

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2022 September 9; 11(5): 385-436



Contents

Bimonthly Volume 11 Number 5 September 9, 2022

FRONTIER

- 385 Childhood constipation: Current status, challenges, and future perspectives
Rajindrajith S, Devanarayana NM, Benninga MA

FIELD OF VISION

- 405 Rational use of antibiotics in children with diabetic ketoacidosis needs attention
Wang X

MINIREVIEWS

- 408 Children with type 1 diabetes in COVID-19 pandemic: Difficulties and solutions
Shi Y, Wu LQ, Wei P, Liao ZH

ORIGINAL ARTICLE

Retrospective Study

- 419 Utilization of chest tube as an esophagus stent in pediatric caustic injuries: A retrospective study
Salimi M, Hosseinpour H, Shahriarirad R, Esfandiari S, Pooresmael F, Sarejloo S, Foroutan H

CASE REPORT

- 429 Three novel homozygous *ITGB2* mutations among two patients with leukocyte adhesion defect type-1: Two case reports
Suksawat Y, Pacharn P, Siripattanamongkol N, Boonyawat B

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Pediatrics*, Jianxiang Liao, MD, PhD, Professor, Chief, Department of Pediatric Neurology, 9th floor of Building B, Shenzhen Children's Hospital, 7019 Yitian Road, Futian District, Guangdong Province, China 518038. liaojianxiang@vip.sina.com

AIMS AND SCOPE

The primary aim of the *World Journal of Clinical Pediatrics* (WJCP, *World J Clin Pediatr*) is to provide scholars and readers from various fields of pediatrics with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCP mainly publishes articles reporting research results and findings obtained in the field of pediatrics and covering a wide range of topics including anesthesiology, cardiology, endocrinology, gastroenterology, hematology, immunology, infections and infectious diseases, medical imaging, neonatology, nephrology, neurosurgery, nursing medicine, perinatology, pharmacology, respiratory medicine, and urology.

INDEXING/ABSTRACTING

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

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Xiang-Di Zhang; Production Department Director: Xu Guo; Editorial Office Director: Yu-Jie Ma.

NAME OF JOURNAL

World Journal of Clinical Pediatrics

ISSN

ISSN 2219-2808 (online)

LAUNCH DATE

June 8, 2012

FREQUENCY

Bimonthly

EDITORS-IN-CHIEF

Toru Watanabe, Consolato M Sergi, Elena Daniela Serban, Surjit Singh

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2219-2808/editorialboard.htm>

PUBLICATION DATE

September 9, 2022

COPYRIGHT

© 2022 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

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

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/gerinfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/gerinfo/288>

PUBLICATION MISCONDUCT

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

ARTICLE PROCESSING CHARGE

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

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/gerinfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Childhood constipation: Current status, challenges, and future perspectives

Shaman Rajindrajith, Niranga Manjuri Devanarayana, Marc A Benninga

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): D

Grade E (Poor): 0

P-Reviewer: Khayyat YM, Saudi Arabia; Shahini E, Italy; Tong WD, China

Received: November 6, 2021

Peer-review started: November 9, 2021

First decision: December 12, 2021

Revised: January 24, 2022

Accepted: July 6, 2022

Article in press: July 6, 2022

Published online: September 9, 2022



Shaman Rajindrajith, Department of Paediatrics, Faculty of Medicine, University of Colombo, Colombo 00800, Sri Lanka

Shaman Rajindrajith, University Paediatric Unit, Lady Ridgeway Hospital for Children, Colombo 00800, Sri Lanka

Niranga Manjuri Devanarayana, Department of Physiology, Faculty of Medicine, University of Kelaniya, Ragama 11010, Sri Lanka

Marc A Benninga, Department of Pediatric Gastroenterology and Nutrition, Emma Children Hospital, Amsterdam University Medical Center, Amsterdam 1105AZ, The Netherlands

Corresponding author: Shaman Rajindrajith, MD, PhD, Chair Professor, Department of Paediatrics, Faculty of Medicine, University of Colombo, 25, Kynsey Road, Colombo 00800, Sri Lanka. shamanrajindrajith4@gmail.com

Abstract

Constipation in children is a major health issue around the world, with a global prevalence of 9.5%. They present to clinicians with a myriad of clinical signs. The Rome IV symptom-based criteria are used to diagnose functional constipation. Functional constipation is also a huge financial burden for healthcare system and has a detrimental impact on health-related quality of life of children. There are various risk factors identified globally, including centrally connected factors such as child abuse, emotional and behavioral issues, and psychological stress. Constipation is also precipitated by a low-fiber diet, physical inactivity, and an altered intestinal microbiome. The main pathophysiological mechanism is stool withholding, while altered rectal function, anal sphincter, pelvic floor, and colonic dysfunction also play important roles. Clinical evaluation is critical in making a diagnosis, and most investigations are only required in refractory patients. In the treatment of childhood constipation, both nonpharmacological (education and demystification, dietary changes, toilet training, behavioral interventions, biofeedback, and pelvic floor physiotherapy), and pharmacological (osmotic and stimulant laxatives and novel drugs like prucalopride and lubiprostone) interventions are used. For children with refractory constipation, transanal irrigation, botulinum toxin, neuromodulation, and surgical treatments are reserved. While frequent use of probiotics is still in the experimental stage, healthy dietary habits, living a healthy lifestyle and limiting exposure to stressful events, are all beneficial preventive measures.

Key Words: Constipation; Children; Functional gastrointestinal disorders; Psychological stress; Treatment; Surgical interventions

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Constipation is a public health problem. It has a high prevalence and a multitude of risk factors. The main pathophysiological mechanisms are stool withholding and colonic and anorectal dysfunction in younger and older children, respectively. Constipation is a clinical diagnosis based on the Rome IV criteria. Polyethylene glycol-based therapy is the mainstay in the management of constipation, while other osmotic and stimulant laxatives are used as adjunct therapies. Colonic washouts and surgical interventions are reserved for refractory constipation. A well-planned preventive strategy is useful in preventing functional constipation in children and would be able to reduce healthcare costs and improve health-related quality of life.

Citation: Rajindrajith S, Devanarayana NM, Benninga MA. Childhood constipation: Current status, challenges, and future perspectives. *World J Clin Pediatr* 2022; 11(5): 385-404

URL: <https://www.wjgnet.com/2219-2808/full/v11/i5/385.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v11.i5.385>

INTRODUCTION

Childhood functional constipation (FC) is characterized by the presence of infrequent, and painful bowel motions, fecal incontinence, stool withholding behavior, and occasional passage of large diameter stools. Epidemiologically it amounts to a global health problem as developed and developing countries show a high prevalence[1]. Children with constipation suffer from a variety of symptoms unrelated to their gastrointestinal system and the disease detrimentally affects their quality of life, often unrecognized by the healthcare systems[2]. A large sum of public funds is also being spent on caring for children with constipation due to repeated hospital admissions, emergency room visits, and regular clinic visits because of recurrent exacerbations of their symptoms[3]. All these factors demand a fresh look at childhood constipation. Therefore, in this frontier article, we critically review the current literature to develop a new paradigm on epidemiology and risk factors, pathophysiology, investigations, and management of children with constipation.

Identifying children with constipation: The Rome criteria

Constipation had been defined using a large number of definitions. An unambiguous, universal definition was needed for epidemiological, pathophysiological, and clinical trials at the turn of the century. These demands paved the way to defining functional gastrointestinal disorders (FGIDs) in the Rome process. In 2006, Rome III criteria were established to diagnose childhood constipation. The duration of constipation was reduced from 3 mo used in Rome II criteria to 2 mo, clearly defining constipation in a more practical way[4]. Rome III criteria were more useful in clinical diagnosis of constipation in children and has a good construct validity. However, the inter- and intra-observer reliability of Rome criteria has been poor, indicating the necessity to develop more robust, clinically valuable criteria[5]. The Rome IV criteria were released in 2016[6] (Table 1). Apart from changing the duration of symptoms from 2 mo to 1 mo from onset to diagnosis, the other criteria remain as the same in Rome III. The change has not increased the number of children diagnosed with constipation, and both Rome III and Rome IV criteria were in excellent agreement[7]. However, the reduction of the duration of symptoms required to diagnose constipation is an important move as it is essential to start therapeutic interventions as early as possible to minimize both physiological and psychological consequences of late diagnosis and treatments.

Epidemiology

FC is a common FGID throughout childhood. In the last 2 decades, several systematic reviews reported that the prevalence of FC changes with the definition used, but prevalence does not change with age or sex and FC is found all over the world. The prevalence of FC is lower in Asian children compared to American and European children. Although the exact reason for this observation is not clear, it is possible that dietary, cultural factors, and social factors related to toilet training may play a role[1,8]. The relationship between socioeconomic status and FC is controversial. Several studies have reported that FC is not associated with low level of parental education, low family income, or maternal and paternal employment[9,10]. However, a Nigerian study reported a higher prevalence among children

Table 1 Rome IV diagnostic criteria for constipation in children

Diagnostic criteria must include at least 2 of the following features of constipation in a child with a development age of at least 4 yr with insufficient criteria to diagnose irritable bowel syndrome

Two or fewer defecations in the toilet per week
History of retentive posturing or excessive volitional stool retention
History of painful or hard bowel motion
Presence of a large fecal mass in the rectum
History of large diameter stools which may obstruct the toilet
After appropriate evaluation, the fecal incontinence cannot be explained by another medical condition

with low social class[11]. Other important factors reported in epidemiological studies include positive family history and health problems among family members[9,10]. Recent studies using Rome IV criteria reported a significantly high prevalence of FC in infants and young children. A study from China noted that 7% of children aged 0-4 years were suffering from FC and among infants in Malaysia it was 1.1% [12,13]. A systematic review on FGIDs in infants and toddlers reported a prevalence of FC as 11.6% at the age of 3 mo according to Rome III criteria[14].

Risk factors for constipation

Several risk factors for FC have been identified. All these factors finally lead to anorectal dysfunction and fecal retention in the rectum and the colon leading to passage of infrequent, hard, and painful stools. It is understood that FC is a disorder of gut brain interactions. Therefore, the risk factors involving childhood FC is divided into two main categories namely, centrally mediated and gut related mechanisms.

CENTRAL RISK FACTORS

Stressful life event

Subtle perceived stressors, such as separation from best friend, failure in exam in school, being bullied at school, and change of school and home related stressors, such as divorce or separation of parents, loss of job of a parent, and severe illnesses in the family may precipitate FC[15]. Other home related risk factors reported were frequent domestic fights, marital disharmony, and sibling rivalry[16,17].

Abuse and child maltreatment

Psychological trauma associated with abuse and maltreatment is known to associate with FC. A study from Sri Lanka reported exposure to all three major forms of abuse (physical, emotional, and sexual) predispose children to develop FC[18]. It also showed that these children had more severe bowel symptoms and somatization. At the molecular level, abuse influences DNA methylation and lead to changes in epigenetic structure and mechanisms[19]. Stress generated during the period of exposure to abuse and psychological influences that last longer and changes in the epigenetic structure may contribute to permanent alterations in the dialogue between the brain and the large bowel leading to FC.

Other psychological and behavioral factors

Studying children with FC using the child behavior check list, several authors reported behavioral traits such as internalization and externalization are more frequent among these children[20,21]. FC is also associated with psychological maladjustment, anxiety, and depression[22-24]. Using the strength and difficulty questionnaire, Cagan-Appak and co-workers[25] noted emotional and peer problems to be more common among children with FC.

Parental rearing style and psychological state

The rearing style of parents is a significant factor during the early life of a child, particularly during the time of toilet training. Parents with high autonomy may try to train their children too strictly and parents with lower autonomy could neglect toilet training leading to fecal retention and constipation.

Studies have noted that parents of children with FC have strict and authoritative parenting styles and are over protective and have rigid attitudes[21,25,26]. In addition, FC in children is also associated with depression and anxiety of parents[25]. All these factors could negatively affect the developing minds of children, adversely affecting their brain-gut connections and lead to FC.

Toilet training

Poor toilet training is a major risk factor for the development of FC in toddlers. Toilet training/potty training should be started between 18-30 mo[27]. However, socioeconomic factors and cultural norms also play a significant role in determination of the timing. Indeed, a comparative study between children from Vietnam and Sweden reported that toilet training was started at 6 mo of age in 89% of Vietnamese children and was achieved in 98% of children by 24 mo, whereas only 5% of Swedish children had started training by 24 mo[28]. Some young children develop stool toileting refusal due to fear of defecation using the toilet or strained family dynamics which enhances withholding behavior [27].

PERIPHERAL RISK FACTORS

Diet

Several dietary factors have been identified as increasing the risk to develop FC. Fiber is an important component of the human diet. Several studies have shown an association between consumption of a diet low in fiber content, including fruits and vegetables, and FC in children[9,10,29]. An observational study noted an association between consumption of fast food and FC[30]. Cow's milk protein allergy is also considered as a potential risk factor for FC in children. Several studies have reported the association between consumption of cow's milk and FC[31-33]. In an elegant study, Borrelli *et al*[32] showed that children with cow's milk allergy-related constipation had increased rectal mast cell density and increased spatial interaction between mast cells and nerve fibers. In addition, anorectal motor abnormalities were found which may result in constipation. These abnormalities resolved on an elimination diet.

Physical activity

Physical activity is an integral part of day-to-day life and has a number of positive health benefits including improved cardiometabolic and bone health. Sedentary lifestyle has been associated with FC [30,34]. Likewise, others have also noted the beneficial effects of physical activity in preventing FC[35, 36].

Abnormal microbiota

The microbiome of the large intestine plays a crucial role in health and disease. Its concentration is estimated up to 10^{11} - 10^{12} cell/g luminal content in the large bowel[37]. This large body of live organisms serves the human body with a variety of physiological functions including digestion and absorption, immunity, prevention of growth of pathogenic organisms, and production of multiple bioactive products. In addition, the microbiome significantly contributes to the stool bulk. de Meij and co-workers [38] reported increased *Bacteroides* (*B. fragilis*, *B. ovatus*) and *Bifidobacteria* (*B. longum*) in children with FC. Another study reported increased *Bifidobacteria* and *Clostridia* in children with FC[39]. In contrast a reduction of *Bifidobacteria* and *Lactobacilli* were noted in adults with FC[40]. When summarizing these data, it is not possible to clearly identify a pattern of organisms associated with FC. Therefore, there is no definitive evidence that the microbiome contributes significantly to predispose children to develop FC.

Pathophysiology

The etiology of FC in children is largely unknown. However, the understanding of the potential pathophysiological mechanisms is rapidly advancing with the aid of evolving novel technological advances, such as high resolution anorectal and colonic manometry and functional magnetic resonance imaging (fMRI) imaging. Growing evidence suggests that voluntary withholding, anorectal dysfunctions (altered sensation, increased compliance, anal achalasia, and dyssynergic defecation), colonic dysfunctions (altered electrophysiology and altered motility), and central mechanisms operating through the brain-gut-microbiota axis and hypothalamo-pituitary-adrenal axis contribute to the pathophysiological mechanisms.

STOOL WITHHOLDING

Stool withholding is the commonest pathophysiological mechanism for developing FC in young children. Faulty toilet training and painful defecation due to passage of hard and large fecal masses lead children to withhold stools. The rectal mucosa, which is designed to absorb water in stools, absorbs water in feces, and the fecal mass in the rectum becomes rock hard and difficult to evacuate. Occasional passage of the fecal mass causes pain in the perianal region, which further aggravates withholding. The rectal wall stretches due to the enlarging fecal mass and accommodates more fecal matter, sometimes leading to a megarectum, which further reduces the desire to pass stools, and augmenting symptoms

[41]. Stretched rectal walls may lose its normal contractility, which is necessary to propel feces. All these pathophysiological factors set up a vicious cycle of stool withholding, painful defecation, and alteration of rectal physiology.

ALTERED RECTAL COMPLIANCE

Increased rectal compliance was noted in children with long-standing fecal impaction. It is difficult to determine whether altered rectal compliance is a primary pathology leading to fecal impaction or secondary to bowel damage caused by prolonged fecal stasis. Children with higher rectal compliance have more severe symptoms, such as fecal incontinence[42]. However, it had been shown that increased rectal compliance has no relationship to the treatment success by noticing that children with high rectal compliance also recovered fully despite their abnormal physiology[42]. In addition, it is important to note that high rectal compliance persists in some children despite them being successfully treated and having no features of FC for many years[43].

ANAL SPHINCTER AND PELVIC FLOOR DYSFUNCTION

During the act of defecation, when the intra-rectal pressure rises to a critical point anal sphincters need to be relaxed to facilitate expulsion of feces. In a subset of children with FC, a paradoxical contraction of external anal sphincter was observed with an increase of intra-rectal pressure, widely known as dyssynergic defecation. Both conventional manometry and the novel three-dimensional high-resolution anorectal manometry have shown the existence of dyssynergic defecation due to dysfunction of the sphincter complex, puborectalis muscle, and internal anal sphincter achalasia[44]. Internal anal sphincter achalasia is a rare condition, which could present with refractory FC. The exact pathophysiological mechanism has not been delineated and the condition is thought to be due to altered intramuscular innervation leading to a dysfunctional anal sphincter[45].

COLONIC DYSFUNCTION

One of the main physiological functions of the colon is to store and propel fecal matter. Several pathological processes, such as neuropathies, myopathies, and reduction of the number of Intestinal Cells of Cajal, which are considered as the pacemaker cells of the large intestine, could contribute to poor colonic transit. Studies have shown that children with intractable constipation have slow colonic transit using nuclear transit studies[46]. Other methods, such as conventional and high-resolution colonic manometry studies, have shown the lack of high amplitude propagatory contractions, reduction in retrograde cyclic motor pattern, and failure to induce a meal response with cyclic motor pattern in children with constipation[47]. Accumulation of feces might lead to dilatation and elongation of the colon leading to premature termination of high amplitude propagatory contractions and the release of nitric oxide, which inhibits myenteric neurons inducing secondary colonic dysfunction[48].

