress and suffering. *World J Clin Pediatr* 2018; 7(3): 75-82 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i3/75.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i3.75>

INTRODUCTION

The history of medicine is riddled with successes and failures with exciting innovations and untold suffering. The contrast between the hopes pinned on innovation and the prolonged suffering in real life is particularly reflected by the experience of suffering from complex and rare disorders. It has been argued that the timetable of research sadly does not fit the life expectancy of patients. Even when progress seems to make headway, we can identify at least three groups of patients: those who are too late to benefit from novel treatments, those who will witness the success of innovative therapies, and those who will journey on the bumpy ride of innovation too slowly, facing new medical problems and ethical concerns. Subjects in the third group call for attention, as their lives will be challenged by difficult choices, whether to accept the risks brought on by changes, often ignoring whether innovation will have results of improvement that are clinically relevant. Moreover, they must cope with the difficulties of obtaining novel medications, which may be offered to them following a label prescription or as part of clinical trials that can require extraordinary willingness to cooperate and sometimes are never granted marketing authorization^[1-3]. Doctors will inform patients and/or their caregivers about the costs/benefits of the new treatments, based on the best expertise at any given moment. However, the partial medical knowledge and highly heterogeneous progression of the disease in addition to the response to treatments may hinder a reliable prediction of the disease outcome. This is particularly true for those patients with severe rare diseases. Even if regulatory agencies established robust rules to protect patients, their journey across major changes in medical knowledge and practice can be full of unforeseen difficulties.

In the first part of this article we mention two stories from the past, which both raised bioethical concerns and received media attention. For both cases, significant advances in medical care were paralleled by the personal stories of patients, who lived during remarkable scientific innovation. During this period, these patients went through moments of great hope and painful ad-

versity. In retrospect, our judgment concerning their cases cannot be impartial to the respective clinical outcomes and the social achievements during that time, in particular concerning birth control, prenatal genetic testing, and facing the prospect of death. However, it is not our intention to judge, but just to remember how difficult it can be to make the right choice. Even if each disease is considered in its own right, in the second part of the article we discuss how these lessons learnt from history can help us to cope with new challenges, such as the medical innovation that is on its way regarding spinal muscular atrophy (SMA).

DISCUSSION CASE #1

The case

These are the days of miracle and wonder, Simon

P: The bubble boy: Immunodeficiencies at the time of molecular immunology. The story of David Vetter, also known as "the bubble boy", has been described in detail elsewhere, both in scientific manuscripts and across some of the world's magazines, as well as in a movie (*The Boy in the Plastic Bubble*, 1976, by Douglas Day Stewart) and in a documentary (*PBS American Experience*, 2006)^[4-6]. The life of the boy inside a plastic bubble was at the same time a theme for scientific and ethical debate and also a popular real show, probably offering a much more cheerful portrait than in reality.

David's parents had their first son in 1970. Unfortunately, he died of severe combined immunodeficiency (SCID). Since there was no family history for immunodeficiency and the molecular defects underlying SCID were still unknown, it was impossible to predict the exact risk of familial recurrence of the disease. However, doctors informed the Vettters that, if they would have another child with SCID, the newborn could be delivered by cesarean section and immediately placed in a sterile environment by means of a plastic "isolator" that would protect him from infections until a cure was found. Being animated by a catholic sense of procreation and a fair trust in the doctors, the Vettters soon had a second boy, David, who was also diagnosed with SCID. The isolation of David in a sterile environment was made possible due to a dedicated research project at the Children Hospital in Houston. Despite great efforts to create a domestic environment in the bubble, the life inside could not have been so comfortable, not only because of the difficulty to interact with others, but also for the constant noise of the bubble's blower motors, turning the room into a scientific laboratory. As a research project, it led to several scientific publications, but also to ethical debates^[4,5,7-12].

It is difficult to try and interpret David's story only from indirect data. However, much of his life was dominated by the conflict between his natural curiosity about the world and the fear of microbes, which was taught to him to decrease his desire to come out of the bubble. When he was six years old, National Aeronautics and Space Administration (NASA) made him a special spacesuit coat to allow for safe walking outside of the

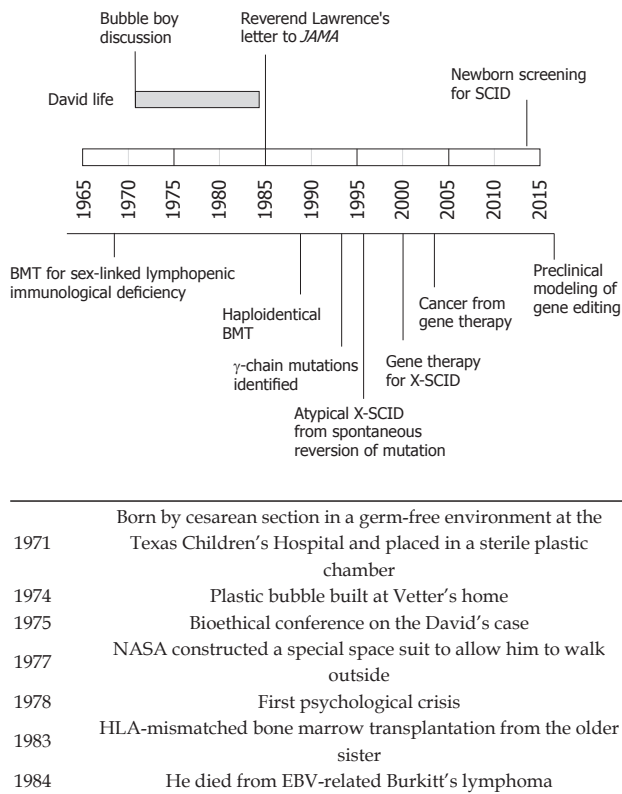


Figure 1 The timeline of David's life paralleled by the most significant advances in understanding and treating X-severe combined immunodeficiency. SCID: Severe combined immunodeficiency; BMT: Bone marrow transplantation; HLA: Histocompatibility leukocyte antigen; EBV: Epstein-Barr virus; NASA: National Aeronautics and Space Administration.

bubble (the so called "Mobile Biological Isolation System"). His reluctance to use this device only after several walks reflects the contrast between his fears and his dreams. As he grew older, he would live through even more conflicts. He soon became aware of how his life was different from his peers and how senseless it was to study things that he could not experience in reality. It does not come as a surprise that he started developing unbearable sadness and depression despite the support from Mary Murphy, a psychologist dedicated to the prevention and treatment of emotional crises. Murphy wrote a concerning tale about her experience with the boy, which was never published due to the contrariety of the parents and the medical staff. She also wrote a scientific manuscript about David's psychological development^[13].

At the age of 12 years, due to the untenable life conditions and recent medical advances, David underwent histocompatibility leukocyte antigen (HLA)-mismatched bone marrow transplantation from his older sister. Unfortunately, he developed Burkitt's lymphoma and died a few months later in February 1984. His death was followed by a scientific and ethical debate with several contributions in *JAMA*^[14-16]. Great attention was given to a letter from the Reverend Raymond J Lawrence, the chaplain of the Houston Children Hospital, who manifested

his disappointment in the case, criticizing the excessive trust in science that had led a boy to be conceived "for research", not considering the potential damages that a possible medical failure could cause to him^[14].

It will remain a matter for debate whether the case of David represents more of a triumph for technology or an error in estimating the power of medicine. Even if ethical issues were discussed at a conference in 1975, years before the death of the boy, a different outcome after transplantation could probably have influenced everyone's judgment. What remains true, apart from any ethical considerations on the case, is the fact that David lived through a period of great changes, both in medical science and in bioethics.

The context

This story is well placed at the beginning of a scientific revolution that witnessed memorable breakthroughs in the field of immunology. Some of his doctors even envisaged the possibility that, once the causative gene would be identified (and it would only be identified in 1993)^[17] the disease could be cured with gene therapy. In Figure 1, the life of David is paralleled by a brief history of knowledge on X-SCID. Only a few babies, before David, survived SCID due to bone marrow transplantation from matched related or unrelated donors^[18-21]. More recently, several reports showed that the outcome of hematopoietic stem cell transplantation has greatly improved in the last two decades. The early diagnosis, thanks to neonatal screening or based on family history, is a major determinant of this success, allowing the procedure to be performed before the development of chronic infections, which are the greatest threat to the patients' survival^[22,23]. Hematopoietic stem cell protocols have been optimized in such a way that matched unrelated donors are now considered a suitable source of stem cells, with a rate of success not much lower than for HLA-matched siblings. Gene therapy was accomplished at the turn of the third millennium, and X-SCID was one of the first applications for this technology^[24]. Indeed, the observation of attenuated X-SCID phenotypes in subjects who developed T cell clones with spontaneous reversion of the genetic mutation highlighted a favorable proliferative fitness of corrected cells and predicted the success of gene therapy^[25]. However, initial attempts of gene therapy were burdened by the development of leukemia due to insertional activation of the LMO2 oncogene^[26]. The simultaneous improvements in the outcome of bone marrow transplantation hindered further applications of gene therapy for X-SCID until recent advances of the development of safer vectors and of the preclinical development of gene editing approaches^[27,28].

CASE DISCUSSION #2

The case

You are soul's unbreakable, Muse: The history of Khaled, an "immortal" boy. This is the history of a boy born in 1962 who was affected by severe anemia due

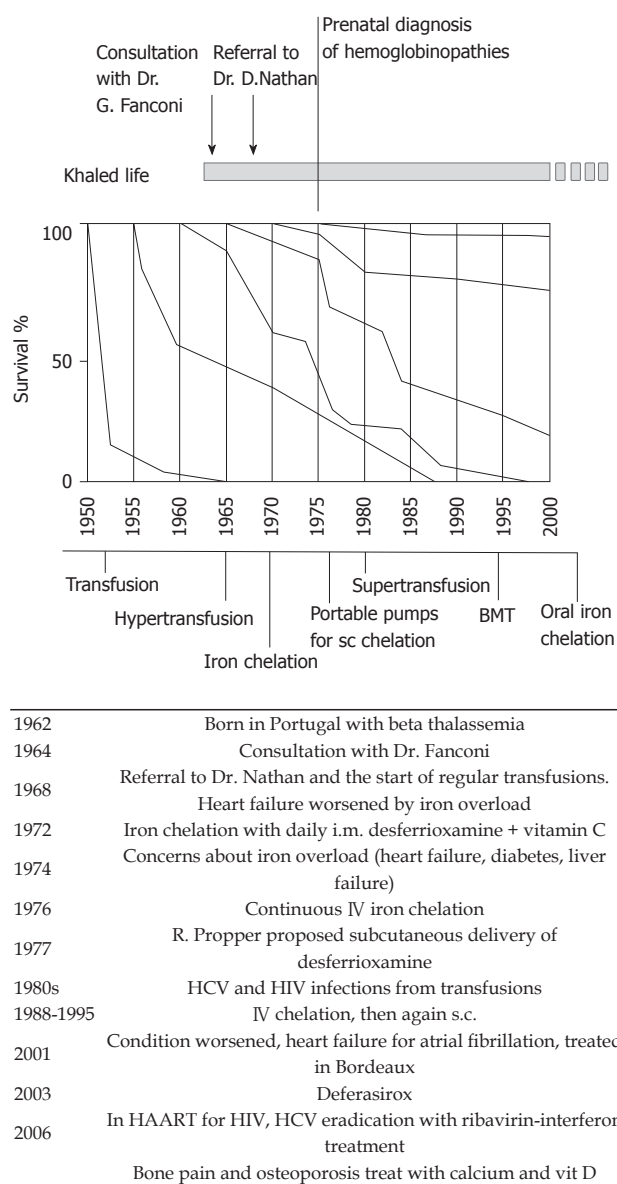


Figure 2 The timeline of Khaled's life paralleled by the most significant advances in understanding and treating Beta thalassemia major. BMT: Bone marrow transplantation; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HAART: Highly active antiretroviral therapy.

to beta thalassemia^[29,30]. His parents were Jewish and of Syrian and Iranian lineage living in Portugal. At that time, thalassemia major was invariably fatal in infancy. Subjects with the most severe form of thalassemia had only transient benefits from transfusions, which were quickly outweighed by the consequences of iron overload. Indeed, when Khaled's parents sought the opinion of the foremost pediatric hematologist in Europe, Guido Fanconi at the Kinderspital in Zurich, he explained to them that there was no recommendation on treating the boy with transfusions. Blood transfusions could allow him to survive several years longer but there would be complications and suffering from enriched iron overload. There was also the possibility that he could have had a milder form of the disease than was first thought,

and therefore he could survive without transfusions. Dr. Fanconi gave a well thought out opinion, following the best of the available expertise, based both on science and humanity. Four years later, the boy had survived, albeit with severe anemia, hepatosplenomegaly, gross bone deformities and recurrent fractures. Thus, the parents decided to seek the attention of David G Nathan, a hematologist in Boston, who was making significant progress with the treatment of thalassemia. As shown in Figure 2, patients' survival was slowly increasing in the cohort of patients born in the late 1960s. However, there was no medication available to efficiently reduce iron overload, and thus it was hard to predict possible changes in the natural history of the disease in subsequent years. When Dr. Nathan decided to start regular transfusions, the increasing iron overload contributed to the possibility of heart failure making the treatment even more challenging. Fortunately, iron chelation was entering clinical protocols for thalassemia major, even if intramuscular administration of the drug allowed insufficient urinary excretion of the metal^[31,32]. Great advances were achieved with continuous intravenous administration, and in 1977 subcutaneous delivery of the medication was implemented. Patients were required to stay at the hospital for long periods until portable infusion pumps were designed and became available. As shown in Figure 2, Khaled's life paralleled the most significant advances in the treatment of the disease, witnessed by a continuous improvement in life expectancy in subsequent generations. Dr. Nathan^[29] characterized this story in a beautiful book, showing how the life of his patient paralleled the history of medical successes and defeats (like viral infections) in thalassemia. An update of this story can be read in the Harvard magazine^[30].

The context

The graph in Figure 2 summarizes the experience of Vullo and his collaborators, in Ferrara Italy, but it can also fit in the experience of other groups dealing with this disease^[33]. Indeed, most pediatricians caring for patients with thalassemia experienced these exciting changes. Only an effective super-transfusion iron chelation regimen can completely suppress the patient's hemopoiesis and prevent the complex cascade typical of the disease: inhibition of hemopoiesis prevented both anemia and bone deformities; iron chelation prevented organ damage to the heart, liver and endocrine glands^[34-38].

Today the burden of beta thalassemia has been greatly reduced because of several factors including careful identification of the carriers, birth prevention of newborns with beta thalassemia major, early treatment of patients with blood transfusion and iron chelators, in some cases with bone marrow transplantation, and gene therapy^[39]. Fortunately, the incidence of thalassemia major has decreased in countries with a higher prevalence of heterozygous individuals due to public information campaigns, population screenings, genetic counseling, and prenatal diagnosis, either voluntary or through

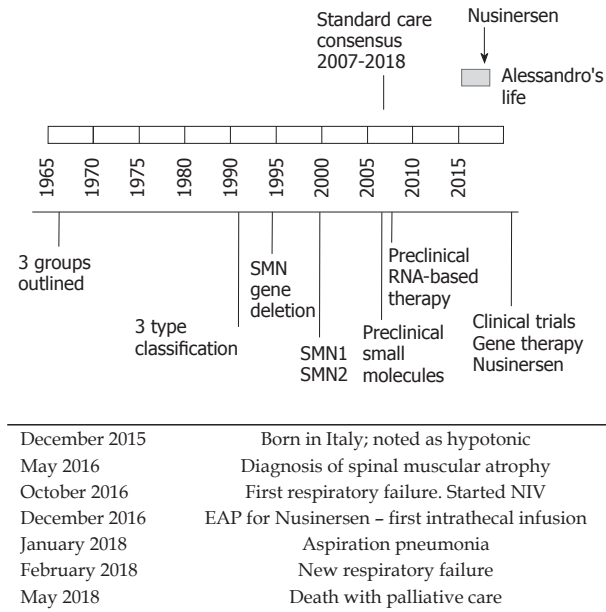


Figure 3 The timeline of Alessandro's life paralleled by the most significant advances in understanding and treating spinal muscular atrophy 1. NIV: Non-invasive ventilation; EAP: Expanded access program.

institutional basis^[40,41].

CASE DISCUSSION #3

The case

"How many roads must a man walk down before you call him a man?" Dylan B: A case of SMA at the time of a major medical progress. The story of Alessandro begins on a night in December 2015 in Italy. Following reduced fetal movements and the mother's hypertension, he was born prematurely at 32 wk of gestation. After birth, severe hypotonia was noted. Alessandro spent his first two months of life in a neonatal intensive care unit with a breathing machine and a feeding tube to sustain his vital functions. After a hard and complicated time, he was discharged with persisting hypotonia. He never achieved enough strength to sustain his head and his parents became aware that something was wrong. At 6 mo old, he was diagnosed with SMA. At that time, no cure for SMA was available and the treatment was based on respiratory and feeding assistance (standard care, see Figure 3). At 7 mo old, the parents took part in a special program on how to assist children with SMA and learned how to manage the ordinary and extraordinary practice of their child's daily life. At 10 mo old, Alessandro had his first breathing failure and a non-invasive ventilation (NIV) was started. This experience led his parents to understand the meaning of palliative care. They refused aggressive treatment and tracheotomy. However, in the same month Nusinersen, a new and promising drug for SMA became available, and the parents entered into the expanded access program (EAP) for this drug. At 12 mo old, Alessandro received the first intrathecal drug

infusion. After the fourth infusion, positive results became evident: small limb movements reappeared, NIV was reduced from 18 h/d to 10 h/d, and the ability to swallow was effectively increased. Nusinersen infusion, a lifelong treatment, was continued for another year and albeit further small improvements were noticed. The child also took part in an advertising campaign, which aimed to gather funds for research in SMA. In January 2018, at 25 mo old, Alessandro had aspiration pneumonia. He was hospitalized for three weeks, and he lost the strength and confidence gained in the previous year. NIV was necessarily increased to 16 h/d, and a percutaneous gastrostomy was proposed to reduce the stress of eating. After 15 d, the child was hospitalized again because of a new respiratory failure. Alessandro and his parents' state of mind completely changed in the last two months: they faced the prospect of death as they realized that SMA was getting worse despite Nusinersen. The drug was able to improve the quality of life, but it was not a cure. The last respiratory failure was crucial in the parents' choice. With great pain and fear, but also with the peacefulness of having accepted the fatal course of the disease, the parents chose palliative care. A few days later Alessandro died without pain. His mother said, "I never allowed a cold to tear away my son, but I also never asked him to win the Olympic games just for the fear of living with torment. Love also means letting it go".

The context

SMA is the most common genetic cause of infant mortality in developed countries. The first International Consensus Statement for Standard of Care in SMA in 2007 has represented a fundamental milestone in the history of SMA^[42]. In fact, the large variation in the disease phenotype of SMA hinders a reliable prediction of the natural course of the disease in each case. Moreover, the existence of relevant differences in clinical care at different hospitals is a serious challenge for families in making a balanced decision. Until recent developments, almost all subjects with SMA1 died in their first year of life due to respiratory failure and infections. SMA does not affect cognitive development, making it even more painful when considering the conflict in children between their growing interests and their limited abilities. Death usually occurs after prolonged agonies in children receiving quite aggressive care with artificial nutrition and ventilation. Thus, in SMA1, this point has been and still is critical to determine the threshold for choosing between palliative care and intervention, considering caregivers beliefs and opinions, as well as their capacity to shoulder the burden of the disease^[43]. Parents/caregivers must receive complete information on the possible treatment options. Facing these ethical problems is part of the experience of most pediatricians as described in the example by Gray and his collaborators^[44]. To make matters even more difficult, we are now living in a period of significant medical advances for the treatment of SMA, thus the threshold for decision-making may change

accordingly within the lifespan of patients^[45]. For example, pharmacologic treatment with Nusinersen may improve motor skills and prolong life expectancy, but in the most severe cases it is not clear if these effects can represent a desirable benefit or therapeutic persecution. Sometimes it may just be impossible to know. Moreover, the launch of Nusinersen for SMA raised several medical concerns^[46]. First, the primary outcome of the ENDEAR trial, which led to the authorization of the drug, was changed while the study was ongoing^[47,48]. Even though the overall survival, free of permanent mechanical ventilation, was the original primary outcome, this was shifted during the trial to “motor milestone response”, which is defined as “more milestones improved than worsened” (considering the following milestones from the Hammersmith Infant Neurological Examination: kicking, head control, rolling, sitting, crawling, standing, and walking). The result of this change was the approval of the drug based on marginal albeit significant improvements in motor function. Based on the result of the ENDEAR trial and on other uncontrolled trials, Nusinersen was granted marketing authority for all types of SMA. However, the achievements shown in ENDEAR were not as clearly proven for all types of the disease and at any age^[46]. Secondly, whilst the proof of efficacy of the drug was obtained in subjects with SMA1 who were younger than 6 mo old at the time Nusinersen was first administered, the drug had been approved for all types of the disease. Thirdly, the extremely high costs of the treatment risked making it not equitably distributable. Moreover, it is even debatable if the same amount of money could not have been used in better ways to improve the care for patients. Finally, the most serious concern is that Nusinersen does not represent a cure and in some cases may be too risky. Paradoxically, the availability of Nusinersen may have an unpredictable impact on decisions about prenatal screening. It is of note that the availability of iron chelators, increasing chronicity, and healthcare costs in beta thalassemia had a role in driving prevention programs in Cyprus, where the disease is prevalent^[49]. Similarly, it could be expected that the availability of Nusinersen may increase screening programs for SMA. Some would argue that Nusinersen may increase patients’ survival to allow for better care (perhaps gene therapy) in the near future. However there is no reliable prediction about this. Thus, we must recognize that children with SMA are living today during major periods of change, like in other stories described in this article^[50].

CONCLUSION

Making the best choice during periods of mounting medical advances among prenatal screening, palliative care, and aggressive treatment can be difficult when dealing with severe diseases. On the one hand, medical progress is increasing the probability of survival for children with severe genetic disorders; on the other, genetic screenings are offering a way to reduce the birth of newborns with

relatively common severe disorders like cystic fibrosis, SMA, and thalassemia^[51,52]. It may be difficult to find the correct direction between full fruition of life and the maintenance of some vital function with unbearable sufferance. Parents’ ethical, cultural, and religious feelings should be considered together with the best medical evidence to elaborate shared bioethical opinions in each case.

ACKNOWLEDGEMENTS

We acknowledge all the patients and families who have gone through so much, facing the challenges of coping with a rare disease, and whose entire life have been paralleled by major medical changes with the opportunities and the challenges.

REFERENCES

- 1 **Dooms M**, Carvalho M. Compounded medication for patients with rare diseases. *Orphanet J Rare Dis* 2018; **13**: 1 [PMID: 29301541 DOI: 10.1186/s13023-017-0741-y]
- 2 **Kempf L**, Goldsmith JC, Temple R. Challenges of developing and conducting clinical trials in rare disorders. *Am J Med Genet A* 2018; **176**: 773-783 [PMID: 28815894 DOI: 10.1002/ajmg.a.38413]
- 3 **Giannuzzi V**, Landi A, Bosone E, Giannuzzi F, Nicotri S, Torrent-Farnell J, Bonifazi F, Felisi M, Bonifazi D, Ceci A. Failures to further developing orphan medicinal products after designation granted in Europe: an analysis of marketing authorisation failures and abandoned drugs. *BMJ Open* 2017; **7**: e017358 [PMID: 28893754 DOI: 10.1136/bmjopen-2017-017358]
- 4 **Malinak LR**, Wilson R, South MA, Montgomery JR, Mumford DM, Flowers CE Jr. Germ-free delivery. The initiation of management of infants with a high probability of congenital immune deficiency states. *Am J Obstet Gynecol* 1973; **116**: 201-204 [PMID: 4703999 DOI: 10.1016/0002-9378(73)91051-X]
- 5 **Bealmear PM**, South MA, Wilson R. David’s story: the gift of 12 years, 5 months, and 1 day. *Prog Clin Biol Res* 1985; **181**: 475-489 [PMID: 4023007]
- 6 **Kirk RG**. “Life in a germ-free world”: isolating life from the laboratory animal to the bubble boy. *Bull Hist Med* 2012; **86**: 237-275 [PMID: 23000838 DOI: 10.1353/bhm.2012.0028]
- 7 **Mukhopadhyay N**, Richie E, Mackler BF, Montgomery JR, Wilson R, Fernbach DJ, South MA. A longitudinal study of T and B lymphocytes from a three-year-old patient with severe combined immunodeficiency (SCID) in ‘gnotobiotic protection’. *Exp Hematol* 1978; **6**: 129-134 [PMID: 304811]
- 8 **Mukhopadhyay N**, Richie E, Montgomery JR, Wilson R, Fernbach DJ. Letter: T and B cell characteristics in combined immunodeficiency. *N Engl J Med* 1974; **291**: 678 [PMID: 4546854 DOI: 10.1056/NEJM197409262911313]
- 9 **Mukhopadhyay N**, Richie E, Montgomery J, Wilson R, Fernbach DJ, South MA. Peripheral blood T and B cell characteristics in a patient with severe combined immune deficiency (SCID) maintained in a gnotobiotic environment. *Exp Hematol* 1976; **4**: 1-9 [PMID: 56280]
- 10 **Freedman DA**, Montgomery JR, Wilson R, Bealmear PM, South MA. Further observations on the effect of reverse isolation from birth on cognitive and affective development. *J Am Acad Child Psychiatry* 1976; **15**: 593-603 [PMID: 993485 DOI: 10.1097/00004583-197601540-00001]
- 11 **Simmons K**. ‘Bubble boy’ reacts well to marrow transplant. *JAMA* 1983; **250**: 2751 [PMID: 6358540 DOI: 10.1001/jama.250.20.2751]
- 12 **South MA**. David the bubble boy: some lessons he has taught us. *Cutis* 1977; **19**: 568, 572, 574 [PMID: 301080]
- 13 **Murphy MA**, Vogel JB. Looking out from the isolator: David’s

- perception of the world. *J Dev Behav Pediatr* 1985; **6**: 118-121 [PMID: 4008655 DOI: 10.1097/00004703-198506000-00004]
- 14 **Lawrence RJ**. David the “Bubble Boy” and the boundaries of the human. *JAMA* 1985; **253**: 74-76 [PMID: 3964901 DOI: 10.1001/jama.253.1.74]
 - 15 **Rennie D**. “Bubble Boy”. *JAMA* 1985; **253**: 78-80 [PMID: 3964903 DOI: 10.1001/jama.253.1.78]
 - 16 **Bubble Boy**. *JAMA* 1985; **254**: 1036-1037 [PMID: 4021039 DOI: 10.1001/jama.1985.03360080046022]
 - 17 **Puck JM**, Deschênes SM, Porter JC, Dutra AS, Brown CJ, Willard HF, Henthorn PS. The interleukin-2 receptor gamma chain maps to Xq13.1 and is mutated in X-linked severe combined immunodeficiency, SCIDX1. *Hum Mol Genet* 1993; **2**: 1099-1104 [PMID: 8401490 DOI: 10.1093/hmg/2.8.1099]
 - 18 **Gatti RA**, Meuwissen HJ, Allen HD, Hong R, Good RA. Immunological reconstitution of sex-linked lymphopenic immunological deficiency. *Lancet* 1968; **2**: 1366-1369 [PMID: 4177932 DOI: 10.1016/S0140-6736(68)92673-1]
 - 19 **Meuwissen HJ**, Gatti RA, Terasaki PI, Hong R, Good RA. Treatment of lymphopenic hypogammaglobulinemia and bone-marrow aplasia by transplantation of allogeneic marrow. Crucial role of histocompatibility matching. *N Engl J Med* 1969; **281**: 691-697 [PMID: 4186068 DOI: 10.1056/NEJM196909252811302]
 - 20 **Rubinstein A**, Speck B, Jeannet M. Successful bone-marrow transplantation in a lymphopenic immunologic deficiency syndrome. *N Engl J Med* 1971; **285**: 1399-1402 [PMID: 4399267 DOI: 10.1056/NEJM197112162852503]
 - 21 **Buckley RH**, Amos DB, Kremer WB, Stickel DL. Incompatible bone-marrow transplantation in lymphopenic immunologic deficiency. Circumvention of fatal graft-versus-host disease by immunologic enhancement. *N Engl J Med* 1971; **285**: 1035-1042 [PMID: 4937691 DOI: 10.1056/NEJM197111042851901]
 - 22 **Gennery AR**, Slatter MA, Grandin L, Taupin P, Cant AJ, Veys P, Amrolia PJ, Gaspar HB, Davies EG, Friedrich W, Hoenig M, Notarangelo LD, Mazzolari E, Porta F, Bredius RG, Lankester AC, Wulffraat NM, Seger R, Güngör T, Fasth A, Sedlacek P, Neven B, Blanche S, Fischer A, Cavazzana-Calvo M, Landais P, Inborn Errors Working Party of the European Group for Blood and Marrow Transplantation; European Society for Immunodeficiency. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? *J Allergy Clin Immunol* 2010; **126**: 602-10.e1-11 [PMID: 20673987 DOI: 10.1016/j.jaci.2010.06.015]
 - 23 **Heimall J**, Logan BR, Cowan MJ, Notarangelo LD, Griffith LM, Puck JM, Kohn DB, Pulsipher MA, Parikh S, Martinez C, Kapoor N, O'Reilly R, Boyer M, Pai SY, Goldman F, Burroughs L, Chandra S, Kletzel M, Thakar M, Connelly J, Cuvelier G, Davila Saldana BJ, Shereck E, Knutsen A, Sullivan KE, DeSantes K, Gillio A, Haddad E, Petrovic A, Quigg T, Smith AR, Stenger E, Yin Z, Shearer WT, Fleisher T, Buckley RH, Dvorak CC. Immune reconstitution and survival of 100 SCID patients post-hematopoietic cell transplant: a PIDTC natural history study. *Blood* 2017; **130**: 2718-2727 [PMID: 29021228 DOI: 10.1182/blood-2017-05-781849]
 - 24 **Cavazzana-Calvo M**, Hachein-Bey S, de Saint Basile G, Gross F, Yvon E, Nusbaum P, Selz F, Hue C, Certain S, Casanova JL, Bousso P, Deist FL, Fischer A. Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. *Science* 2000; **288**: 669-672 [PMID: 10784449 DOI: 10.1126/science.288.5466.669]
 - 25 **Stephan V**, Wahn V, Le Deist F, Dirksen U, Broker B, Müller-Fleckenstein I, Horneff G, Schroten H, Fischer A, de Saint Basile G. Atypical X-linked severe combined immunodeficiency due to possible spontaneous reversion of the genetic defect in T cells. *N Engl J Med* 1996; **335**: 1563-1567 [PMID: 8900089 DOI: 10.1056/NEJM199611213352104]
 - 26 **Hachein-Bey-Abina S**, von Kalle C, Schmidt M, Le Deist F, Wulffraat N, McIntyre E, Radford I, Villeval JL, Fraser CC, Cavazzana-Calvo M, Fischer A. A serious adverse event after successful gene therapy for X-linked severe combined immunodeficiency. *N Engl J Med* 2003; **348**: 255-256 [PMID: 12529469 DOI: 10.1056/NEJM200301163480314]
 - 27 **De Ravin SS**, Wu X, Moir S, Anaya-O'Brien S, Kwatema N, Littel P, Theobald N, Choi U, Su L, Marquesen M, Hilligoss D, Lee J, Buckner CM, Zarembek KA, O'Connor G, McVicar D, Kuhns D, Throm RE, Zhou S, Notarangelo LD, Hanson IC, Cowan MJ, Kang E, Hadigan C, Meagher M, Gray JT, Sorrentino BP, Malech HL, Kardava L. Lentiviral hematopoietic stem cell gene therapy for X-linked severe combined immunodeficiency. *Sci Transl Med* 2016; **8**: 335ra57 [PMID: 27099176 DOI: 10.1126/scitranslmed.aad8856]
 - 28 **Alzubi J**, Pallant C, Mussolino C, Howe SJ, Thrasher AJ, Cathomen T. Targeted genome editing restores T cell differentiation in a humanized X-SCID pluripotent stem cell disease model. *Sci Rep* 2017; **7**: 12475 [PMID: 28963568 DOI: 10.1038/s41598-017-12750-4]
 - 29 **Nathan DG**. Genes, blood, and courage : a boy called Immortal Sword. Cambridge, Mass.: Harvard University Press, 1995
 - 30 **Nathan DG**. Lessons from an Unexpected Life. Harvard Magazine. Boston: Harvard University, 2009: 36-41
 - 31 **McDonald R**. Deferoxamine and diethylenetriaminepentaacetic acid (DTPA) in thalassemia. *J Pediatr* 1966; **69**: 563-571 [PMID: 5921331 DOI: 10.1016/S0022-3476(66)80041-0]
 - 32 **Diwany M**, Gabr M, el Hefni A, Mokhtar N. Desferrioxamine in thalassaemia. *Arch Dis Child* 1968; **43**: 340-343 [PMID: 5652711 DOI: 10.1136/adc.43.229.340]
 - 33 **Borgna-Pignatti C**, Rugolotto S, De Stefano P, Piga A, Di Gregorio F, Gamberini MR, Sabato V, Melevendi C, Cappellini MD, Verlato G. Survival and disease complications in thalassemia major. *Ann N Y Acad Sci* 1998; **850**: 227-231 [PMID: 9668544 DOI: 10.1111/j.1749-6632.1998.tb10479.x]
 - 34 **Propper RD**, Button LN, Nathan DG. New approaches to the transfusion management of thalassemia. *Blood* 1980; **55**: 55-60 [PMID: 7350942]
 - 35 **Smith CH**, SCHULMAN I, ANDO RE, STERN G. Studies in Mediterranean (Cooley's) anemia. II. The suppression of hematopoiesis by transfusions. *Blood* 1955; **10**: 707-717 [PMID: 14389383]
 - 36 **Cazzola M**, De Stefano P, Ponchio L, Locatelli F, Beguin Y, Dessi C, Barella S, Cao A, Galanello R. Relationship between transfusion regimen and suppression of erythropoiesis in beta-thalassaemia major. *Br J Haematol* 1995; **89**: 473-478 [PMID: 7734344 DOI: 10.1111/j.1365-2141.1995.tb08351.x]
 - 37 **De Sanctis V**, Roos M, Gasser T, Fortini M, Raiola G, Galati MC; Italian Working Group on Endocrine Complications in Non-Endocrine Diseases. Impact of long-term iron chelation therapy on growth and endocrine functions in thalassaemia. *J Pediatr Endocrinol Metab* 2006; **19**: 471-480 [PMID: 16759032]
 - 38 **Olivieri NF**, Brittenham GM, McLaren CE, Templeton DM, Cameron RG, McClelland RA, Burt AD, Fleming KA. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. *N Engl J Med* 1998; **339**: 417-423 [PMID: 9700174 DOI: 10.1056/NEJM199808133390701]
 - 39 **Thompson AA**, Walters MC, Kwiatkowski J, Rasko JEJ, Ribeil JA, Hongeng S, Magrin E, Schiller GJ, Payen E, Semeraro M, Moshous D, Lefrere F, Puy H, Bourget P, Magnani A, Caccavelli L, Diana JS, Suarez F, Monpoux F, Brousse V, Poirot C, Brouzes C, Meritet JF, Pondarré C, Beuzard Y, Chrétien S, Lefebvre T, Teachey DT, Anurathapan U, Ho PJ, von Kalle C, Kletzel M, Vichinsky E, Soni S, Veres G, Negre O, Ross RM, Davidson D, Petrusich A, Sandler L, Asmal M, Hermine O, De Montalembert M, Hachein-Bey-Abina S, Blanche S, Leboulch P, Cavazzana M. Gene Therapy in Patients with Transfusion-Dependent β -Thalassemia. *N Engl J Med* 2018; **378**: 1479-1493 [PMID: 29669226 DOI: 10.1056/NEJMoa1705342]
 - 40 **Cao A**, Furbetta M, Galanello R, Melis MA, Angius A, Ximenes A, Rosatelli C, Ruggeri R, Addis M, Tuvieri T, Falchi AM, Paglietti E, Scalas MT. Prevention of homozygous beta-thalassemia by carrier screening and prenatal diagnosis in Sardinia. *Am J Hum Genet* 1981; **33**: 592-605 [PMID: 7258188]
 - 41 **Angastiniotis M**, Kyriakidou S, Hadjiminis M. The Cyprus Thalassemia Control Program. *Birth Defects Orig Artic Ser* 1988; **23**: 417-432 [PMID: 3390571]
 - 42 **Wang CH**, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, Aloysius A, Morrison L, Main M, Crawford TO, Trela A; Participants of the International Conference on SMA Standard of

- Care. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol* 2007; **22**: 1027-1049 [PMID: 17761659 DOI: 10.1177/0883073807305788]
- 43 **Mercuri E**, Bertini E, Iannaccone ST. Childhood spinal muscular atrophy: controversies and challenges. *Lancet Neurol* 2012; **11**: 443-452 [PMID: 22516079 DOI: 10.1016/S1474-4422(12)70061-3]
- 44 **Gray K**, Isaacs D, Kilham HA, Tobin B. Spinal muscular atrophy type I : do the benefits of ventilation compensate for its burdens? *J Paediatr Child Health* 2013; **49**: 807-812 [PMID: 24131113 DOI: 10.1111/jpc.12386]
- 45 **van der Ploeg AT**. The Dilemma of Two Innovative Therapies for Spinal Muscular Atrophy. *N Engl J Med* 2017; **377**: 1786-1787 [PMID: 29091554 DOI: 10.1056/NEJMe1712106]
- 46 **Burgart AM**, Magnus D, Tabor HK, Paquette ED, Frader J, Glover JJ, Jackson BM, Harrison CH, Urion DK, Graham RJ, Brandsema JF, Feudtner C. Ethical Challenges Confronted When Providing Nusinersen Treatment for Spinal Muscular Atrophy. *JAMA Pediatr* 2018; **172**: 188-192 [PMID: 29228163 DOI: 10.1001/jamapediatrics.2017.4409]
- 47 **Gerrity MS**, Prasad V, Obley AJ. Concerns About the Approval of Nusinersen Sodium by the US Food and Drug Administration. *JAMA Intern Med* 2018; **178**: 743-744 [PMID: 29710299 DOI: 10.1001/jamainternmed.2018.0869]
- 48 **inkel RS**, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, Chiriboga CA, Saito K, Servais L, Tizzano E, Topaloglu H, Tulinius M, Montes J, Glanzman AM, Bishop K, Zhong ZJ, Gheuens S, Bennett CF, Schneider E, Farwell W, De Vivo DC; ENDEAR Study Group. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med* 2017; **377**: 1723-1732 [PMID: 29091570 DOI: 10.1056/NEJMoa1702752]
- 49 **Ashiotis T**, Zachariadis Z, Sofroniadou K, Loukopoulou D, Stamatoyannopoulos G. Thalassaemia in Cyprus. *Br Med J* 1973; **2**: 38-42 [PMID: 4695698 DOI: 10.1136/bmj.2.5857.38]
- 50 **Groen EJM**, Talbot K, Gillinwater TH. Advances in therapy for spinal muscular atrophy: promises and challenges. *Nat Rev Neurol* 2018; **14**: 214-224 [PMID: 29422644 DOI: 10.1038/nrneurol.2018.4]
- 51 **Boardman FK**, Sadler C, Young PJ. Newborn genetic screening for spinal muscular atrophy in the UK: The views of the general population. *Mol Genet Genomic Med* 2018; **6**: 99-108 [PMID: 29169204 DOI: 10.1002/mgg3.353]
- 52 **Archibald AD**, Smith MJ, Burgess T, Scarff KL, Elliott J, Hunt CE, Barns-Jenkins C, Holt C, Sandoval K, Siva Kumar V, Ward L, Allen EC, Collis SV, Cowie S, Francis D, Delatycki MB, Yiu EM, Massie RJ, Pertile MD, du Sart D, Bruno D, Amor DJ. Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy in Australia: outcomes of 12,000 tests. *Genet Med* 2018; **20**: 513-523 [PMID: 29261177 DOI: 10.1038/gim.2017.134]

P- Reviewer: Pandey A, Teng RJ, Watanabe T

S- Editor: Ji FF **L- Editor:** Filipodia **E- Editor:** Song H



Clinical features of acute kidney injury in patients with Kawasaki disease

Toru Watanabe

Toru Watanabe, Department of Pediatrics, Niigata City General Hospital, Niigata City 950-1197, Japan

ORCID number: Toru Watanabe (0000-0003-3326-4144).

Author contributions: Watanabe T solely contributed to this paper.

Conflict-of-interest statement: None.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Toru Watanabe, MD, PhD, Doctor, Department of Pediatrics, Niigata City General Hospital, 463-7 Shumoku, Chuo-ku, Niigata City, 950-1197, Japan. twata@hosp.niigata.niigata.jp
Telephone: +81-25-2815151
Fax: +81-25-2815169

Received: June 19, 2018

Peer-review started: June 20, 2018

First decision: June 19, 2018

Revised: August 1, 2018

Accepted: August 6, 2018

Article in press: August 7, 2018

Published online: August 30, 2018

Abstract

Although acute kidney injury (AKI) is a common complication in hospitalized children, AKI has rarely been reported in patients with Kawasaki disease (KD). Herein, we review the clinical trajectories of AKI in patients with KD. A total

of 39 patients with KD who developed AKI have been reported in 28 publications as case reports. The causes of AKI include prerenal AKI associated with acute heart failure (AHF), intrinsic AKI caused by tubulointerstitial nephritis (TIN), acute nephritic syndrome (ANS), hemolytic uremic syndrome (HUS), immune complex-mediated nephropathy, rhabdomyolysis, and KD shock syndrome (KDSS). Six of the 39 patients (15.4%) underwent renal replacement therapy. While AHF and multiple organ dysfunction syndrome developed in 41% and 68% of KD patients with AKI, respectively, all patients recovered without any renal sequelae. Although the precise pathogenic mechanism underlying the development of AKI in patients with KD is unknown, several possible mechanisms have been proposed, including T-cell-mediated immunologic abnormalities for TIN, renal and glomerular endothelial injury resulting from vasculitis for HUS, immune complex-mediated kidney injury for immune complex-mediated nephropathy and ASN, and capillary leak and an increased release of cytokines with myocardial dysfunction for KDSS.

Key words: Kawasaki disease; Acute kidney injury; Kidney involvement; Multiple organ dysfunction syndrome

© The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Acute kidney injury (AKI) has rarely been reported in patients with Kawasaki disease (KD). We review the clinical characteristics of AKI in patients with KD and show that AKI is caused by a number of pathologic changes induced by KD. Patients with KD and AKI had good outcomes, despite the development of multiple organ dysfunction syndrome. The possible mechanisms underlying the development of AKI in KD include T-cell-mediated immunologic abnormalities, renal and glomerular endothelial injury resulted from vasculitis, immune complex-mediated kidney injury, and capillary leak and the increased release of cytokines with myocardial dysfunction.

Watanabe T. Clinical features of acute kidney injury in patients with Kawasaki disease. *World J Clin Pediatr* 2018; 7(3): 83-88 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i3/83.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i3.83>

INTRODUCTION

Kawasaki disease (KD) is a systemic vasculitis that occurs mainly in infants and children^[1]. Although clinical and epidemiologic studies suggest an infectious etiology, the causative agent has yet to be determined^[2]. Recent studies have suggested that an immunologic reaction is induced in genetically-susceptible hosts upon exposure to the KD trigger^[2]. Because KD is a systemic vasculitis, KD can involve multiple organs and tissues, including the kidneys^[3].

Kidney complications in KD include pyuria, trace proteinuria, prerenal acute kidney injury (AKI), intrinsic AKI resulted from tubulointerstitial nephritis (TIN), hemolytic uremic syndrome (HUS), immune complex-mediated nephropathy, intrinsic AKI associated with KD shock syndrome (KDSS), acute nephritic syndrome (ANS), nephrotic syndrome (NS), and renal tubular abnormalities^[4]. Although patients with KD often present with sterile pyuria and trace proteinuria, other kidney complications in KD are uncommon^[4]; however, several laboratory and imaging studies have shown that a number of patients with KD develop subclinical kidney injury^[5,6].

AKI is a common complication in hospitalized children^[7]. Recent studies have shown that AKI developed in 26.9% of children and young adults admitted to the intensive care unit (ICU)^[8], and in at least 5% of non-critically ill hospitalized children and young adults^[9]. Because AKI is associated with poor outcomes, including a high mortality rate and long-term morbidity^[7,10], it is important to establish the causes and clinical features of hospitalized children with AKI, as well as patients with KD. The clinical trajectories of AKI in patients with KD are the subject of this mini-review.

We conducted a computerized search of the English, French, and Spanish literature using the PubMed database with a search engine and the Japanese literature using the Japan Medical Abstract Society database with a search engine from January 1967 through April 2018. The search used a combination of the following terms: "Kawasaki disease" with "acute kidney injury" or with "acute renal failure". Also, a direct search of cited references was conducted. The clinical criteria in the 2004 American Heart Association/American Academy of Pediatrics guidelines were used to diagnose KD^[11]. AKI is usually defined as serum creatinine level elevation ≥ 1.5 times the baseline level, according to Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Acute Kidney Injury^[12]. Because the baseline level of serum creatinine was not documented in most of the patients searched in this study, AKI was defined as a

serum creatinine level ≥ 1.5 times the upper limit of the normal age-specific serum creatinine reference level^[13,14]. Studies which had insufficient clinical information for each patient were excluded from detailed analysis of the clinical manifestations of KD patients with AKI.

PREVALENCE OF AKI IN PATIENTS WITH KD

Chuang *et al*^[13] studied the clinical characteristics and laboratory data of 336 Taiwanese patients with KD, including serum creatinine levels, and reported that 28% of the patients with KD developed AKI. Moreover, young age and elevated alanine transaminase level were reported to be the main factors associated with AKI. Based on our review of the clinical and laboratory data of 249 Japanese children with KD, however, no patients developed AKI^[15]. Although it is not clear why the two reports yielded a different prevalence for AKI in patients with KD, it is possible that differences in disease severity influenced the results^[15].

EPIDEMIOLOGY

Thirty-nine patients with KD who developed AKI have been reported in 28 publications as case reports^[16-43]. The median age was 4.8 years (range, 3 mo-to-45 years). Twenty-seven patients were male (male-to-female ratio, 2.07:1). Thirty-two patients developed complete KD, while 7 patients had incomplete KD.

CAUSES OF AKI

The causes of AKI are usually divided into the following three pathophysiologic categories: prerenal AKI, which is characterized by effective hypoperfusion of the kidneys and a lack of parenchymal damage to the kidney; intrinsic AKI, which involves renal parenchymal damage; and postrenal AKI, which is associated with acute obstruction of the urinary tract^[44]. In patients with KD, prerenal AKI associated with acute heart failure (AHF)^[16,17] and intrinsic AKI have been reported. The causes of intrinsic AKI in KD include TIN^[18-21], ANS^[22-24], HUS^[25-27], immune complex-mediated nephropathy^[28], rhabdomyolysis^[29], and KDSS^[30-34] (Table 1); however, because only 8 of the reported KD patients with AKI underwent renal biopsies, the etiology of AKI was unknown in 25% of the patients^[35-43].

CLINICAL MANIFESTATIONS

Oliguria, edema, hypotension, and hypertension occurred in 62% (18/29), 31% (2/29), 41% (16/39) and 15.4% (6/39) of the KD patients, respectively, and AHF developed in 41% (16/39) of the KD patients. Based on the Goldstein diagnostic criteria, 68.4% of patients had multiple organ dysfunction syndrome (MODS)^[45], and the median number of affected organs was 2 (range, 1-5).

Table 1 Causes of acute kidney injury in patients with Kawasaki disease

Cause	N
1 Prerenal AKI associated with acute heart failure	2
2 Intrinsic AKI	
Tubulointerstitial nephritis	4
Acute nephritic syndrome	3
Hemolytic uremic syndrome	3
Immune complex-mediated nephritis	1
Rhabdomyolysis	1
Kawasaki disease shock syndrome	14
Undetermined etiology	11

AKI: Acute kidney injury.

The dysfunctional systems included the cardiovascular system in 41% (16/39) of the patients, the respiratory system in 10.2% (4/39), the nervous system in 25.6% (10/39), the hematologic system in 5.1% (2/39), and the hepatobiliary system in 33.3% (13/39).

The median blood urea nitrogen level was 58 mg/dL (range, 8-194 mg/dL), and the median serum creatinine level was 2.2 mg/dL (range, 0.5-7.43 mg/dL). Sixteen of 20 patients (80%) had hyponatremia (serum sodium < 135 mEq/L), 82.1% had proteinuria, 46.4% (13/28) had hematuria, and 73.9% (17/23) had pyuria. Three patients with KDSS developed NS, and 3 patients with ANS had macroscopic hematuria.

Only 8 patients underwent renal biopsies, which revealed TIN in 4 patients, ATN in 2, immune complex-mediated nephropathy in 1, and minor abnormalities in 1. Thirty of the 39 patients (76.9%) underwent intravenous immunoglobulin (IVIG) therapy. IVIG therapy was effective in 73.3% (22/30) of the patients, while 26.7% (8/30) were IVIG-resistant. Six of the 39 patients (15.4%) had renal replacement therapy, which included hemodialysis in 4 patients, continuous hemodialysis in 1, and peritoneal dialysis in 1.

All patients recovered from AKI without any renal sequelae. Although transient coronary artery dilatation occurred in 28.2% (11/39) of the patients, coronary artery aneurysms (CAAs) developed in 5.1% (2/39).

Prerenal AKI

Two patients with KD who developed prerenal AKI have been reported. Senzaki *et al*^[16] reported an 8-year-old boy with KD who developed AHF and AKI. The results of the fractional excretion of sodium (0.04%), the renal failure index (0.02), the urine-to-plasma creatinine ratio (54), and the urine-to-plasma osmolality ratio (1.7) were consistent with prerenal AKI. Adachi described a 2-year-old girl with KD who developed prerenal AKI caused by hypovolemia due to gastrointestinal losses and AHF^[17]. An intravenous fluid infusion and IVIG therapy resolved AKI following improvement of AHF in both patients, probably due to correction of hypovolemia and myocardial dysfunction, respectively.

AHF causes renal hypoperfusion due to decreased cardiac output^[44]. In addition, KD is associated with

hypovolemia due to decreased oral intake, gastrointestinal losses, or third spacing resulting from increased vascular permeability^[16]. Therefore, both hypovolemia and AHF may have central roles in the development of prerenal AKI in patients with KD.