IMPACT OF FC

Economic and burden on hospitals

Being one of the commonest FGIDs, FC has serious ramifications on existing healthcare systems across the world. Emergency room visits for fecal impaction and abdominal pain, regular clinic visits, regular medications (which could be needed for months), sophisticated investigations, such as anorectal and colonic manometry, and occasional surgical intervention in refractory cases, contribute to the cost. In addition, analysis of national emergency department data from the US showed that fecal impaction due to FC is an important reason to visit the emergency room[49]. In a birth cohort study of children younger than 5 years, FC was reported to have the highest number of first-time medical visits compared to other chronic gastrointestinal disorders, including abdominal pain and gastroesophageal reflux[50]. A study conducted in Victoria, Australia, noted that FC represented 6.7% of annual hospital admission with annual cost of 5.5 million Australian dollars[3]. Using a nationally representative household survey, the annual cost of managing FC in children in the US was noted to be 3.9 billion for urinary stone disease[51]. All these studies indicate the economic burden of FC on healthcare systems and on national healthcare expenditure.

QUALITY OF LIFE AND IMPACT ON EDUCATION

Health related quality of life (HRQoL) is an indirect measure of the impact of a disease in a given individual. It is calculated as a composite numerical figure, including several components such as social, emotional, physical, and school functions. HRQoL has also been identified as one of the secondary outcome measures in clinical trials of FC. Several studies have reported poor HRQoL in children with FC. In a case-controlled study, Youssef reported that children with FC have a lower HRQoL than children with severe organic diseases, such as inflammatory bowel disease or gastroesophageal reflux, indicating the magnitude of the problem[52]. A hospital-based, case-control study from China also reported poor physical, emotional, social, and school related quality of life in children with FC[53]. A recent systematic review and a meta-analysis has clearly emphasized the negative impact of FC on HRQoL in children[2]. There are multitude of reasons for this observation. Symptoms of FC, such as pain during defecation and lower abdominal discomfort due to fecal impaction, could be troublesome to children. Associated fecal incontinence (FI) also leads to significant embarrassment and shame. Finally, psychological comorbidities associated with FC, including emotional and behavioral issues, maladjustment, and abnormal personality traits, also could negatively affect the quality of life of children[20,22,23].

Clinical evaluation

A thorough history and a complete physical examination are sufficient to diagnose constipation. The main components of the clinical history are given in the Table 2. The modified Bristol Stool Scale Form can be used to identify the type of stools in children to facilitate the diagnosis[54]. A complete physical examination, specifically designed to spot general growth and dysmorphic syndromes that could be associated with constipation, should be undertaken as a part of clinical evaluation (Table 3). Alarm features that indicate possible organic diseases also will be revealed during clinical evaluation (Table 4). Presence of such features demands further evaluation of the child for possible organic disorders. In the majority of children with FC, it is not necessary for such investigations; however, a thorough understanding of anorectal physiology, neurophysiology, and morphology is essential when symptoms become refractory despite adequate medical interventions.

COMMON INVESTIGATIONS

Several reviews have summarized the value of plain abdominal radiograph in identifying FC[55,56]. According to these reviews and clinical experiences, a plain abdominal radiograph does not provide any useful insights for management. Similarly, most of the routine blood tests, such as thyroid function tests, screening for cow's milk allergy or celiac disease, and checking for electrolyte abnormalities (hypokalemia, hypercalcemia) are not very helpful in day-to-day management of FC[55].

COLONIC FUNCTION

Colonic transit time

Colonic transit studies measure the ability of the colon to propel fecal matter and are useful in assessing overall colonic motor function. Delayed colonic transit time (CTT) was noted in children with FC due to anorectal dysfunction as well as colonic dysfunction[57]. Currently CTT is utilized only to differentiate constipation associated fecal incontinence from functional nonretentive fecal incontinence when a clinical differentiation is not possible[56].

Colonic manometry

Colonic physiology in children with FC is poorly understood. High-resolution colonic manometry is a valuable method to study physiological function, including motor and propulsive activity of the colon. In the beginning, the fasting motility is recorded, and the gastrocolic reflexes are assessed after a meal. Bisacodyl is instilled into the colon only when high amplitude propagatory contractions are not identified after a meal. Absence of high amplitude propagatory contractions, generalized colonic hypomotility, absence of response stimulant laxatives, and lack of increase in the cyclic retrograde propagatory motor patterns after a test meal are characteristic features in children with FC indicating neuromuscular dysfunction. In addition, premature termination of the propagation of contractions possibly indicates the presence of a segmental dysmotility[58]. These observations are helpful in decision making in management, such as surgery of refractory cases. However, there are several limitations, including limited availability, need for general anesthesia, high initial cost, and lack of normal data in children.

Table 2 Clinical history-taking

Component and subcomponents
Onset of symptoms and duration of the disease
Bowel habits
Frequency of stools
Nature of the stools
Fecal incontinence
Blood in stools
Passage of meconium
Other associated symptoms
Withholding behavior
Somatic symptoms
Past medical and surgical history
Bowel surgeries
Medications
Neuromuscular diseases
Dietary history
Fiber content in the diet
Frequency of junk food
Family history
Psychological history
Developmental history

ANORECTAL FUNCTION

Anorectal manometry

Anorectal manometry provides details on the length of the anal canal, rectal sensation, and squeeze sphincter pressures, rectoanal reflexes, and pressure changes in attempted balloon expulsion mimicking defecation. However, its main use is to exclude Hirschsprung disease in young children with constipation by demonstrating the absence of the rectoanal inhibitory reflex[55]. It is generally measured using either solid state or water perfused catheters.

Wireless motility capsule

The wireless motility capsule (WMC) is useful in measuring the transit through the different parts of the gastrointestinal transit. It is a non-invasive test that does not expose the patient to radiation. The pediatric studies using WMC, on the other hand are still in the early phase and have only been described as case studies[59]. The test is well tolerated up until the age of 8 years. WMC is beneficial in detecting the delayed colonic transit time in children with refractory constipation, and the results show a strong correlation with colonic transit time evaluated using radiopaque markers[60]. Therefore, the utility of WMC in children with FC should be investigated in future studies, particularly when FC is resistant to standard management strategies.

OTHER INVESTIGATIONS

Lower GI contrast studies in children are used to differentiate FC from Hirschsprung disease and assess the length of the aganglionic segment in Hirschsprung disease. However, the test is insensitive, and once a transitional zone is detected, a biopsy is needed to confirm the diagnosis. Defecography is not useful in the day-to-day management of constipation in children as the procedure exposes children to a significant amount of radiation and rectoceles, and rectal intussusceptions are rare in children. Similarly endoscopy is also not recommended in children with FC[61]. Although the use of ultrasonography in diagnosing FC has been reported, further refinements of the technique are needed before it is used in

Table 3 Physical examination

Component and subcomponents
General examination
Assessment of growth
Assessment of development
Abdominal examination
Abdominal distension
Surgical scars
Palpable fecal masses
Perianal observation
Position of the anus
Perianal excoriation and dermatitis
Scars, fissures, and tags
Patulous anus
Neurological evaluation
Spine
Lower limb neurological assessment

Table 4 Red flag features and their clinical relevance

Features and subfeatures
Hirschsprung disease
Delayed passage of meconium
Positive family history
Ribbon like stools
Significant abdominal distension
Child sexual abuse
Extreme fear of anal examination
Scars in the perianal region
Fissures in children > 2 yr of age
Neurological abnormalities
Hair tuft/hemangioma/scars on spine
Abnormal anal and cremasteric reflex
Deficiencies in lower limb neurology
Developmental delay
Other organic disorders
Bilious vomiting
Blood in stools
Failure to thrive
Malposition of the thyroid gland

current clinical practice[62]. MRI of the spine is only indicated in children who show features of intractable constipation and features suggestive of spinal anomaly indicated by a tuft of hair, hemangiomas, or scars in the lower spine and neurological signs in lower limbs.

Management

Clinical management of constipation has several facets. The main approaches are non-pharmacological interventions (education and demystification, dietary adjustment, toilet training, behavioral interventions, use of biofeedback, and pelvic floor physiotherapy), pharmacological interventions (oral and/or rectal laxatives, including novel drugs such as prucalopride and lubiprostone), and surgical interventions (antegrade enema and bowel resection), and other novel modalities, such as neuromodulation (Figure 1). The majority respond to one or combination of above-mentioned therapeutic strategies. It is crucial to understand that untreated or poorly managed children with FC tend to have significant complications. Therefore, it is quite important to treat these children effectively at the early stages to relieve symptoms.

POOR PROGNOSTIC FACTORS

Presence of poor prognostic factors may interfere with treatment success. Table 5 provides the possible factors that could influence prognosis[55]. It is imperative that the clinician looks into these factors at the initial assessment and use these factors in decision making while determining therapeutic options.

CLEAN UP THE RECTUM AND COLON

The majority of children with FC have a large fecal mass in their rectum. Therefore, the first step in the management is to clean up the rectal fecal mass and the impacted colon as much as possible. This facilitates the passage of stools during the maintenance phase as the colon and rectum impacted with hard fecal matter may not respond to the drugs commonly used in the management of FC. In a comparative study, both polyethylene glycol (PEG, 1.5 g/kg) and enemas for 3-6 d were equally effective in disimpaction. Both modalities had similar frequency of adverse effects with the exception of fecal incontinence, which was significantly more common in the group receiving PEG[63]. However, the oral route is generally well tolerated in children and therefore should be the first line therapy when available. In children where medical therapy is not effective or the rectum is impacted with an enormous scybalous, manual evacuation of impacted feces in the rectum is recommended.

MAINTENANCE THERAPY

In the maintenance stage, children are encouraged to pass stools regularly while using laxatives for at least 2 mo. This is to keep stools soft and make defecations less painful and less frightening. After disimpaction, this is achieved by using both pharmacological and proven nonpharmacological interventions using a step-down model with gradual tailing off of laxatives. Once regular defecation pattern is established, children with FC are managed with regular use of toilet and a balanced diet with adequate fluid and fiber intake.

NONPHARMACOLOGICAL INTERVENTIONS

Toilet training

The majority (80%-100%) of young children with FC demonstrate features of stool withholding and most of the stool withholders (> 80%) refuse to pass stools in the toilet (stool toileting refusal)[64]. Parents should encourage their child to sit on the potty or toilet for 5 min after waking and after lunch and dinner. They need to be instructed on proper seating method, how to keep legs and feet relaxed, how to relax the perineum, and how to strain to expel stools using a model toilet or a video. The process needs to be a conscious effort, and using mobile phones or tabs as rewards while sitting on the potty would be counterproductive. It is also imperative to counsel parents to reinforce the positive behavior of the child, especially when the child passes stools in the toilet/potty[65].

Behavioral and psychological intervention

There are many learned behavioral problems related to FC. They include toilet refusal, stress, and fear related to defecation. These behavior traits frequently lead to development and perpetuation of symptoms of FC. Therefore, in some children behavior therapy might be helpful in addition to medical treatment[66]. Novel therapeutic interventions, such as the use of principles of positive psychology, including resilience, optimism, and self-regulation providing a framework to achieve subjective well-being. These treatment modalities, when starting early in the disease process might be able to prevent the patient developing maladaptive coping habits, engage in high physical and psychological symptom

Table 5 Factors negatively affect the prognosis of functional constipation

Factor
Constipation during the 1st yr of life
Longer duration of symptoms before presentation
Low defecation frequency at presentation
Presence of fecal incontinence
Large diameter stools
Stool withholding
Nighttime urinary incontinence
Presence of fecal mass in abdomen/rectum
Prolonged colonic transit > 100 h
Failed balloon expulsion test

reporting, and exhibit poor, costly disease outcomes[67]. These new therapeutic modalities need to be explored in children with FC early in the disease process before bowel and psychological damage take place leading to poor long-term prognosis.

Dietary interventions

Fiber is an important dietary component with significant long term health benefits. The current recommendation from the American Health Foundation is to consume at least “age in years plus 5 g – 10 g” of fiber per day for children over 2 years[68]. Low fiber intake is a risk factor to develop FC in children[10]. In the last decades, 9 different fiber types have been tried as therapeutic agents for children with FC. They include cocoa husk, glucomannan, partially hydrolyzed guar gum, combination of acacia fiber, corn fiber, soy fiber, psyllium fiber, and fructose, galactooligosaccharides, and inulin-type fructose. A systematic review studying 10 randomized trials showed some beneficial effects of using fiber in treating children with FC. However, due to different types of fibers, different study designs, and small sample size, it is difficult to make strong recommendations[69]. Indeed, the ESPGHAN/NAPGHAN guideline recommends ensuring normal amount of dietary fiber intake for children with FC[55].

Probiotics

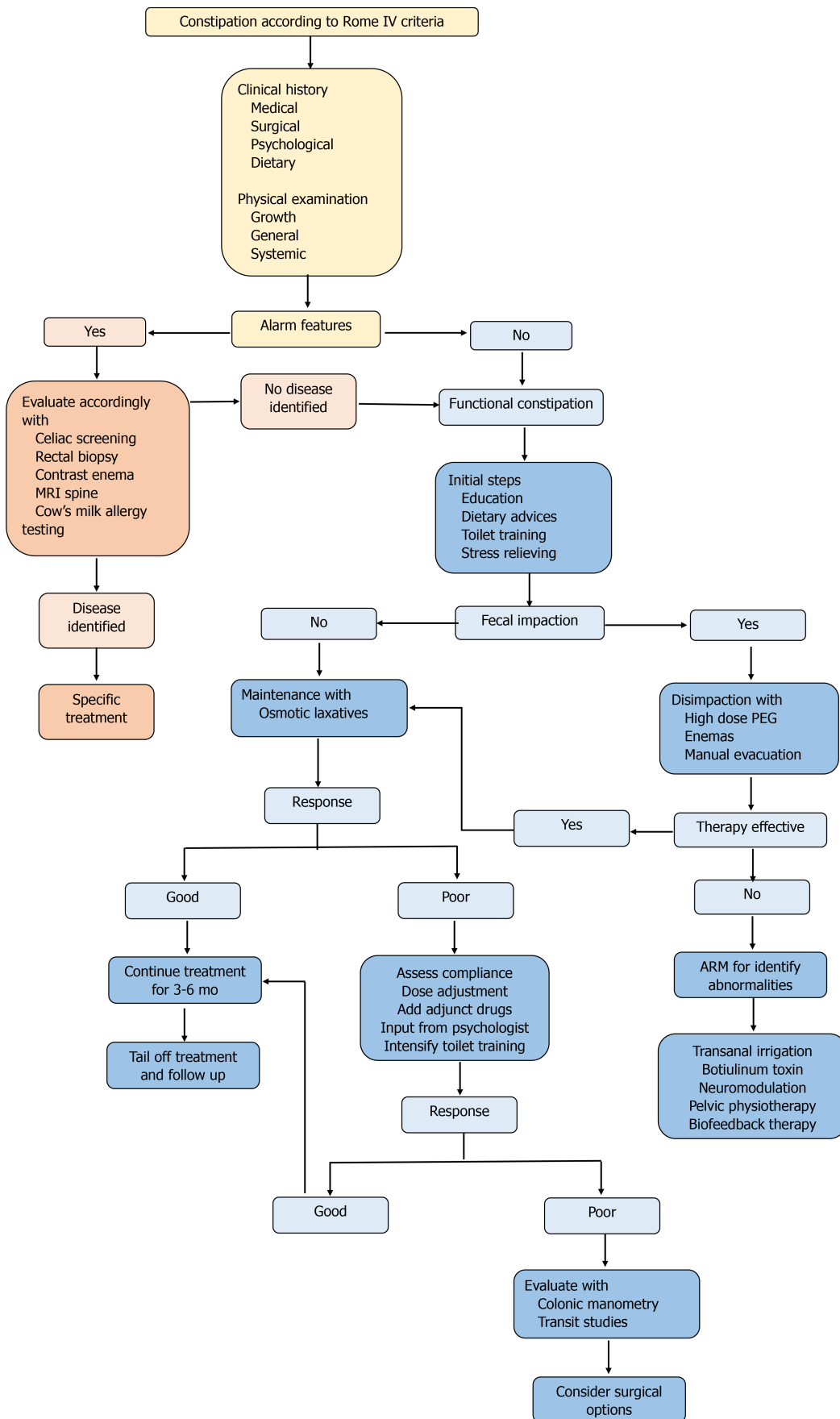
Dysbiosis is known to occur in children, although our knowledge of this important area is still in its infancy[38]. A systematic review published in 2017 assessed seven randomized controlled trials (RCTs) using probiotics for FC. In this systematic review the authors found that *Lactobacillus rhamnosus casei* Lcr35 is no more effective than a placebo in treating FC in children. None of the probiotics were effective in reducing frequency of fecal incontinence[70]. Other studies showed that *Lactobacillus rhamnosus* GG was not effective as adjunct therapy or with polyethylene glycol[71] in treating FC.

Other dietary modifications

Cow’s milk protein allergy had been considered as a possible associated factor with FC. Two studies evaluated the clinical utility of cow’s milk elimination diet in treating children with FC with variable results[72,73]. A recent trial conducted by Bourkheili *et al*[74], showed the efficacy of cow’s milk elimination diet in children who did not respond to laxatives. However, the open-label nature of the study leads to a high degree of bias in their findings. The ESPGHAN-NASPGHAN guideline recommends cow’s milk protein-free diet only in laxative resistant constipation and under the guidance of an expert[55]. Increasing water intake or hyperosmolar fluid has no significant effect on defecation frequency or improvement of consistency of stools[75]. The ESPGHAN-ESPGHAN guideline does not support the use of extra fluid intake in the treatment of FC[55]. Other studies of dietary interventions, such as Cassia Fistula emulsion and Descurainia Sophia seeds, showed high risk of bias and, therefore, could not recommended as therapeutic interventions[76,77].

Biofeedback and pelvic floor physiotherapy

Biofeedback gives a visual display of physiological monitoring of anorectal function while providing input by a therapist to retrain anorectal and perineal muscles. A systematic review concluded that biofeedback is not recommended for children with FC[78]. Similarly, the ESPGHAN-NASPGHAN guideline also does not recommend biofeedback as a therapeutic intervention for children with FC[55]. Pelvic floor physiotherapy uses motor relearning. The components of pelvic floor physiotherapy include supporting toilet training, increase awareness of sensation, and pelvic floor muscle training. A



DOI: 10.5409/wjcp.v11.i5.385 Copyright ©The Author(s) 2022.

Figure 1 Management flow chart of childhood constipation.

pragmatic trial using the Dutch pelvic floor physiotherapy protocol compared pelvic floor physiotherapy plus standard medical care with standard medical care. The primary outcome of the study was defined as the absence of FC according to the 6 Rome III criteria. In this study 24 out of 26 (92.3%) children receiving pelvic floor physiotherapy with standard medical care showed treatment success compared to 17/27 (63.0%) who received standard medical care (adjusted OR 11.7; 95%CI 1.8-78.3; $P = 0.011$)[79]. However, there are several limitations in this trial, including lack of blinding, small sample size, and alteration and adjustment of the protocol during the trial. Potential benefits of pelvic floor physiotherapy as a therapeutic option for FC need further elaboration.

Pharmacological interventions

Pharmacological interventions are the mainstay of therapy for childhood FC. There are several therapeutic agents that can effectively and safely be used either alone or in combination.

OSMOTIC LAXATIVES

A Cochrane systematic review reported that polyethylene glycol (PEG) was found to be superior to placebo, lactulose, and milk of magnesia to improve stool frequency[80]. In addition, they showed that a high dose of (0.7 g/kg) PEG was more effective at increasing stool frequency than a low dose (0.3 g/kg). The common adverse effects of PEG include flatulence, abdominal pain, nausea, diarrhea, and headache. Another meta-analysis found that PEG is also more effective in disimpaction than non-PEG laxatives, such as lactulose, magnesium hydroxide, and liquid paraffin[81]. Based on the current evidence, PEG is the most suitable drug for both disimpaction and maintenance of FC in children.

There are no RCTs comparing lactulose with placebo. Two trials compared lactulose with liquid paraffin[82,83]. When pooling the data using a fixed-effect model, liquid paraffin was shown to be more effective than lactulose in increasing stool frequency[80]. Other trials comparing lactulose with partially hydrolyzed guar gum found no difference in clinical efficacy between those therapeutic modalities and lactulose[84]. Lactulose is recommended to use as the first line maintenance therapy when PEG is not available[55].

STIMULANT LAXATIVES AND FECAL SOFTENERS

Bisacodyl is a stimulant laxative. It has a local prokinetic effect and stimulates intestinal secretion. Bisacodyl is a useful adjunct drug to osmotic laxatives in treating children with FC[55]. Senna is a natural laxative made from the leaves and fruits of the senna plant and is another stimulant laxative that is frequently used in treating children with FC. In a retrospective chart review from the US, it was noted that senna was effective as a laxative in the treatment of FC, and only 15% of the patients reported significant side effects, including abdominal cramps and diarrhea. None of the patients had to stop the laxative due to adverse effects[85]. Sodium picosulphate is the other available stimulant laxative used in clinical practice. Mineral oil is a time-tested fecal softener and is only recommended as an add-on therapy in the maintenance phase when the response to osmotic laxatives is suboptimal[55].

NOVEL THERAPEUTIC OPTIONS

Several prosecretory agents have shown to be effective in treating constipation in adults. They include prucalopride, lubiprostone, linaclotide, and plecanatide. These agents stimulate secretory function of the intestine at various levels and improve stool consistency and stool volume, leading to increase bowel movements. Prucalopride is a highly affinity 5-HT₄ receptor agonist with significant prokinetic properties. Studies in adults have shown beneficial effects of prucalopride in treating chronic constipation[86,87]. However, a large multicenter placebo-controlled randomized trial including 213 children (6-18 years) showed no significant difference in improvement in stool frequency and episodes of fecal incontinence between prucalopride and placebo[88]. Differences in mechanisms of constipation between children and adults, usage of different end points between studies (*e.g.*, inclusion of fecal incontinence in the pediatric study), and inclusion of a large number of children with refractory constipation may have contributed to the lack of response of prucalopride in childhood constipation.

Lubiprostone is a CIC-2 chloride channel activator and cystic fibrosis transmembrane conductance regulator. Studies in adults have shown clinical efficacy of lubiprostone in adults with chronic constipation, as well as IBS-C[89-91]. A large double-blind, placebo-controlled, multicenter study including more than 600 children with FC fulfilling the Rome IV criteria showed that 12 wk of lubiprostone treatment did not result in a statistically significant improvement in bowel movement frequency (to more than three times per week) in children with FC compared to placebo[92]. The reasons for not observing the desirable outcome of the trial may be similar to the prucalopride trial.

Linaclotide and plecanatide are guanylate cyclase C receptor agonists that promote secretion of fluid into the intestine. Although studies in adults show the efficacy of these two drugs in relieving constipation, no pediatric trials have been conducted. A retrospective chart review of 60 children with FC on linaclotide revealed that 45% had a positive response at 2.5 mo after starting the drug. However, about 1/3 of children on linaclotide had adverse events such as diarrhea, abdominal pain nausea, and bloating severe enough to stop treatment[93]. It is imperative to understand why these novel therapies are not working in children and find a way forward. Although the drugs make stools less hard and improve colonic motility by stimulating smooth muscles, none of these drugs address the main pathophysiological mechanisms of FC specially in younger children, *i.e.* stool withholding.

TRANSANAL IRRIGATION

Transanal irrigation systems irrigate the rectum and colon to clear accumulated feces. It is useful in children with constipation with severe recurrent fecal impaction resistant to conventional medical management. Three retrospective studies including children with constipation and FI (both organic and functional) have demonstrated improvement of FI when using transanal irrigation[94,95].

Surgical interventions

Surgical interventions are generally reserved for children whose symptoms are refractory to medical interventions. Around 10% of constipated children referred to a pediatric surgeon require some form of surgical intervention[96]. All these children need colonic and anorectal manometry and contrast enema of the lower bowel to delineate the physiological function and the anatomy before embarking into invasive surgical procedures.

ANTEGRADE CONTINENT ENEMA

In antegrade continent enema (ACE), a stoma is usually created to flush the colon from proximal to the distal direction using several surgical techniques. The initial procedure described was the Malone appendicocostomy, where the appendix is brought out through the umbilicus, creating a conduit with a valve through which a catheter can be passed to irrigate the colon[97], or cecostomy, where a catheter is kept permanently. Novel techniques, such as creating a neoappendix using a colonic flap, laparoscopic-assisted cecostomy tube insertion, and inserting a percutaneous cecostomy button following interventional radiological procedures, have also been invented to establish the flushing mechanism [98]. A systematic review showed that both procedures (appendicostomy and cecostomy) are equally effective achieving continence (80% *vs* 70%, respectively)[99].

SURGICAL RESECTION AND STOMAS

Several surgical resection techniques have been described in the management of intractable constipation. They include segmental resection, including proctocolectomy with reservoir and ileoanal anastomosis, laparoscopic or open sigmoidectomy with or without ACE, laparoscopic low anterior resection, ileostomy, and colostomy[100]. However, there is no consensus on the definition of intractable constipation, and the type of surgical pathway that should follow. The decision that has to be taken after careful discussion between a motility specialist and pediatric surgeon. The physiological function of the colon needs to be carefully studied using contrast studies, transit studies, defecography and, when available, colonic manometry. However, complications, such as fecal incontinence, persistence of constipation following surgery, leaking from stomas, stoma prolapse, and small bowel obstructions, are known complications of these surgical interventions.

BOTULINUM TOXIN INJECTION

Botulinum toxin A is a neurotoxin, and acts as a muscle relaxant. When injected into intersphincteric area, botulinum toxin relaxes the internal anal sphincter and facilitates the passage of stools. The intervention is reported to be successful in the majority of children with constipation and only a few who received the first dose needed a second injection[58]. Minor complications such as pain, transient urinary and fecal incontinence are known to occur in some children. Large prospective placebo-controlled trials with a long follow-up are needed to evaluate the true effectiveness of this invasive and costly treatment.

NEUROMODULATION

Neuromodulation is an evolving therapeutic modality where a selective group of nerve fibers is electrically stimulated to alter the physiological function of a desired organ through neural activity. This can be achieved using transcutaneous stimulation of the posterior tibial nerve, transabdominal stimulation, and an electrode insertion surgically into the sacral foramen. Sacral neuromodulation improves colonic motility by increasing both antegrade and retrograde propagatory contractions[101, 102]. Neuromodulation has been shown to be clinically effective (improving number of bowel motions and reducing frequency of fecal incontinence) in treating children with intractable constipation and slow transit constipation[103,104]. In addition, several systematic reviews have also shown the benefits of neuromodulation in children with constipation[105,106]. However, most of these studies are underpowered with a small number of patients, some were retrospective studies, and the majority had number of biases. In addition, there is no consensus on the frequency of stimulation or the duration of therapy. Therefore, it is difficult to draw firm conclusions in using neuromodulation as a treatment for chronic constipation in children.

Preventive measures

It is important to consider possible preventive measures that could be implemented for reducing incidence of FC in children. It is well known that stress, in any form, predisposes children to develop constipation. These events include minor home and school related events, child maltreatment, and exposure to civil unrest[107]. It is imperative to understand that most of these events are beyond the control of children. Teaching coping strategies with stress should be a part of modern school curricula, and through early psychological interventions, it may be possible to prevent constipation that is associated with psychological stress. In addition, identifying and addressing other psychological factors, such as anxiety, depression, internalization, and externalization, which are common in children with FC, need to be recognized and addressed early as primary or secondary preventive strategies[20,22,25,108]. Indrio and co-workers[109] provided evidence that prophylactic use of probiotics also would be able to prevent developing FC in young children with significant reduction in healthcare cost. The mechanisms of how probiotics play a role in prevention of FC is not entirely evident. However, it could possibly be through improvement of intestinal permeability, reduction of visceral sensitivity, changing mast cell density, and altering the cross talk between the brain and the gut through the brain-gut-microbiota axis. More research into this unexplored area with more convincing evidence would provide a potential window of opportunity to prevent constipation in the future. Improper or inadequate toilet training is a common risk factor for children to develop FC. Raising public awareness regarding the importance of timely toilet training would also help to reduce the prevalence of constipation. Additionally, educating parents and children about the importance of eating a balanced diet with the recommended amount of fiber and avoiding "junk food" is a critical step. Several studies have shown the association between sedentary lifestyle and constipation in children[30,34]. Therefore, encouraging physical activity in children would help in reducing the prevalence of FC. It is critical to recognize that, in today's competitive society, parents are compelled to work longer hours and spend less time with their children. Attention, attachment, appropriate parenting styles, and assisting children in developing desirable core lifestyles by setting a healthy example with proper dietary and physical activity patterns are also helpful in reducing the prevalence of FC.

Way forward into the future

It is evident that FC is a global public health problem with a significant physical, psychological, economic, and societal burden. Furthermore, at individual levels, chronic FC leads to physical and psychological consequences. The HRQoL of children is significantly affected due to both intestinal and extraintestinal symptoms of FC. Therefore, clinicians, and public health experts need to understand the gravity of the problem. Early aggressive, and effective medical therapy and other individualized non-pharmacological treatments need to be commenced as early as possible to prevent progressive bowel dysfunction and psychological consequences. Several therapeutic interventions may be used at the beginning of treatment, with gradual reduction of interventions as the child respond to treatment. Most of the novel investigations are only needed in children who do not respond to initial treatment. High resolution colonic and anorectal manometry are important investigations and will further improve the understanding of pathophysiology of chronic FC in children. In combination with a detailed clinical history and thorough physical examination, these novel investigation modalities reveals most of the pathophysiological processes that a clinician needs in decision making. The key drug in the medical management of FC in children will be PEG during for the foreseeable future. The other novel drugs will only be adjunct therapies. Researchers need to identify this reality, and novel drugs need to be tested in combination with PEG in randomized trials to improve the therapeutic armory. Surgical interventions are only needed in a minority of patients who are having severe and refractory constipation. Most of the described surgical interventions are studied in a non-randomized manner for several reasons. We believe more evidence is needed in major surgical procedures in the future to optimize the management of FC. Clinical validity of novel treatment options, such as pelvic floor physiotherapy and botulinum

toxin injection to the anal sphincter, need to be explored in well-designed randomized trials, as these treatments can be made available to many centers with collaborative training. Preventive measures should be explored widely across the world to minimize societal and economic burden of FC in children.

CONCLUSION

Childhood FC is a common health problem across the globe. The high prevalence is partly due to a multitude of risk factors which are highly prevalent among children. The aetiology of FC in children is not clearly understood. Stool withholding play a major role in developing FC in younger children while anorectal dysfunction, and colonic dysmotility significantly contribute to the development of FC in older children. FC is a clinical diagnosis established using the standard Rome IV criteria after a thorough clinical evaluation using clinical history and physical examination. Although commonly used most of the routine investigations are not helpful in diagnosing or day to day management. Anorectal, and colonic manometry are useful only in children who are refractory to conventional management strategies. The majority of children have fecal impaction when they present to a clinician. The first step in the management is to evacuate the rectal fecal mass either with oral PEG or enemas. The maintenance therapy using either osmotic laxatives alone or osmotic laxatives combined with stimulant laxatives aimed to prevent reaccumulation of fecal matter in the colon and the rectum. Although it may subject to variations, most children recover within 3-6 mo of therapy. Novel pharmacological interventions such as prucalopride, lubiprostone, and linaclotide need further clinical trials to prove their efficacy in children. The surgical options such as antegrade continent enema, creation of stomas, and bowel resection are only rarely needed in children and only reserved for refractory FC. It is imperative to understand that FC contributes to a significant healthcare expenditure, and reduction of HRQoL. Therefore, researchers should focus on developing preventive strategies to alleviate both the societal and healthcare burden of FC in children.

FOOTNOTES

Author contributions: Rajindrajith S developed the concept and wrote the initial manuscript; Devanarayana NM and Benninga MA edited the manuscript with significant intellectual contribution; All authors fulfilled the criteria for authorship established by the International Committee of Medical Journal Editors and verify the validity of the article.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (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: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Sri Lanka

ORCID number: Shaman Rajindrajith 0000-0003-1379-5052; Niranga Manjuri Devanarayana 0000-0002-2988-110X; Marc A Benninga 0000-0001-9406-9188.

S-Editor: Xing YX

L-Editor: Filipodia

P-Editor: Xing YX

REFERENCES

- 1 **Koppen IJN**, Vriesman MH, Saps M, Rajindrajith S, Shi X, van Etten-Jamaludin FS, Di Lorenzo C, Benninga MA, Tabbers MM. Prevalence of Functional Defecation Disorders in Children: A Systematic Review and Meta-Analysis. *J Pediatr* 2018; **198**: 121-130.e6 [PMID: 29656863 DOI: 10.1016/j.jpeds.2018.02.029]
- 2 **Vriesman MH**, Rajindrajith S, Koppen IJN, van Etten-Jamaludin FS, van Dijk M, Devanarayana NM, Tabbers MM, Benninga MA. Quality of Life in Children with Functional Constipation: A Systematic Review and Meta-Analysis. *J Pediatr* 2019; **214**: 141-150 [PMID: 31399248 DOI: 10.1016/j.jpeds.2019.06.059]
- 3 **Ansari H**, Ansari Z, Lim T, Hutson JM, Southwell BR. Factors relating to hospitalisation and economic burden of paediatric constipation in the state of Victoria, Australia, 2002-2009. *J Paediatr Child Health* 2014; **50**: 993-999 [PMID: 24976312 DOI: 10.1111/jpc.12675]