Intrinsic AKI

TIN: AKI due to TIN has been reported in 5 patients with KD. None of the patients had a *Yersinia pseudotuberculosis* infection^[46]. Veiga *et al*^[18] reported a 2-year-old boy with KD who developed AKI based on a renal biopsy, which showed diffuse interstitial infiltration of mononuclear and polymorphonuclear leukocytes. The patient was treated with IVIG, oral aspirin, fluid restriction, and furosemide, and recovered without any untoward sequelae. Kawamura^[19] reported a 9-year-old girl with KD who developed AKI based on a renal biopsy, which showed mild interstitial mononuclear cell infiltration. The patient underwent hemodialysis and recovered without any renal sequelae. Ashida *et al*^[20] reported a 5-year-old boy with KD who developed AKI based on a renal biopsy, which revealed interstitial infiltration of mononuclear cells. After fluid restriction and IVIG therapy, the boy recovered without sequelae. Bonany *et al*^[21] reported an 8-year-old boy with KD who developed AKI and NS based on a renal biopsy, which showed TIN and acute tubular necrosis; the patient recovered with supportive care alone.

TIN is an immune-mediated cause of AKI that is characterized by the presence of an inflammatory cell infiltrate in the interstitium of the kidney^[47]. Although acute TIN is largely due to medications, autoimmune diseases are associated with acute TIN, including anti-tubular basement membrane disease, TIN with uveitis, and KD^[48]. Although the pathogenesis underlying TIN has not been completely described, T cell activation and the resultant cytokine and protease activity may play central roles in TIN. Because T cell activation and extensive cytokine release also occur in KD^[1,2], these immunologic abnormalities may cause acute TIN in some patients with KD.

ANS: AKI due to ANS has been reported in 3 patients with KD. Suzue *et al*^[22] reported a 5-mo-old boy with KD who developed AKI due to ANS 2 wk after IVIG therapy with a transient decrease in serum C3 and C4 levels. The patient recovered with supportive care alone. Yoshida *et al*^[23] reported a 3-mo-old girl with KD who developed AHF and AKI due to ANS 6 d after IVIG therapy with a transient decrease in serum C3 and C4 levels. While the pathogenesis underlying the development of ANS in these patients with KD was not established, an immune complex-mediated mechanism was suspected because both patients had transient hypocomplementemia following IVIG therapy.

In contrast, Motoyama *et al*^[24] reported a 6-year-old boy with ANS and AKI who subsequently developed KD. The patient was administered intravenous corti-

costeroids and oral aspirin and recovered without any sequelae.

HUS: AKI due to HUS has been reported in 3 patients with KD. Ferriero and Wolfsdorf^[25] reported a 2-year-old girl with KD who developed AKI and metabolic encephalopathy due to HUS. She recovered with supportive care alone^[25]. Heldrich *et al*^[26] reported a 3-year-old girl with KD who developed AKI due to HUS and Henoch-Schönlein purpura, which required adjustment to therapy. Saviour *et al*^[27] reported a 2-year-old boy with KD who developed AKI due to HUS. The patient underwent IVIG therapy and supportive management of fluids and electrolytes. She recovered without any sequelae.

Without renal biopsy findings, the pathogenesis of HUS in patients with KD cannot be ascertained; however, it is possible that vasculitis-associated KD may involve the kidney causing injury to the renal and glomerular endothelium, thus leading to HUS^[25].

Immune complex-mediated nephropathy: Nagamatsu *et al*^[28] reported a 3-year-old boy with KD who developed AKI. The patient was treated with IVIG, dopamine, and furosemide. Electron microscopy of a renal biopsy specimen showed electron-dense deposits in the subepithelial spaces and podocytes, which suggested the possibility of glomerular derangement by immune complexes.

Rhabdomyolysis: Sevin *et al*^[29] reported a 10-year-old girl with KD who developed AKI due to rhabdomyolysis that was possibly caused by hyperthermia. A renal biopsy showed renal tubular necrosis without glomerular or vascular changes^[29]. The patient recovered from AKI with IVIG and supportive care alone.

KDSS: KDSS is a condition characterized by systolic hypotension or clinical signs of poor perfusion in patients with KD^[49,50]. Although the pathogenesis underlying KDSS is unknown, intensive vasculitis with capillary leak and hypercytokinemia with myocardial dysfunction may cause KDSS^[49-51].

Mac Ardle *et al*^[30] reported a 2-year-old boy with KDSS who developed encephalopathy, respiratory failure and AKI. A renal biopsy showed normal glomeruli and a patchy immune-type infiltrate consisting of plasma cells and eosinophils, with evidence of recovering acute tubular necrosis. The patient received an intravenous fluid infusion, underwent peritoneal dialysis, and was mechanically ventilated. The boy recovered with mild neurologic sequelae. Nakanishi *et al*^[31] reported a 12-year-old boy with KDSS who developed AHF, a coagulopathy, and AKI. A renal biopsy showed no glomerular or tubular abnormalities. The patient recovered with IVIG, hemodialysis, and the intravenous administration of catecholamines. An 11-year-old girl with KDSS who developed AKI and AHF due to myocarditis was reported^[32]. The patient was mechanically ventilated,

and received a diuretic intravenously, and IVIG therapy. She recovered but had CAAs. Umei *et al*^[33] reported a 12-year-old boy with KDSS who developed AHF, hepatic dysfunction, a coagulopathy, and AKI. The patient was treated with IVIG, plasma exchange, continuous hemodialysis, and the intravenous administration of catecholamines. He recovered without any sequelae. Gatterre *et al*^[34] studied 11 patients with KDSS and reported that 10 developed AKI. Nine of the patients had proteinuria, 3 of whom exhibited NS. All of the patients underwent IVIG therapy and recovered without sequelae.

Undetermined etiologies: Eleven patients with AKI of unknown etiologies have been reported. Yamawaki *et al*^[35] reported a 5-year-old boy with KD who developed oliguric AKI. The patient underwent hemodialysis and recovered without any sequelae. Nardi *et al*^[36] reported a 6-year-old girl with KD who developed oliguric AKI and hepatic dysfunction. The patient recovered with supportive care alone. Lande *et al*^[37] reported a 3-year-old girl with KD who developed oliguric AKI. The patient received IVIG and underwent hemodialysis. She recovered without any sequelae. Ashida *et al*^[20] reported a 3-year-old boy with KD who developed AKI. He was treated with IVIG and recovered without any sequelae. El Karoui *et al*^[38] reported a 45-year-old man with adult-onset KD who developed AKI. He was treated with IVIG, which resulted in rapid improvement and recovery of normal renal function. Nandi and Mondal^[39] reported a 4-year-old boy with KD who developed oliguric AKI. The patient recovered with supportive care alone. Keeswijk and Walle^[40,41] reported a 2-year-old boy with KD who developed oliguric AKI. The patient recovered completely with IVIG therapy, fluid restriction, and a diuretic. Tiewsoh *et al*^[42] reported 3 boys with incomplete KD who developed AKI. All of the patients were treated with IVIG and recovered without any sequelae. Martínez Vázquez *et al*^[43] reported a 9-year-old girl with KD who developed oliguric AKI and cholestasis. The patient was treated with IVIG and intravenous pulses of methylprednisolone, which led to an improvement in the AKI and clinical features of KD, but she had CAAs.

THERAPEUTIC STRATEGIES TO KD PATIENTS WITH AKI

Treatment of KD patients with prerenal AKI and AHF consists of appropriate restoration of the normal circulating blood volume, heart function support^[44], and specific therapy for KD^[44]. Among KD patients with intrinsic AKI, renal damage results from vasculitis of the renal arteries, or T cell- or B cell-mediated immunoregulatory abnormalities caused by KD. Therefore, treatments adapted to the severity of KD can improve AKI in addition to supportive therapies to ameliorate derangements of fluid and electrolyte homeostasis, which include fluid restriction, diuretic usage and renal replacement therapy^[10,44].

CONCLUSION

AKI in patients with KD is uncommon and includes the following conditions: prerenal AKI; intrinsic AKI caused by TIN; ANS; HUS; immune complex-mediated nephropathy; rhabdomyolysis; KDSS; and undetermined etiologies.

Although the pathogenic mechanism underlying renal involvement in patients with KD who develop AKI is unknown, several possible mechanisms have been proposed, which include T-cell-mediated immunologic abnormalities for TIN, muscle injury caused by hyperthermia for rhabdomyolysis, renal and glomerular endothelial injury resulting from vasculitis for HUS, immune complex-mediated kidney injury for immune-complex mediated nephropathy and ANS, and capillary leak and hypercytokinemia with myocardial dysfunction induced by intensive vasculitis for KDSS.

REFERENCES

- Newburger JW, Takahashi M, Burns JC. Kawasaki Disease. *J Am Coll Cardiol* 2016; **67**: 1738-1749 [PMID: 27056781 DOI: 10.1016/j.jacc.2015.12.073]
- Shulman ST, Rowley AH. Kawasaki disease: insights into pathogenesis and approaches to treatment. *Nat Rev Rheumatol* 2015; **11**: 475-482 [PMID: 25907703 DOI: 10.1038/nrrheum.2015.54]
- Watanabe T, Abe Y, Sato S, Uehara Y, Ikeno K, Abe T. Sterile pyuria in patients with Kawasaki disease originates from both the urethra and the kidney. *Pediatr Nephrol* 2007; **22**: 987-991 [PMID: 17323086 DOI: 10.1007/s00467-007-0449-7]
- Watanabe T. Kidney and urinary tract involvement in kawasaki disease. *Int J Pediatr* 2013; **2013**: 831834 [PMID: 24288547 DOI: 10.1155/2013/831834]
- Wang JN, Chiou YY, Chiu NT, Chen MJ, Lee BF, Wu JM. Renal scarring sequelae in childhood Kawasaki disease. *Pediatr Nephrol* 2007; **22**: 684-689 [PMID: 17151872 DOI: 10.1007/s00467-006-0385-y]
- Wu JM, Chiou YY, Hung WP, Chiu NT, Chen MJ, Wang JN. Urinary cytokines and renal Doppler study in Kawasaki disease. *J Pediatr* 2010; **156**: 792-797 [PMID: 20171655 DOI: 10.1016/j.jpeds.2009.11.046]
- Sutherland SM, Kwiatkowski DM. Acute Kidney Injury in Children. *Adv Chronic Kidney Dis* 2017; **24**: 380-387 [PMID: 29229169 DOI: 10.1053/j.ackd.2017.09.007]
- Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL; AWARE Investigators. Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults. *N Engl J Med* 2017; **376**: 11-20 [PMID: 27959707 DOI: 10.1056/NEJMoa1611391]
- McGregor TL, Jones DP, Wang L, Danciu I, Bridges BC, Fleming GM, Shirey-Rice J, Chen L, Byrne DW, Van Driest SL. Acute Kidney Injury Incidence in Noncritically Ill Hospitalized Children, Adolescents, and Young Adults: A Retrospective Observational Study. *Am J Kidney Dis* 2016; **67**: 384-390 [PMID: 26319754 DOI: 10.1053/j.ajkd.2015.07.019]
- Bellomo R, Kellum JA, Ronco C. Acute kidney injury. *Lancet* 2012; **380**: 756-766 [PMID: 22617274 DOI: 10.1016/S0140-6736(11)61454-2]
- Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, Shulman ST, Bolger AF, Ferrieri P, Baltimore RS, Wilson WR, Baddour LM, Levison ME, Pallasch TJ, Falace DA, Taubert KA; Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease; Council on Cardiovascular Disease in the Young; American Heart Association; American Academy of Pediatrics. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 2004; **110**: 2747-2771 [PMID: 15505111 DOI: 10.1161/01.CIR.0000145143.19711.78]
- Kellum JA, Lameire N, Aspelin P, Barsoum R, Burdmann E, Goldstein S, Herzog C, Joannidis M, Kribben A, Levey A, MacLeod A, Mehta R, Murray P, Naicker S, Opal S, Schaefer F, Schetz M, Uchino S. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group: KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012; **2**: 1-138
- Chuang GT, Tsai IJ, Lin MT, Chang LY. Acute kidney injury in patients with Kawasaki disease. *Pediatr Res* 2016; **80**: 224-227 [PMID: 27064240 DOI: 10.1038/pr.2016.81]
- Søby K, Jensen PB, Werge T, Sørensen S. Mining of hospital laboratory information systems: a model study defining age- and gender-specific reference intervals and trajectories for plasma creatinine in a pediatric population. *Clin Chem Lab Med* 2015; **53**: 1621-1630 [PMID: 25719320 DOI: 10.1515/cclm-2014-0949]
- Watanabe T, Abe T, Tsukano S. Acute kidney injury occurs only rarely in patients with Kawasaki disease. *Pediatr Res* 2017; **82**: 890-891 [PMID: 28817559 DOI: 10.1038/pr.2017.191]
- Senzaki H, Suda M, Noma S, Kawaguchi H, Sakakihara Y, Hishi T. Acute heart failure and acute renal failure in Kawasaki disease. *Acta Paediatr Jpn* 1994; **36**: 443-447 [PMID: 7942014 DOI: 10.1111/j.1442-200X.1994.tb03220.x]
- Adachi K. A two-year-old girl with Kawasaki disease who developed acute renal failure (in Japanese). *Prog Med* 1998; **18**: 394-395
- Veiga PA, Pieroni D, Baier W, Feld LG. Association of Kawasaki disease and interstitial nephritis. *Pediatr Nephrol* 1992; **6**: 421-423 [PMID: 1457322 DOI: 10.1007/BF00873999]
- Kawamura I. A case of acute renal failure, anemia and thrombophlebitis in a patient with Kawasaki disease (in Japanese). *Shoni Zinfuzen Kenkyukai Shi* 1993; **13**: 158-160
- Ashida A, Katayama H, Nakamura H, Tamai K, Yoshikawa K, Takahashi T. Acute renal failure in patients with Kawasaki disease (in Japanese). *Shoni Zinfuzen Kenkyukai Shi* 2000; **20**: 169-172
- Bonany PJ, Bilkis MD, Gallo G, Lago N, Dennehy MV, Sosa del Valle JM, Vallejo G, Cánepa C. Acute renal failure in typical Kawasaki disease. *Pediatr Nephrol* 2002; **17**: 329-331 [PMID: 12042888 DOI: 10.1007/s00467-002-0844-z]
- Suzue T, Ohuchi T, Ichioka T, Tamura Y, Tsuno K. An infant with Kawasaki disease associated with nephritis (in Japanese). *Shonika Rinsho* 1989; **42**: 2196-2200
- Yoshida S, Ai Y, Imai K, Mimasu S. A case of Kawasaki disease complicated by acute glomerulonephritis (in Japanese). *Progress in Medicine* 2002; **22**: 1598-1593
- Motoyama O, Tarui H, Ishihara C, Komatsu H, Matsuyama G, Sawada K, Tateno A, Iitaka K. Kawasaki disease presenting with macroscopic hematuria. *Pediatr Int* 2008; **50**: 260-261 [PMID: 18353075 DOI: 10.1111/j.1442-200X.2008.02566.x]
- Ferriero DM, Wolfsdorf JL. Hemolytic uremic syndrome associated with Kawasaki disease. *Pediatrics* 1981; **68**: 405-406 [PMID: 7279468]
- Heldrich FJ, Jodorkovsky RA, Lake AM, Parnes CA. Kawasaki syndrome: HUS and HSP complicating its course and management. *Md Med J* 1987; **36**: 764-766 [PMID: 3683104]
- Saviour MJ, Hassan S. Kawasaki Disease Presenting with Bloody Diarrhea and Acute Renal Failure: First Case. *Pediatr Rep* 2017; **9**: 7163 [PMID: 28706619 DOI: 10.4081/pr.2017.7163]
- Nagamatsu K, Ikuta K, Aoki S, Sakata K, Onouchi Z. An acute renal disease which developed in 3-year-old boy during Kawasaki disease. *J Clin Electron Microscopy* 1990; **23**: 5-6
- Sevin C, Heidet L, Gagnadoux MF, Chéron G, Niaudet P. [Acute renal insufficiency in Kawasaki disease]. *Arch Fr Pediatr* 1993; **50**: 505-507 [PMID: 8135613]
- Mac Ardle BM, Chambers TL, Weller SD, Tribe CR. Acute renal failure in Kawasaki disease. *J R Soc Med* 1983; **76**: 615-616 [PMID: 6876053 DOI: 10.1177/014107688307600718]
- Nakanishi S, Iwasaki T, Koga Y, Kamishiro M, Yamagishi M. A case of acute renal failure probably due to Kawasaki disease (in Japanese). *Shoni Zinfuzen Kenkyukai Shi* 1994; **14**: 53-56

- 32 Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 36-1998. An 11-year-old girl with fever, hypotension, and azotemia. *N Engl J Med* 1998; **339**: 1619-1626 [PMID: 9867524 DOI: 10.1056/NEJM199811263392208]
- 33 Umei N, Atagi K, Shimaoka H, Kinishi Y, Suga T, Otsuka Y, Uziro A. A case of Kawasaki disease initially diagnosed as septic shock (in Japanese). *J Jpn Soc Intensive Care Med* 2012; **19**: 405-408 [DOI: 10.3918/jsicm.19.405]
- 34 Gatterre P, Oualha M, Dupic L, Iserin F, Bodemer C, Lesage F, Hubert P. Kawasaki disease: an unexpected etiology of shock and multiple organ dysfunction syndrome. *Intensive Care Med* 2012; **38**: 872-878 [PMID: 22273753 DOI: 10.1007/s00134-012-2473-8]
- 35 Yamawaki Y, Hattori M, Nishikawa R, Chishiro H, Fujizaki Y. A case of MCLS with acute renal failure (in Japanese). *Shonika Shinryo* 1984; **47**: 350-353
- 36 Nardi PM, Haller JO, Friedman AP, Slovis TL, Schaffer RM. Renal manifestations of Kawasaki's disease. *Pediatr Radiol* 1985; **15**: 116-118 [PMID: 3883299 DOI: 10.1007/BF02388716]
- 37 Lande MB, Gleeson JG, Sundel RP. Kawasaki disease and acute renal failure. *Pediatr Nephrol* 1993; **7**: 593 [PMID: 8251330 DOI: 10.1007/BF00852560]
- 38 El Karoui K, Servais A, Fadel F, Jablonski M, Fakhouri F, Lesavre P, Hummel A. Acute renal failure and febrile rash--infectious or not? Adult Kawasaki disease (KD). *Nephrol Dial Transplant* 2007; **22**: 949-951 [PMID: 17210597 DOI: 10.1093/ndt/gfl792]
- 39 Nandi M, Mondal R. Acute renal failure in a child with Kawasaki disease. *East J Med* 2010; **15**: 122-124
- 40 Keenswijk W, Walle JV. An atypical case of a 2-year-old boy with acute kidney injury: a race against time. Questions. *Pediatr Nephrol* 2017; **32**: 1175-1176 [PMID: 27704254 DOI: 10.1007/s00467-016-3497-z]
- 41 Keenswijk W, Walle JV. An atypical case of a 2-year-old boy with acute kidney injury: a race against time. Answers. *Pediatr Nephrol* 2017; **32**: 1177-1179 [PMID: 27704255 DOI: 10.1007/s00467-016-3516-0]
- 42 Tiewsoh K, Sharma D, Jindal AK, Bhisikar S, Suri D, Singh S. Acute Kidney Injury in Kawasaki Disease: Report of 3 Cases From North India and a Brief Review of Literature. *J Clin Rheumatol* 2018; **24**: 231-234 [PMID: 29293117 DOI: 10.1097/RHU.0000000000000687]
- 43 Martínez Vázquez JA, Sánchez García C, Rodríguez Muñoz L, Martínez Ramírez RO. Acute kidney injury and cholestasis associated with Kawasaki disease in a 9-year-old: Case report. *Reumatol Clin* 2017; pii: S1699-258X(17)30282-6 [PMID: 29254742 DOI: 10.1016/j.reuma.2017.11.008]
- 44 Sharfuddin AA, Weisbord SD, Palevsky PM, Molitoris BA. Acute kidney injury. In: Skorecki K, Chertow GM, Marsden PA, Taal MW, Yu ASL. Brenner and Rector's the kidney. 2nd ed. Philadelphia: Elsevier, 2016: 958-1011
- 45 Goldstein B, Giroir B, Randolph A; International Consensus Conference on Pediatric Sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. *Pediatr Crit Care Med* 2005; **6**: 2-8 [PMID: 15636651 DOI: 10.1097/01.PCC.0000149131.72248.E6]
- 46 Watanabe T. Acute renal failure in Kawasaki disease. *Pediatr Nephrol* 2003; **18**: 200; author reply 201 [PMID: 12579412 DOI: 10.1007/s00467-002-1027-7]
- 47 Ulinski T, Sellier-Leclerc AL, Tudorache E, Bensman A, Aoun B. Acute tubulointerstitial nephritis. *Pediatr Nephrol* 2012; **27**: 1051-1057 [PMID: 21638156 DOI: 10.1007/s00467-011-1915-9]
- 48 Neilson EG. Tubulointerstitial nephritis. In: Goldman L, Schafer AI. Goldman's Cecil medicine. 25th ed. Philadelphia: Elsevier, 2016: 793-799
- 49 Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, Watson VE, Best BM, Burns JC. Recognition of a Kawasaki disease shock syndrome. *Pediatrics* 2009; **123**: e783-e789 [PMID: 19403470 DOI: 10.1542/peds.2008-1871]
- 50 Taddio A, Rossi ED, Monasta L, Pastore S, Tommasini A, Lepore L, Bronzetti G, Marrani E, Mottolese BD, Simonini G, Cimaz R, Ventura A. Describing Kawasaki shock syndrome: results from a retrospective study and literature review. *Clin Rheumatol* 2017; **36**: 223-228 [PMID: 27230223 DOI: 10.1007/s10067-016-3316-8]
- 51 Natterer J, Perez MH, Di Bernardo S. Capillary leak leading to shock in Kawasaki disease without myocardial dysfunction. *Cardiol Young* 2012; **22**: 349-352 [PMID: 21933461 DOI: 10.1017/S1047951111001314]

P- Reviewer: Agrawal A, Das RR, Teng RJ, Tommasini A, Uwaezuoke SN S- Editor: Ji FF L- Editor: A E- Editor: Song H





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>



World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2018 October 25; 7(4): 89-104





REVIEW

- 89 Perianal infectious dermatitis: An underdiagnosed, unremitting and stubborn condition
Serban ED

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Pediatrics*, Stanley P Galant, MD, Full Professor, Pediatrics, Childrens Hospital of Orange County University of California Irvine, Orange, CA 92868, United States

AIM AND SCOPE

World Journal of Clinical Pediatrics (*World J Clin Pediatr*, *WJCP*, online ISSN 2219-2808, DOI: 10.5409) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCP covers a variety of clinical medical topics, including fetal diseases, inborn, newborn diseases, infant diseases, genetic diseases, diagnostic imaging, endoscopy, and evidence-based medicine and epidemiology. Priority publication will be given to articles concerning diagnosis and treatment of pediatric diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJCP*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Clinical Pediatrics is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Shu-Yu Yin*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Ying Dou*
Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL

World Journal of Clinical Pediatrics

ISSN

ISSN 2219-2808 (online)

LAUNCH DATE

June 8, 2012

EDITORS-IN-CHIEF

Consolato M Sergi, FRCP(C), MD, PhD, Professor, Department of Lab Medicine and Pathology, University of Alberta, Alberta T6G 2B7, Canada

Toru Watanabe, MD, PhD, Professor, Department of Pediatrics, Niigata City General Hospital, Niigata 950-1197, Japan

EDITORIAL BOARD MEMBERS

All editorial board members resources online at <http://www.wjgnet.com/2219-2808/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director
World Journal of Clinical Pediatrics
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLISHER

Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLICATION DATE

October 25, 2018

COPYRIGHT

© 2018 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

<http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION

<http://www.f6publishing.com>

Perianal infectious dermatitis: An underdiagnosed, unremitting and stubborn condition

Elena Daniela Serban

Elena Daniela Serban, 2nd Department of Pediatrics, "Iuliu Hatieganu" University of Medicine and Pharmacy, Emergency Hospital for Children, Cluj-Napoca 400177, Romania

ORCID number: Elena Daniela Serban (0000-0003-0906-1232).

Author contributions: Serban ED contributed to the paper's conception and design, the data collection, extraction, analysis and evaluation, the interpretation of results, and the manuscript's preparation, critical revision, editing and final submission.

Conflict-of-interest statement: The author declares there are no potential conflicts of interest relevant to this publication.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Elena Daniela Serban, MD, PhD, Associate Professor, Pediatric Gastroenterologist, 2nd Department of Pediatrics, "Iuliu Hatieganu" University of Medicine and Pharmacy, Emergency Hospital for Children, 5 Crisan Street, Cluj-Napoca 400177, Romania. daniela.serban@umfcluj.ro
Telephone: +40-264-532216
Fax: +40-264-590478

Received: June 24, 2018

Peer-review started: June 25, 2018

First decision: August 2, 2018

Revised: August 23, 2018

Accepted: October 8, 2018

Article in press: October 9, 2018

Published online: October 25, 2018

ficial inflammation of the perianal skin, which is of bacterial origin (classically, *group A beta-hemolytic streptococci*). This narrative review aims to critically review and summarize the available scientific literature regarding pediatric PID, being the first of its kind, to the best of the author's knowledge. It also reports the first cases of Romanian children with PID. Multiple databases were subjected to systematic literature search (from 1966 to April 30, 2018) to identify studies and case reports of children with PID. As such, this review provides updated information about essential aspects of PID (epidemiology, etiology, pathogenesis, as well as clinical features, required investigations and therapeutic options) and of diagnostic pitfalls. Although a well-defined entity, PID remains largely underdiagnosed. PID may mimic other common conditions with skin manifestations (like candidiasis, pinworms, eczema, irritant dermatitis, anal fissure, hemorrhoids, Crohn's disease, psoriasis, seborrheic dermatitis, zinc deficiency dermatosis and even sexual abuse), with consequent unnecessary, sometimes expensive and invasive investigations and futile therapies, which cause patients and families discomfort and distress. Since PID has an unremitting course, early recognition is imperative, as it allows for prompt and efficacious antibiotic therapy. However, PID represents a stubborn condition and, even if properly treated, its recurrence rate remains high. Further well-designed prospective randomized controlled trials, with adequate follow-up, are required in order to formulate the optimum personalized antibiotic therapy (oral alone or in association with topical medication), able to prevent recurrences. Awareness of this condition by healthcare professionals should improve patient outcomes.