- 4 **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](#)]
- 5 **Chogle A**, Dhroove G, Sztainberg M, Di Lorenzo C, Saps M. How reliable are the Rome III criteria for the assessment of functional gastrointestinal disorders in children? *Am J Gastroenterol* 2010; **105**: 2697-2701 [PMID: [20808296](#) DOI: [10.1038/ajg.2010.350](#)]
- 6 **Hyams JS**, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Functional Disorders: Children and Adolescents. *Gastroenterology* 2016 [DOI: [10.1053/j.gastro.2016.02.015](#)]
- 7 **Russo M**, Strisciuglio C, Scarpato E, Bruzzese D, Casertano M, Staiano A. Functional Chronic Constipation: Rome III Criteria Versus Rome IV Criteria. *J Neurogastroenterol Motil* 2019; **25**: 123-128 [PMID: [30646483](#) DOI: [10.5056/jnm18035](#)]
- 8 **Mugie SM**, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. *Best Pract Res Clin Gastroenterol* 2011; **25**: 3-18 [PMID: [21382575](#) DOI: [10.1016/j.bpg.2010.12.010](#)]
- 9 **Park M**, Bang YG, Cho KY. Risk Factors for Functional Constipation in Young Children Attending Daycare Centers. *J Korean Med Sci* 2016; **31**: 1262-1265 [PMID: [27478337](#) DOI: [10.3346/jkms.2016.31.8.1262](#)]
- 10 **Inan M**, Aydiner CY, Tokuc B, Aksu B, Ayvaz S, Ayhan S, Ceylan T, Basaran UN. Factors associated with childhood constipation. *J Paediatr Child Health* 2007; **43**: 700-706 [PMID: [17640287](#) DOI: [10.1111/j.1440-1754.2007.01165.x](#)]
- 11 **Udoh EE**, Rajindrajith S, Devanarayana NM, Benninga MA. Prevalence and risk factors for functional constipation in adolescent Nigerians. *Arch Dis Child* 2017; **102**: 841-844 [PMID: [28446425](#) DOI: [10.1136/archdischild-2016-311908](#)]
- 12 **Huang Y**, Tan SY, Parikh P, Buthmanaban V, Rajindrajith S, Benninga MA. Prevalence of functional gastrointestinal disorders in infants and young children in China. *BMC Pediatr* 2021; **21**: 131 [PMID: [33731059](#) DOI: [10.1186/s12887-021-02610-6](#)]
- 13 **Chew KS**, Em JM, Koay ZL, Jalaludin MY, Ng RT, Lum LCS, Lee WS. Low prevalence of infantile functional gastrointestinal disorders (FGIDs) in a multi-ethnic Asian population. *Pediatr Neonatol* 2021; **62**: 49-54 [PMID: [32891528](#) DOI: [10.1016/j.pedneo.2020.08.009](#)]
- 14 **Ferreira-Maia AP**, Matijasevich A, Wang YP. Epidemiology of functional gastrointestinal disorders in infants and toddlers: A systematic review. *World J Gastroenterol* 2016; **22**: 6547-6558 [PMID: [27605889](#) DOI: [10.3748/wjg.v22.i28.6547](#)]
- 15 **Devanarayana NM**, Rajindrajith S. Association between constipation and stressful life events in a cohort of Sri Lankan children and adolescents. *J Trop Pediatr* 2010; **56**: 144-148 [PMID: [19696192](#) DOI: [10.1093/tropej/fmp077](#)]
- 16 **Sujatha B**, Velayutham DR, Deivamani N, Bavanandam S. Normal Bowel Pattern in Children and Dietary and Other Precipitating Factors in Functional Constipation. *J Clin Diagn Res* 2015; **9**: SC12-SC15 [PMID: [26266179](#) DOI: [10.7860/JCDR/2015/13290.6025](#)]
- 17 **Oswari H**, Alatas FS, Hegar B, Cheng W, Pramadyani A, Benninga MA, Rajindrajith S. Epidemiology of Paediatric constipation in Indonesia and its association with exposure to stressful life events. *BMC Gastroenterol* 2018; **18**: 146 [PMID: [30285647](#) DOI: [10.1186/s12876-018-0873-0](#)]
- 18 **Rajindrajith S**, Devanarayana NM, Lakmini C, Subasinghe V, de Silva DG, Benninga MA. Association between child maltreatment and constipation: a school-based survey using Rome III criteria. *J Pediatr Gastroenterol Nutr* 2014; **58**: 486-490 [PMID: [24253365](#) DOI: [10.1097/MPG.0000000000000249](#)]
- 19 **Cecil CAM**, Zhang Y, Nolte T. Childhood maltreatment and DNA methylation: A systematic review. *Neurosci Biobehav Rev* 2020; **112**: 392-409 [PMID: [32081689](#) DOI: [10.1016/j.neubiorev.2020.02.019](#)]
- 20 **Rajindrajith S**, Ranathunga N, Jayawickrama N, van Dijk M, Benninga MA, Devanarayana NM. Behavioral and emotional problems in adolescents with constipation and their association with quality of life. *PLoS One* 2020; **15**: e0239092 [PMID: [33044960](#) DOI: [10.1371/journal.pone.0239092](#)]
- 21 **Kilincaslán H**, Abali O, Demirkaya SK, Bilici M. Clinical, psychological and maternal characteristics in early functional constipation. *Pediatr Int* 2014; **56**: 588-593 [PMID: [24373103](#) DOI: [10.1111/ped.12282](#)]
- 22 **Ranasinghe N**, Devanarayana NM, Benninga MA, van Dijk M, Rajindrajith S. Psychological maladjustment and quality of life in adolescents with constipation. *Arch Dis Child* 2017; **102**: 268-273 [PMID: [27402734](#) DOI: [10.1136/archdischild-2016-310694](#)]
- 23 **van Dijk M**, Benninga MA, Grootenhuis MA, Last BF. Prevalence and associated clinical characteristics of behavior problems in constipated children. *Pediatrics* 2010; **125**: e309-e317 [PMID: [20083527](#) DOI: [10.1542/peds.2008-3055](#)]
- 24 **Waters AM**, Schilpzand E, Bell C, Walker LS, Baber K. Functional gastrointestinal symptoms in children with anxiety disorders. *J Abnorm Child Psychol* 2013; **41**: 151-163 [PMID: [22773359](#) DOI: [10.1007/s10802-012-9657-0](#)]
- 25 **Çağan Appak Y**, Yalın Sapmaz Ş, Doğan G, Herdem A, Özyurt BC, Kasırga E. Clinical findings, child and mother psychosocial status in functional constipation. *Turk J Gastroenterol* 2017; **28**: 465-470 [PMID: [29086714](#) DOI: [10.5152/tjg.2017.17216](#)]
- 26 **van Dijk M**, de Vries GJ, Last BF, Benninga MA, Grootenhuis MA. Parental child-rearing attitudes are associated with functional constipation in childhood. *Arch Dis Child* 2015; **100**: 329-333 [PMID: [25359759](#) DOI: [10.1136/archdischild-2014-305941](#)]
- 27 **Pediatrics AAO**. Guide to toilet training. New York: Penguin Random House, 2016
- 28 **Duong TH**, Jansson UB, Holmdahl G, Sillén U, Hellström AL. Urinary bladder control during the first 3 years of life in healthy children in Vietnam—a comparison study with Swedish children. *J Pediatr Urol* 2013; **9**: 700-706 [PMID: [23759503](#) DOI: [10.1016/j.jpuro.2013.04.022](#)]
- 29 **Asakura K**, Todoriki H, Sasaki S. Relationship between nutrition knowledge and dietary intake among primary school children in Japan: Combined effect of children's and their guardians' knowledge. *J Epidemiol* 2017; **27**: 483-491 [PMID: [28576447](#) DOI: [10.1016/j.je.2016.09.014](#)]
- 30 **Olaru C**, Diaconescu S, Trandafir L, Gimiga N, Stefanescu G, Ciubotariu G, Burlea M. Some Risk Factors of Chronic Functional Constipation Identified in a Pediatric Population Sample from Romania. *Gastroenterol Res Pract* 2016; **2016**: 3989721 [PMID: [27994619](#) DOI: [10.1155/2016/3989721](#)]

- 31 **Daher S**, Tahan S, Solé D, Naspitz CK, Da Silva Patricio FR, Neto UF, De Moraes MB. Cow's milk protein intolerance and chronic constipation in children. *Pediatr Allergy Immunol* 2001; **12**: 339-342 [PMID: [11846872](#) DOI: [10.1034/j.1399-3038.2001.0o057.x](#)]
- 32 **Borrelli O**, Barbara G, Di Nardo G, Cremon C, Lucarelli S, Frediani T, Paganelli M, De Giorgio R, Stanghellini V, Cucchiara S. Neuroimmune interaction and anorectal motility in children with food allergy-related chronic constipation. *Am J Gastroenterol* 2009; **104**: 454-463 [PMID: [19174791](#) DOI: [10.1038/ajg.2008.109](#)]
- 33 **El-Hodhod MA**, Younis NT, Zaitoun YA, Daoud SD. Cow's milk allergy related pediatric constipation: appropriate time of milk tolerance. *Pediatr Allergy Immunol* 2010; **21**: e407-e412 [PMID: [19555354](#) DOI: [10.1111/j.1399-3038.2009.00898.x](#)]
- 34 **Chien LY**, Liou YM, Chang P. Low defaecation frequency in Taiwanese adolescents: association with dietary intake, physical activity and sedentary behaviour. *J Paediatr Child Health* 2011; **47**: 381-386 [PMID: [21309885](#) DOI: [10.1111/j.1440-1754.2010.01990.x](#)]
- 35 **Asakura K**, Masayasu S, Sasaki S. Dietary intake, physical activity, and time management are associated with constipation in preschool children in Japan. *Asia Pac J Clin Nutr* 2017; **26**: 118-129 [PMID: [28049271](#) DOI: [10.6133/apjcn.112015.02](#)]
- 36 **Seidenfaden S**, Ormarsson OT, Lund SH, Björnsson ES. Physical activity may decrease the likelihood of children developing constipation. *Acta Paediatr* 2018; **107**: 151-155 [PMID: [28898506](#) DOI: [10.1111/apa.14067](#)]
- 37 **Zhao Y**, Yu YB. Intestinal microbiota and chronic constipation. *Springerplus* 2016; **5**: 1130 [PMID: [27478747](#) DOI: [10.1186/s40064-016-2821-1](#)]
- 38 **de Meij TG**, de Groot EF, Eck A, Budding AE, Kneepkens CM, Benninga MA, van Bodegraven AA, Savelkoul PH. Characterization of Microbiota in Children with Chronic Functional Constipation. *PLoS One* 2016; **11**: e0164731 [PMID: [27760208](#) DOI: [10.1371/journal.pone.0164731](#)]
- 39 **Zoppi GC**, M. ; Luciano, A. ; Benini, A. ; Muner, A. ; Bertazzoni M.E. The intestinal ecosystem in chronic constipation. *Acta Paediatr* 1998; **87**(8): 836-841 [DOI: [10.1080/080352598750013590](#)]
- 40 **Khalif IL**, Quigley EM, Konovitch EA, Maximova ID. Alterations in the colonic flora and intestinal permeability and evidence of immune activation in chronic constipation. *Dig Liver Dis* 2005; **37**: 838-849 [PMID: [16169298](#) DOI: [10.1016/j.dld.2005.06.008](#)]
- 41 **Baaleman DFR**, Rajindrajith S, Devanarayana NM, Di Lorenzo C, Benninga MA. Defecation Disorders in Children: Constipation and Fecal Incontinence. In: Guandalini SD A, editor Textbook of Pediatric Gastroenterology, Hepatology, and Nutrition A Comprehensive Guide to Practice. Second Edition ed. New York: Springer International Publishing AG Switzerland, 2021: 247-260 [DOI: [10.1007/978-3-030-80068-0_21](#)]
- 42 **van den Berg MM**, Bongers ME, Voskuijl WP, Benninga MA. No role for increased rectal compliance in pediatric functional constipation. *Gastroenterology* 2009; **137**: 1963-1969 [PMID: [19699738](#) DOI: [10.1053/j.gastro.2009.08.015](#)]
- 43 **van den Berg MM**, Voskuijl WP, Boeckstaens GE, Benninga MA. Rectal compliance and rectal sensation in constipated adolescents, recovered adolescents and healthy volunteers. *Gut* 2008; **57**: 599-603 [PMID: [17965058](#) DOI: [10.1136/gut.2007.125690](#)]
- 44 **van der Plas RN**, Benninga MA, Büller HA, Bossuyt PM, Akkermans LM, Redekop WK, Taminiu JA. Biofeedback training in treatment of childhood constipation: a randomised controlled study. *Lancet* 1996; **348**: 776-780 [PMID: [8813983](#) DOI: [10.1016/s0140-6736\(96\)03206-0](#)]
- 45 **Doodnath R**, Puri P. Internal anal sphincter achalasia. *Semin Pediatr Surg* 2009; **18**: 246-248 [PMID: [19782306](#) DOI: [10.1053/j.sempedsurg.2009.07.006](#)]
- 46 **Hutson JM**, Chase JW, Clarke MC, King SK, Sutcliffe J, Gibb S, Catto-Smith AG, Robertson VJ, Southwell BR. Slow-transit constipation in children: our experience. *Pediatr Surg Int* 2009; **25**: 403-406 [PMID: [19396449](#) DOI: [10.1007/s00383-009-2363-5](#)]
- 47 **Giorgio V**, Borrelli O, Smith VV, Rampling D, Köglmeier J, Shah N, Thapar N, Curry J, Lindley KJ. High-resolution colonic manometry accurately predicts colonic neuromuscular pathological phenotype in pediatric slow transit constipation. *Neurogastroenterol Motil* 2013; **25**: 70-8.e8 [PMID: [23030503](#) DOI: [10.1111/nmo.12016](#)]
- 48 **Dickson EJ**, Hennig GW, Heredia DJ, Lee HT, Bayguinov PO, Spencer NJ, Smith TK. Polarized intrinsic neural reflexes in response to colonic elongation. *J Physiol* 2008; **586**: 4225-4240 [PMID: [18635646](#) DOI: [10.1113/jphysiol.2008.155630](#)]
- 49 **Corban C**, Sommers T, Sengupta N, Jones M, Cheng V, Friedlander E, Bollom A, Lembo A. Fecal Impaction in the Emergency Department: An Analysis of Frequency and Associated Charges in 2011. *J Clin Gastroenterol* 2016; **50**: 572-577 [PMID: [26669560](#) DOI: [10.1097/MCG.0000000000000458](#)]
- 50 **Chitkara DK**, Talley NJ, Weaver AL, Katusic SK, De Schepper H, Rucker MJ, Locke GR 3rd. Incidence of presentation of common functional gastrointestinal disorders in children from birth to 5 years: a cohort study. *Clin Gastroenterol Hepatol* 2007; **5**: 186-191 [PMID: [16901769](#) DOI: [10.1016/j.cgh.2006.06.012](#)]
- 51 **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](#)]
- 52 **Youssef NN**, Langseder AL, Verga BJ, Mones RL, Rosh JR. Chronic childhood constipation is associated with impaired quality of life: a case-controlled study. *J Pediatr Gastroenterol Nutr* 2005; **41**: 56-60 [PMID: [15990631](#) DOI: [10.1097/01.mpg.0000167500.34236.6a](#)]
- 53 **Wang C**, Shang L, Zhang Y, Tian J, Wang B, Yang X, Sun L, Du C, Jiang X, Xu Y. Impact of Functional Constipation on Health-Related Quality of Life in Preschool Children and Their Families in Xi'an, China. *PLoS ONE* 2013; **8**(10) [DOI: [10.1371/journal.pone.0077273](#)]
- 54 **Gulati R**, Komuravelly A, Leb S, Mhanna MJ, Ghori A, Leon J, Needlman R. Usefulness of Assessment of Stool Form by the Modified Bristol Stool Form Scale in Primary Care Pediatrics. *Pediatr Gastroenterol Hepatol Nutr* 2018; **21**: 93-100 [PMID: [29713606](#) DOI: [10.5223/pghn.2018.21.2.93](#)]
- 55 **Tabbers MM**, DiLorenzo 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]
- 56 **Benninga MA**, Tabbers MM, van Rijn RR. How to use a plain abdominal radiograph in children with functional defecation disorders. *Arch Dis Child Educ Pract Ed* 2016; **101**: 187-193 [PMID: 27325615 DOI: 10.1136/archdischild-2015-309140]
 - 57 **Southwell BR**, Clarke MC, Sutcliffe J, Hutson JM. Colonic transit studies: normal values for adults and children with comparison of radiological and scintigraphic methods. *Pediatr Surg Int* 2009; **25**: 559-572 [PMID: 19488763 DOI: 10.1007/s00383-009-2387-x]
 - 58 **Lu PL**, Mousa HM. Constipation: Beyond the Old Paradigms. *Gastroenterol Clin North Am* 2018; **47**: 845-862 [PMID: 30337036 DOI: 10.1016/j.gtc.2018.07.009]
 - 59 **Fritz T**, Hünseler C, Broekaert I. Assessment of whole gut motility in adolescents using the wireless motility capsule test. *Eur J Pediatr* 2022; **181**: 1197-1204 [PMID: 34786599 DOI: 10.1007/s00431-021-04295-6]
 - 60 **Rodriguez L**, Heinz N, Colliard K, Amicangelo M, Nurko S. Diagnostic and clinical utility of the wireless motility capsule in children: A study in patients with functional gastrointestinal disorders. *Neurogastroenterol Motil* 2021; **33**: e14032 [PMID: 33184926 DOI: 10.1111/nmo.14032]
 - 61 **Excellence NifHaC**. Constipation in children and young people: diagnosis and management. 26th May 2010 ed. London: Royal College of Obstetricians and Gynaecologists, 2010
 - 62 **Bijoś A**, Czerwionka-Szaflarska M, Mazur A, Romańczuk W. The usefulness of ultrasound examination of the bowel as a method of assessment of functional chronic constipation in children. *Pediatr Radiol* 2007; **37**: 1247-1252 [PMID: 17952426 DOI: 10.1007/s00247-007-0659-y]
 - 63 **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]
 - 64 **Loening-Baucke V**. Constipation in early childhood: patient characteristics, treatment, and longterm follow up. *Gut* 1993; **34**: 1400-1404 [PMID: 8244110 DOI: 10.1136/gut.34.10.1400]
 - 65 **Taubman B**, Blum NJ, Nemeth N. Stool toileting refusal: a prospective intervention targeting parental behavior. *Arch Pediatr Adolesc Med* 2003; **157**: 1193-1196 [PMID: 14662573 DOI: 10.1001/archpedi.157.12.1193]
 - 66 **van Dijk M**, Benninga MA, Grootenhuis MA, Nieuwenhuizen AM, Last BF. Chronic childhood constipation: a review of the literature and the introduction of a protocolized behavioral intervention program. *Patient Educ Couns* 2007; **67**: 63-77 [PMID: 17374472 DOI: 10.1016/j.pec.2007.02.002]
 - 67 **Keefer L**. Behavioural medicine and gastrointestinal disorders: the promise of positive psychology. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 378-386 [PMID: 29651112 DOI: 10.1038/s41575-018-0001-1]
 - 68 **Williams CL**, Bollella M, Wynder EL. A new recommendation for dietary fiber in childhood. *Pediatrics* 1995; **96**: 985-988 [PMID: 7494677]
 - 69 **Axelrod CH**, Saps M. The Role of Fiber in the Treatment of Functional Gastrointestinal Disorders in Children. *Nutrients* 2018; **10** [PMID: 30400292 DOI: 10.3390/nu10111650]
 - 70 **Wojtyński K**, Szajewska H. Systematic review: probiotics for functional constipation in children. *Eur J Pediatr* 2017; **176**: 1155-1162 [PMID: 28762070 DOI: 10.1007/s00431-017-2972-2]
 - 71 **Wegner A**, Banaszkiewicz A, Kierkus J, Landowski P, Korlatowicz-Bilar A, Wiecek S, Kwiecien J, Gawronska A, Dembinski L, Czaja-Bulsa G, Socha P. The effectiveness of Lactobacillus reuteri DSM 17938 as an adjunct to macrogol in the treatment of functional constipation in children. A randomized, double-blind, placebo-controlled, multicentre trial. *Clin Res Hepatol Gastroenterol* 2018; **42**: 494-500 [PMID: 29650440 DOI: 10.1016/j.clinre.2018.03.008]
 - 72 **Dehghani SM**, Ahmadpour B, Haghighat M, Kashef S, Imanieh MH, Soleimani M. The Role of Cow's Milk Allergy in Pediatric Chronic Constipation: A Randomized Clinical Trial. *Iran J Pediatr* 2012; **22**: 468-474 [PMID: 23429756]
 - 73 **Iacono G**, Cavataio F, Montalto G, Florena A, Tumminello M, Soresi M, Notarbartolo A, Carroccio A. Intolerance of cow's milk and chronic constipation in children. *N Engl J Med* 1998; **339**: 1100-1104 [PMID: 9770556 DOI: 10.1056/NEJM199810153391602]
 - 74 **Mohammadi Bourkheili A**, Mehrabani S, Esmaeili Dooki M, Haji Ahmadi M, Moslemi L. Effect of Cow's-milk-free diet on chronic constipation in children: A randomized clinical trial. *Caspian J Intern Med* 2021; **12**: 91-96 [PMID: 33680404 DOI: 10.22088/cjim.12.1.91]
 - 75 **Young RJ**, Beerman LE, Vanderhoof JA. Increasing oral fluids in chronic constipation in children. *Gastroenterol Nurs* 1998; **21**: 156-161 [PMID: 9849179 DOI: 10.1097/00001610-199807000-00002]
 - 76 **Mozaffarpur SA**, Naseri M, Esmaeilidooki MR, Kamalinejad M, Bijani A. The effect of cassia fistula emulsion on pediatric functional constipation in comparison with mineral oil: a randomized, clinical trial. *Daru* 2012; **20**: 83 [PMID: 23351337 DOI: 10.1186/2008-2231-20-83]
 - 77 **Nimrouzi M**, Sadeghpour O, Imanieh MH, Shams Ardekani M, Salehi A, Minaei MB, Zarshenas MM. Flixweed vs. Polyethylene Glycol in the Treatment of Childhood Functional Constipation: A Randomized Clinical Trial. *Iran J Pediatr* 2015; **25**: e425 [PMID: 26196006 DOI: 10.5812/ijp.425]
 - 78 **Brazzelli M**, Griffiths PV, Cody JD, Tappin D. Behavioural and cognitive interventions with or without other treatments for the management of faecal incontinence in children. *Cochrane Database Syst Rev* 2011; CD002240 [PMID: 22161370 DOI: 10.1002/14651858.CD002240.pub4]
 - 79 **van Engelenburg-van Lonkhuyzen ML**, Bols EM, Benninga MA, Verwij WA, de Bie RA. Effectiveness of Pelvic Physiotherapy in Children With Functional Constipation Compared With Standard Medical Care. *Gastroenterology* 2017; **152**: 82-91 [PMID: 27650174 DOI: 10.1053/j.gastro.2016.09.015]
 - 80 **Gordon M**, MacDonald JK, Parker CE, Akobeng AK, Thomas AG. Osmotic and stimulant laxatives for the management of childhood constipation. *Cochrane Database Syst Rev* 2016; CD009118 [PMID: 27531591 DOI: 10.1002/14651858.CD009118.pub3]
 - 81 **Chen SL**, Cai SR, Deng L, Zhang XH, Luo TD, Peng JJ, Xu JB, Li WF, Chen CQ, Ma JP, He YL. Efficacy and

- complications of polyethylene glycols for treatment of constipation in children: a meta-analysis. *Medicine (Baltimore)* 2014; **93**: e65 [PMID: [25310742](#) DOI: [10.1097/MD.0000000000000065](#)]
- 82 **Farahmand F.** A randomised trial of liquid paraffin versus lactulose in the treatment of chronic functional constipation in children. *Acta Medica Iranica* 2007; **45**: 183-188
 - 83 **Urganci N, Akyildiz B, Polat TB.** A comparative study: the efficacy of liquid paraffin and lactulose in management of chronic functional constipation. *Pediatr Int* 2005; **47**: 15-19 [PMID: [15693860](#) DOI: [10.1111/j.1442-200x.2004.02001.x](#)]
 - 84 **Üstündağ G, Kuloğlu Z, Kirbaş N, Kansu A.** Can partially hydrolyzed guar gum be an alternative to lactulose in treatment of childhood constipation? *Turk J Gastroenterol* 2010; **21**: 360-364 [PMID: [21331988](#) DOI: [10.4318/tjg.2010.0121](#)]
 - 85 **Vilanova-Sanchez A, Gasior AC, Toocheck N, Weaver L, Wood RJ, Reck CA, Wagner A, Hoover E, Gagnon R, Jaggars J, Maloof T, Nash O, Williams C, Levitt MA.** Are Senna based laxatives safe when used as long term treatment for constipation in children? *J Pediatr Surg* 2018; **53**: 722-727 [PMID: [29429768](#) DOI: [10.1016/j.jpedsurg.2018.01.002](#)]
 - 86 **Camilleri M, Kerstens R, Rykx A, Vandeplasseche L.** A placebo-controlled trial of prucalopride for severe chronic constipation. *N Engl J Med* 2008; **358**: 2344-2354 [PMID: [18509121](#) DOI: [10.1056/NEJMoa0800670](#)]
 - 87 **Quigley EM, Vandeplasseche L, Kerstens R, Ausma J.** Clinical trial: the efficacy, impact on quality of life, and safety and tolerability of prucalopride in severe chronic constipation--a 12-week, randomized, double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2009; **29**: 315-328 [PMID: [19035970](#) DOI: [10.1111/j.1365-2036.2008.03884.x](#)]
 - 88 **Mugie SM, Korczowski B, Bodi P, Green A, Kerstens R, Ausma J, Ruth M, Levine A, Benninga MA.** Prucalopride is no more effective than placebo for children with functional constipation. *Gastroenterology* 2014; **147**: 1285-95.e1 [PMID: [25239590](#) DOI: [10.1053/j.gastro.2014.09.005](#)]
 - 89 **Barish CF, Drossman D, Johanson JF, Ueno R.** Efficacy and safety of lubiprostone in patients with chronic constipation. *Dig Dis Sci* 2010; **55**: 1090-1097 [PMID: [20012484](#) DOI: [10.1007/s10620-009-1068-x](#)]
 - 90 **Drossman DA, Chey WD, Johanson JF, Fass R, Scott C, Panas R, Ueno R.** Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome--results of two randomized, placebo-controlled studies. *Aliment Pharmacol Ther* 2009; **29**: 329-341 [PMID: [19006537](#) DOI: [10.1111/j.1365-2036.2008.03881.x](#)]
 - 91 **Johanson JF, Morton D, Geenen J, Ueno R.** Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. *Am J Gastroenterol* 2008; **103**: 170-177 [PMID: [17916109](#) DOI: [10.1111/j.1572-0241.2007.01524.x](#)]
 - 92 **Benninga MA, Hussain SZ, Sood MR, Nurko S, Hyman P, Clifford RA, O'Gorman M, Losch-Beridon T, Mareya S, Lichtlen P, Di Lorenzo C.** Lubiprostone for Pediatric Functional Constipation: Randomized, Controlled, Double-Blind Study With Long-term Extension. *Clin Gastroenterol Hepatol* 2022; **20**: 602-610.e5 [PMID: [33838349](#) DOI: [10.1016/j.cgh.2021.04.005](#)]
 - 93 **Baaleman DF, Gupta S, Benninga MA, Bali N, Vaz KH, Yacob D, Di Lorenzo C, Lu PL.** The Use of Linacotide in Children with Functional Constipation or Irritable Bowel Syndrome: A Retrospective Chart Review. *Paediatr Drugs* 2021; **23**: 307-314 [PMID: [33876403](#) DOI: [10.1007/s40272-021-00444-4](#)]
 - 94 **Ng J, Ford K, Dalton S, McDowell S, Charlesworth P, Cleeve S.** Transanal irrigation for intractable faecal incontinence and constipation: outcomes, quality of life and predicting non-adopters. *Pediatr Surg Int* 2015; **31**: 729-734 [PMID: [26163087](#) DOI: [10.1007/s00383-015-3735-7](#)]
 - 95 **Nasher O, Hill RE, Peeraully R, Wright A, Singh SJ.** Peristeen (□) transanal irrigation system for paediatric faecal incontinence: a single centre experience. *Int J Pediatr* 2014; **2014**: 954315 [PMID: [24895498](#) DOI: [10.1155/2014/954315](#)]
 - 96 **Wood RJ, Yacob D, Levitt MA.** Surgical options for the management of severe functional constipation in children. *Curr Opin Pediatr* 2016; **28**: 370-379 [PMID: [26963948](#) DOI: [10.1097/MOP.0000000000000345](#)]
 - 97 **Malone PS, Ransley PG, Kiely EM.** Preliminary report: the antegrade continence enema. *Lancet* 1990; **336**: 1217-1218 [PMID: [1978072](#) DOI: [10.1016/0140-6736\(90\)92834-5](#)]
 - 98 **Lawal TA, Rangel SJ, Bischoff A, Peña A, Levitt MA.** Laparoscopic-assisted Malone appendicostomy in the management of fecal incontinence in children. *J Laparoendosc Adv Surg Tech A* 2011; **21**: 455-459 [PMID: [21366440](#) DOI: [10.1089/lap.2010.0359](#)]
 - 99 **Li C, Shanahan S, Livingston MH, Walton JM.** Malone appendicostomy versus cecostomy tube insertion for children with intractable constipation: A systematic review and meta-analysis. *J Pediatr Surg* 2018; **53**: 885-891 [PMID: [29519574](#) DOI: [10.1016/j.jpedsurg.2018.02.010](#)]
 - 100 **Vilanova-Sanchez A, Levitt MA.** Surgical Interventions for Functional Constipation: An Update. *Eur J Pediatr Surg* 2020; **30**: 413-419 [PMID: [32987436](#) DOI: [10.1055/s-0040-1716729](#)]
 - 101 **Dinning PG, Fuentealba SE, Kennedy ML, Lubowski DZ, Cook JJ.** Sacral nerve stimulation induces pan-colonic propagating pressure waves and increases defecation frequency in patients with slow-transit constipation. *Colorectal Dis* 2007; **9**: 123-132 [PMID: [17223936](#) DOI: [10.1111/j.1463-1318.2006.01096.x](#)]
 - 102 **Patton V, Wiklendt L, Arkwright JW, Lubowski DZ, Dinning PG.** The effect of sacral nerve stimulation on distal colonic motility in patients with faecal incontinence. *Br J Surg* 2013; **100**: 959-968 [PMID: [23536312](#) DOI: [10.1002/bjs.9114](#)]
 - 103 **Veiga ML, Lordêlo P, Farias T, Barroso U Jr.** Evaluation of constipation after parasacral transcutaneous electrical nerve stimulation in children with lower urinary tract dysfunction--a pilot study. *J Pediatr Urol* 2013; **9**: 622-626 [PMID: [22857873](#) DOI: [10.1016/j.jpuro.2012.06.006](#)]
 - 104 **van Wunnik BP, Peeters B, Govaert B, Nieman FH, Benninga MA, Baeten CG.** Sacral neuromodulation therapy: a promising treatment for adolescents with refractory functional constipation. *Dis Colon Rectum* 2012; **55**: 278-285 [PMID: [22469794](#) DOI: [10.1097/DCR.0b013e3182405c61](#)]
 - 105 **Lu ML, He J, Lu S.** Electrical stimulation therapy for slow transit constipation in children: a systematic review. *Int J Colorectal Dis* 2015; **30**: 697-702 [PMID: [25772272](#) DOI: [10.1007/s00384-015-2180-3](#)]
 - 106 **Iacona R, Ramage L, Malakounides G.** Current State of Neuromodulation for Constipation and Fecal Incontinence in Children: A Systematic Review. *Eur J Pediatr Surg* 2019; **29**: 495-503 [PMID: [30650450](#) DOI: [10.1055/s-0038-1677485](#)]
 - 107 **Liyanarachchi H, Rajindrajith S, Kuruppu C, Chathurangana P, Ranawaka R, Devanarayana NM, Benninga MA.** Association between childhood constipation and exposure to stressful life events: a systematic review. *Neurogastroenterol*

- Motil* 2022; **34**: e14231 [PMID: [34415089](#) DOI: [10.1111/nmo.14231](#)]
- 108 **Zhao W**, Jin H, Xu M, Wang D, Liu Y, Tang Y, Zhang Q, Hua J, Wang B. Sleep Quality of Functional Gastrointestinal Disorder Patients in Class-Three Hospitals: A Cross-Sectional Study in Tianjin, China. *Biomed Res Int* 2018; **2018**: 3619748 [PMID: [29977909](#) DOI: [10.1155/2018/3619748](#)]
- 109 **Indrio F**, Di Mauro A, Riezzo G, Civardi E, Intini C, Corvaglia L, Ballardini E, Bisceglia M, Cinquetti M, Brazzoduro E, Del Vecchio A, Tafuri S, Francavilla R. Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation: a randomized clinical trial. *JAMA Pediatr* 2014; **168**: 228-233 [PMID: [24424513](#) DOI: [10.1001/jamapediatrics.2013.4367](#)]



Rational use of antibiotics in children with diabetic ketoacidosis needs attention

Xu Wang

Specialty type: Medicine, general and internal

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Cure E, Turkey; dildar S, Pakistan

Received: March 14, 2022

Peer-review started: March 14, 2022

First decision: May 11, 2022

Revised: June 20, 2022

Accepted: July 8, 2022

Article in press: July 8, 2022

Published online: September 9, 2022



Xu Wang, Department of Endocrinology, Children's Hospital of Nanjing Medical University, Nanjing 210008, China

Corresponding author: Xu Wang, MD, PhD, Doctor, Department of Endocrinology, Children's Hospital of Nanjing Medical University, No. 72 Guangzhou Road, Nanjing 210008, Jiangsu Province, China. sepnine@njmu.edu.cn

Abstract

Diabetic ketoacidosis (DKA) in children may lead to acute kidney injury (AKI). Among 45 children with DKA in our center, eight cases had AKI on admission, and in one child, his kidney function did not recover until 3 mo after discharge. This child was treated with antibiotics (cephalosporin), and we cannot rule out delayed AKI recovery due to the combined effects of the drug and the disease. Pediatricians should be concerned about the impact of nephrotoxic drug and disease interactions on children's kidney function, and need to follow up children with DKA and AKI to determine the development of AKI.

Key Words: Diabetic ketoacidosis; Acute kidney injury; Antibiotics; Nephrotoxic; Follow up

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Pediatricians should pay attention to the prevention of further damage to kidney function in children with Diabetic ketoacidosis (DKA) and acute kidney injury (AKI), and it is necessary to rationally use PK model to achieve drug safety. It is of concern that children with DKA and AKI events must be followed up to determine the development of AKI. Risk factors that may further affect kidney function also need to be avoided.

Citation: Wang X. Rational use of antibiotics in children with diabetic ketoacidosis needs attention. *World J Clin Pediatr* 2022; 11(5): 405-407

URL: <https://www.wjgnet.com/2219-2808/full/v11/i5/405.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v11.i5.405>

INTRODUCTION

Diabetic ketoacidosis (DKA) is a serious endocrine disease in children. DKA in children may present with obvious symptoms of dehydration, and even lead to acute kidney injury (AKI). We observed that among 45 children with DKA in our center, Children's Hospital of Nanjing Medical University, eight cases had AKI on admission, and 2 wk after DKA correction, seven cases had AKI recovery, and one case still had AKI on discharge. At follow-up 3 mo after discharge, the child's kidney function returned to normal. This child was treated with antibiotics (cephalosporin), and we cannot rule out delayed AKI recovery due to the combined effects of the drug and the disease. It is suggested that most children with DKA have prerenal volumic reactive injury, and a few children with DKA may experience endogenous renal tubule injury leading to AKI, which may be caused by disease and drug interaction. This highlights the need for rational use of antibiotics in specific disease states.

Because of the limited research on pharmacokinetics, pharmacodynamics and drug-disease interactions in children, drug dose selection for children is extremely challenging. Antibiotic is a kind of drugs with potential kidney toxicity. In the absence of specific dose regimen of antibiotics for children, a simple linear relationship between body weight and drug pharmacokinetics was assumed based on experience, and the dose for children was inferred from adult data. However, in the case with DKA and AKI, the kidney function of children has been impaired, and therapy of antibiotics based on experience may result in overdosing or underdosing. Once the fragile kidney function of children is further impaired by antibiotics therapy, it may exacerbate pharmacokinetic changes, such as antibiotics accumulation, and increased nephrotoxicity. Therefore, pediatricians should be concerned about the impact of nephrotoxic drug and disease interactions on children's kidney function.

The concept of prevention for drug-related kidney injury is important. Detailed history and holistic assessment can help identify the risk of nephrotoxicity from antibiotic therapy. Antibiotic dosages can be determined based on therapeutic drug concentration monitoring (TDM)[1]. However, the limitation of pediatric TDM is that most antibiotic target concentrations are derived from adult patients rather than measured from pediatric data. Pharmacokinetic models (PK) that are used in adults can be extended to pediatric patients through comparative studies of antibiotic pharmacokinetics between children and adults[2]. For the use of nephrotoxic antibiotic, PK model can quantify the effect of kidney injury on drugs[3,4] and promote the optimal use of antibiotics in children with DKA and AKI.

The purpose of this vision is to emphasize that pediatricians should pay attention to the prevention of further damage to kidney function in children with DKA and AKI, and it is necessary to rationally use PK model to achieve drug safety. It is of concern that children with DKA and AKI events must be followed up to determine the development of AKI. Risk factors that may further affect kidney function also need to be avoided.