Key words: Perianal dermatitis; Perianal streptococcal dermatitis; *Beta-hemolytic streptococci*; *Staphylococcus aureus*; Perineal streptococcal dermatitis; Perianal swab culture; Differential diagnosis; Antibiotic therapy; Perianal streptococcal disease

Abstract

Perianal infectious dermatitis (PID) represents a super-

© **The Author(s) 2018.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Perianal infectious dermatitis (PID) represents a superficial inflammation of the perianal skin, which is of bacterial origin. This narrative review aims to summarize the available literature regarding pediatric PID, being the first of its kind, to the best of the author's knowledge. An updated insight into the main features of PID is provided, including diagnostic pitfalls. PID may mimic other common conditions with skin manifestations, with consequent application of a treatment that is wrong. The unremitting course of PID makes early recognition and antibiotic therapy crucial. Recurrence rates of PID remain high. Awareness of this condition should improve patient outcomes.

Serban ED. Perianal infectious dermatitis: An underdiagnosed, unremitting and stubborn condition. *World J Clin Pediatr* 2018; 7(4): 89-104 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i4/89.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i4.89>

INTRODUCTION

Perianal infectious dermatitis (PID) represents a superficial inflammation of the perianal skin, which is of bacterial origin^[1]. The first cases of pediatric PID, all caused by *group A beta-hemolytic streptococci* (GAS), were published more than 50 years ago^[2]. Still today, the clinical hallmark of PID is represented by a characteristic well-demarcated perianal edematous erythema, extending 2-4 cm around the anus^[1-10], sometimes with white exudate, pseudo-membranes and superficial anal fissures or cracks^[1,10-12]. Despite its typical features, PID is still unrecognized by many healthcare professionals^[13], as a result, patients are submitted to unnecessary investigations, sometimes invasive and costly (*i.e.*, upper and lower digestive endoscopies under general anesthesia, and magnetic resonance enterography), as well as to various therapies. Delays in diagnosis and treatment increase patient discomfort and stress, which can also affect the patient's family.

The aim of this narrative review, therefore, is to summarize the currently available scientific literature regarding pediatric PID-as an alert to the medical community-to help ensure more instances of correct management. The author provides updated knowledge of essential aspects of PID (epidemiology, etiology, pathogenesis, as well as clinical characteristics, investigations required and therapeutic options) and of diagnostic pitfalls.

LITERATURE SEARCH

Published full manuscripts and abstracts were identified by a systematic literature search up to the date of April 30, 2018 for MEDLINE (PubMed), Web of Science and Mendeley (starting from 1966), EMBASE (starting from 1974), The Cochrane Library (starting from 1992), Google

Scholar (starting from 2004), and Research Gate (starting from 2008) databases. Titles, abstracts and full-texts were searched without any language restriction. The reference lists from the selected studies were manually examined to identify additional research studies. Duplicates were excluded. The search included the following items/key words: "perianal cellulitis", "perianal dermatitis", "perianal disease", "perianal infection", "perineal dermatitis", "perianal streptococcal cellulitis", "perianal streptococcal infection", "perianal streptococcal dermatitis", "perianal streptococcal disease", "perineal streptococcal disease", "perineal streptococcal dermatitis", "anitis", and "anusitis". Only papers clearly presenting PID [as case reports, case series/observational studies or randomized controlled trials (RCTs)] and focused on children were retained for detailed analysis.

Data extraction

The following data were extracted: Last name of the first author; publication year; country; authors' field of medical practice and working department; study design; characteristics of the included population (*i.e.*, sample size, age, sex); symptoms and signs; etiology of the PID; presence or absence of pharyngitis or other site infections; results of throat culture and other relevant laboratory investigations; duration until diagnosis; important data concerning infections in family/community; previous investigations, diagnoses and therapies; type and duration of medication used to cure the PID; presence and rate of recurrence; medication used for recurrences; potential limits of the studies; and, any other relevant data regarding PID.

Characteristics of included studies

Sixty-four full-text articles reporting on pediatric cases of PID were included, being available from either the mentioned databases or (for older papers) by personally contacting their authors (email and/or phone). Only one reported on a RCT^[12] (including 35 children); the remaining represented descriptive observational prospective studies/case series [6 articles, comprising a total of 351 patients (between 10 and 150/study)]^[2,6,11,14-16], descriptive observational retrospective studies/case series [16 articles, comprising a total of 549 patients (between 6 and 157/study)]^[4,5,8,10,17-28], and case reports [41, comprising a total of 75 patients (between 1 and 4 cases/report)]^[3,7,9,13,29-65]. Three cases diagnosed by this author were also added, giving a total of 78 case reports that were analyzed in this review. Ultimately, the analysis in this review involved the 78 patients from the case reports, 35 from RCTs, 549 from retrospective studies and 351 from prospective studies, giving a total number of PID pediatric cases of 1013.

The main characteristics of the included studies/case series are presented in Tables 1 and 2, and of the case reports in Tables 3 and 4. Four cases presented as case reports did not have the full-text manuscript available in electronic form^[35,48,64]; however, they are described in Tables 3 and 4, are included in the total number of

Table 1 Studies/case series with perianal infectious dermatitis: Clinical and bacteriological patient characteristics

Name, yr, country, study design	Population size; age; sex	Symptoms/signs ¹ ; symptom duration	Etiology of PID	Other findings ²
Amren, 1966, United States, PS ^[2]	10; 1-8 yr, half < 5 yr; 90% M	Painful defecation, constipation, anal pruritus, perianal pain, mucoid or bloody anal discharge; 1 F also with vulvo-vaginitis	GAS (culture)	Throat GAS positive: 28% (no symptoms)
Spear, 1985, United States, RS ^[26]	14; mean age 3.9 yr (1-10 yr); 11 M	Painful defecation (14), constipation (6), bloody stool (7), anal fissure (5); mean duration: 6.2 mo (range: 1-12 mo)	GAS (culture)	
Kokx, 1987, United States, RS ^[4]	31; 7 mo to 8 yr (mean 4.25 ± 1.8 yr); 77% M	Perianal itching (78%), rectal pain (52%), and blood-streaked stool (35%)	GAS and RADT	Throat GAS positive: 64%; identical perianal and pharyngeal T-type (T28, 5 cases; T4, 4; T2, 1)
Krol, 1990, Canada, RS ^[20]	8; 8 mo to 10 yr; 6 M	Perianal pruritus (8); painful defecation (4); anal fissure (2); bloody stool (1); 3 wk to 6 mo	GAS (culture)	
Grant, 1993, United Kingdom, RS ^[10]	20; 5 mo to 12 yr (mean 5 yr); 75% M	Perianal discomfort (14) and itch (13), fresh blood per rectum (12), pain on defecation (10), perianal pain (4), anal mucus discharge (2); 3 wk to 1 yr (mean 3 mo)	GAS (culture)	
Patrizi, 1994, Italy, RS ^[22]	1. 10 yr, M 2. 4 yr, F 3. 5 yr, F 4. 9 yr, M 5. 7 yr, M	1. Pruritus, tenesmus, constipation, acute GP and mild balanitis 2. Anal pruritus, vulvar and perineal erythema, and GP; 4 mo 3. PID and GP 4. Painful defecation, GP; 1 mo 5. PID and balanitis	GAS (culture)	1. Throat GAS negative; penile GAS: same antibiogram 2. Throat GAS negative 3. Throat GAS positive 4. Throat GAS positive 5. GAS tonsillitis 3 mo before; penile GAS and mother with cervical GAS (child and mother bathing together)
Wright, Australia, 1994, PS ^[11]	22; 5 mo to 8 yr (mean 41 mo); 13 M	Painful defecation, bleeding ± anal pain, perianal pruritus, constipation	Culture: 12 GAS, 1 GBS, 1 GCS	
Mostafa, 1997, Egypt, PS ^[15]	150; 2 mo to 11 yr (mean 3.8 ± 2.1 yr); 75% M	Perianal itching (15%), gastroenteritis (34%)	BHS: 35.3%, <i>S. aureus</i> 3.4%	Throat: BHS 44% (GAS 21.3%, non-GAS 22.7%); PID caused by GAS: 53.8% with same GAS in the throat
Barzilai, 1998, Israel, PS ^[14]	18; 7 mo to 5.4 yr; 10 M	Perianal pruritus (50%); painful defecation or constipation (44%); anal fissure (39%); purulent secretion (27%); rectal bleeding (16%); 2 GP	GAS	GAS in other locations: 72%; 4 siblings throat GAS positive (no symptoms)
Mogielnicki, 2000, United States, RS ^[5]	23; mean age 5 yr (1-11 yr); 13 F	13 only PID; 2 PID + vulvo-vaginitis; 8 only vulvo-vaginitis	GAS (culture)	Throat GAS positive: 92% (± symptoms)
Mateo, 2002, Spain, RS ^[19]	10; 9 mo to 7 yr; 6 M	Oozing and rectal bleeding, anal pruritus, pain on defecation; 1 M also GP; 20 d to 2 yr	GAS	Throat GAS positive: 3/6
Petersen, 2003, Denmark, RS ^[27]	17; mean age 6 yr (3-13 yr)	Painful defecation, fresh blood on stool	GAS 12 (11 M) T28	Throat GAS positive 12%; 6/12 with T28 from kindergarten
Landolt, 2005, Switzerland, RS ^[17]	13; 7 F	Obstipation (58%), painful defecation (50%), perianal itching (25%), melena (25%); 10 cases with > 1 symptom	GAS positive in 12	
Echeverría Fernández, 2006, Spain, PS ^[6]	19; 6 mo to 4 yr (median age 12 mo)	Anal pruritus (19), constipation (9), anal fissures (5), rectal bleeding (4), vulvo-vaginitis (2)	GAS (RADT and culture)	Throat GAS positive: 80%; GAS pharyngitis: 1 case
Meury, 2008, Switzerland, RCT ^[12]	35; 1-16 yr	Either typical erythema or at least 2 of: perianal itching, rectal pain, painful defecation, constipation, blood-streaked stool, rectal mucopurulent discharge, or anal fissure	GAS	
Jongen, 2008, Germany, RS ^[8]	21; < 14 yr (mean age 6.3 yr); 76% M	Perianal itching, sore anus, bleeding and pain at defecation; mean duration of 6.6 months (2 wk to 2 yr)	17 GAS, 4 GBS (culture)	
Shouval, 2008, Israel, RS ^[18]	11; 6 mo to 4 yr (mean 24 mo); 73% M	Irritability (all), perianal itching (6) and pain (3); < 28 d	GAS (RADT)	
Heath, 2009, United States, RS ^[26]	26; 5 mo to 12 yr; 15 F	Anal erythema or recurrent buttocks dermatitis; in PID caused by <i>S. aureus</i> : specific small papules and pustules of the buttocks or extension of the erythema to adjacent buttock skin	<i>S. aureus</i> 82%, GAS, GBS	
Olson, 2011, United States, RS ^[25]	81; mean age, M: 4.1 yr and F: 4.6 yr; 58% M	(86.4%) perianal involvement; (22.2%) symptoms for at least 2 wk (6.2% with symptoms for at least 4 wk); the rest: duration < 1 wk	GAS	
Clegg, 2015, United States, RS ^[23]	157; 18 d to 12.5 yr, mean 4.8 yr, 53% M	Predominant site of involvement: M: perianal (86%) and F: perivaginal area (62%); 9.8 d	GAS	Throat GAS positive: 95%; 100% concordance between perineal and pharyngeal GAS

Cohen, 2015, France, PS ^[16]	132; mean age 46.6 ± 23.5 mo; 64% M	Painful defecation, anal fissure, bloody stools; 4 also vulvo-vaginitis; 2 wk	GAS (RADT and culture)	
Garcia, 2015, Spain, RS ^[21]	6; 9 mo to 5 yr (mean age 3 yr); 5 M	Perianal rash (6), rectal pain (3), itching (2), vaginitis (1)	GAS	GAS pharyngitis: 30%
Sterbenc, 2016, Slovenia, RS ^[24]	89 cases < 15 yr (84.7%); median age 5 yr		GAS, GBS, GCS, GGS	

¹Besides typical perianal erythema; ²Especially throat culture and infections in the family/community. AB: Antibiotic; BHS: Beta-hemolytic streptococci; F: Female; GAS: Group A beta-hemolytic streptococci; GBS: Group B beta-hemolytic streptococci; GCS: Group C beta-hemolytic streptococci; GP: Guttate psoriasis; M: Male; Pen: Penicillin; PID: Perianal infectious dermatitis; PS: Prospective study; RADT: Rapid antigen detection test; RCT: Randomized controlled trial; RS: Retrospective study; *S. aureus*: *Staphylococcus aureus*; T2: T-type 2 of GAS; T28: T-type 28 of GAS; T4: T-type 4 of GAS.

patients analyzed, and provided epidemiological, clinical and bacteriological data. Five papers found as references in other reports could not be included, as their abstracts and full-text manuscripts were not available in electronic format and there was also no reply to this author's inquiry, initially made in December 2016^[66-70]. Table 5 presents previous investigations, diagnoses and therapies in children finally diagnosed with PID.

DEFINITIONS AND TERMS USED

Initially, the PID condition was described as "perianal cellulitis" in 1996 by Amren *et al*^[2]; this term has since been used by other authors^[10,14,28-31,38,56,59,61,63]. However, the term "cellulitis" was later considered inaccurate, since inflammation involves only the skin^[4,20]. The more appropriate term of "perianal streptococcal dermatitis" was introduced by Krol^[20] in 1990 and used both in pediatric^[8,9,12,13,17,19,20,22,24,34-36,39-47,49,51-53,55] and adult cases^[71-75]. The terms "anitis"^[13,55] and "anusitis"^[67] were also used, but only in a few papers. Other authors preferred to name this condition "perianal streptococcal infection"^[7,11,16,18,27,33,37,50,60,65,76,77] or "perianal streptococcal disease", as introduced in 1987 by Kokx *et al*^[4,62,64,78]. Mogielnicki *et al*^[5] introduced the term "perineal streptococcal disease", as the infection may extend to genital organs. Others preferred "perineal streptococcal infection"^[23] or "perineal streptococcal dermatitis"^[3,25,79]. Recently, the proposed term is "PID"^[1], as other infectious bacterial agents have also been proven to cause this condition^[3,8,24,26,32,58].

EPIDEMIOLOGY

The incidence of pediatric PID is unknown. With so many terms used for the same condition, it is not surprising that its frequency is not determined. However, the main reason for this unknown incidence is considered the fact that PID remains too often unrecognized by healthcare professionals. PID appears all over the world and has been reported by authors in various countries from different continents, including the United States^[2,4,5,23,25,26,28,32,38,43,46,57,59,61-63], Canada^[3,20,40], Australia^[11,33], Africa (Egypt^[15]), Europe (United Kingdom^[7,10,29,30,65],

Spain^[6,19,21,31,42,64], Italy^[22,35,39,47,48], The Netherlands^[36,60], Finland^[37], Sweden^[41,50], Germany^[8,9,45], Denmark^[27], Switzerland^[12,17,54], France^[13,16,55], Greece^[58], Asia (India^[44], Taiwan^[49], Japan^[51,52], Iran^[56]), Israel^[14,18] and Turkey^[53]. It appears that no cases have been published from Eastern Europe.

Considering incidence of PID caused by GAS among all pediatric consultations in different services, rates have varied from 1 case/2000 patients (May 1964 through July 1965 in a pediatric department in the United States^[2] and in a study published in 2015 from another pediatric center in the United States^[23]) to 1 case/400 outpatient visits (January through March 1990 in a pediatric hospital in the United States)^[80], 1 case/218 patients (October 1985 through June 1986 in a pediatric hospital in the United States)^[4], 1 case/200 patients (during the year 1997 in a department of pediatrics and community and family medicine in the United States)^[5] and 1 case/20 patients (October 2000 through May 2001 in a pediatric clinic in Switzerland)^[17]. As seen, most data have originated from the United States, with only one report being from Europe. The only other European paper reporting frequency of PID was a German case series, albeit from a colorectal surgery clinic. PID was detected in 16% of patients aged a maximum of 14 year with anorectal complaints, from February 2003 through September 2006^[8]. In a rural area of Denmark, the annual incidence was determined to be 2-7 in 1000 children^[27]. From a survey performed among general practitioners in 1996 in an urban area of the United Kingdom, it was concluded that PID might be seen, on average, once or twice a year. Lack of awareness was considered the main reason for PID being missed in primary care^[7].

Regarding age, PID is particularly encountered in children, especially between the ages of 6 mo and 10 years^[2-4,8,11,20,22,28], with a maximum incidence peak between 3 years and 6 years^[24]. However, cases have been described in infants less than 6 mo of age^[15,23,26,43,57] or older than 10 years^[5,10,15,23,26,27,39,48,62], and even in adults^[52,61,71-78,81-84].

Boys have been initially described as predominantly affected by PID, representing about or more than 70%-80% of cases^[2,4,8,10,15,18,20,21,28] (Table 1). Also, most

Table 2 Studies/case series with perianal infectious dermatitis: Therapy and follow-up of patients

Name, yr, country	Therapy of PID and results	Follow-up of PID
Amren, 1966, United States ^[2]	IM Pen, 10 d plus oral Pen, 10 d: disappearance of symptoms in 2-3 d	After therapy: 2 cases GAS positive; 10 d of Pen (same type): Effective in eradicating GAS in both cases
Spear, 1985, United States ^[28]	Oral Pen: rapid resolution of PID	Recurrence of infection: Not uncommon, requiring a repeated course of oral AB
Kokx, 1987, United States ^[4]	Oral Pen or amoxicillin, 10 d: clinical and bacteriological clearance in 61%	39% relapses, treated with IM or oral Pen; 4 children failed; 3 successfully treated with oral clindamycin, 10 d; 4 th case successfully treated with oral Pen (10 d) and rifampin (last 4 d)
Krol, 1990, Canada ^[20]	Oral Pen, 10 d plus topical mupirocin in 4 cases (these 4 without recurrence)	2 cases: 2 nd course of therapy within 1 mo
Grant, 1993, United Kingdom ^[10]	Oral Pen, 3 wk: 14 responded (6 plus topical fucidin)	6 cases: No complete response; successful 2 nd course of oral Pen and topical fucidin
Patrizi, 1994, Italy ^[22]	1. Oral erythromycin, 14 d 2. Oral Pen, 2 wk 3. Oral erythromycin, 2 wk 4. Oral erythromycin and topical mupirocin, 2 wk 5. Amoxicillin, 2 wk: good results	1. 4 wk later, GP and PID disappeared and all swabs negative 2. Lesions improved, but swab positive: erythromycin, 2 wk: complete healing (including negative GAS) 3. Lesions disappeared in maximum 5 wk 4. 4 wk later, lesions and culture negative 5. 4 wk later, perianal GAS, no lesions; 2 nd course of amoxicillin: good results
Wright, Australia, 1994 ^[11]	Oral amoxicillin - clavulanate plus topical bacitracin, 2 wk	50%: Response to treatment in 2 wk; no recurrence
Barzilai, 1998, Israel ^[14]	Oral amoxicillin, 10 d and topical mupirocin: 16 patients clinically cured; perianal cultures GAS negative: days 3-5 of therapy and weeks 2 to 3 post-therapy	Recurrence: 2 cases (clinical and culture); successfully retreated 1 wk after finishing first therapy
Mateo, 2002, Spain ^[19]	IM Pen (1), oral amoxicillin (5), topical mupirocin (4)	All with favorable response and no recurrence
Petersen, 2003, Denmark ^[27]	Oral Pen, 10 d: ineffective in 3 cases	3 cases: Clarithromycin, 7 d; no recurrence
Landolt, 2005, Switzerland ^[17]	10 with > 1 symptom: oral Pen, 10 d; 3: oral or IV amoxicillin-clavulanate	4 with persistent symptoms: 2 nd course of AB - oral Pen (3 cases), 14 d and oral clarithromycin (1 case), 10 d; 1 mo later: all 4 healed
Echeverría Fernández, 2006, Spain ^[6]	Oral Pen, 10 d	Favorable in 85%, perianal GAS negative in 95%
Meury, 2008, Switzerland ^[12]	15 cases: oral Pen, 10 d and 14 cases: oral cefuroxime, 7 d	Clinical improvement: More rapid in the cefuroxime group ($P = 0.028$) and perianal GAS negative the last day of therapy in 93% on cefuroxime vs 47% on Pen ($P < 0.01$)
Jongen, 2008, Germany ^[8]	Oral Pen ± local polihexanid, 10-14 d	1 case: New GAS associated PID 5 mo later; successfully treated with oral AB
Shouval, 2008, Israel ^[18]	Oral amoxicillin, 10 d and topical mupirocin (8/11); complete healing in 73%	Recurrence: 3/11; 2 nd course of AB administered
Heath, 2009, United States ^[26]	Oral cephalexin for <i>S. aureus</i> : Successful in all but one; 4 cases with <i>S. aureus</i> cleared on topical mupirocin and 1 on bleach baths and topical steroids	1 case with MRSA: 2 nd course of oral AB required
Olson, 2011, United States ^[25]	Oral AB alone: 81.4%; topical agent alone: 2.5%; both: 16%; duration: oral beta-lactams 10 d, azithromycin 5 d, cephalexin 5 d, oral Pen 14 d	Recurrence 32.1%; recurrence within 6 wk 69.2%; recurrence rate: After Pen or amoxicillin 38.1% vs 27.8% after a beta-lactamase resistant AB (adjusted odds ratio: 2.02)
Clegg, 2015, United States ^[23]	Amoxicillin 82.2%; cephalexin 11%; other AB 7%; topical therapy: 6%	Recurrence rate (symptomatic PID) 6 mo after the initial episode: 13.4% after any AB, 12.4% after amoxicillin, 29.4% after cephalexin, and 0% after all other AB (oral Pen, amoxicillin-clavulanate, azithromycin, clarithromycin, cefprozil and cefdinir)
García, 2015, Spain ^[21]	Oral AB (Pen 5, amoxicillin 1), plus 4 topical mupirocin and 3 clotrimazole	Satisfactory; 1 recurrence
Sterbenc, 2016, Slovenia ^[24]		All BHS: susceptible to Pen; all GAS susceptible to clindamycin, 1.4% resistant to erythromycin; GBS resistant to erythromycin in 14.8% and clindamycin in 7.4% of cases

AB: Antibiotic; BHS: Beta-hemolytic streptococci; GAS: Group A beta-hemolytic streptococci; GBS: Group B beta-hemolytic streptococci; GP: Guttae psoriasis; IM: Intramuscular; IV: Intravenous; Pen: Penicillin; MRSA: Methicillin-resistant *S. aureus*; PID: Perianal infectious dermatitis.

case reports have presented male patients (Table 3). No precise reason has been found for this predominance; hormones and immune factors may contribute to it^[52]. However, other series showed smaller rates of male predominance (53%^[23], 55.5%^[14], 58%^[25], 59%^[11],

60%^[19] and 64%^[16]), while four studies reported a slight female predominance (54%^[17], 57%^[5,26] and 63%^[6]).