CONCLUSION

In conclusion, in our study, of the 8 children with DKA complicated with AKI, 7 case did not receive antibiotics and 1 received cephalosporin, and the cephalosporin treated child showed delayed recovery from AKI. The selection of antibiotics in children is more challenging in special disease states, and we emphasize that pediatricians should pay attention to the impact of potentially nephrotoxic drug and disease interactions on children's renal function. Among them, vancomycin and ceftriaxone can be regarded as representative drugs for exacerbating AKI in special disease states, which is worthy of academic attention. In addition, since most antibiotics have varying degrees of renal toxicity, we aim to stress the rational use of PK model to achieve drug safety.

FOOTNOTES

Author contributions: Wang X conceptualized and designed the study, and drafted and revised the manuscript.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (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: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Xu Wang 0000-0002-1861-5922.

S-Editor: Liu JH

L-Editor: A

P-Editor: Liu JH

REFERENCES

- 1 **De Rose DU**, Cairoli S, Dionisi M, Santisi A, Massenzi L, Goffredo BM, Dionisi-Vici C, Dotta A, Auriti C. Therapeutic Drug Monitoring Is a Feasible Tool to Personalize Drug Administration in Neonates Using New Techniques: An Overview on the Pharmacokinetics and Pharmacodynamics in Neonatal Age. *Int J Mol Sci* 2020; **21** [PMID: [32824472](#) DOI: [10.3390/ijms21165898](#)]
- 2 **Maharaj AR**, Edginton AN. Physiologically based pharmacokinetic modeling and simulation in pediatric drug development. *CPT Pharmacometrics Syst Pharmacol* 2014; **3**: e150 [PMID: [25353188](#) DOI: [10.1038/psp.2014.45](#)]
- 3 **Emoto C**, Fukuda T, Johnson TN, Adams DM, Vinks AA. Development of a Pediatric Physiologically Based Pharmacokinetic Model for Sirolimus: Applying Principles of Growth and Maturation in Neonates and Infants. *CPT Pharmacometrics Syst Pharmacol* 2015; **4**: e17 [PMID: [26225230](#) DOI: [10.1002/psp4.17](#)]
- 4 **Yang F**, Tong X, McCarver DG, Hines RN, Beard DA. Population-based analysis of methadone distribution and metabolism using an age-dependent physiologically based pharmacokinetic model. *J Pharmacokinet Pharmacodyn* 2006; **33**: 485-518 [PMID: [16758333](#) DOI: [10.1007/s10928-006-9018-0](#)]



Children with type 1 diabetes in COVID-19 pandemic: Difficulties and solutions

Yue Shi, Li-Qun Wu, Peng Wei, Ze-Huan Liao

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): E

P-Reviewer: Abdelbasset WK, Saudi Arabia; Moshref RH, Saudi Arabia; Virarkar M, United States

Received: February 26, 2022

Peer-review started: February 26, 2022

First decision: April 17, 2022

Revised: June 1, 2022

Accepted: August 22, 2022

Article in press: August 22, 2022

Published online: September 9, 2022



Yue Shi, Li-Qun Wu, Second Clinical Medical College, Beijing University of Chinese Medicine, Beijing 100078, China

Peng Wei, School of Traditional Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100029, China

Ze-Huan Liao, School of Biological Sciences, Nanyang Technological University, Singapore 637551, Singapore

Ze-Huan Liao, Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm 17177, Sweden

Corresponding author: Ze-Huan Liao, BSc, Teaching Assistant, School of Biological Sciences, Nanyang Technological University, No. 60 Nanyang Distinct, Singapore 637551, Singapore. liao0058@e.ntu.edu.sg

Abstract

Children/adolescents with type 1 diabetes (T1D) require holistic approach and continuous care. However, the coronavirus disease 2019 (COVID-19) pandemic has made challenges for the T1D children and their caregivers, professionals, and the healthcare system. This minireview aims to consolidate and discuss the difficulties and solutions of children with type 1 diabetes in the COVID-19 pandemic. T1D has been the most common type of diabetes in children and adolescents and the last decades has seen a rapid increase in the prevalence of T1D in youths worldwide, which deserves a public concern particularly in the COVID-19 pandemic. As reported in previous studies, T1D is a risk factor related to severe cases, while the virus may induce new-onset diabetes and serious complications. Moreover, restriction strategies influence medical availability and lifestyle, impact glycemic control and complication management, and thus pose stress on families and health providers of youths with T1D, especially on those with certain fragile conditions. Therefore, special treatment plans are required for children provided by caregivers and the local health system. Latest health tools such as improved medical devices and telemedicine service, as well as a combined support may benefit in this period. This minireview emphasises that continued medical access and support are required to prevent deteriorated condition of children and adolescents with diabetes throughout this pandemic. Therefore, strategies are supposed to be formulated to mitigate the difficulties and stress among this group, particularly in the most at-risk population. Proposed solutions in this minireview may help individuals and the health system to overcome these

problems and help youths with T1D in better diabetes management during such emergency situations.

Key Words: Type 1 diabetes; Pediatrics; COVID-19 pandemic; Diabetes management; Glycemic control; Telemedicine

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: There are several reviews in the literature discussing the difficulties or solutions to the life of children with type 1 diabetes (T1D). However, this is the first review to collect and analyse the latest studies on which sub-groups of children with T1D are more likely to be influenced, how the coronavirus disease 2019 pandemic affects the treatment of children with T1D and the life of their caregivers, and what measures are supposed to be applied to deal with these dilemmas.

Citation: Shi Y, Wu LQ, Wei P, Liao ZH. Children with type 1 diabetes in COVID-19 pandemic: Difficulties and solutions. *World J Clin Pediatr* 2022; 11(5): 408-418

URL: <https://www.wjgnet.com/2219-2808/full/v11/i5/408.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v11.i5.408>

INTRODUCTION

Type 1 diabetes (T1D) is a heterogeneous disorder characterized by destruction of pancreatic beta cells, culminating in absolute insulin deficiency. It accounts for 5- 10% of the total cases of diabetes worldwide corresponding to 21-42 million people, while type 2 diabetes (T2D), characterized by a combination of resistance to insulin action and inadequate compensatory insulin secretory response, is the more prevalent category[1]. Particularly, in children and adolescents, T1D has been the most prevalent type of diabetes and 15%-20% of newly diagnosed patients are under age 5. Children with T1D and their caregivers are faced with challenges from various aspects such as physiology, psychology, and development[2].

The coronavirus disease 2019 (COVID-19) has been regarded as a global pandemic since 2020, leading to strict control policy and interrupted health care services, which contribute to challenges such as disruption in follow-up visits, restricted availability of medicines, and changes in lifestyle, particularly for those with chronic illnesses such as T1D[3,4].

Although there have already been some attempts to help to address these dilemmas, a systematic review on this issue has not been carried out. Since there are a large number of children and adolescents with T1D, who have specific concerns during the ongoing pandemic, we review the existing literature, related websites, and relevant guidelines to form this minireview to help resolve key questions in this area.

T1D and its treatments

T1D is a frequent chronic diseases in infants and the most common endocrinal disease in children and adolescents[5]. To diagnose the diabetes syndrome, both the history and check results are clues: A family history of diabetes is important, while a history of previous early childhood deaths or miscarriages is relevant. Pointers in the examination include evidence of sensorineural hearing loss or vision defects or developmental delay. Useful investigations include autoantibodies to glutamic acid decarboxylase, islet cells, audiogram and visual evoked responses, and fasting insulin and C-peptide. Further specialized checks include an echocardiogram, bone marrow aspirate, skeletal survey, and genetic testing[6].

Diabetes management mandates adherence to insulin, balanced diet, regular physical activity, and self-monitoring of blood glucose to achieve good glycemic control and prevent the development of short-term and long-term complications[7]. Pediatric diabetes management needs continuous parental supervision and confronts the whole family in challenges in the daily life, including regular blood glucose monitoring, insulin application, dietary indications, *etc*[8]. To achieve a favorable control, it is necessary to monitor blood sugar on a regular basis in a day, while for the patients who have erratic glycemic control or intermittent hypoglycemia, it is recommended to monitor at least 4 times a day and an additional check should be performed when there are signs or symptoms related to hypoglycemia [8]. In addition, children and adolescents with T1D require multiple daily insulin injections: The major organizations recommend one to two basal insulin injections with at least three regular or rapid acting insulin injections[8].

Unsatisfying metabolic control may result in the acute complications of hypoglycemia and ketoacidosis, poor growth, and chronic microvascular and macrovascular complications. Due to the fact that children and adolescents are more sensitive to a lack of insulin than adults, the youths are at higher risk of a rapid and dramatic development of diabetic ketoacidosis. Episodes of severe hypoglycemia or ketoacidosis especially in young children are risk factors for structural brain abnormalities and impaired cognitive function[9].

Challenges of type 1 diabetes in children during COVID-19 pandemic

Risk of contracting COVID-19 in patients with T1D: Diabetes can affect the immune response to pathogens and thus make patients vulnerable to the infections[10,11]. Diabetic patients are exposed to a higher risk of being infected compared to the healthy group and the risk is even greater in T1D children than in those with T2D, which may be attributed to immune dysfunction, micro- and macro-angiopathies induced by hyperglycemia, and more needs for medical interventions in this group[12,13]. Analyses carried out in many countries revealed that people with diabetes hospitalized for COVID-19 have a greater chance to suffer more severe outcomes, including twice the risk of requiring intensive unit care and increased risk of death[14-19]. It can be attributed to free radical overproduction due to viral infection, which can burden the oxidative stress, leading to pulmonary oxidative injury and inflammation[20]. Furthermore, the virus causes glucose metabolism disorders, which may entangle the pre-existing diabetes in complications[21].

Effect of COVID-19 on development of T1D: Viral infections are associated with the development of pancreatic autoantibodies leading to T1D in genetically susceptible children, and coronavirus family was considered to be an incriminating pathogen[22]. Viral infections trigger autoimmune insulinitis and pancreatic β -cell destruction by directly damaging β -cells, increasing the risk of autoantibody generation, and activating cytokine release and T cells[23]. According to previous surveys, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) binds to angiotensin-converting enzyme 2 receptors in the pancreas, consequently damaging islet cells and reduced insulin release[24]. During the COVID-19 pandemic, similar associations have been made for children[25,26].

The data in [Figure 1](#) represent the situation in Western Greece. The median ages of the patients are 10.94 years old and 12.07 years old in pre-COVID-19 years and COVID-19 years, respectively.

Cautions against COVID-19 on complications of T1D: Chloroquine and hydroxychloroquine are increasingly administered to treat COVID-19. However, these drugs may increase the incidence of hypoglycemia in diabetes patients[27]. Chloroquine stimulates insulin secretion, glucose uptake, and glycogen synthase, while hydroxychloroquine decreases insulin degradation, increases intracellular insulin accumulation, and stimulates insulin-mediated glucose transport[27,28]. All these functions can lead to a low blood glucose level and therefore, patients with T1D who use these agents need should be monitored for hypoglycemia ([Figure 2](#)).

Risk of diabetic ketoacidosis: COVID-19 can increase the opportunity of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state even in people without previously diagnosed diabetes[29]. Meanwhile, patients with T1D are at a greater risk of developing DKA especially in youths, and there are reports of prevalence of severe DKA in COVID children with established T1D[21,30,31]. Moreover, researchers have found that delayed diagnosis of new-onset T1D can lead to severe DKA, which may be due to reduced clinical visit for fear of being infected by SARS-CoV2, less access to emergency departments, closure of non-COVID-19-related hospital services, preoccupied doctors, and potential changes in access to insulin or self-monitoring of blood glucose test strips[32,33]. Certain features of DKA overlap with viral illnesses in youths and pediatricians should pay attention to symptoms including polyuria, polydipsia, weight loss, and Kussmaul breathing, as well as a fruity odour in breath. Ultimately, the standard of care for DKA to apply intravenous insulin may lead to a dilemma in the present pandemic because it often requires ICU admission. However, beds may be occupied for COVID-19 patients[31,34].

Influence of restriction strategies on individual T1D management: Strict isolation measures interrupt access to routine health care and social activities, thus increasing stress and anxiety among children and adolescents with T1D and their caregivers[4]. Since T1D is dominantly affected by alterations in daily routine, isolation measures pose a negative effect in glycemic control. However, interestingly, several researchers have reported contrary results that there was no deterioration or even improvement in glycemic management ([Table 1](#)).

Factors that worsen glycemic control: Difficulties in access to medical care was particularly prevalent in families with a lower socio-economic condition[35,36]. The COVID-19 pandemic has led to an economic crisis, and those whose financial stability was already difficult were first to suffer[37]. Researchers found that minority children had a higher glycosylated hemoglobin (HbA1c) level both in the pre-pandemic and the lockdown period than white race[38-40]. Similarly, patients with medical aid had a notably higher HbA1c and increase in HbA1c during the lockdown than those with private insurance[38]. Other publications have also indicated that youth whose families are in a disadvantaged financial condition

Table 1 Pros and cons of various methods in different groups

Target group	Methods	Pros	Cons
Patients	Routine glycemic management	Provide a more convenient and comfortable alternative	
	Sick day management	Avoid glycemic fluctuations and subsequent risk of complications	Need regular education and more rigorous adherence
	Psychosocial aids	May help to vent out distress	
	Physical activities	May help to reduce stress and achieve a healthy BMI	May be hard to perform because of the restriction in outdoor activities
Caregivers	Channels for voice and guidance	Eliminate the sense of overload	
	Provision of multidisciplinary ways	Provide economically accessible information	
	Groups on social media	Share perceptions and help each other	
Medical providers	Collaboration and intervals	Improve patient care equality, provide the learning opportunities to establish a holistic view	
	Financial and social stressors inquiries	Affect family engagement with healthcare providers	
	Persistent efforts	May help to get desired outcomes	
Telemedicine users		May help to get diabetes reviews, self-management support, and timely professional intervention with the minimised risk of virus transmission	Have difficulty to perform a suitable physical examination, lack widespread availability, have obstacles to gain collaboration, cannot replace the in-clinic visits in several circumstances

BMI: Body mass index.

have poorer glucose control[38-40]. The reason can be ascribed to the fact that many of those are supported by various programs for regular supply of insulin and glucose meterstrips[41]. However, these medicine and devices may be unavailable because of closure of nodal healthcare facilities and local transport facilities during the lockdown. Sequentially, the limited availability and the fear of shortage of medical supply forced these children with T1D to reduce glucose monitoring, which caused more frequent hypo-/hyperglycemic excursions[42]. Moreover, consequent DKA may emerge with unavailability of any type of insulin or technology-related problems such as pump dysfunction[43].

Female gender was a risk factor for unfavorable glycaemic control due to more mental effect[44,45]. Glycemic control interacts with stress, which may directly disturb glucose regulation, or indirectly result in non-adherence to treatment and unhealthy daily routine[46]. Previous epidemiological publications reported that females are at a greater risk for psychological disorders and perceived stress is more prevalent among females compared with males in the lockdown[47]. Interestingly, one study indicated that the glycemic control of males was more adversely affected in this period, which may be ascribed to more changes in almost all aspects of lifestyle among boys compared to girls[36].

Factors that improve glycemic control: Glycemic level in the school age children had significantly improved during the lockdown period, which may be attributed to more supervision of insulin injections and overall health care from their parents[48]. On the contrary, the pubertal adolescents group showed an adverse trend, which may be attributed to a change in independence from the parents during this age and more pressure from peer and themselves[36].

Although children and adolescents performed less physical activity and engaged in more sedentary behavior during the lockdown which impeded glycemic control, the changes in eating habits seemed to play a more essential role in glycemic management[49]. Healthy diet is essential for glycemic control. Evidence revealed that hyperglycemia is a significant predictor of some viral infections including COVID-19 which can exacerbate the complications of diabetes mellitus (DM)[50]. According to the literature review, adequate intake of dietary protein, fiber, essential fatty acids, and some micronutrients especially vitamins D, C, and B12, folate, zinc and selenium are beneficial to the prevention and treatment of COVID-19 in diabetic patients through modulation of innate and adaptive immune responses or direct effects on virus enzymes or cell entrance[50]. Due to home confinement, parents may monitor their children's behavior throughout the day. Particularly, compared to those with a longer duration of the disease, children with newly diagnosed or less than a year diabetes got more benefit from improvement in eating behaviors, which may be partially ascribed by taking over diabetes control from their caregivers[51]. Furthermore, outside dining and junk food consumption are prone to be

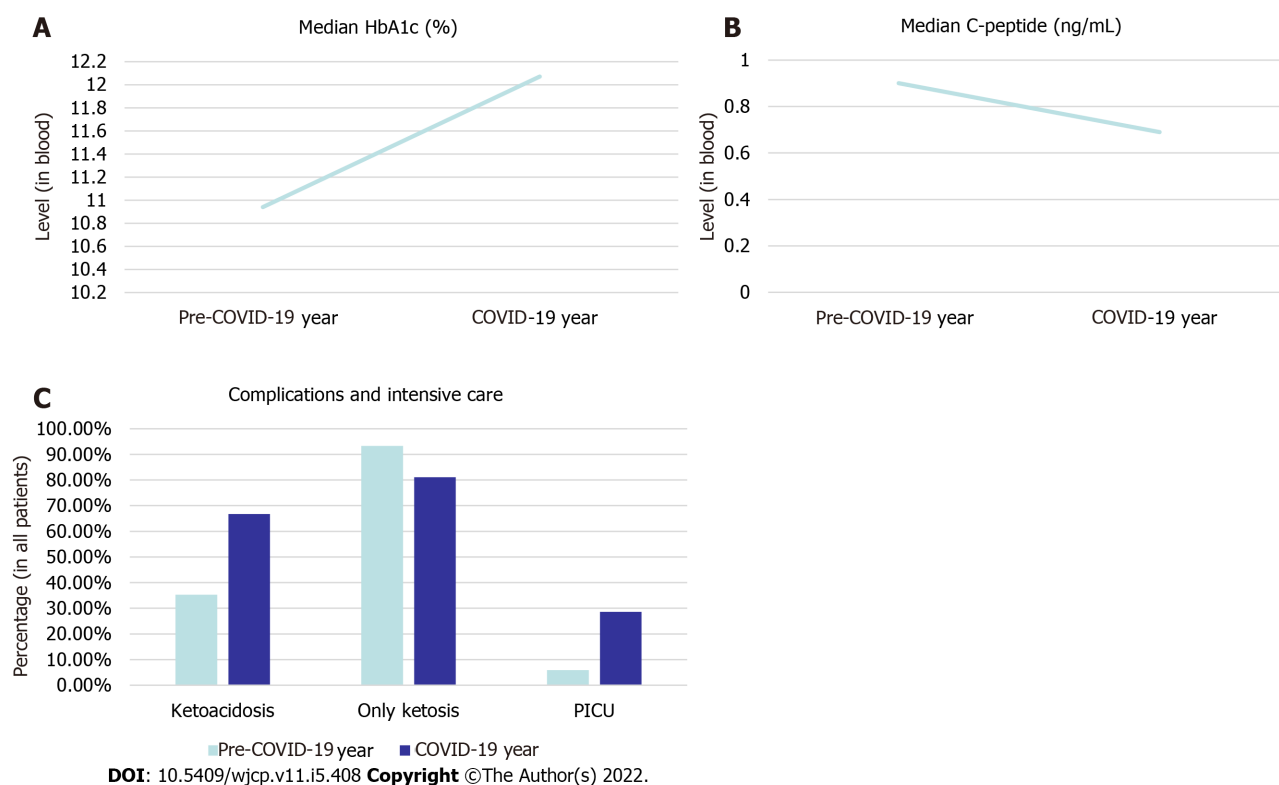


Figure 1 Characteristics of children and adolescents diagnosed with type 1 diabetes mellitus during the coronavirus disease 2019 year and pre-coronavirus disease 2019 year. A: Median higher glycosylated hemoglobin; B: Median C-peptide; C: Complications and intensive care. HbA1c: Higher glycosylated hemoglobin; COVID-19: The coronavirus disease 2019; PICU: Pediatric intensive care unit.