Concerning seasons, most cases of PID caused by GAS appeared in winter^[2,5,8,19] and spring^[2,5,24], when GAS infections of the upper respiratory tract are also more

Table 3 Case reports with perianal infectious dermatitis: Clinical and bacteriological patient characteristics

Name, yr, country	Case age, sex	Symptoms/signs ¹ ; symptom duration	Etiology of PID	Other findings ²
Hirschfeld, 1970, United States ^[59]	1-2. 6 yr, F and 3 yr brother 3-4. 5 yr and 3 yr brothers (unrelated family)	1-2. Painful defecation; several days 3-4. Same history and symptoms	GAS (culture)	1-2. Both had sore throats 2 wk prior 3-4. Throat GAS positive (1 case)
Farmer, 1987, United Kingdom ^[65]	1. 4 yr, M 2. 5 yr, F	1. White anal discharge, perianal pustules; 3 wk 2. Perianal itching, pain on defecation, dysuria; vulva affected; 3 wk	GAS (culture)	
Rehder, 1998, United States ^[61]	1. 3 yr, M 2. 3 yr, M 3. 4 yr, M 4. 1 yr, F	1. Rectal irritation; 6 mo 2. Perianal pain and itching; 5 wk 3. Perirectal pain; 6 wk 4. GP; 3 wk	GAS (culture)	1. Sibling, 6 yr: GAS pharyngitis recently 2. Patient: throat GAS positive; sibling with recent sore throat 3. Identical GAS from anus and throat
Honig, 1988, United States ^[62]	4; 15 mo, 6, 8 and 12 yr; 3 M	Anal pruritus, bloody anal discharge; GP: 2 cases, appeared 9 mo after onset of PID; 1 M with PID history of 2 yr	GAS (culture)	
Marks, 1988, United States ^[63]	5 yr, M	Perianal irritation and pruritus, bloody discharge; 2 wk	GAS (culture)	
Guerrero - Vázquez 1989, Spain ^[64]	2 cases	Perianal irritation in both; seropurulent anal and balano-preputial discharge in 1 case	GAS (culture)	
Duhra, 1990, United Kingdom ^[29]	5 yr, M	Painful defecation, micturition, bloody stool; penile erythema swelling; 4 wk	GAS (culture)	GAS positive from penile skin; members of patient's family: severe sore throat recently
Goodyear, 1991, United Kingdom ^[30]	4 yr, M	Painful defecation, blood-streaked liquid stool; fecal incontinence; 6 wk	GAS (culture)	
Medina, 1992, Spain ^[31]	4 yr, M	Perianal pruritus and bleeding; 3 mo	GAS (culture)	
Montemaranano, 1993, United States ^[32]	3 yr, M	Painful perianal area, satellite pustules; 2 mo	<i>S. aureus</i> (culture)	<i>S. aureus</i> positive in anterior nares and satellite pustule
Guppy, 1993, Australia ^[33]	1. 7 yr, M 2-3. His 2 brothers, 5 and 2.5 yr 4. 4 yr, M 3 yr, M	1. Perianal excoriation; 8 wk 2-3. Similar history 4. Typical PID; penis lesions later; 4 wk Perianal itching; 2 mo	GAS (culture)	The three siblings bathing together
Paradisi, 1993, Italy ^[34]	1. 3 yr, F 2. 5 ½ yr, M, brother	Painful defecation, perianal itching, rectal bleeding, constipation	GAS	
van Zeijl, 1996, Netherlands ^[36]	4; 3 M (1, 6 and 8 yr, the last 2 brothers); 1 F (2 yr)	Constipation, painful defecation, diarrhea	GAS (culture)	Brothers shared same toilet
Saxen, 1997, Finland ^[37]	1. 3 yr, M 2-3. Other cases	1. Itchy anus and bloody stool; 1 w 2. Same symptoms	GAS (T28)	2. Throat GAS positive, identical (T28)
Berlin, 1997, United States ^[38]	3 yr, M	Constipation, myositis	GAS (culture)	His mother had sore throat GAS positive
Bugatti, 1998, Italy ^[39]	12 yr, M	Perianal discharge, 1 mo	GAS (culture)	
Adams, 1999, Canada ^[40]	1 yr, M	Typical PID	GAS (culture)	
Roos, 1999, Sweden ^[41]	5 yr, M	Anal pruritus	GAS T28 (culture)	Case: throat GAS negative; mother: GAS tonsillitis positive; anal and throat GAS identical
Velez, 1999, Spain ^[42]	2 yr, M	Fever 39-40 °C, erythema: perianal, genitalia and proximal thighs	GAS (culture)	Throat negative
Herbst, 2000, Germany ^[9]	4 yr, M	GP; 6 w history; PID discovered at physical exam	GAS (culture)	Patient and family members: Negative GAS throat
Brilliant, 2000, United States ^[43]	1. 4 yr, M 2-3. 2 mo and 30 mo 4. 4 yr, F	1. Rectal itching and pain, scant mucoid discharge 2-3. Several days later with similar symptoms 4. Plus vulvitis	GAS (RADT + culture)	2-3. Siblings of case 1 4. Neighbor of the 3 cases
Balasubramanian, 2000, India ^[44]	1. 13 mo, M 2. 11 mo, M 3. 13 mo, F	1. Fever, painful defecation, anal pruritus; 2 d 2-3. Fever, painful defecation	GAS (culture)	
Heidelberger, Germany, 2000 ^[45]	1. 6 yr, M 2. 9 yr, M	1. Anal itching and burning; 3 mo 2. Balanitis and impetigo	GAS (culture)	

Nowicki, 2000, United States ^[46]	7 yr, M	Perianal itching, painful defecation; 10 d	GAS (culture)	Throat GAS negative
Soulliet, 2000, France ^[13]	7 yr, F	Vulvar erythema, perirectal pain, painful defecation, constipation; perioral impetigo; 3 wk	GAS (culture)	Perioral GAS positive
Lunghi, 2001, Italy ^[47]	Brother (4 yr) and sister (6 yr)	1 also vulvo-vaginitis; 4 mo	GAS (culture)	Throat GAS positive in both patients
Romano, 2002, Italy ^[48]	12 yr, M	PID and GP	GAS	
Huang, 2003, Taiwan ^[49]	6 yr, M	Perianal itching, painful defecation, scant mucoid discharge	GAS (culture)	Throat GAS positive
Reimer, 2004, Sweden ^[50]	1. 4 yr, M 2. 6 yr, M	1. Perianal discomfort 2. Purulent discharge plus balanitis	1. GAS (RADT) 2. GAS	2. Penis culture GAS positive; father treated for GAS pharyngitis; brother, 4 yr with GAS PID and brother 2 yr with GAS pharyngitis
Takeshita, 2006, Japan ^[51]	3. 4 yr, F 1. 2 yr, F	3. Perianal pain, vulvar erythema and pain 1. PID; 2 wk	3. GAS GAS (culture)	
Usuki, 2006, Japan ^[52]	2. 6 mo, M 5 yr, F	2. PID; 1 wk PID	GAS (RADT)	4 d later: Father with symptoms of PID and GAS positive
Ulger, 2007, Turkey ^[53]	3 yr, M	Pain on defecation, anal pruritus; 8 d; GP; 2 d	GAS (culture)	Sore throat 2 wk before; no culture, no therapy needed
Greisser, 2008, Swiss ^[54]	7 yr, M	Perianal pain and pruritus, yellow discharge; 3 d	GAS (RADT + culture)	Throat GAS negative
Lehman, 2009, United Kingdom ^[7]	3 yr, F	Itchy bottom and painful defecation; 2 wk	GAS (culture)	
Ledoux, 2009, France ^[55]	4 yr, M	PID for 2 wk; lesions of GP since second week	GAS (culture)	
Rasi, 2009, Iran ^[56]	4 yr, M	Rectal itching and burning, pain on defecation; plaque type psoriasis; 3 mo	GAS (RADT)	
Block, 2013, United States ^[57]	1. 2 mo, F 2. 4 mo, F	1. PID and vulvar erythema 2. Blood in diaper	GAS	1. 8 yr sibling: previous GAS pharyngitis
Theotokatou, 2014, Greece ^[58]	1. 8 yr, M	1. Perianal itching, constipation, blood-streaked stool; 3 wk	<i>Enterococcus faecalis</i> (culture) in both)	
Zhang 2016, Canada ^[3]	2. 10 yr, M, brother 1. 4 yr, M	2. Perianal itching and mucous discharge (2 wk after onset of symptoms of his brother) 1. Painful defecation, GP, penile erythema	1. GAS and <i>S. aureus</i> 2. GBS 3. GCS	1. Throat GAS positive 2. Throat culture negative 3. Throat culture negative; vulvar culture few GCS and scant <i>S. aureus</i>
Garritsen, 2017, Netherlands ^[60]	2. 4 yr, M 3. 3 yr, F 19 mo, M	2. Painful defecation, GP 3. Perivulvar erythema, small amount of greenish-yellowish vaginal discharge PID and 1 wk later: GP	GAS	
Serban, present study, Romania	1. 9 yr 4 mo, M 2. 9 yr 6 mo, M 3. 11 yr 9 mo, M	1. Perianal pain and pruritus, anal mucous and bloody discharge, painful defecation; 6 wk 2. Anal pruritus, painful defecation, anal mucous and bloody discharge 3. Anal pruritus, mucous and bloody discharge, painful defecation, constipation	1. GBS and <i>S. aureus</i> (culture) 2. GAS (culture) 3. GAS (culture)	1. Throat GAS, GBS and <i>S. aureus</i> negative 2. Throat GAS positive 3. Throat GAS negative

¹Besides typical perianal erythema; ²Especially throat culture and infections in the family/community. F: Female; GAS: Group A beta-hemolytic streptococci; GBS: Group B beta-hemolytic streptococci; GCS: Group C beta-hemolytic streptococci; GP: Guttate psoriasis; M: Male; PID: Perianal infectious dermatitis; RADT: Rapid antigen detection test; *S. aureus*: *Staphylococcus aureus*; T28: T-type 28 of GAS.

prevalent. Only 30% of cases were reported in June and July in the initial paper by Amren *et al*^[2], while the rest were during spring and winter. A recent prospective study found most cases in autumn (peak of 21% in November)^[16], while a report published that same year showed a maximum incidence between October and March (65% of cases)^[23]. Interestingly, PID caused by group B streptococci (GBS) also had a maximum incidence during winter and spring^[24].

Cases of PID in the same family and/or with inter-familial spread have been extensively documented, transmitted from children to parents^[52] or *vice versa*^[22,38,50] or between siblings^[14,33,35,36,43,47,50,58,59] or other family

members^[26] or friends^[43]. In the study by Kokx *et al*^[4], among 31 children from 19 families, intrafamilial spread was detected only in siblings and occurred in 50% of the possible situations, with 7 families representing multiple cases of PID. Also, small epidemics (outbreaks) in daycare centers have been published^[5,27,37]. In the study reported by Mogielnicki *et al*^[5], of 23 cases, 10 had contact with someone with PID. Saxén *et al*^[37] showed that a small outbreak of 3 culture-confirmed PID cases caused by GAS and 2 non-verified clinical PID cases occurred within 9 d in a group of 20 daycare children. The following risk factors for PID have been described: perianal skin lesions; poor hygiene; poor living conditions; overcrowded houses;

Table 4 Case reports with perianal infectious dermatitis: Therapy and follow-up of patients

Name, yr, country	Case age, sex	Therapy of PID and results	Follow-up of PID
Hirschfeld, 1970, United States ^[59]	1-2. 6 yr, F and 3 yr brother 3-4. 5 yr and 3 yr brothers (unrelated family)	Oral Pen	
Farmer, 1987, United Kingdom ^[65]	1. 4 yr, M 2. 5 yr, F	1. Oral Pen: prompt and complete recovery 2. Oral Pen, 1 wk: asymptomatic	
Rehder, 1998, United States ^[61]	1. 3 yr, M 2. 3 yr, M 3. 4 yr, M	1. Oral Pen, 2 wk 2. Oral Pen, 2 wk 3. Oral Pen, 3 wk	1. 2 wk later, erythema and GAS positive: erythromycin, for 1 mo; no recurrence (including culture) 2. No recurrence (including cultures) 3. Perianal cultures positive after 2 and 3 wk: erythromycin, 10 d: negative culture 4. All negative
Honig, 1988, United States ^[62]	4; 15 mo, 6, 8 and 12 yr; 3 M	4. Oral Pen, 3 wk: both conditions cleared Oral Pen, 10 d; PID cleared in 3 cases within 10-14 d	The 4 th case with PID history of 2 Y: 10 d of erythromycin, cleared PID and negative culture; psoriasis cleared 14-35 d after institution of therapy
Marks, 1988, United States ^[63]	5 yr, M	Oral Pen, 14 d; rash progressively healed (completely in 17 d)	
Duhra, 1990, UK ^[29]	5 yr, M	Oral Pen, 3 wk: clearance of penile lesion (2 wk), but not perianal, also with positive GAS	Other 2 wk of oral Pen cleared PID and GAS
Goodyear, 1991, United Kingdom ^[30]	4 yr, M	Oral Pen, 10 d; completely resolved in 2 wk	Follow up 2 mo later: clinically well
Medina, 1992, Spain ^[31]	4 Y, M	Topical mupirocin, 10 d: Completely resolved	Negative cultures 1 wk and 1 mo later
Montemarano, 1993, United States ^[32]	3 Y, M	Oral erythromycin, 10 d: Rapid cure	
Guppy, 1993, Australia ^[33]	1. 7 yr, M 2-3. His 2 brothers, 5 and 2.5 yr	1. Oral Pen, 10 d 2. Oral Pen, 10 d 3. Oral Pen, 10 d, initially improved	1. After stopping Pen, rectal bleeding: Cefaclor, 10 d, no recurrence 2. No recurrence 3. 3 mo later: Persistent perianal infection: erythromycin
Paradisi M, 1993, Italy ^[34]	4. 4 yr, M 3 yr, M	4. Oral Pen, 2 wk, incomplete resolution Topical erythromycin, 15 d: Complete clinical and bacteriologic resolution	4. Erythromycin, 4 wk: Complete resolution No recurrence
van Zeijl, 1996, Netherlands ^[36]	4; 3 M (1, 6 and 8 yr, the last 2 brothers); 1 F (2 yr)	Oral Pen, 10 d ± mupirocin or fucidin Oral amoxicillin + fucidin	
Saxen, 1997, Finland ^[37]	1. 3 yr, M	1. Oral Pen, 10 d: clearance within 2 d	1. 1 wk after stopping Pen: PID recurrence, with GAS positive; oral cephalixin: good results
Berlin, 1997, United States ^[38]	3 yr, M	IV antibiotics (not mentioned)	Symptoms resolved entirely after 2 wk
Bugatti, 1998, Italy ^[39]	12 yr, M	Amoxicillin, 10 d: Rapid resolution of symptoms	
Adams, 1999, Canada ^[40]	1 yr, M	Oral Pen and topical mupirocin, 10 d	
Roos, 1999, Sweden ^[41]	5 yr, M	Cefadroxil plus topical fucidin, 10 d	No recurrence
Velez, 1999, Spain ^[42]	2 yr, M	Cefaclor, 10 ds: complete healing	2 wk after therapy: Acral (hands and feet) scarlatiniform desquamation
Herbst, 2000, Germany ^[9]	4 yr, M	Oral Pen and topical fucidin, 2 wk: Complete healing (including culture)	
Brilliant, 2000, United States ^[43]	1. 4 yr, M 2-3. 2 mo and 30 mo 4. 4 yr, F	1. Oral amoxicillin, dramatic improvement 1 d 2-3. Same effective therapy 4. Same effective therapy	
Balasubramanian, 2000, India ^[44]	1. 13 mo, M 2. 11 mo, M 3. 13 mo, F	Oral Pen, 10 d; symptoms clearance in 3 d	
Heidelberger, Germany, 2000 ^[45]	1. 6 yr, M 2. 9 yr, M	1: Oral Pen, 10 d 2. Same plus topical clioquinol; in both cases, all lesions disappeared	
Nowicki, 2000, United States ^[46]	7 yr, M	Oral Pen: Symptoms and signs disappeared	1 wk following Pen, peeling from his fingers tip (toes not involved)
Soulliet, 2000, France ^[13]	7 yr, F	Amoxicillin, 10 d; perianal lesions cleared by day 2	
Lunghi, 2001, Italy ^[47]	Brother (4 yr) and sister (6 yr)	IM Pen, 4 wk, plus local mupirocin	Complete resolution (with negative culture) within 4 wk; no relapse in 4 mo

Huang, 2003, Taiwan ^[49]	6 yr, M	Oral Pen and topical mupirocin, 14 d: clinical healing after 4 d	After starting Pen: desquamation of fingers and perioral skin
Reimer, 2004, Sweden ^[50]	1. 4 yr, M 2. 6 yr, M 3. 4 yr, F	Oral Pen in all cases: quickly healed	
Takeshita, 2006, Japan ^[51]	1. 2 yr, F 2. 6 mo, M	Oral antibiotics: rapid resolution of the condition	
Usuki, 2006, Japan ^[52]	5 yr, F	Oral and topical antibiotics	
Ulger, 2007, Turkey ^[53]	3 yr, M	Oral Pen, 2 wk; topical corticosteroids for GP; all lesions healed	No recurrence
Greisser, 2008, Swiss ^[54]	7 yr, M	Oral amoxicillin, 6 d: Rapid improvement	No recurrence
Ledoux, 2009, France ^[55]	4 yr, M	Josamycin 1 mo and desonide for GP: All symptoms subsided	No relapse in 6 mo
Rasi, 2009, Iran ^[56]	4 yr, M	Oral amoxicillin, 10 d: Clinical response within 3 d, healed in 3 wk; GAS negative after 3 wk	No improvement of psoriatic lesions
Block, 2013, United States ^[57]	1. 2 mo, F 2. 4 mo, F	Amoxicillin, 10 d, in both patients	No recurrence in both cases
Theotokatou, 2014, Greece ^[58]	1. 8 yr, M 2. 10 yr, M, brother	Oral cefuroxime and topical mupirocin for both brothers: effective by day 4	
Zhang 2016, Canada ^[3]	1. 4 yr, M 2. 4 yr, M 3. 3 yr, F	1. Oral cefuroxime, 7 d plus topical fucidin 2. Oral cefuroxime, 7 d plus betamethasone for GP 3. Oral cefuroxime, 7 d plus topical fucidin; persistent erythema and discharge	1. 3 mo later: Throat and anus GAS negative; PID cleared 2. 2 wk later, perianal GBS positive: topical Fucidin; 3 mo later: GBS negative and cleared GP 3. Vulvar culture: GCS and GBS, perianal culture: GCS; culture from vaginal introitus: positive GAS: oral amoxicillin, 10 d
Garritsen, 2017, Netherlands ^[60]	19 mo, M	Oral Pen plus mometasone for GP; 4 wk: PID and GP significantly improved	
Serban, present study, Romania	1. 9 yr 4 mo, M 2. 9 yr 6 mo, M 3. 11 yr 9 mo, M	1. Spiramycin and topical mupirocin, 2 wk: improvement after 2 d; perianal culture negative on day 7; completely healed after 12 d 2. Spiramycin, 2 wk: improvement since day 2; negative perianal culture on day 7; completely healed after 1 wk 3. Spiramycin and topical bacitracin plus neomycin, 3 wk: improvement after 5 d; negative perianal culture on day 7; healed completely after 2 wk	1. No recurrence after 2 yr 2. No recurrence after 7 mo 3. No recurrence after 2 mo

F: Female; GAS: Group A beta-hemolytic streptococci; GBS: Group B beta-hemolytic streptococci; GCS: Group C beta-hemolytic streptococci; GP: Guttate psoriasis; IM: Intramuscular; IV: Intravenous; M: Male; Pen: Penicillin; PID: Perianal infectious dermatitis.

atopic dermatitis; chronic dialysis; and, malnutrition.

ETIOLOGY

The vast majority of cases in the pediatric literature are caused by GAS (Tables 1 and 3). It has been considered that the type T28 emm 28 of GAS (one of the most detected types causing PID) harbors unique properties, which may increase the likelihood of perineal infection^[4,5,27,37,41]. However, other agents have been detected as well, like GBS^[3,8,11,26] (such cases include 1 from this author's own experience), group C streptococci (GCS)^[3], group G streptococci (GGS)^[11], *Staphylococcus aureus* (*S. aureus*)^[15,26,32], and *Enterococcus faecalis* (*E. faecalis*)^[58]. Mostafa *et al*^[15] reported 150 children with PID, over a period of 4 mo, from which 35.3% were positive for beta-hemolytic streptococci (BHS) (GAS representing 21.3% and non-GAS representing 18%) and 3.4% for *S. aureus*. In a retrospective 10-year study of patients with PID, 105 BHS were isolated from the perianal area of the same number of patients. GAS, GBS, GCS and

GGS were cultured in 69.5%, 25.7%, 2.8% and 2%, respectively^[24].

PATHOGENESIS

A few theories have been suggested for the infection of the perianal area, especially for GAS. They include spread by hand contact with the oral cavity and then perianal area, deglutition of GAS with dissemination along the gastrointestinal tract, contaminated fomites (communal bathtubs or toilets), and airborne spread^[3,5,79,85,86]. GAS are not considered part of the perianal skin flora^[2] and asymptomatic carriage is exceedingly rare^[22].

Digital oral-anal contact is a well-documented route^[5,8,24]. The perianal area could be infected by scratching with hands containing bacteria from mouth or nose or other skin infected sites. Bacteria could belong to the same person (autoinoculation)^[2] or to other people^[1,5,8,24], either from respiratory tract (aerosols), flatulence^[86] or direct touch (*i.e.*, kisses from a sibling)^[57]. Some children with PID caused by GAS had other members of the family

Table 5 Previous investigations, diagnoses and therapies in children with perianal infectious dermatitis

Name, yr, country	Population size; age; sex	Previous performed investigations and/or suspected diagnosis	Previous therapy
Spear, 1985, United States ^[28]	14; mean age 3.9 yr (range: 1-10 yr); M/F: 3.7/1	2 proctoscopies under general anesthesia, upper gastrointestinal x-ray series, barium enema; anal fissure, IBD, behavior disturbance, psychogenic stool holding, psoriasis, candidiasis, ammoniacal diaper dermatitis	Laxatives, suppositories, hydrocortisone, polymyxin, bacitracin and neomycin, povidone-iodine, triamcinolone
Farmer, 1987, United Kingdom ^[65]	1. 4 yr, M 2. 5 yr, F	1. Anal pinworms (negative) 2. Anal pinworms (negative)	1. Piperazine, miconazole, and hydrocortisone cream 2. Clotrimazole cream
Kokx, 1987, United States ^[4]	31; 7 mo to 8 yr, mean 4.25 ± 1.8 yr; M 77%	Hemorrhoids, poor hygiene, perianal allergy to toilet paper perfumes, rectal fissures, and/or constipation	
Rehder, 1998, United States ^[61]	1. 3 yr, M 2. 3 yr, M 3. 4 yr, M	 3. Pinworms	1. Soaks, topical antifungals and corticosteroids 2. Topical hydrocortisone, nystatin, triamcinolone and zinc oxide 3. Oral cefaclor, with clearing of erythema, but recurrence
Marks, 1988, United States ^[63]	5 yr, M	Pinworms and stool for ova and parasites: negative	Topical A and D ointment, hydrocortisone, ketoconazole
Duhra, 1990, United Kingdom ^[29]	5 yr, M	Considered as possible case of sexual abuse; threadworms, candidiasis, psoriasis and eczema	Treatment for threadworms, candidiasis, psoriasis and eczema
Goodyear, 1991, United Kingdom ^[30]	4 yr, M	Examination under anesthesia and proctoscopy	Stool softeners, stimulant laxatives, topical anesthetics, steroid and antifungal creams
Montemarano, 1993, United States ^[32]	3 yr, M		Topical and oral nystatin
Grant, 1993, United Kingdom ^[10]	20; 5 mo to 12 yr; 75% M	2 cases: suspected Crohn's disease 1 case: suspected sexual abuse	3 patients treated for worms, 7 treated for constipation, 5 topical treatment (steroids, lignocaine, eosin, fucidin)
Guppy, 1993, Australia ^[33]	1. 7 yr, M 2-3. 5 and 2.5 yr 4. 4 yr, M		1. Topical antifungal, antibacterial and steroid creams, oral pyrantel embonate and metronidazole 2-3. Various antifungal, antibacterial and steroid creams, oral pyrantel embonate 4. Local nystatin, hydrocortisone; oral pyrantel embonate
Patrizi, 1994, Italy ^[22]	5; 4-10 yr; 3 M		Topical agents, including steroid cream
Bugatti, 1998, Italy ^[39]	12 yr, M		Topical antifungal agents
Adams, 1999, Canada ^[40]	1 yr, M		Topical corticosteroids and clotrimazole
Roos, 1999, Sweden ^[41]	5 yr, M		Topical steroids
Herbst, 2000, Germany ^[9]	4 yr, M		Various ointments for the last several months
Brilliant, 2000, United States ^[43]	1. 4 yr, M 4. 4 yr, F		1. Topical ointment and baby powder, topical antifungal 4. Topical antifungal
Heidelberger, 2000, Germany ^[45]	1. 6 yr, M 2. 9 yr, M		1. Tannolact seat baths and topical tetracycline 2. Tannolact seat baths and topical clotrimazole
Soulliet, 2000, France ^[13]	7 yr, F	Candidiasis	Nystatin unsuccessful for suspected candidiasis
Lunghi, 2001, Italy ^[47]	Brother (4 yr) and sister (6 yr)		Both: Local and oral antifungal drugs for 4 mo
Mateo, 2002, Spain ^[19]	10; 9 mo to 7 yr; 6 M		4 cases: 2 steroids cream, 1 clotrimazole cream and 1 betamethasone and clotrimazole cream
Reimer, 2004, Sweden ^[50]	1. 4 yr, M 3. 4 yr, F	1. Pinworms (negative)	3. Local ointment (kenacutan)
Jongen, 2008, Germany ^[8]	21; < 14 yr (mean age 6.3 yr), 76% M	Anoscopy and rectoscopy: negative	Topical agents (zinc paste, corticosteroids, antimycotic ointments)
Rasi, 2009, Iran ^[56]	4 yr, M		Topical antibiotics, steroids and antifungal creams, 3 mo
Zhang, 2016, Canada ^[3]	1: 4 yr, M 3: 3 yr, F		1. Topical terbinafine and hydrocortisone acetate 3. Gentle skin care, zinc barrier cream, topical antifungals, corticosteroids, and mupirocin
Garritsen, 2017, Netherlands ^[60]	19 mo, M		Topical corticosteroids and antimycotic agents

Serban, present paper, Romania	1. 9 yr 4 mo, M	1. Psoriasis, pinworms, candidiasis, eczema; Hospitalization in 6 public clinics and 2 private hospitals; upper and lower endoscopy under general anesthesia; magnetic resonance enterography – all negative; considered as Crohn's disease and sent to our clinic	1. Topical antibiotics, steroids, antifungal and anesthetics creams; oral antiallergics
	2. 9 yr 6 mo, M	2. Pinworms, intestinal dysbiosis	2. Oral probiotics and therapy against worms; topical baneocin and neomycin, cortisone and anti-hemorrhoids
	3. 11 yr 9 mo, M	3. Eczema, anal fissure, constipation	3. Oral probiotics, osmotic laxatives and stool softeners; topical hydrocortisone, cicatrizants

F: Female; IBD: Inflammatory bowel disease; M: Male.