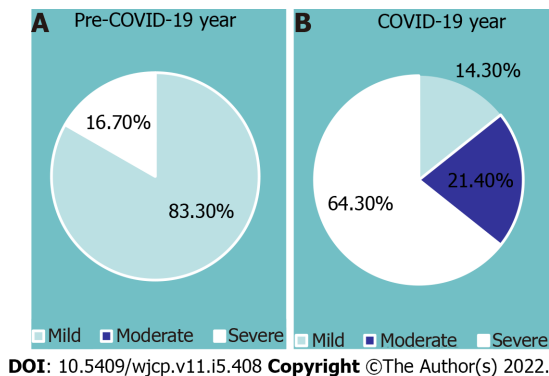


Figure 2 Severity of diabetic ketoacidosis in children and adolescents diagnosed with type 1 diabetes mellitus during the coronavirus disease 2019 year and pre-coronavirus disease 2019 year. A: Pre-coronavirus disease 2019 (COVID-19) year; B: COVID-19 year. COVID-19: The coronavirus disease 2019.

limited due to the lockdown, which may have reduced opportunities to adopt or engage in the unhealthy dietary habits or weight control practices that have been frequently observed in youths with diabetes[43,52]. In addition, the isolation measures may have reduced or canceled activities and contexts typically linked to social situation with peers that usually challenge good diabetes management and lead to behaviors negatively influencing glycemic control[53]. However, in certain areas, because of strict lockdown and suspension of food supplies, regular supply of important components of their healthy diet plan may be not available, which obstructs medical nutrition therapy and deserves the concern of government[54].

Hard time for caregivers of T1D children: Before the pandemic, caregivers played a fundamental role in family diabetes control and short or long-term consequence resolving[55]. Pediatric T1D is a very fragile context, in which the pandemic can lead to emotional adaptation disorders[56]. In some families of children and adolescents with T1D, the school nurse provided most of the diabetes care. However, because of the sudden closure of school, parents who needed extra help may have less access to

adequate training[38]. The unavailability of medical appointments, the lack of information about the relationship between COVID-19 and T1D, the difficulty in obtaining specialized support, and the inability to provide quality food and supplies for diabetes during the pandemic may generate negative feelings and insecurity in these caregivers[57,58]. Ultimately, the emotional burden of caregivers might not only influence the parents' mental health, but also negatively affect blood sugar control of their children[59].

Challenges related to the healthcare system: Patients with T1DM require continuous access to healthcare services. However, the lockdown and closure of healthcare centers may deprive these patients of access to medical support for their daily disease management and complication treatment. In addition, emergency issues like hypoglycemia or DKA requiring hospitalization may be precipitated, while infections such as COVID-19 or any other cases, may also lead to glycemic fluctuations and increase the risk of hospitalization[43,60]. How to deal with all the factors mentioned above poses challenges for the healthcare system.

Possible solutions for the difficulties

Self-management: Patients with T1DM need to adhere to frequent glucose monitoring, proper dietary behaviors, adequate hydration, and dose titration of glucose-lowering medication. As signified in publications, the up-to-date medical devices and test methods may bring convenience to these procedures. For instance, continuous glucose monitoring (CGM) and fast glucose monitoring systems are proved to be useful[61]. Moreover, percentage time in range and other CGM-derived metrics are the substitutes of HbA1c in the absence of routine laboratory tests related to the pandemic, which are potential to monitor the glycemic control[62]. Meanwhile, transitioning to CGM indicates "fewer finger punctures and less pain" for children and caregivers can constantly monitor the insulin level with the device[63]. In addition, the insulin pump allows T1D patients to achieve a better control as it tracks the glucose level and injects a proper dose of insulin automatically, thus generating a more comfortable alternative compared to multiple daily insulin injections[64].

The importance of management in sick days should be highlighted to avoid glycemic fluctuations and subsequent risk of DKA or hypoglycemia. As mentioned in publications, when children with T1D are under stress and acute infections, less food intake and more stress hormones may affect glycemic control, therefore it should be cautioned about the rising risk of either hyperglycemia or hypoglycemia [65]. Moreover, patients are recommended to take symptomatic therapy to reduce fever[66]. Ultimately, regular education about diabetes-related symptoms may contribute to a faster diagnosis of T1D and reduce the prevalence of DKA in children and adolescents, along with more rigorous adherence to "sick-day rules" which are recommended to diagnosed T1D patients[67].

Mental outcomes of the COVID-19 pandemic should be taken into consideration in the further treatment plan for children and adolescents with T1D[56]. To vent out distress, the most common method was sharing problems with companions[68].

Physical activities: As recommended by the World Health Organization, young people are supposed to practice more than 1 h per day, doing moderate or vigorous intensity physical activity[69]. However, the physical activity level of T1D children was low before the lockdown and further reduced in the pandemic[36]. Therefore, innovative methods such as appropriate indoor exercises may be a potential way to maintain or lift physical activity levels during the restriction of outdoor activities[36]. For instance, taking online physical training which provides various indoor exercise selections could be a beneficial choice for teenagers.

Use of telemedicine: A move towards telemonitoring to provide healthcare services for patients with diabetes has been part of a long-term plan in the management of the disease[70]. Hopefully, the public health emergency of the COVID-19 pandemic has accelerated the process[71]. Telemedicine services means that digital services substitute for the routine care to offer reviews and self-management advice on diabetes[71]. Telemedicine consultation minimizes the risk of virus transmission by maintaining physical distancing, while remote monitoring of electronic data enables health-care workers to provide in-time support in patients with worsening condition based on available data, which may benefit clinical outcomes[72].

However, there are still limitations in telemedicine including unavailability to perform a suitable physical examination, obstacles in wide spread because of difficulty of Internet construction in certain regions and populations, and challenges in establishing harmonious relationship with patients or helping resolve behavior problems or making effective communication and gaining collaboration[73, 74]. In addition, it should be emphasized that in-clinic visits are indispensable in some care processes at a certain frequency. Meanwhile, patients with a more acute disease including DKA or hyperosmolar hyperglycemic state should not simply adapt the transition to telemedicine[75]. Moreover, insulin initiation in new-onset T1D is typically required in in-clinic attendance and face-to-face training. Therefore, in the future, telemedicine is not merely about keeping patients away from hospitals, but it is about knowing who should be asked to come to the clinic and when at the same time[71].

Relieving the stress of caregivers: There are several possible strategies that should be used to reduce the mental impact on caregivers[58]. To begin with, channels for these caregivers' voice and guidance on emotional self-relief should be provided to eliminate the sense of overloading[58]. In addition, the multidisciplinary ways which provide physical, psychological, and nutritional guidance for children and adolescents with T1D should be economically accessible[58]. Nevertheless, creating social media groups to promote peer interaction in communicating their perceptions and helping each other could be beneficial[58].

Responsibility of medical providers: The whole is greater than the sum of its parts. To provide efficient help, local support groups should coordinate with the hospital team for better T1D management[43]. Interdisciplinary collaboration *via* staff meetings or other forms at a regular basis improves patient care equality, allowing medical providers to learn from others and perform medical service from a more holistic view[74,76]. To connect with individual patients, clinics should ask families about stress on finance and society due to the pandemic, which may influence their coordination with medical providers as well[74].

Furthermore, it was reported that interventions of glycemic management employed during the first two cycles did not produce satisfying outcomes for any target. However, in the 3rd cycle of intervention, the screening and consultation rates increased[74]. Therefore, it should be highlighted that persistent efforts make sense.

Limitations

The minireview is based on the articles mostly reported in English, which limits the extrapolation of results across the globe. Moreover, in most of the research, assessments of glycemic control were only based on HbA1c instead of the home blood glucose levels due to a variety of reasons. Additionally, albeit the use of self-reported measures administered online overcomes the impossibility of conducting a traditional paper survey during the pandemic, it may lead to imprecise ratings of specific anthropometric and clinical data, and subjective perceptions and behaviors. Similarly, thoughts and feelings may not have been sincerely, accurately, or fully revealed[77]. Notwithstanding the above limitations, all studies provide an invaluable report about the difficulties met by youths with T1D and promising solutions.

CONCLUSION

T1D is one of the most common endocrine metabolic disorders around the world[78]. Children with T1D are imperiled by psychological issues, owing to the underlying disease and the complex management of diabetes[79]. As discussed in the minireview, children and adolescents with diabetes are vulnerable to the COVID-19 pandemic resulting in worsening healthcare and would need specific medical access in this period for health advice and support. In addition, they are encouraged to keep a healthy lifestyle whenever possible during these difficult times. In addition, emotional overload leads to exhaustion in youths with T1D diabetes and those who are responsible to take care of them. More than ever, the mental well-being of T1D children and adolescents and their caregivers should be prioritized, and coping strategies should be advocated[58]. Moreover, the COVID-19 pandemic is an opportunity for telemedicine development and puts it to the forefront of diabetes management. Besides distant management of diabetes, identifying the at-risk groups to provide in-person consultation and care is also the value of routine telemonitoring[71]. Ultimately, cooperation and continuous effort should be made among medical providers, families with T1D youths, and the whole society.

In summary, we can conclude that youths with T1D require continuous care and attention during the COVID-19 pandemic because of various issues as discussed above. Proposed solutions in this article may assist them to resolve these obstacles in diabetes management to reduce the risk of complications particularly DKA during such emergency situations. Furthermore, proper prospective studies need to be conducted to identify the challenges faced by youths with T1DM during lockdown and their influence on glycemic control and complications, which may help us to come to more precise solutions to improve the welfare of children and adolescents with T1D during such pandemic.

FOOTNOTES

Author contributions: Shi Y drafted the review and performed the majority of the writing; Wu LQ, Wei P, and Liao ZH contributed to the writing and editing of the manuscript; Liao ZH accepted the editor invitation, conceptualized the topic, and proofread the manuscript; both Wei P and Liao ZH provided supervision and approved the submission of this minireview.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (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: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Singapore

ORCID number: Yue Shi 0000-0003-0225-0305; Li-Qun Wu 0000-0002-0840-2157; Peng Wei 0000-0002-3721-7014; Ze-Huan Liao 0000-0002-7500-1521.

Corresponding Author's Membership in Professional Societies: Associate Member of American Association for Cancer Research, 1075629.

S-Editor: Wang LL

L-Editor: Wang TQ

P-Editor: Wang LL

REFERENCES

- 1 DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet* 2018; **16**: 2449-2462 [PMID: 29916386 DOI: 10.1016/S0140-6736(18)31320-5]
- 2 Writing Group for the SEARCH for Diabetes in Youth Study Group. Dabelea D, Bell RA, D'Agostino RB Jr, Imperatore G, Johansen JM, Linder B, Liu LL, Loots B, Marcovina S, Mayer-Davis EJ, Pettitt DJ, Waitzfelder B. Incidence of diabetes in youth in the United States. *JAMA* 2007; **297**: 2716-2724 [PMID: 17595272 DOI: 10.1001/jama.297.24.2716]
- 3 WHO. Coronavirus disease 2019 (COVID-19): situation report, 75. [cited 20 April 2022]. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>
- 4 Kretzschmar IA, Asiedu-Danso M, Kretzschmar JP. Medication management and adherence during the COVID-19 pandemic: Perspectives and experiences from low-and middle-income countries. *Res Social Adm Pharm* 2021; **17**: 2023-2026 [PMID: 32307319 DOI: 10.1016/j.sapharm.2020.04.007]
- 5 DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet* 2018; **16**: 2449-2462 [PMID: 29916386 DOI: 10.1016/S0140-6736(18)31320-5]
- 6 Donaghue KC, Marcovecchio ML, Wadwa RP, Chew EY, Wong TY, Calliari LE, Zabeen B, Salem MA, Craig ME. ISPAD Clinical Practice Consensus Guidelines 2018: Microvascular and macrovascular complications in children and adolescents. *Pediatr Diabetes* 2018; **19** Suppl 27: 262-274 [PMID: 30079595 DOI: 10.1111/pedi.12742]
- 7 Noser AE, Patton SR, Van Allen J, Nelson MB, Clements MA. Evaluating Parents' Self-Efficacy for Diabetes Management in Pediatric Type 1 Diabetes. *J Pediatr Psychol* 2017; **42**: 296-303 [PMID: 27550634 DOI: 10.1093/jpepsy/jsw072]
- 8 Ferguson SC, Blane A, Wardlaw J, Frier BM, Perros P, McCrimmon RJ, Deary IJ. Influence of an early-onset age of type 1 diabetes on cerebral structure and cognitive function. *Diabetes Care* 2005; **28**: 1431-1437 [PMID: 15920064 DOI: 10.2337/diacare.28.6.1431]
- 9 Orioli L, Hermans MP, Thissen JP, Maiter D, Vandeleene B, Yombi JC. COVID-19 in diabetic patients: Related risks and specifics of management. *Ann Endocrinol (Paris)* 2020; **81**: 101-109 [PMID: 32413342 DOI: 10.1016/j.ando.2020.05.001]
- 10 Knapp S. Diabetes and infection: is there a link? *Gerontology* 2013; **59**: 99-104 [PMID: 23182884 DOI: 10.1159/000345107]
- 11 Carey IM, Critchley JA, DeWilde S, Harris T, Hosking FJ, Cook DG. Risk of Infection in Type 1 and Type 2 Diabetes Compared With the General Population: A Matched Cohort Study. *Diabetes Care* 2018; **41**: 513-521 [PMID: 29330152 DOI: 10.2337/dc17-2131]
- 12 Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: A review of pathogenesis. *Indian J Endocrinol Metab* 2012; **16** Suppl 1: S27-S36 [PMID: 22701840 DOI: 10.4103/2230-8210.94253]
- 13 Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]
- 14 Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, Klonoff DC. Glycemic Characteristics and Clinical Outcomes of COVID-19 Patients Hospitalized in the United States. *J Diabetes Sci Technol* 2020; **14**: 813-821 [PMID: 32389027 DOI: 10.1177/1932296820924469]
- 15 Chen Y, Yang D, Cheng B, Chen J, Peng A, Yang C, Liu C, Xiong M, Deng A, Zhang Y, Zheng L, Huang K. Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication. *Diabetes Care* 2020; **43**: 1399-1407 [PMID: 32409498 DOI: 10.2337/dc20-0660]
- 16 Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, Barron E, Bakhai C, Khunti K, Wareham NJ, Sattar N, Young B, Valabhji J. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol* 2020; **8**: 823-833 [PMID: 32798471 DOI: 10.1016/S2213-8587(20)30271-0]
- 17 Paternoster G, Sartini C, Pennacchio E, Lisanti F, Landoni G, Cabrini L. Awake pronation with helmet continuous positive airway pressure for COVID-19 acute respiratory distress syndrome patients outside the ICU: A case series. *Med Intensiva (Engl Ed)* 2020 [PMID: 33067029 DOI: 10.1016/j.medin.2020.08.008]