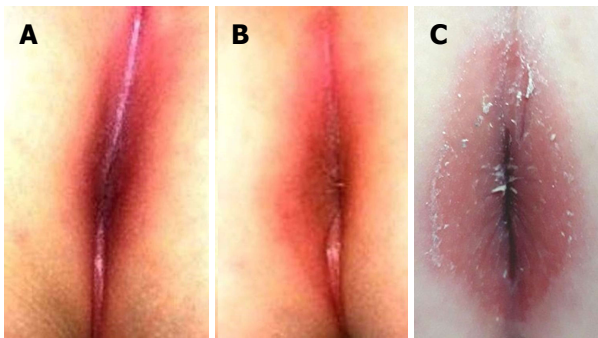


Figure 1 Perianal infectious dermatitis. A, B, C: Well-demarcated perianal erythema; B, C: With white exudate. Personal cases from the author (Elena Daniela Serban).

recently diagnosed with GAS pharyngitis (siblings^[57,61], mother^[38,41] or father^[50]). Self-inoculation has been reported in studies showing positive throat culture for GAS when PID was diagnosed. The rates of isolation of GAS from the throat of these children (with or without concomitant pharyngitis) have varied from 28%^[2] to 38%^[14], 50%^[19], 53.8%^[15], 64%^[4], 80%^[6], 92%^[5] and 95%^[23]. The high pharyngeal carrier frequency found in the studies by Mogielnicki *et al*^[5] and Clegg *et al*^[23] was considered very suggestive for PID, leading to a quick diagnosis (only 9.8 d)^[23]. Also, case reports showed the same finding - concomitant positive throat culture for GAS^[3,13,22,37,47,49,59,61] and 1 case from this author) and presence of *S. aureus* in the anterior nares^[32].

Eradication from pharynx could be more rapid than from the perineal area, explaining the various frequencies^[5]. Conversely, only 6% of children with GAS pharyngitis are anal carriers of GAS^[87]. In one study, the T-types of the pharyngeal and perianal GAS were identical^[4]. Other authors also showed that the same perianal GAS was found in the throat^[15,23,37,61]. Mostafa *et al*^[15] reported 3.4% of PID caused by *S. aureus*, with the same bacteria in the throat in 2.7% of cases.

Children may infect the perianal skin also while using a shared toilet (sitting on it or cleaning the area after touching toilet, without washing hands) and/or communal baths^[4,22,33,36], facts that could also explain the intrafamilial or interfamilial spread^[1,27,37]. During the outbreak in a daycare center, the transmission route was reported to be most likely the common toilet and especially its GAS-

contaminated plastic toilet seat^[37].

Also, it had previously been suggested that oral bacteria can pass intact into the digestive tract and colonize the anus; however, this hypothesis is not accepted anymore^[56].

CLINICAL PRESENTATION

Specifically, symptoms appear in otherwise healthy children, without fever, malaise or other systemic symptoms^[1,33,44]. Symptoms like anal pruritus (itching), painful defecation with consequent retentive constipation, anal pain, mucous (sometimes purulent)^[12,14] and/or bloody anal discharge (blood-streaked stools) are usually present^[2,4-8,10,28,43,59]. Very rarely, abdominal pain (related to defecation or to retention to defecation)^[21], fecal incontinence^[2,21,30] or tenesmus^[21,22] could be associated. Exceptionally, other symptoms have been reported, including fever^[21,44], irritability^[18], diarrhea^[15,36] and muscular pain^[38]. Synthesizing data from the literature (Tables 1 and 3), the following frequencies of symptoms and signs are detected: perianal itching (78%-100%); painful defecation (50%); constipation (47%-58%); blood-streaked stools (21%-60%); purulent secretion (27%); anal fissures (26%-40%); perianal pain (20%); and, mucous discharge at the anal margin (10%)^[4-8,10,11,14,17,20,21].

The hallmark of PID (found in all included cases) is represented by the aspect of the perianal area - superficial, intense edematous vivid red erythema (like "raw beef"), rarely pink, sharply demarcated, extending 2-4 cm around the anus^[1-10]. The area is sometimes extremely tender, rendering physical examination very difficult. White exudate, pseudomembranes and superficial anal fissures or cracks could also be detected^[1,10-12]. Three cases of PID from this author's experience are illustrated in Figure 1. The typical appearance could change, however, after applying various topical creams, rendering the diagnosis more difficult.

Infection can extend to genital organs, resulting in vulvo-vaginitis^[2,3,5,6,13,16,21-23,43,47,50,57,65] or balanitis^[3,22,23,29,33,42,45,50,64], and cultures from these areas grow same type of bacteria^[2,22,29]. Small papules or pustules on the buttocks are suggestive for *S. aureus*^[26,32]. Sometimes, extraperineal rash (mostly papulo-pustular or impetiginous) could also be associated, up to 35.8% in a recent series^[25]. Another cutaneous finding, acral

desquamation (following therapy for PID caused by GAS and concomitant with resolution of PID) was reported by three authors; these included fingers^[42,46,49], toes^[42], and perioral skin^[49]. The presence of acral desquamation has been suggested to be the effect of streptococcal exotoxin^[42,46,49]. Rarely, when PID is diagnosed early, concomitant pharyngitis may be found^[6,21,22,25].

INVESTIGATIONS

Simple methods are required to diagnose PID (Tables 1 and 3). Culture of anal, perianal and perineal swabs represent the best option for diagnosis^[3]. Physicians should specifically ask for *BHS* culture, on blood agar plates, as laboratories do not adequately search for them in the evaluation of routine perianal swabs^[8,11,20,28,57,59]. Culture allows detection of the bacteria causing PID, besides GAS (including *non-GAS*, *S. aureus* and *E. faecalis*)^[3,26,32,58]. Moreover, it allows identification of their sensitivity to antibiotics, given that antibiotic resistance has become a seriously increasing issue across the world. Stool culture is not recommended^[24].

For GAS, the rapid antigen detection test (RADT) of the swab could be used, allowing a quicker diagnosis^[24]. Depending on the method of RADT, the sensitivity for extrapharyngeal GAS ranges from 77.9% to 98.0%, suggesting that this test may represent a rapid, practical and accurate diagnostic tool for point-of-care differentiation of GAS associated PID from other conditions with similar presentations^[88]. A recent French prospective multicenter study showed RADT to have a sensitivity of 98% and a specificity of 72.8%^[16]. However, RADT does not have formal approval for extrapharyngeal testing^[16,57]. A negative RADT result needs additional testing by bacterial culture^[3,23,74].

Sophisticated tests, like pulse field gel electrophoresis, allowing genotyping of the bacteria, are reserved for research studies^[37], especially to determine if types of bacteria are identical in outbreaks.

DIAGNOSIS

As shown, with a high index of suspicion, the simple culture (or RADT) of the perianal skin confirms the PID diagnosis^[28]. Although most patients included in this review were seen primarily by their pediatrician or family physician, only three papers were published by physicians from primary healthcare facilities^[5,7,50]. Most published reports diagnosing PID have come from dermatologists, working in dermatology university centers^[3,15,20,22,31,34,35,40,42,45,52,56,63,79] or hospitals^[29,32,47,55], as well as from those in pediatric dermatology university centers^[49,53,54,60-62] or hospitals^[13,19,26,30]. Also, many of the patients were diagnosed by physicians from pediatric university centers^[6,17,18,21,23,25,27,44,57] or hospitals^[4,10,16,33,36,39,64,65]. There were four reports of PID diagnosed in surgery services^[8,11,51,58]. Only one paper was published, respectively, by authors from a pediatric

gastroenterology clinic^[46], pediatric radiology clinic^[38], pediatric infectious clinic^[14], ear nose and throat clinic^[41] and from an emergency medicine hospital^[43].

Characteristically, a delay in diagnosis is reported by most authors (mean of 6 mo, ranging from 1 mo to 1 year)^[28]. As such, many children undergo unnecessary investigations and therapies^[33]. A few reports showed a 2-year delay to diagnosis^[8,19,62]. However, diagnosis is sometimes established within 1 mo (e.g., 3 wk^[13,19,58,61,65], 2 wk^[7,8,16,25,51,55,63], 10 d^[23,46], 1 wk^[25,37,52], 3 d^[54] and 2 d^[53]). Table 5 presents previous suspected diagnoses and performed tests in children with PID (including the present cases). As shown, PID was misdiagnosed most often as candidiasis^[13,28,29], pinworms^[50,61,65], anal fissure^[4,28], psoriasis^[28,29], possible sexual abuse^[10,29], eczema/atopic dermatitis^[29], constipation^[4], Crohn's disease^[10], inflammatory bowel disease, ammoniacal diaper dermatitis, psychogenic stool holding^[28], threadworms^[29], hemorrhoids, poor hygiene, perianal allergy^[4], and gut dysbiosis. As seen, not only can misdiagnosis lead to improper therapies but also to potential severe consequences on family harmony and to legal issues. Just carrying out anal tests for pinworms appears far less erroneous, costly and/or invasive than performing lower and upper endoscopies under general anesthesia^[8,28,30], upper gastrointestinal X-ray series and barium enema^[28], as well as magnetic resonance enterography.

DIFFERENTIAL DIAGNOSIS

As anticipated from the previous paragraph, differential diagnosis of PID is vast and, unfortunately, patients are commonly overlooked^[4,43,57,58]. Besides the conditions already mentioned, differential diagnosis encompasses seborrheic dermatitis, Langerhans cell histiocytosis, zinc deficiency dermatosis^[43,54,88], intertrigo^[18], redness from vigorous wiping, fecal incontinence^[11], and lichen planus^[1].

DISEASE COURSE AND COMPLICATIONS

PID does not resolve spontaneously. The longer the time until correct diagnosis and therapy, the higher is the risk for discomfort and complications. Complications related to streptococcal infections include impetigo^[13,25,45] and immunological conditions, like post-streptococcal acute glomerulonephritis (commonly known as PSAGN) and rheumatic fever. Although among the included studies, no such immunological complications were found, a urine analysis may be performed to screen for possible PSAGN^[7,79]. GAS-associated PID may trigger acute guttate psoriasis (GP)^[3,9,19,22,48,53,55,60-62,83], plaque-psoriasis^[56] or pustular psoriasis^[77]. Treating PID also resolves the skin disease, as was mostly reported, except for 1 case of GP^[3] and 1 of plaque-psoriasis^[56]. Among the cases with GBS-associated PID, GP developed in 1 child^[3] and one adult^[83]. GP could be determined by stimulation of T cells by superantigens, in GAS infections; however, GBS do not produce superantigenic exotoxins^[3]. In patients with GP, the perianal/perineal area should be carefully inspected,

and cultured when appropriate, to exclude PID as a triggering factor^[20,60].

TREATMENT

Since PID usually goes unrecognized for a long time, patients are erroneously treated for other conditions, as shown in Table 5 (including the present cases). The most used topical agents were antifungal agents^[3,13,16,22,27,31-33,35,36,42,43,47,49,51,61,64,65] and corticosteroids^[3,4,8,10,19,22,28-30,33,40,41,56,60,61]. Other topical agents were represented by antibiotics^[3,10,28,33,45,56], antiseptics, suppositories^[10,28], zinc oxide^[3,4,8], anesthetics^[10,30], kenacutan^[50], tannate^[45], vitamins A and D^[61], antihemorrhoidals and cicatrizants. Oral medication included laxatives^[10,28,30], anthelmintics^[10,33,65], antibiotics^[4,33], nystatin^[32,47], antihistaminic agents and probiotics. A survey on general practitioners from an area in the United Kingdom appears as very illustrative for the various modalities of managing this peculiar condition. After a case with PID was presented, physicians were asked what their management would be at the first consultation. Their answers included "anthelmintics (54%), stool softeners (52%), taking a perianal swab (31%), topical anesthetics (28%), antifungal cream (22%), looking for possible sexual abuse (17%), topical antiseptics (11%), systemic antibiotics (7%), and looking for inflammatory bowel disease (7%)"^[7]. This highlights PID as being largely unknown still; and, more worrisomely, almost one-fifth of the general practitioners considered investigating for possible sexual abuse.

Conversely, an early correct antibiotic therapy leads to a dramatic and rapid improvement of symptoms, in 1 d^[43], 2 d^[2,13,37,39] or 3 d^[2,44,56], with reports showing healing of PID after 4 d^[49,58] (Tables 2 and 4). The actual goal of therapy is represented by complete healing (CH), meaning disappearance of clinical signs and eradication of perianal bacteria. CH has been reported 2 wk^[4,9,14,30,61,62] to 4 wk after starting therapy^[47].

Two studies mentioned obtaining CH with topical antibiotics as a sole therapy (erythromycin^[34] and mupirocin^[31]); however, oral antibiotics are considered the medication of choice^[13,25,79]. Classically, the medication of choice against GAS consisted of oral penicillin (Pen)^[2,4,8,10,12,17,20-22,25,27-30,33,37,45,46,50,53,59-63] (Tables 2 and 4). Duration of Pen therapy ranged from 7 d^[65] to 10 d^[2,4,6,8,12,17,20,27,30,33,36,37,44,45,62], 2 wk^[8,22,33,53,61,63], 3 wk^[10,29,61] and 4 wk^[22]. Amoxicillin has been considered a good alternative^[19,21,43], given for 6 d^[54], 10 d^[4,13,36,39,56,57] or 2 wk^[22]. Other authors used cefaclor^[42], amoxicillin-clavulanate^[11,17], erythromycin^[22], or josamycin^[55]. In many cases, oral antibiotic was used in combination with a topical agent. Pen was associated with topical antibiotics (mupirocin^[20,21,36,40] or fucidin^[9,10,36]) or antiseptics (clioquinol^[45] or polyhexanid^[8]). Amoxicillin was combined with fucidin^[36] or mupirocin^[14,18] and amoxicillin-clavulanate with topical bacitracin^[11]. As for macrolides, erythromycin was associated with mupirocin^[22] and spiramycin was used in the cases belonging to the present

author, in combination with mupirocin and bacitracin plus neomycin, respectively. Cefadroxil was associated with fucidin^[41] and cefuroxime with fucidin^[3] or mupirocin^[58]. Cefuroxime plus topical fucidin was used in PID caused by GAS and *S. aureus*, by GBS and by GCS^[3]. In cases with *S. aureus* only, oral erythromycin and cephalexin were used^[26,32].

It is quite difficult to appreciate the treatment efficacy, since some authors reported only clinical healing, while others considered CH and others did not mention the type of healing. CH was reported after Pen^[22], amoxicillin^[56], cefaclor^[42], Pen combined with fucidin^[9], erythromycin with mupirocin^[22], spiramycin with mupirocin or with bacitracin plus neomycin. More details about the CH are presented in Tables 2 and 4^[4,6,14,18].

Some patients required a second course of antibiotic, either to cure symptoms or to eradicate perianal bacteria, or both. Some authors preferred to use the same antibiotic (Pen^[2,17,20,29], amoxicillin^[22] or cephalexin^[26]), detailed in Tables 2 and 4. Other authors chose a different antibiotic for the second course. After ineffective oral Pen, erythromycin^[22,61], cefaclor^[37] or clarithromycin^[17,27] determined CH. In a GCS-associated PID case, after oral cefuroxime plus topical fucidin being ineffective, oral amoxicillin lead to CH^[3].

The only published RCT, by Meury *et al*^[12], compared 15 children treated with oral Pen with 14 cases with cefuroxime, all with GAS-associated PID. Both clinical improvement and eradication of perianal GAS were significantly higher with cefuroxime *versus* Pen (Table 2). However, the study was not blinded and there was no follow-up after the end of treatment, precluding evaluation of optimal duration for the cefuroxime therapy^[12].

PROGNOSIS

From the data presented, it appears that most cases are easy to cure (*i.e.*, reaching CH). However, recurrence (clinical and/or bacteriological) may occur and a repeated course of antibiotics is required^[4]. Assessing recurrence rate appears rather difficult, as most cases did not have a precise follow-up period. No clinical recurrence was reported after oral Pen^[30], amoxicillin-clavulanate^[11] and cefadroxil plus topical fucidin^[11]. No clinical and bacteriological recurrence was detected after topical mupirocin^[31] and josamycin^[17]. In the study by Kokx *et al*^[4], the 39% relapses were treated with Pen. In children treated with amoxicillin plus mupirocin, the recurrence rate varied between 11%^[14] and 27%^[18]. In a series of 21 cases treated with oral Pen plus topical polihexanid, only 5% showed recurrence^[8].

In one of the largest published studies of GAS-associated PID (81 cases), recurrence was detected in 32% of cases, significantly higher after Pen or amoxicillin *vs* a beta-lactamase-resistant antibiotic (Table 2). A meta-analysis performed by the same authors showed that the pooled recurrence rate after Pen or amoxicillin was significantly higher than after a beta-lactamase-resistant antibiotic (odds ratio: 2.39, 95%CI: 1.18-4.81)^[25]. In

the largest (157 cases with GAS-associated PID) and most recent series, patients were treated with various antibiotics. The clinical recurrence rate, 6 mo after the first episode, was much higher after using cephalexin *versus* amoxicillin (Table 2). Recurrence after amoxicillin was predicted by a delayed diagnosis and having a sibling with PID around the time of the first episode^[23].

Recurrences appearing soon after therapy may be due to poor compliance with antibiotics or their inadequate dosage. Alternatively, some recurrences could be the result of a reinfection in the context of a continuous exposure (intrafamilial or close contact), due to poor hygiene^[4]. Therefore, in those with frequent relapses, it is recommended to screen (and eventually treat) other members of the family^[57]. Improvement of personal (hands washing, individual use of toothbrush, towels, toilets, etc.) and collective hygiene is indispensable.

CONCLUSION

To the best of the author's knowledge, this is the first narrative review of all published available pediatric cases with PID, to date. Although the clinical characteristics of PID are well-defined, it still remains a misdiagnosed entity, with an underestimated frequency. PID could appear at any age and affect females as well. Given its infectious origin, PID may have intra- and/or interfamily spread. The vast majority of cases are caused by GAS; however, other BHS (like GBS, GCS and GGS) and *S. aureus* have been described. These bacteria could also be found in the upper respiratory tract. Since PID may mimic other common conditions with skin manifestations, laboratory tests are required for correct diagnosis. RADT could suffice to identify GAS, but bacterial culture is the most reliable tool for diagnosis. If not properly diagnosed and treated, PID has a chronic, unrelmitting course.

Oral Pen or amoxicillin could be used for the initial treatment of BHS-associated PID; however, the recurrence rate is high (up to 40%). Various beta-lactamase-resistant antibiotics could be used instead (like cephalosporines, amoxicillin-clavulanate, macrolides and clindamycin). Combining oral antibiotics with topical antiseptics or antibiotics may accelerate bacterial clearance. Duration of therapy should be 14-21 d. Therapeutic efficacy should be appreciated both clinically and bacteriologically; throat culture should also be repeated, if it was positive. Recurrence rates of PID remain high. Improvement of personal and collective hygiene is essential.

RESEARCH PERSPECTIVES

Prospective well-designed (multicenter) clinical trials are required in order to detect the incidence of this condition. Moreover, randomized controlled studies, with adequate follow-up, should be performed in order to formulate the optimum personalized antibiotic therapy (oral alone or in association with topical medication) able to induce complete healing and prevent recurrences. An interesting topic of future research will be determining

whether the same bacteria cause recurrences.

REFERENCES

1. Juern AM, Drolet BA. Cutaneous bacterial infections. In: Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, editors. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Elsevier, 2016: 3209
2. Amren DP, Anderson AS, Wannamaker LW. Perianal cellulitis associated with group A streptococci. *Am J Dis Child* 1966; **112**: 546-552 [PMID: 5928818 DOI: 10.1001/archpedi.1966.02090150090007]
3. Zhang C, Haber RM. The ABCs of Perineal Streptococcal Dermatitis. *J Cutan Med Surg* 2017; **21**: 102-107 [PMID: 27628908 DOI: 10.1177/1203475416670369]
4. Kokx NP, Comstock JA, Facklam RR. Streptococcal perianal disease in children. *Pediatrics* 1987; **80**: 659-663 [PMID: 3313256]
5. Mogielnicki NP, Schwartzman JD, Elliott JA. Perineal group A streptococcal disease in a pediatric practice. *Pediatrics* 2000; **106**: 276-281 [PMID: 10920151 DOI: 10.1542/peds.106.2.276]
6. Echeverría Fernández M, López-Menchero Oliva JC, Marañón Pardillo R, Míguez Navarro C, Sánchez Sánchez C, Vázquez López P. [Isolation of group A beta-hemolytic Streptococcus in children with perianal dermatitis]. *An Pediatr (Barc)* 2006; **64**: 153-157 [PMID: 16527068 DOI: 10.1157/13084175]
7. Lehman R, Pinder S. Streptococcal perianal infection in children. *BMJ* 2009; **338**: b1517 [PMID: 19416994 DOI: 10.1136/bmj.b1517]
8. Jongen J, Eberstein A, Peleikis HG, Kahlke V, Herbst RA. Perianal streptococcal dermatitis: an important differential diagnosis in pediatric patients. *Dis Colon Rectum* 2008; **51**: 584-587 [PMID: 18324440 DOI: 10.1007/s10350-008-9237-0]
9. Herbst RA, Hoch O, Kapp A, Weiss J. Guttate psoriasis triggered by perianal streptococcal dermatitis in a four-year-old boy. *J Am Acad Dermatol* 2000; **42**: 885-887 [PMID: 10767696 DOI: 10.1016/S0190-9622(00)90263-9]
10. Grant HW, MacKinlay GA, Bisset WH, Uttley WS. Perianal cellulitis in children caused by group A streptococcus. *Pediatr Surg Int* 1993; **8**: 410-411 [DOI: 10.1007/BF00176730]
11. Wright JE, Butt HL. Perianal infection with beta haemolytic streptococcus. *Arch Dis Child* 1994; **70**: 145-146 [PMID: 8129441 DOI: 10.1136/adc.70.2.145]
12. Meury SN, Erb T, Schaad UB, Heininger U. Randomized, comparative efficacy trial of oral penicillin versus cefuroxime for perianal streptococcal dermatitis in children. *J Pediatr* 2008; **153**: 799-802 [PMID: 18692203 DOI: 10.1016/j.jpeds.2008.06.035]
13. Souillet AL, Truchot F, Jullien D, Dumas V, Faure M, Floret D, Claudy A. [Perianal streptococcal dermatitis]. *Arch Pediatr* 2000; **7**: 1194-1196 [PMID: 11109946 DOI: 10.1016/S0929-693X(00)00129-9]
14. Barzilai A, Choen HA. Isolation of group A streptococci from children with perianal cellulitis and from their siblings. *Pediatr Infect Dis J* 1998; **17**: 358-360 [PMID: 9576401 DOI: 10.1097/00006454-199804000-00024]
15. Mostafa WZ, Arnaut HH, el-Lawindi MI, el-Abidin YM. An epidemiologic study of perianal dermatitis among children in Egypt. *Pediatr Dermatol* 1997; **14**: 351-354 [PMID: 9336803 DOI: 10.1111/j.1525-1470.1997.tb00979.x]
16. Cohen R, Levy C, Bonacorsi S, Wollner A, Koskas M, Jung C, Béchet S, Chalumeau M, Cohen J, Bidet P. Diagnostic accuracy of clinical symptoms and rapid diagnostic test in group A streptococcal perianal infections in children. *Clin Infect Dis* 2015; **60**: 267-270 [PMID: 25313248 DOI: 10.1093/cid/ciu794]
17. Landolt M, Heininger U. Prevalence of perianal streptococcal dermatitis in children and adolescents. *Praxis (Bern 1994)* 2005; **94**: 1467-1471 [PMID: 16209362 DOI: 10.1024/0369-8394.94.38.1467]
18. Shouval DS, Schurr D, Nussinovitch M. Presentation of perianal group A streptococcal infection as irritability among children. *Pediatr Dermatol* 2008; **25**: 568-570 [PMID: 18950404 DOI: 10.1111/j.1525-1470.2008.00737.x]
19. Mateo JR, Carrero González PA, Pérez ES. Dermatitis estreptocócica perianal. *Actas Dermosifiliogr* 2002; **93**: 243-246 [DOI: 10.1016/S0001-7310(02)76565-4]
20. Krol AL. Perianal streptococcal dermatitis. *Pediatr Dermatol* 1990; **7**: 97-100 [PMID: 2359737 DOI: 10.1111/j.1525-1470.1990.tb00662.x]

- 21 **García Osés I**, Martínez de Zabarte Fernández JM, Puig García C, Arnal Alonso JM. Pensando en la dermatitis perianal. *Pediatría Atención Primaria* 2015; **17**: 51-55 [DOI: 10.4321/S1139-76322015000100012]
- 22 **Patrizi A**, Costa AM, Fiorillo L, Neri I. Perianal streptococcal dermatitis associated with guttate psoriasis and/or balanoposthitis: a study of five cases. *Pediatr Dermatol* 1994; **11**: 168-171 [PMID: 8041660 DOI: 10.1111/j.1525-1470.1994.tb00574.x]
- 23 **Clegg HW**, Giftos PM, Anderson WE, Kaplan EL, Johnson DR. Clinical Perineal Streptococcal Infection in Children: Epidemiologic Features, Low Symptomatic Recurrence Rate after Treatment, and Risk Factors for Recurrence. *J Pediatr* 2015; **167**: 687-93.e1-2 [PMID: 26095284 DOI: 10.1016/j.jpeds.2015.05.034]
- 24 **Šterbenc A**, Seme K, Lah LL, Točkova O, Kamhi Trop T, Švent-Kučina N, Pirš M. Microbiological characteristics of perianal streptococcal dermatitis: a retrospective study of 105 patients in a 10-year period. *Acta Dermatovenol Alp Pannonica Adriat* 2016; **25**: 73-76 [PMID: 28006879 DOI: 10.15570/actaapa.2016.21]
- 25 **Olson D**, Edmonson MB. Outcomes in children treated for perineal group A beta-hemolytic streptococcal dermatitis. *Pediatr Infect Dis J* 2011; **30**: 933-936 [PMID: 21747323 DOI: 10.1097/INF.0b013e318228492a]
- 26 **Heath C**, Desai N, Silverberg NB. Recent microbiological shifts in perianal bacterial dermatitis: Staphylococcus aureus predominance. *Pediatr Dermatol* 2009; **26**: 696-700 [PMID: 20199443 DOI: 10.1111/j.1525-1470.2009.01015.x]
- 27 **Petersen JP**, Kaltoft MS, Misfeldt JC, Schumacher H, Schønheyder HC. Community outbreak of perianal group A streptococcal infection in Denmark. *Pediatr Infect Dis J* 2003; **22**: 105-109 [PMID: 12586971 DOI: 10.1097/01.inf.0000048907.22286.b5]
- 28 **Spear RM**, Rothbaum RJ, Keating JP, Blaufuss MC, Rosenblum JL. Perianal streptococcal cellulitis. *J Pediatr* 1985; **107**: 557-559 [PMID: 4045605 DOI: 10.1016/S0022-3476(85)80019-6]
- 29 **Duhra P**, Ilchyshyn A. Perianal streptococcal cellulitis with penile involvement. *Br J Dermatol* 1990; **123**: 793-796 [PMID: 2265096 DOI: 10.1111/j.1365-2133.1990.tb04199.x]
- 30 **Goodyear HM**, Knowles L, Harper JJ. Faecal incontinence due to perianal cellulitis. *Acta Paediatr Scand* 1991; **80**: 1107-1108 [PMID: 1750350 DOI: 10.1111/j.1651-2227.1991.tb11794.x]
- 31 **Medina S**, Gómez MI, de Misa RF, Ledo A. Perianal streptococcal cellulitis: treatment with topical mupirocin. *Dermatology* 1992; **185**: 219 [PMID: 1446090 DOI: 10.1159/000247453]
- 32 **Montemarano AD**, James WD. Staphylococcus aureus as a cause of perianal dermatitis. *Pediatr Dermatol* 1993; **10**: 259-262 [PMID: 8415304 DOI: 10.1111/j.1525-1470.1993.tb00372.x]
- 33 **Guppy DH**. Perianal group A streptococcal infection. *J Paediatr Child Health* 1993; **29**: 144-145 [PMID: 8489795 DOI: 10.1111/j.1440-1754.1993.tb00468.x]
- 34 **Paradisi M**, Cianchini G, Angelo C, Conti G, Puddu P. Efficacy of topical erythromycin in treatment of perianal streptococcal dermatitis. *Pediatr Dermatol* 1993; **10**: 297-298 [PMID: 8415314 DOI: 10.1111/j.1525-1470.1993.tb00384.x]
- 35 **Paradisi M**, Cianchini G, Angelo C, Conti G, Puddu P. Perianal streptococcal dermatitis: two familial cases. *Cutis* 1994; **54**: 341-342 [PMID: 7835063]
- 36 **van Zeijl JH**, Korver CR. [Perianal streptococcal dermatitis in children]. *Ned Tijdschr Geneesk* 1996; **140**: 2191-2193 [PMID: 8984357]
- 37 **Saxén H**, Muotiala A, Rostila T, Vuopio-Varkila J. Outbreak of perianal Streptococcus pyogenes infection in a day-care center. *Pediatr Infect Dis J* 1997; **16**: 247-249 [PMID: 9041610 DOI: 10.1097/00006454-199702000-00016]
- 38 **Berlin SC**, Morrison SC, Myers MT, Sivitt CJ, Weinert DM. Pediatric case of the day. Streptococcal myositis and perianal cellulitis. *AJR Am J Roentgenol* 1997; **169**: 303, 306-307 [PMID: 9207558 DOI: 10.2214/ajr.169.1.9207558]
- 39 **Bugatti L**, Filosa G, Ciattaglia G. Perianal dermatitis in a child. Perianal streptococcal dermatitis (PSD). *Arch Dermatol* 1998; **134**: 1147, 1150 [PMID: 9762032 DOI: 10.1001/archderm.134.9.1145-c]
- 40 **Adams SP**. Dermacase. Perianal streptococcal dermatitis. *Can Fam Physician* 1999; **45**: 2059, 2066 [PMID: 10509216]
- 41 **Roos K**, Lind L, Holm SE, Grahn-Håkansson E. Perianal streptococcal dermatitis. The possible protective role of alpha-streptococci against spread and recurrence of group A streptococcal throat infection. *Scand J Prim Health Care* 1999; **17**: 46-48 [PMID: 10229993 DOI: 10.1080/028134399750002890]
- 42 **Vélez A**, Moreno JC. Febrile perianal streptococcal dermatitis. *Pediatr Dermatol* 1999; **16**: 23-24 [PMID: 10027994 DOI: 10.1046/j.1525-1470.1999.99006.x]
- 43 **Brilliant LC**. Perianal streptococcal dermatitis. *Am Fam Physician* 2000; **61**: 391-393, 397 [PMID: 10670505]
- 44 **Balasubramanian S**, Padmasani LN, Mouli NC. Perianal streptococcal dermatitis. *Indian Pediatr* 2000; **37**: 433-435 [PMID: 10781241]
- 45 **Heidelberger A**, Cremer H, Ring J, Abeck D. [Perianal streptococcal dermatitis]. *Hautarzt* 2000; **51**: 86-89 [PMID: 10743579 DOI: 10.1007/s001050050018]
- 46 **Nowicki MJ**, Bishop PR, Parker PH. Digital desquamation--a new finding in perianal streptococcal dermatitis. *Clin Pediatr (Phila)* 2000; **39**: 237-239 [PMID: 10791137 DOI: 10.1177/000992280003900408]
- 47 **Lunghi F**, Finzi M, Frati C. Two familial cases of perianal streptococcal dermatitis. *Cutis* 2001; **68**: 183-184 [PMID: 11579781]
- 48 **Romano I**, Venturi C, Bassissi P. Perianal streptococcal dermatitis and guttate psoriasis. Case report. *Eur J Pediatr Dermatol* [Internet] 2002; **2**: 93-96
- 49 **Huang TJ**, Liu TY, Chen FL. Perianal streptococcal dermatitis. *Dermatol Sin* [Internet] 2003; **21**: 142-145
- 50 **Reimer M**. Perianal/vulvovaginal/penile streptococcal infection. A childhood disease easily diagnosed with rapid testing. *Lakartidningen* 2004; **101**: 3327-3328 [PMID: 15543955]
- 51 **Takeshita T**, Gondo H, Tsuji G, Furue M. Three cases of perianal streptococcal dermatitis. *Nishi Nihon Hifuka* 2006; **68**: 644-647 [DOI: 10.2336/nishinihonhifu.68.644]
- 52 **Usuki K**. Perianal streptococcal dermatitis in father and daughter. *Nishi Nihon Hifuka* 2006; **68**: 512-514 [DOI: 10.2336/nishinihonhifu.68.512]
- 53 **Ulger Z**, Gelenava T, Kosay Y, Darcan S. Acute guttate psoriasis associated with streptococcal perianal dermatitis. *Clin Pediatr (Phila)* 2007; **46**: 70-72 [PMID: 17164513 DOI: 10.1177/1084713806297157]
- 54 **Greisser J**, Niederer-Loher A, Kernland Lang K. Perianal erythema in a child--group A streptococci?!. *Praxis (Bern 1994)* 2008; **97**: 143-145 [PMID: 18549015 DOI: 10.1024/1661-8157.97.3.143]
- 55 **Ledoux M**, Chazerain V, Saiag P, Mahé E. [Streptococcal perianal dermatitis and guttate psoriasis]. *Ann Dermatol Vénereol* 2009; **136**: 37-41 [PMID: 19171228 DOI: 10.1016/j.annder.2008.06.013]
- 56 **Rasi A**, Pour-Heidari N. Association between plaque-type psoriasis and perianal streptococcal cellulitis and review of the literature. *Arch Iran Med* 2009; **12**: 591-594 [PMID: 19877754]
- 57 **Block SL**. Perianal dermatitis: much more than just a diaper rash. *Pediatr Ann* 2013; **42**: 12-14 [PMID: 23316826 DOI: 10.3928/00904481-20121221-05]
- 58 **Theotokatou S**, Saravakos P, Niopa M, Kallinikos A. Bacterial perianal dermatitis caused by Enterococcus faecalis with intrafamily spread: Report of a rare case. *J Pediatr Infect Dis* 2015; **9**: 043-046 [DOI: 10.3233/JPI-140407]
- 59 **Hirschfeld AJ**. Two family outbreaks of perianal cellulitis associated with group A beta-hemolytic streptococci. *Pediatrics* 1970; **46**: 799-802 [PMID: 4991446]
- 60 **Garritsen FM**, Kraag DE, de Graaf M. Guttate psoriasis triggered by perianal streptococcal infection. *Clin Exp Dermatol* 2017; **42**: 536-538 [PMID: 28543851 DOI: 10.1111/ced.13129]
- 61 **Rehder PA**, Eliezer ET, Lane AT. Perianal cellulitis. Cutaneous group A streptococcal disease. *Arch Dermatol* 1988; **124**: 702-704 [PMID: 3129994 DOI: 10.1001/archderm.124.5.702]
- 62 **Honig PJ**. Guttate psoriasis associated with perianal streptococcal disease. *J Pediatr* 1988; **113**: 1037-1039 [PMID: 3057157 DOI: 10.1016/S0022-3476(88)80577-8]
- 63 **Marks VJ**, Maksimik M. Perianal streptococcal cellulitis. *J Am Acad Dermatol* 1988; **18**: 587-588 [PMID: 3280624 DOI: 10.1016/

- S0190-9622(88)80298-6]
- 64 **Guerrero Vázquez J**, Sebastián Planes M, de Paz Aparicio P, Garcés Ramos A, Luengo Casasola JL, Valera Pascual MT, Peñalba Moreno G, Olmedo Sanlaureano S. Streptococcal perianal disease and balanoposthitis. *An Esp Pediatr* 1989; **30**: 198-200 [PMID: 2729790]
 - 65 **Farmer G**. Perianal infection with group A streptococcus. *Arch Dis Child* 1987; **62**: 1169-1170 [PMID: 3318714 DOI: 10.1136/adc.62.11.1169]
 - 66 **Castro R**, Rivera J. Recurrent perianal streptococcal cellulitis. *Del Med J* 1988; **60**: 421-422 [PMID: 3044853]
 - 67 **Ellett ML**. Anusitis associated with group A beta-hemolytic streptococci. *Gastroenterol Nurs* 1989; **12**: 53-54 [PMID: 2487812 DOI: 10.1097/00001610-198907000-00014]
 - 68 **Putto-Laurila A**, Ruuskanen O, Mertsola J. Perianal infection caused by group A beta-hemolytic Streptococcus on children. *Duodecim* 1995; **111**: 361-364 [PMID: 8654306]
 - 69 **Broberg A**, Mobacken H. Perianal streptococcal dermatitis is a possibility in therapy-resistant anal redness. *Lakartidningen* 1992; **89**: 3955-3956 [PMID: 1461011]
 - 70 **Teillac-Hamel D**, de Prost Y. Perianal streptococcal dermatitis in children. *Eur J Dermatol* 1992; **2**: 71-74
 - 71 **Neri I**, Bardazzi F, Marzaduri S, Patrizi A. Perianal streptococcal dermatitis in adults. *Br J Dermatol* 1996; **135**: 796-798 [PMID: 8977685 DOI: 10.1046/j.1365-2133.1996.d01-1082.x]
 - 72 **Scheiba N**, Hartschuh W. Perianal streptococcal dermatitis caused by beta-hemolytic group G streptococci in two adults. *Hautarzt* 2011; **62**: 131-133 [PMID: 20835811 DOI: 10.1007/s00105-010-1977-9]
 - 73 **Abdolrasouli A**, Hemmati Y, Amin A, Roushan A, Butler I. Lancefield group G Streptococcus dysgalactiae subsp. equisimilis: an unusual aetiology of perianal streptococcal dermatitis acquired from heterosexual oral-anal intercourse. *Int J STD AIDS* 2012; **23**: 911-912 [PMID: 23258838 DOI: 10.1258/ijsa.2012.012112]
 - 74 **Kahlke V**, Jongen J, Peleikis HG, Herbst RA. Perianal streptococcal dermatitis in adults: its association with pruritic anorectal diseases is mainly caused by group B Streptococci. *Colorectal Dis* 2013; **15**: 602-607 [PMID: 23216793 DOI: 10.1111/codi.12089]
 - 75 **Maatouk I**, Moutran R. Perianal streptococcal dermatitis due to Streptococcus dysgalactiae ssp. Equisimilis in a man who has sex with men. *J Sex Med* 2013; **10**: 2351-2352 [PMID: 23845120 DOI: 10.1111/jsm.12243]
 - 76 **Mahendran R**, Highet AS. Acute perianal streptococcal infection in an adult. *Clin Exp Dermatol* 2002; **27**: 69 [PMID: 11952678 DOI: 10.1046/j.0307-6938.2001.00936.x]
 - 77 **Maiolo C**, Kwok SM, Ross C, Ibbetson J. Perianal streptococcal infection precipitating pustular psoriasis in an adult. *JAAD Case Rep* 2016; **2**: 281-283 [PMID: 27504479 DOI: 10.1016/j.jidcr.2016.05.010]
 - 78 **Orden B**, Manjavacas CG, Mombiola T, Martinez R, Franco A. Streptococcal perianal disease in two healthy adult women. *Clin Microbiol Infect* 1996; **2**: 142 [PMID: 11866832 DOI: 10.1111/j.1469-0691.1996.tb00220.x]
 - 79 **Herbst R**. Perineal streptococcal dermatitis/disease: recognition and management. *Am J Clin Dermatol* 2003; **4**: 555-560 [PMID: 12862498 DOI: 10.2165/00128071-200304080-00005]
 - 80 **Combs JT**. Perianal streptococcal disease. *Clin Pediatr (Phila)* 2000; **39**: 500 [PMID: 10961825 DOI: 10.1177/000992280003900814]
 - 81 **Bafounta ML**, Bloch P, Kernbaum S, Saia P. Group A beta-hemolytic Streptococcus: an unusual etiology of perianal dermatitis in an adult?. *Ann Dermatol Venereol* 1998; **125**: 902-904 [PMID: 9922865]
 - 82 **Tonkovic-Capin V**, Fleming MG, Kleven-Kranz K, Lund MR. Vulvovaginitis and perineal cellulitis due to group A streptococcus in an adult woman. *Arch Dermatol* 2005; **141**: 790-792 [PMID: 15967936 DOI: 10.1001/archderm.141.6.790]
 - 83 **Ergin S**, Elçin G, Sahin S. Guttate psoriasis triggered by perianal cellulitis due to group B streptococci [Turkish]. *Turkish J Dermatology [Internet]* 2009; **3**: 70-72
 - 84 **Kallini JR**, Cohen PR. Perianal and periumbilical dermatitis: Report of a woman with group G streptococcal infection and review of perianal and periumbilical dermatoses. *Dermatol Online J* 2013; **19**: 3 [PMID: 24021363]
 - 85 **McIntyre DM**. An epidemic of Streptococcus pyogenes puerperal and postoperative sepsis with an unusual carrier site—the anus. *Am J Obstet Gynecol* 1968; **101**: 308-314 [PMID: 4967751 DOI: 10.1016/0002-9378(68)90056-2]
 - 86 **Schaffner W**, Lefkowitz LB Jr, Goodman JS, Koenig MG. Hospital outbreak of infections with group A streptococci traced to an asymptomatic anal carrier. *N Engl J Med* 1969; **280**: 1224-1225 [PMID: 4889553 DOI: 10.1056/NEJM196905292802209]
 - 87 **Asnes RS**, Vail D, Grebin B, Sprunt K. Anal carrier rate of group A beta-hemolytic streptococci in children with streptococcal pharyngitis. *Pediatrics* 1973; **52**: 439-441 [PMID: 4581122]
 - 88 **Clegg HW**, Dallas SD, Roddey OF, Martin ES, Swetenburg RL, Koonce EW, Felkner MB, Ryan AG, Presbyterian Pediatric Research Group. Extrapharyngeal group A Streptococcus infection: diagnostic accuracy and utility of rapid antigen testing. *Pediatr Infect Dis J* 2003; **22**: 726-731 [PMID: 12913775 DOI: 10.1097/01.inf.0000078835.72497.ab]

P- Reviewer: Agrawal A, Nkachukwu SN S- Editor: Ji FF
L- Editor: A E- Editor: Yin SY





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>



World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2018 November 12; 7(5): 105-110





EDITORIAL

- 105 Promptly reporting of critical laboratory values in pediatrics: A work in progress

Sergi C

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Pediatrics*, Tuna Kenar, MD, MSc, Assistant Professor, Doctor, Otolaryngology Clinic, Private Denizli Cerrahi Hospital, Denizli 20010, Turkey

AIM AND SCOPE

World Journal of Clinical Pediatrics (*World J Clin Pediatr*, *WJCP*, online ISSN 2219-2808, DOI: 10.5409) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCP covers a variety of clinical medical topics, including fetal diseases, inborn, newborn diseases, infant diseases, genetic diseases, diagnostic imaging, endoscopy, and evidence-based medicine and epidemiology. Priority publication will be given to articles concerning diagnosis and treatment of pediatric diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJCP*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Clinical Pediatrics is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Yun-XiaoJian Wu*
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Ying Dou*
Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL

World Journal of Clinical Pediatrics

ISSN

ISSN 2219-2808 (online)

LAUNCH DATE

June 8, 2012

EDITORS-IN-CHIEF

Consolato M Sergi, FRCP(C), MD, PhD, Professor, Department of Lab Medicine and Pathology, University of Alberta, Alberta T6G 2B7, Canada

Toru Watanabe, MD, PhD, Professor, Department of Pediatrics, Niigata City General Hospital, Niigata 950-1197, Japan

EDITORIAL BOARD MEMBERS

All editorial board members resources online at <http://www.wjnet.com/2219-2808/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director
World Journal of Clinical Pediatrics
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjnet.com>

PUBLISHER

Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjnet.com>

PUBLICATION DATE

November 12, 2018

COPYRIGHT

© 2018 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS

<http://www.wjnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION

<http://www.f6publishing.com>

Promptly reporting of critical laboratory values in pediatrics: A work in progress

Consolato Sergi

Consolato Sergi, Department of Laboratory Medicine and Pathology, Stollery Children's Hospital, University of Alberta, Edmonton, AB T6G 2B7, Canada

ORCID number: Consolato Sergi (0000-0002-2779-7879).

Author contributions: Sergi C conceived the study, drafted the manuscript and approved the final version of the article.

Conflict-of-interest statement: The author has no conflict of interest to declare in a relationship with the topic discussed in this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Consolato Sergi, FRCP (C), MD, MSc, PhD, Full Professor, Department of Laboratory Medicine and Pathology, Stollery Children's Hospital, University of Alberta, Edmonton, AB T6G 2B7, Canada. sergi@ualberta.ca
Telephone: +1-780-4077951

Received: May 22, 2018

Peer-review started: May 23, 2018

First decision: June 14, 2018

Revised: September 30, 2018

Accepted: October 17, 2018

Article in press: October 17, 2018

Published online: November 12, 2018

in clinical pediatrics. Pre-analytical, analytical, and post-analytical matters will consolidate or undermine the fate of any laboratory process. Pre-analytical issues need to be cleared off before the laboratory physician can dispatch the result to the pediatrician in charge. Once it is cleared off, the classification of essential laboratory results is paramount. It is more than an academic exercise and may be subdivided in the order of priority we handle it to inform promptly and safely the primary physicians. Currently, we are applying new modes of making sure relevant information is transmitted without interrupting the standard workflow of the primary physicians in charge for the child, who eventually need a fast line of action for results that may be life-threatening.

Key words: Communication; Laboratory; Healthcare; Prioritization; Quality

© The Author(s) 2018. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Communication is crucial in pediatrics, not only in the emergency departments. A fast line of action needs to be in place but needs to rely on pediatric laboratory physicians. The interaction between pediatrics and pediatric laboratory will build a center of excellence identifying critical values that need to be transmitted promptly from the bench to bedside.

Sergi C. Promptly reporting of critical laboratory values in pediatrics: A work in progress. *World J Clin Pediatr* 2018; 7(5): 105-110 Available from: URL: <http://www.wjgnet.com/2219-2808/full/v7/i5/105.htm> DOI: <http://dx.doi.org/10.5409/wjcp.v7.i5.105>

Abstract

In the 21st century, the determination of alert thresholds remains the most challenging and controversial issue

INTRODUCTION

Children's hospitals are very busy healthcare institutions that have targets to meet regarding quality

Table 1 The Sydney Triage to Admission Risk Toll examples in pediatrics

Critical (must know now): Amniotic fluid, blood culture, hemoglobin, pH, sodium, potassium
Urgent (must know): Coombs test for newborn hemolysis
Important (should know): Sideremia (iron)

care and waiting list probably not comparable to any other healthcare institutions. Children's hospitals are unique institutions and provide immediate attention to thousands of newborns and kids every year. The application of correct triage protocols is crucial to avoid chaos^[1-5]. Risk-stratification is essential for the accurate management of diseases. The term triage has been used, and we are accustomed to using it in several disciplines to better manage sick patients. In clinics, triage is the assignment in a determinate time frame of degrees of urgency to a different degree of body/mind illnesses or wound/damage to choose the appropriate order of treatment of patients in non-war settings or casualties in a disaster or war setting. Triage has its origin during the wars of Napoleon Bonaparte arising from the terrific work of Dominique Jean Larrey (1766, Baudéan, France - 1842, Lyon). Further, the term "triage" was used during World War I (WWI)^[6]. At this war, the personnel classified the wounded soldiers into three categories according to the degree of injury and potential outcome. The first category entailed victims "who are likely to survive", probably irrespective of what kind of therapy they receive. The second category addressed the victims who were "unlikely to survive", apparently unrelatedly of what therapy they could receive, and, finally, the third category included injured soldiers for whom immediate care might make a positive difference in the outcome. It is paramount to understand that the third category is critical. Many emergency medical services (EMS) systems, worldwide, still use a similar model^[7-13]. First responders may use START, which is an acronym for simple triage and rapid treatment^[14-18]. Although criticized and, sometimes, vehemently discussed, the START is a relatively proper procedure. It is used by first personnel to rapidly classify victims during a mass casualty incident according to the severity of the injury (immediate/red, delayed/yellow/walking wounded/minor/green, and deceased/expectant/black)^[18-21]. Since 1983, the year when staff members of Hoag Hospital and Newport Beach Fire Department located in California, developed START, this triage protocol or its modified version is currently widely used in the United States and Canada^[16,21-24]. Similarly, laboratory diagnostics has faced the importance to establish laboratory triage system. Doubtlessly, laboratory diagnostics play a significant role in the correct triage of sick children. Values associated with imminent danger/death of the child (unless acted upon promptly) require to be identified as critical values and need to be punctually referred to the EMS personnel or attending physicians.

CRITICAL VALUES IN LABORATORY DIAGNOSTICS

The procedures of laboratory diagnostics do play a central role in clinical decision making and managing the care of numerous pediatric disorders, particularly life-threatening diseases. A mixture of issues is entailed in the total quality of the testing process, beginning with the appropriateness of test ordering in pre-analytical phase of the process and concluding with the timely and efficient communication of test results to the physicians who oversee the pediatric patient in the post-analytical phase of the process^[25]. Numerous studies point to the sensitive time's frames of the pre-analytical and post-analytical phases for most of the diagnostic errors^[26-30]. The identification and effective communication of the "highly abnormal" values have raised the threshold of attention of numerous physicians because this activity is essential to good laboratory practice and for the accreditation of the hospitals. Despite several efforts in improving laboratory standardization using several accreditation models, the improvement of laboratory standardization, effectiveness, and efficiency is an ongoing quality process, and the list of the harmonized critical values in pediatrics is a continuing debate. Probably, first and foremost risk-stratifying patients regarding sepsis is a mandatory process because of the cardiovascular dysfunction associated with sepsis^[31]. A serum test of lactate is often established in the emergency to diagnose enteral ischemia and as a serological marker of end-organ perfusion. However, it seems to be highly nonspecific. Lactate level is a classic example of critical values. In fact, values more or equal to 4 mmol/L are considered to require early and aggressive resuscitation procedures, whereas values less than 4 mmol/L are associated with patients who do not require the typical interventions in the early management of sepsis. The use of serum lactate should probably be addressed in patients who have signs of a septic infection. This test should be based on the degree of suspect specific diseases^[32]. Substantially, critical values may be segmented into tiers of severity, including the critical at a high level "must know now" results, the "must know" results with less critical value, and the "should know" results or, also called, "courtesy" calls by Dietzen^[33,34]. The last category entails the least severe results. Although there are numerous references for adults, sources are quite scarce in Pediatrics. In the following table, we list some examples of START in Pediatrics (Table 1).

The first tier, *i.e.*, the life-and-death critical values of

the original Lundberg's definition^[35] need to be referred to as "must know now" results. The second tier, those values with highly significant data of a severe disease without the burden of an immediate response need to be referred to as "must know" results. The "should know" results or "courtesy" calls may include abnormal results that incorporate a specific intervention as a mandate but remain dependent from the context where are generated. Despite the controversy raised recently, we agree that the lactate level is a "must know now" result. Other pediatric examples of critical values with "must know now" level of the critical setting include total bilirubin and ammonia, while the conjugated bilirubin concentration may be considered a "must know" result. Critical values are also analytes such as potassium and TCO₂, which is an amount of carbon dioxide in several states total carbon dioxide. In an emergency, the measurement of TCO₂ is key because it is part of an electrolyte profile, which is advantageous in evaluating HCO₃⁻ concentration. TCO₂ and HCO₃⁻ are mandatory elements to properly assess the acid-base imbalance along with pH and PCO₂ partial pressure of carbon dioxide and electrolyte imbalance. The Coombs test for newborn hemolysis is an urgent value that often has been part of litigation because it has been classified as "important" but not "urgent". Maternal alloimmunization toward antigens of erythrocytes causes hemolytic Disease of the Fetus and Newborn (HDFN). In severe cases, HDFN may lead to life-threatening fetal anemia and severe forms of neonatal hyperbilirubinemia with a risk for the baby developing kernicterus. In the most severe cases, there is an etiology linked to anti-D, despite the introduction of antenatal and postnatal anti-D immunoglobulin prophylaxis. Erythrocytes antibody screening programmes are aimed to detect maternal alloimmunization early in pregnancy with the aim to identify high-risk cases to timely start antenatal and postnatal treatment^[36-38]. An abnormal result in an indirect Coombs test means that the patient has circulating antibodies to any erythrocytes that are considered foreign to the body. Depending on the age and events, this circumstance may indicate erythroblastosis fetalis, an incompatible blood match for receiving a blood transfusion, or hemolytic anemia due to an autoimmune reaction or drug toxicity. There is a visible risk for kernicterus, and this critical value needs to be reported urgently.

Another abnormal result that needs particular attention is the ferritin value in the setting of hemophagocytic lymphohistiocytosis or lymphohistiocytic syndromes (HLH syndromes) ("must know now" value). Hyperferritinemia, which is usually with a value greater than 10000 ng/mL, is a crucial hallmark in HLH. It is used as an indicator triggering a macrophage activation syndrome leading to HLH. Measurement of serum ferritin can be used in both diagnosis and prognosis in the setting of HLH. Hyperferritinemia is a significant contributor to manage appropriately critically ill children and should be communicated urgently to the pediatric

emergency team or a professional team of a pediatric intensive care unit.

In 1991, Kost *et al*^[39] reviewed critical limits of 39 children's hospital across the United States. These authors listed glucose, potassium, calcium, and sodium as high critical limits in children, whereas critical limits for newborns were glucose, potassium, hemoglobin, platelets, hematocrit, and white blood cell counts. Both the presence of blasts on the blood smear and abnormal cerebrospinal fluid findings are qualitative critical results. Children's hospitals target foremostly critical limits for surveillance in the setting of the evaluation of kidney function, coagulation, and potassium. In the 39 children's hospitals reviewed, the number of tests ranged from 3 to 50. Currently, the number of critical values may easily go over 100, and, indeed, it may become a nightmare for a laboratory physician. The increase in the number of critical values is due to the improvements in health care, transplantation program, and stem cell therapy protocols. Indeed, there is a high subjectivity in addressing tests and thresholds in several hospitals, and the specialization of the hospital may condition the choice of level of critical value. About a decade ago, Dietzen evaluated four pediatric institutions, in addition to three adult hospitals. The results are part of the critical tests of the 4th edition (now adjourned 6th edition) of "Tietz Textbook of Clinical Chemistry and Molecular Diagnosis"^[34,40]. The number of tests ranged from 12 to 45. Eleven values, including total bilirubin, conjugated bilirubin, ammonia, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sweat chloride, iron, gamma-glutamyl-transferase (GGT), fibrinogen, and lactate dehydrogenase (LDH), were identified as unique in a pediatric setting. The high variability of critical values identified by Kost *et al*^[39], Dietzen^[34] and others^[41,42] point to the high variability of the critical value assignment. Prompt interventions to prevent kernicterus include phototherapy and exchange transfusion total bilirubin concentrations are values that physicians must know now. A mildly increased value of unconjugated hyperbilirubinemia may be found in the neonatal period, but an increased value of conjugated bilirubin almost always indicates pathology and surgically correctable diseases need to be ruled out^[43-45]. The diagnosis of biliary atresia, which is a perinatal necro-inflammatory process involving the extra- and intra-hepatic biliary system with progressive ductopenia and obliterative cholangiopathy needs to be targeted properly. The failure to recognize within 30-45 d after birth determines an irreversible liver damage and cirrhosis. The child's fate is, then, linked to liver transplantation. As indicated by Dietzen^[34], conjugated bilirubin rates are critical values that pediatricians must know. However, these results may not necessarily be communicated "now", because biliary atresia is a life-threatening disease but not imminently. The course of action should be straightforward, but not instantaneous. Many inborn errors of metabolism may result in life-threatening

accumulation of toxic intermediates. A critical value that pediatricians need to know now is the ammonia level. In consideration that hyperammonemia occurs in defects of the urea cycle or secondary to hepatocellular dysfunction and is extremely toxic to the newborn brain, an immediate and straightforward line of action must be put in place to prevent irreversible neurologic damage. The number of new devices, including digital droplet PCR, has increased in the last decade and accuracy and precision are the criteria to receive Food and Drug Administration approval^[46]. Chief instances are disorders of the urea cycle, phenylketonuria, and galactosemia. Physicians "must know" about the rates of the substances "now" to prevent calamitous sequelae for the child. Fatty acid oxidation defects include medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. MCAD may remain asymptomatic for a long time. Nevertheless, a severe hypoglycemia may result in neuro-disability and death in case of a prolonged fast,. In such situations, parents may be unaware of this catastrophic cascade. In case of such a tragedy, the pediatric pathology services will play a substantial role in helping the family to find the etiology and eventually target the specific genes. In newborn screening programs, some diseases progress slowly, whereas some others eventually lead to severe multi-organ dysfunction. The result of mucoviscidosis is not a critical value that pediatricians need to know now. Mucoviscidosis or cystic fibrosis (CF) entails insufficiency of the exocrine pancreas and chronic pulmonary disease leading to failure of the lung in the 3rd or 4th decade of life. Acute life-threatening complications may occur in newborns but are highly infrequent. Another similar endocrinological disorder that does not reach the level of highest priority is congenital hypothyroidism. A different value is given to lysosomal storage diseases, such as sialidosis^[47]. In sialidosis, there is a deficiency of the enzyme neuraminidase, which ends in the abnormal accumulation of toxic compounds in several organs, mainly brain and liver, although other organs are also affected^[48,49]. In fact, sialidosis may be considered a critical diagnosis that physicians must know now. In inborn errors of metabolism with target organs, including brain, heart, and liver, priority is the highest. Finally, drug monitoring and toxicology results are results with the most top priority because life-threatening imbalances can occur at any time. The pharmacological history is mandatory in evaluating the interaction of drugs with herbals or food in pediatrics more than in any other medical area^[50,51]. Metabolomics is playing a central role in inborn errors of metabolism^[52-54]. The severe potential of these disorders dictates that physicians know about these conditions at the time the value of the test becomes known to the laboratory physician. My clinical and research experience in several countries (Italy, Germany, United Kingdom, Austria, Canada) has been crucial in understanding the role of communication of critical values to emergency physicians or to a professional team of pediatric intensive care units.

Although a table would be beneficial, it does not fit all children's hospital priorities, because some institutions have different priorities with some providing primary care and some tertiary care. However, I am a strong advocate in considering that the laboratory physician team liaise with the clinical physicians to create a list that is specific for that specific institution. In my experience, critical values come to the list once they are set by the laboratory physicians in collaboration with the clinicians. It is not a one-off activity, but it is under continuous review at regular intervals, which is crucial for the accreditation of the institution. It is a dynamic process. Critical values may change over time if critical incidents or "near misses" occur and are discussed in the setting of a comprehensive quality assurance.

Finally, the pre-analytical process is critical because it may require the clinical team to liaise with the laboratory to identify the best way to gather and deliver the sample for analysis (e.g., saline, transport medium, formaldehyde, glutaraldehyde). Another point that remains crucial is the age of the patient. A serum bilirubin value over 300 $\mu\text{mol/L}$ is critical (must know now) for a child during the first 15 d of life, but it is less critical (must know) for older children. Also, even for the same unit or even the same patient, the significance of an abnormal value may change over time. The presence of blastic cells in the peripheral blood is critical at the first diagnosis, but its presence will be less essential once the diagnosis of leukemia has been established. The analytical phase is complicated as it encompasses a whole list of devices and steps in clinical and surgical pathology. The postanalytical phase remains probably the most evolving at this time. The complexity of modern hospitals and inter-disciplinary works may favor the use of electronic ways to communicate the results. Advances in electronics, wireless communication, and personal communicative devices have changed the way we work along with others. Laboratory data can be accessed anytime and anywhere giving the clinical team an opportunity to act immediately on critical values. The next level of essential values in patient care will be dictated by improving the level of communication of the information and, probably, through an interpretation of the value. The phone conversation may remain crucial to discuss and interpret correctly critical values.

CONCLUSION

The original concept of critical value was defined in the 70's of the last century as a value representing an imminent danger on which a physician needs to act promptly^[35]. In pediatrics, failure to provide this value means loss of life or development of mostly neurologic disabilities. Thus, the mandatory prompt intervention infers that the result is communicated precisely very close to the precipitating event. The medical/surgical intervention upon it is unambiguous and abrupt raising the need for an objective treatment. In the 21st century,

the determination of alert thresholds remains the most challenging and controversial issue in clinical pediatrics. In any case, pre-analytical matters need to be cleared off before the laboratory physician can dispatch the life-threatening result. Classification of essential laboratory results is more than an academic exercise. Prioritizing critical calls should be part of the excellent educational training of the resident. In this setting, life hangs in the balance, and life-death decisions need to be taken in seconds not minutes. A phone conversation may be substituted using other alternative alerting functions, including inserting data into the database of electronic medical records or communicating by e-mail. These new methods are modes of making sure relevant information is transmitted without interrupting the standard workflow of the primary physicians in charge of the child.

REFERENCES

- 1 **Allon R**, Feldman O, Karminsky A, Steinberg C, Leiba R, Shavit I. Validity of the Pediatric Canadian Triage Acuity Scale in a tertiary children's hospital in Israel. *Eur J Emerg Med* 2018; **25**: 270-273 [PMID: 28362647 DOI: 10.1097/MEJ.0000000000000464]
- 2 **Westwood A**, Buys H, Cheema B. An adapted triage tool (ETAT) at Red Cross War Memorial Children's Hospital Medical Emergency Unit, Cape Town, South Africa: an evaluation. *S Afr Med J* 2013; **103**: 273 [PMID: 23971102 DOI: 10.7196/samj.6906]
- 3 **Buys H**, Muloiwa R, Westwood C, Richardson D, Cheema B, Westwood A. An adapted triage tool (ETAT) at Red Cross War Memorial Children's Hospital Medical Emergency Unit, Cape Town: an evaluation. *S Afr Med J* 2012; **103**: 161-165 [PMID: 23472679 DOI: 10.7196/samj.6020]
- 4 **Miles H**, Litton E, Curran A, Goldsworthy L, Sharples P, Henderson AJ. The PATRIARCH Study. Using outcome measures for league tables: can a North American prediction of admission score be used in a United Kingdom children's emergency department? PRISA And Triage In A Regional Children's Hospital. *Emerg Med J* 2002; **19**: 536-538 [PMID: 12421779 DOI: 10.1136/emj.19.6.536]
- 5 **Thomas DO**. A children's hospital ED referral/triage form. *J Emerg Nurs* 1996; **22**: 250-251 [PMID: 8949235 DOI: 10.1016/S0099-1767(96)80125-5]
- 6 **Skandalakis PN**, Lainas P, Zoras O, Skandalakis JE, Mirilas P. "To afford the wounded speedy assistance": Dominique Jean Larrey and Napoleon. *World J Surg* 2006; **30**: 1392-1399 [PMID: 16850154 DOI: 10.1007/s00268-005-0436-8]
- 7 **Nakao H**, Ukai I, Kotani J. A review of the history of the origin of triage from a disaster medicine perspective. *Acute Med Surg* 2017; **4**: 379-384 [PMID: 29123897 DOI: 10.1002/ams2.293]
- 8 **Firouzkouhi M**, Zargham-Boroujeni A, Kako M, Abdollahimohammad A. Experiences of civilian nurses in triage during the Iran-Iraq War: An oral history. *Chin J Traumatol* 2017; **20**: 288-292 [PMID: 29032912 DOI: 10.1016/j.cjtee.2017.07.002]
- 9 **Mazer M**, Deroos F, Hollander JE, McCusker C, Peacock N, Perrone J. Medication history taking in emergency department triage is inaccurate and incomplete. *Acad Emerg Med* 2011; **18**: 102-104 [PMID: 21414064 DOI: 10.1111/j.1553-2712.2010.00959.x]
- 10 **Katoch R**, Rajagopalan S. Warfare Injuries: History, Triage, Transport and Field Hospital Setup in the Armed Forces. *Med J Armed Forces India* 2010; **66**: 304-308 [PMID: 27365730 DOI: 10.1016/S0377-1237(10)80003-6]
- 11 **Mitchell GW**. A brief history of triage. *Disaster Med Public Health Prep* 2008; **2** Suppl 1: S4-S7 [PMID: 18769265 DOI: 10.1097/DMP.0b013e3181844d43]
- 12 **Iseron KV**, Moskop JC. Triage in medicine, part I: Concept, history, and types. *Ann Emerg Med* 2007; **49**: 275-281 [PMID: 17141139 DOI: 10.1016/j.annemergmed.2006.05.019]
- 13 **Mackersie RC**. History of trauma field triage development and the American College of Surgeons criteria. *Prehosp Emerg Care* 2006; **10**: 287-294 [PMID: 16801263 DOI: 10.1080/10903120600721636]
- 14 **Ebker-White AA**, Bein KJ, Dinh MM. The Sydney Triage to Admission Risk Tool (START): A prospective validation study. *Emerg Med Australas* 2018; **30**: 511-516 [PMID: 29417732 DOI: 10.1111/1742-6723.12940]
- 15 **Silvestri S**, Field A, Mangalat N, Weatherford T, Hunter C, McGowan Z, Stamile Z, Mattox T, Barfield T, Afshari A, Ralls G, Papa L. Comparison of START and SALT triage methodologies to reference standard definitions and to a field mass casualty simulation. *Am J Disaster Med* 2017; **12**: 27-33 [PMID: 28822212 DOI: 10.5055/ajdm.2017.0255]
- 16 **Claudius I**, Kaji AH, Santillanes G, Cicero MX, Donofrio JJ, Gausche-Hill M, Srinivasan S, Chang TP. Accuracy, Efficiency, and Inappropriate Actions Using JumpSTART Triage in MCI Simulations. *Prehosp Disaster Med* 2015; **30**: 457-460 [PMID: 26323610 DOI: 10.1017/S1049023X15005002]
- 17 **Cross KP**, Petry MJ, Cicero MX. A better START for low-acuity victims: data-driven refinement of mass casualty triage. *Prehosp Emerg Care* 2015; **19**: 272-278 [PMID: 25153986 DOI: 10.3109/10903127.2014.942481]
- 18 **Navin DM**, Sacco WJ, McCord TB. Does START triage work? The answer is clear! *Ann Emerg Med* 2010; **55**: 579-580; author reply 580-581 [PMID: 20494228 DOI: 10.1016/j.annemergmed.2009.11.031]
- 19 **Gebhart ME**, Pence R. START triage: does it work? *Disaster Manag Response* 2007; **5**: 68-73 [PMID: 17719507 DOI: 10.1016/j.dmr.2007.05.002]
- 20 **Wallis L**. START is not the best triage strategy. *Br J Sports Med* 2002; **36**: 473 [PMID: 12453848 DOI: 10.1136/bjism.36.6.473]
- 21 **Benson M**, Koenig KL, Schultz CH. Disaster triage: START, then SAVE--a new method of dynamic triage for victims of a catastrophic earthquake. *Prehosp Disaster Med* 1996; **11**: 117-124 [PMID: 10159733 DOI: 10.1017/S1049023X0004276X]
- 22 **Chang TP**, Santillanes G, Claudius I, Pham PK, Koved J, Cheyne J, Gausche-Hill M, Kaji AH, Srinivasan S, Donofrio JJ, Bir C. Use of a Novel, Portable, LED-Based Capillary Refill Time Simulator within a Disaster Triage Context. *Prehosp Disaster Med* 2017; **32**: 451-456 [PMID: 28345508 DOI: 10.1017/S1049023X17006343]
- 23 **Jain TN**, Ragazzoni L, Stryhn H, Stratton SJ, Della Corte F. Comparison of the Sacco Triage Method Versus START Triage Using a Virtual Reality Scenario in Advance Care Paramedic Students. *CJEM* 2016; **18**: 288-292 [PMID: 26553510 DOI: 10.1017/cem.2015.102]
- 24 **Kahn CA**, Schultz CH, Miller KT, Anderson CL. Does START triage work? An outcomes assessment after a disaster. *Ann Emerg Med* 2009; **54**: 424-430, 430.e1 [PMID: 19195739 DOI: 10.1016/j.annemergmed.2008.12.035]
- 25 **Lippi G**, Adcock D, Simundic AM, Tripodi A, Favaloro EJ. Critical laboratory values in hemostasis: toward consensus. *Ann Med* 2017; **49**: 455-461 [PMID: 28042729 DOI: 10.1080/07853890.2016.1278303]
- 26 **Favaloro EJ**, Lippi G. Post-analytical Issues in Hemostasis and Thrombosis Testing. *Methods Mol Biol* 2017; **1646**: 545-559 [PMID: 28804854 DOI: 10.1007/978-1-4939-7196-1_40]
- 27 **Plebani M**. Towards a new paradigm in laboratory medicine: the five rights. *Clin Chem Lab Med* 2016; **54**: 1881-1891 [PMID: 27732557 DOI: 10.1515/ccmlm-2016-0848]
- 28 **Zemlin AE**, Nutt L, Burgess LJ, Eiman F, Erasmus RT. Potential for medical error: incorrectly completed request forms for thyroid function tests limit pathologists' advice to clinicians. *S Afr Med J* 2009; **99**: 668-671 [PMID: 20073294]
- 29 **Hollensead SC**, Lockwood WB, Elin RJ. Errors in pathology and laboratory medicine: consequences and prevention. *J Surg Oncol* 2004; **88**: 161-181 [PMID: 15562462 DOI: 10.1002/jso.20125]
- 30 **Ricós C**, García-Victoria M, de la Fuente B. Quality indicators and specifications for the extra-analytical phases in clinical laboratory management. *Clin Chem Lab Med* 2004; **42**: 578-582 [PMID: 15259371 DOI: 10.1515/CCLM.2004.100]

- 31 **Sergi C**, Shen F, Lim DW, Liu W, Zhang M, Chiu B, Anand V, Sun Z. Cardiovascular dysfunction in sepsis at the dawn of emerging mediators. *Biomed Pharmacother* 2017; **95**: 153-160 [PMID: 28841455 DOI: 10.1016/j.biopha.2017.08.066]
- 32 **Richards C**, Ishihara K, Grayson C, Lustik M, Yheulon C. Serum lactate predicts resource utilization, but not surgical need, in the emergency department. *J Surg Res* 2018; **226**: 89-93 [PMID: 29661294 DOI: 10.1016/j.jss.2018.01.020]
- 33 **Dietzen DJ**. Fifty Shades of Yellow. *Clin Chem* 2017; **63**: 937-938 [PMID: 28320762 DOI: 10.1373/clinchem.2017.271460]
- 34 **Dietzen D**. Pediatric considerations in critical value assignment. 2009. Available from: URL: <https://acutecaretesting.org/en/articles/pediatric-considerations-in-critical-value-assignment>
- 35 **Lundberg GD**. When to panic over abnormal values. *MLO Med Lab Obs* 1972; **(4)**: 47-54
- 36 **Fasano RM**. Hemolytic disease of the fetus and newborn in the molecular era. *Semin Fetal Neonatal Med* 2016; **21**: 28-34 [PMID: 26589360 DOI: 10.1016/j.siny.2015.10.006]
- 37 **de Haas M**, Thurik FF, Koelewijn JM, van der Schoot CE. Haemolytic disease of the fetus and newborn. *Vox Sang* 2015; **109**: 99-113 [PMID: 25899660 DOI: 10.1111/vox.12265]
- 38 **Thurik FF**, Ait Soussan A, Bossers B, Woortmeijer H, Veldhuisen B, Page-Christiaens GC, de Haas M, van der Schoot CE. Analysis of false-positive results of fetal RHD typing in a national screening program reveals vanishing twins as potential cause for discrepancy. *Prenat Diagn* 2015; **35**: 754-760 [PMID: 25855535 DOI: 10.1002/pd.4600]
- 39 **Kost GJ**. Critical limits for emergency clinician notification at United States children's hospitals. *Pediatrics* 1991; **88**: 597-603 [PMID: 1881742]
- 40 **Rifai N**. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics: Saunders, 2018. Available from: URL: <https://evolve.elsevier.com/cs/product/9780323359214?role=student>
- 41 **Lum G**. Critical limits (alert values) for physician notification: universal or medical center specific limits? *Ann Clin Lab Sci* 1998; **28**: 261-271 [PMID: 9784826]
- 42 **Howanitz PJ**, Steindel SJ, Heard NV. Laboratory critical values policies and procedures: a college of American Pathologists Q-Probes Study in 623 institutions. *Arch Pathol Lab Med* 2002; **126**: 663-669 [PMID: 12033953 DOI: 10.1043/0003-9985(2002)126:0.CO;2]
- 43 **Sergi C**, Benstz J, Feist D, Nutzenadel W, Otto HF, Hofmann WJ. Bile duct to portal space ratio and ductal plate remnants in liver disease of infants aged less than 1 year. *Pathology* 2008; **40**: 260-267 [PMID: 18428045 DOI: 10.1080/00313020801911538]
- 44 **Sergi C**, Adam S, Kahl P, Otto HF. Study of the malformation of ductal plate of the liver in Meckel syndrome and review of other syndromes presenting with this anomaly. *Pediatr Dev Pathol* 2000; **3**: 568-583 [PMID: 11000335 DOI: 10.1007/s100240010104]
- 45 **Sergi C**, Adam S, Kahl P, Otto HF. The remodeling of the primitive human biliary system. *Early Hum Dev* 2000; **58**: 167-178 [PMID: 10936437 DOI: 10.1016/S0378-3782(00)00065-7]
- 46 **Shen F**, Sergi C, Sun HL. Hepatitis B Virus Covalently Closed Circular DNA-Selective Droplet Digital PCR: A Sensitive and Noninvasive Method for Hepatocellular Carcinoma Diagnosis? *J Mol Diagn* 2018; **20**: 277-278 [PMID: 29572198 DOI: 10.1016/j.jmoldx.2018.03.001]
- 47 **Khan A**, Sergi C. Sialidosis: A Review of Morphology and Molecular Biology of a Rare Pediatric Disorder. *Diagnostics* (Basel) 2018; **8**: pii: E29 [PMID: 29693572 DOI: 10.3390/diagnostics8020029]
- 48 **Sergi C**, Penzel R, Uhl J, Zoubaa S, Dietrich H, Decker N, Rieger P, Kopitz J, Otto HF, Kiessling M, Cantz M. Prenatal diagnosis and fetal pathology in a Turkish family harboring a novel nonsense mutation in the lysosomal alpha-N-acetyl-neuraminidase (sialidase) gene. *Hum Genet* 2001; **109**: 421-428 [PMID: 11702224 DOI: 10.1007/s004390100592]
- 49 **Sergi C**, Beedgen B, Kopitz J, Zilow E, Zoubaa S, Otto HF, Cantz M, Linderkamp O. Refractory congenital ascites as a manifestation of neonatal sialidosis: clinical, biochemical and morphological studies in a newborn Syrian male infant. *Am J Perinatol* 1999; **16**: 133-141 [PMID: 10438195 DOI: 10.1055/s-2007-993847]
- 50 **Dinakaran D**, Sergi CM. Co-ingestion of aspirin and acetaminophen promoting fulminant liver failure: A critical review of Reye syndrome in the current perspective at the dawn of the 21st century. *Clin Exp Pharmacol Physiol* 2018; **45**: 117-121 [PMID: 28945927 DOI: 10.1111/1440-1681.12861]
- 51 **Dinakaran D**, Bristow E, Armanious H, Garros D, Yap J, Noga M, Sergi C. Co-ingestion of willow bark tea and acetaminophen associated with fatal infantile fulminant liver failure. *Pediatr Int* 2017; **59**: 743-745 [PMID: 28436611 DOI: 10.1111/ped.13262]
- 52 **Perkins BA**, Caskey CT, Brar P, Dec E, Karow DS, Kahn AM, Hou YC, Shah N, Boeldt D, Coughlin E, Hands G, Lavrenko V, Yu J, Procko A, Appis J, Dale AM, Guo L, Jönsson TJ, Wittmann BM, Bartha I, Ramakrishnan S, Bernal A, Brewer JB, Brewerton S, Biggs WH, Turpaz Y, Venter JC. Precision medicine screening using whole-genome sequencing and advanced imaging to identify disease risk in adults. *Proc Natl Acad Sci USA* 2018; **115**: 3686-3691 [PMID: 29555771 DOI: 10.1073/pnas.1706096114]
- 53 **Caskey T**. Precision Medicine: Functional Advancements. *Annu Rev Med* 2018; **69**: 1-18 [PMID: 29261360 DOI: 10.1146/annurev-med-041316-090905]
- 54 **Guo L**, Milburn MV, Ryals JA, Lonergan SC, Mitchell MW, Wulff JE, Alexander DC, Evans AM, Bridgewater B, Miller L, Gonzalez-Garay ML, Caskey CT. Plasma metabolomic profiles enhance precision medicine for volunteers of normal health. *Proc Natl Acad Sci USA* 2015; **112**: E4901-E4910 [PMID: 26283345 DOI: 10.1073/pnas.1508425112]

P- Reviewer: Kute VB, Lee AC, Lin J, Tommasini A **S- Editor:** Ji FF
L- Editor: A **E- Editor:** Wu YXJ





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