- 18 **Mantovani A**, Byrne CD, Zheng MH, Targher G. Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: A meta-analysis of observational studies. *Nutr Metab Cardiovasc Dis* 2020; **30**: 1236-1248 [PMID: [32571616](#) DOI: [10.1016/j.numecd.2020.05.014](#)]
- 19 **Fadini GP**, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. *J Endocrinol Invest* 2020; **43**: 867-869 [PMID: [32222956](#) DOI: [10.1007/s40618-020-01236-2](#)]
- 20 **Cuschieri S**, Grech S. COVID-19 and diabetes: The why, the what and the how. *J Diabetes Complications* 2020; **34**: 107637 [PMID: [32456846](#) DOI: [10.1016/j.jdiacomp.2020.107637](#)]
- 21 **Caruso P**, Longo M, Esposito K, Maiorino MI. Type 1 diabetes triggered by covid-19 pandemic: A potential outbreak? *Diabetes Res Clin Pract* 2020; **164**: 108219 [PMID: [32442555](#) DOI: [10.1016/j.diabres.2020.108219](#)]
- 22 **Op de Beeck A**, Eizirik DL. Viral infections in type 1 diabetes mellitus--why the β cells? *Nat Rev Endocrinol* 2016; **12**: 263-273 [PMID: [27020257](#) DOI: [10.1038/nrendo.2016.30](#)]
- 23 **Yang WL**, Li Q, Sun J, Huat Tan S, Tang YH, Zhao MM, Li YY, Cao X, Zhao JC, Yang JK. Potential drug discovery for COVID-19 treatment targeting Cathepsin L using a deep learning-based strategy. *Comput Struct Biotechnol J* 2022; **20**: 2442-2454 [PMID: [35602976](#) DOI: [10.1016/j.csbj.2022.05.023](#)]
- 24 **Uto H**, Matsuoka H, Murata M, Okamoto T, Miyata Y, Hori T, Ido A, Hirono S, Hayashi K, Tsubouchi H. A case of chronic hepatitis C developing insulin-dependent diabetes mellitus associated with various autoantibodies during interferon therapy. *Diabetes Res Clin Pract* 2000; **49**: 101-106 [PMID: [10963820](#) DOI: [10.1016/s0168-8227\(00\)00143-1](#)]
- 25 **Doğan Eİ**, Kurt BÖ. New-onset or Exacerbated Occupational Hand Eczema among Healthcare Workers During the COVID-19 Pandemic: A Growing Health Problem. *Acta Dermatovenereol Croat* 2021; **291**: 21-29 [PMID: [34477059](#)]
- 26 **Imanova Yaghji N**, Kan EK, Akcan S, Colak R, Atmaca A. Hydroxychloroquine Sulfate Related Hypoglycemia In A Non-Diabetic COVID-19 Patient: A Case Report and Literature Review. *Postgrad Med* 2021; **133**: 548-551 [PMID: [33583332](#) DOI: [10.1080/00325481.2021.1889820](#)]
- 27 **Halaby MJ**, Kastein BK, Yang DQ. Chloroquine stimulates glucose uptake and glycogen synthase in muscle cells through activation of Akt. *Biochem Biophys Res Commun* 2013; **435**: 708-713 [PMID: [23702482](#) DOI: [10.1016/j.bbrc.2013.05.047](#)]
- 28 **Li J**, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. *Diabetes Obes Metab* 2020; **22**: 1935-1941 [PMID: [32314455](#) DOI: [10.1111/dom.14057](#)]
- 29 **Smith SM**, Boppana A, Traupman JA, Unson E, Maddock DA, Chao K, Dobesh DP, Brufsky A, Connor RI. Impaired glucose metabolism in patients with diabetes, prediabetes, and obesity is associated with severe COVID-19. *J Med Virol* 2021; **93**: 409-415 [PMID: [32589756](#) DOI: [10.1002/jmv.26227](#)]
- 30 **Ho J**, Rosolowsky E, Pacaud D, Huang C, Lemay JA, Brockman N, Rath M, Doulla M. Diabetic ketoacidosis at type 1 diabetes diagnosis in children during the COVID-19 pandemic. *Pediatr Diabetes* 2021; **22**: 552-557 [PMID: [33745226](#) DOI: [10.1111/pedi.13205](#)]
- 31 **Cherubini V**, Gohil A, Addala A, Zanfardino A, Iafusco D, Hannon T, Maahs DM. Unintended Consequences of Coronavirus Disease-2019: Remember General Pediatrics. *J Pediatr* 2020; **223**: 197-198 [PMID: [32437758](#) DOI: [10.1016/j.jpeds.2020.05.004](#)]
- 32 **Croft A**, Bucca A, Jansen JH, Motzkus C, Herbert A, Wang A, Hunter BR. First-time Diabetic Ketoacidosis in Type 2 Diabetics With COVID-19 Infection: A Novel Case Series. *J Emerg Med* 2020; **59**: e193-e197 [PMID: [32912646](#) DOI: [10.1016/j.jemermed.2020.07.017](#)]
- 33 **Dzygalo K**, Nowaczyk J, Szwillig A, Kowalska A. Increased frequency of severe diabetic ketoacidosis at type 1 diabetes onset among children during COVID-19 pandemic lockdown: an observational cohort study. *Pediatr Endocrinol Diabetes Metab* 2020; **26**: 167-175 [PMID: [33554490](#) DOI: [10.5114/pedm.2020.101003](#)]
- 34 **Kostopoulou E**, Eliopoulou MI, Rojas Gil AP, Chrysis D. Impact of COVID-19 on new-onset type 1 diabetes mellitus - A one-year prospective study. *Eur Rev Med Pharmacol Sci* 2021; **25**: 5928-5935 [PMID: [34661251](#) DOI: [10.26355/eurev_202110_26869](#)]
- 35 **Cheng HP**, Wong JSL, Selveindran NM, Hong JYH. Impact of COVID-19 lockdown on glycaemic control and lifestyle changes in children and adolescents with type 1 and type 2 diabetes mellitus. *Endocrine* 2021; **73**: 499-506 [PMID: [34244903](#) DOI: [10.1007/s12020-021-02810-1](#)]
- 36 **Nicola M**, Alsafi Z, Sohrabi C, Kerwan A, Al-Jabir A, Iosifidis C, Agha M, Agha R. The socio-economic implications of the coronavirus pandemic (COVID-19): A review. *Int J Surg* 2020; **78**: 185-193 [PMID: [32305533](#) DOI: [10.1016/j.ijsu.2020.04.018](#)]
- 37 **Gayoso M**, Lim WY, Mulekar MS, Kaulfers AD. Effect of COVID-19 quarantine on diabetes Care in Children. *Clin Diabetes Endocrinol* 2021; **7**: 9 [PMID: [34020722](#) DOI: [10.1186/s40842-021-00122-x](#)]
- 38 **Johns C**, Faulkner MS, Quinn L. Characteristics of adolescents with type 1 diabetes who exhibit adverse outcomes. *Diabetes Educ* 2008; **34**: 874-885 [PMID: [18832292](#) DOI: [10.1177/0145721708322857](#)]
- 39 **Borschuk AP**, Everhart RS. Health disparities among youth with type 1 diabetes: A systematic review of the current literature. *Fam Syst Health* 2015; **33**: 297-313 [PMID: [25984737](#) DOI: [10.1037/fsh0000134](#)]
- 40 **Kumar KM**, Saboo B, Rao PV, Sarda A, Viswanathan V, Kalra S, Sethi B, Shah N, Srikanth SS, Jain SM, Raghupathy P, Shukla R, Jhingan A, Chowdhury S, Jabbar PK, Kanungo A, Joshi R, Kumar S, Tandon N, Khadilkar V, Chadha M. Type 1 diabetes: Awareness, management and challenges: Current scenario in India. *Indian J Endocrinol Metab* 2015; **19**: S6-S8 [PMID: [25941655](#) DOI: [10.4103/2230-8210.155339](#)]
- 41 **Odeh R**, Gharaibeh L, Daher A, Kussad S, Alassaf A. Caring for a child with type 1 diabetes during COVID-19 lockdown in a developing country: Challenges and parents' perspectives on the use of telemedicine. *Diabetes Res Clin Pract* 2020; **168**: 108393 [PMID: [32858098](#) DOI: [10.1016/j.diabres.2020.108393](#)]
- 42 **Jethwani P**, Saboo B, Jethwani L, Kesavadev J, Kalra S, Sahay R, Agarwal S, Hasnani D. Management of children and adolescents having type 1 diabetes during COVID-19 pandemic in India: challenges and solutions. *Int J Diabetes Dev Ctries* 2020; **1-5** [PMID: [32952333](#) DOI: [10.1007/s13410-020-00865-w](#)]
- 43 **Gerstl EM**, Rabl W, Rosenbauer J, Gröbe H, Hofer SE, Krause U, Holl RW. Metabolic control as reflected by HbA1c in children, adolescents and young adults with type-1 diabetes mellitus: combined longitudinal analysis including 27,035 patients from 207 centers in Germany and Austria during the last decade. *Eur J Pediatr* 2008; **167**: 447-453 [PMID: [17811111](#) DOI: [10.1007/s00431-008-0865-5](#)]

- 17924142 DOI: [10.1007/s00431-007-0586-9](https://doi.org/10.1007/s00431-007-0586-9)]
- 44 **Springer D**, Dziura J, Tamborlane WV, Steffen AT, Ahern JH, Vincent M, Weinzimer SA. Optimal control of type 1 diabetes mellitus in youth receiving intensive treatment. *J Pediatr* 2006; **149**: 227-232 [PMID: [16887440](https://pubmed.ncbi.nlm.nih.gov/16887440/) DOI: [10.1016/j.jpeds.2006.03.052](https://doi.org/10.1016/j.jpeds.2006.03.052)]
 - 45 **Agarwal N**, Harikar M, Shukla R, Bajpai A. COVID-19 pandemic: a double trouble for Indian adolescents and young adults living with type 1 diabetes. *Int J Diabetes Dev Ctries* 2020; **40**: 346-352 [PMID: [32963456](https://pubmed.ncbi.nlm.nih.gov/32963456/) DOI: [10.1007/s13410-020-00869-6](https://doi.org/10.1007/s13410-020-00869-6)]
 - 46 **Özdin S**, Bayrak Özdin Ş. Levels and predictors of anxiety, depression and health anxiety during COVID-19 pandemic in Turkish society: The importance of gender. *Int J Soc Psychiatry* 2020; **66**: 504-511 [PMID: [32380879](https://pubmed.ncbi.nlm.nih.gov/32380879/) DOI: [10.1177/0020764020927051](https://doi.org/10.1177/0020764020927051)]
 - 47 **Gao J**, Zheng P, Jia Y, Chen H, Mao Y, Chen S, Wang Y, Fu H, Dai J. Mental health problems and social media exposure during COVID-19 outbreak. *PLoS One* 2020; **15**: e0231924 [PMID: [32298385](https://pubmed.ncbi.nlm.nih.gov/32298385/) DOI: [10.1371/journal.pone.0231924](https://doi.org/10.1371/journal.pone.0231924)]
 - 48 **Dunton GF**, Do B, Wang SD. Early effects of the COVID-19 pandemic on physical activity and sedentary behavior in children living in the U.S. *BMC Public Health* 2020; **20**: 1351 [PMID: [32887592](https://pubmed.ncbi.nlm.nih.gov/32887592/) DOI: [10.1186/s12889-020-09429-3](https://doi.org/10.1186/s12889-020-09429-3)]
 - 49 **Marigliano M**, Maffei C. Glycemic control of children and adolescents with type 1 diabetes improved after COVID-19 lockdown in Italy. *Acta Diabetol* 2021; **58**: 661-664 [PMID: [33532867](https://pubmed.ncbi.nlm.nih.gov/33532867/) DOI: [10.1007/s00592-020-01667-6](https://doi.org/10.1007/s00592-020-01667-6)]
 - 50 **Elhenawy YI**, Eltonbary KY. Glycemic control among children and adolescents with type 1 diabetes during COVID-19 pandemic in Egypt: a pilot study. *Int J Diabetes Dev Ctries* 2021; **41**: 389-395 [PMID: [34257483](https://pubmed.ncbi.nlm.nih.gov/34257483/) DOI: [10.1007/s13410-021-00968-y](https://doi.org/10.1007/s13410-021-00968-y)]
 - 51 **Howe CJ**, Jawad AF, Kelly SD, Lipman TH. Weight-related concerns and behaviors in children and adolescents with type 1 diabetes. *J Am Psychiatr Nurses Assoc* 2008; **13**: 376-385 [PMID: [21672877](https://pubmed.ncbi.nlm.nih.gov/21672877/) DOI: [10.1177/1078390307310154](https://doi.org/10.1177/1078390307310154)]
 - 52 **Palladino DK**, Helgeson VS. Friends or foes? *J Pediatr Psychol* 2012; **37**: 591-603 [PMID: [22460759](https://pubmed.ncbi.nlm.nih.gov/22460759/) DOI: [10.1093/jpepsy/jss009](https://doi.org/10.1093/jpepsy/jss009)]
 - 53 **Smart CE**, Annan F, Higgins LA, Jelleryd E, Lopez M, Acerini CL. ISPAD Clinical Practice Consensus Guidelines 2018: Nutritional management in children and adolescents with diabetes. *Pediatr Diabetes* 2018; **19** Suppl 27: 136-154 [PMID: [30062718](https://pubmed.ncbi.nlm.nih.gov/30062718/) DOI: [10.1111/pedi.12738](https://doi.org/10.1111/pedi.12738)]
 - 54 **Harrington KR**, Boyle CT, Miller KM, Hilliard ME, Anderson BJ, Van Name M, DiMeglio LA, Laffel LM; T1D Exchange Clinic Network. Management and Family Burdens Endorsed by Parents of Youth <7 Years Old With Type 1 Diabetes. *J Diabetes Sci Technol* 2017; **11**: 980-987 [PMID: [28770627](https://pubmed.ncbi.nlm.nih.gov/28770627/) DOI: [10.1177/1932296817721938](https://doi.org/10.1177/1932296817721938)]
 - 55 **Carducci C**, Rapini N, Deodati A, Pampanini V, Cianfarani S, Schiaffini R. Post-traumatic stress disorder (PTSD) in parents of children with type 1 diabetes during COVID-19 pandemic. *Ital J Pediatr* 2021; **47**: 176 [PMID: [34446073](https://pubmed.ncbi.nlm.nih.gov/34446073/) DOI: [10.1186/s13052-021-01126-0](https://doi.org/10.1186/s13052-021-01126-0)]
 - 56 **Commissariat PV**, Harrington KR, Whitehouse AL, Miller KM, Hilliard ME, Van Name M, DeSalvo DJ, Tamborlane WV, Anderson BJ, DiMeglio LA, Laffel LM. "I'm essentially his pancreas": Parent perceptions of diabetes burden and opportunities to reduce burden in the care of children <8 years old with type 1 diabetes. *Pediatr Diabetes* 2020; **21**: 377-383 [PMID: [31808586](https://pubmed.ncbi.nlm.nih.gov/31808586/) DOI: [10.1111/pedi.12956](https://doi.org/10.1111/pedi.12956)]
 - 57 **Alessi J**, de Oliveira GB, Erthal IN, Teixeira JB, Morello MS, Ribeiro RJE, de Carvalho TR, Jaeger EH, Schaan BD, Telo GH. "Not having a minute of self-distancing during the social distancing is exhausting": a qualitative study on the perspective of caregivers of youth with type 1 diabetes during the COVID-19 pandemic. *Acta Diabetol* 2021; **58**: 1533-1540 [PMID: [34132868](https://pubmed.ncbi.nlm.nih.gov/34132868/) DOI: [10.1007/s00592-021-01753-3](https://doi.org/10.1007/s00592-021-01753-3)]
 - 58 **Van Gampelaere C**, Luyckx K, Van Ryckeghem DML, van der Straaten S, Laridaen J, Goethals ER, Casteels K, Vanbesien J, den Brinker M, Cools M, Goubert L. Mindfulness, Worries, and Parenting in Parents of Children With Type 1 Diabetes. *J Pediatr Psychol* 2019; **44**: 499-508 [PMID: [30590544](https://pubmed.ncbi.nlm.nih.gov/30590544/) DOI: [10.1093/jpepsy/isy094](https://doi.org/10.1093/jpepsy/isy094)]
 - 59 **Brink S**, Joel D, Laffel L, Lee WW, Olsen B, Phelan H, Hanas R; International Society for Pediatric and Adolescent Diabetes. ISPAD Clinical Practice Consensus Guidelines 2014. Sick day management in children and adolescents with diabetes. *Pediatr Diabetes* 2014; **15** Suppl 20: 193-202 [PMID: [25182314](https://pubmed.ncbi.nlm.nih.gov/25182314/) DOI: [10.1111/pedi.12193](https://doi.org/10.1111/pedi.12193)]
 - 60 **Caballero AE**, Ceriello A, Misra A, Aschner P, McDonnell ME, Hassanein M, Ji L, Mbanya JC, Fonseca VA. COVID-19 in people living with diabetes: An international consensus. *J Diabetes Complications* 2020; **34**: 107671 [PMID: [32651031](https://pubmed.ncbi.nlm.nih.gov/32651031/) DOI: [10.1016/j.jdiacomp.2020.107671](https://doi.org/10.1016/j.jdiacomp.2020.107671)]
 - 61 **Danne T**, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, Garg S, Heinemann L, Hirsch I, Amiel SA, Beck R, Bosi E, Buckingham B, Cobelli C, Dassau E, Doyle FJ 3rd, Heller S, Hovorka R, Jia W, Jones T, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Maahs D, Murphy HR, Nørgaard K, Parkin CG, Renard E, Saboo B, Scharf M, Tamborlane WV, Weinzimer SA, Phillip M. International Consensus on Use of Continuous Glucose Monitoring. *Diabetes Care* 2017; **40**: 1631-1640 [PMID: [29162583](https://pubmed.ncbi.nlm.nih.gov/29162583/) DOI: [10.2337/dc17-1600](https://doi.org/10.2337/dc17-1600)]
 - 62 **Şahinol M**, Başkavak G. Contested Daily Routines, Contested Care. Children with Type 1 Diabetes in COVID-19 Times. *Childhood Vulnerability* 2021; **3**: 23-40 [DOI: [10.1007/s41255-021-00017-0](https://doi.org/10.1007/s41255-021-00017-0)]
 - 63 **Bergenstal RM**, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, Joyce C, Peoples T, Perkins BA, Welsh JB, Willi SM, Wood MA; STAR 3 Study Group. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med* 2010; **363**: 311-320 [PMID: [20587585](https://pubmed.ncbi.nlm.nih.gov/20587585/) DOI: [10.1056/NEJMoa1002853](https://doi.org/10.1056/NEJMoa1002853)]
 - 64 **Chiang JL**, Maahs DM, Garvey KC, Hood KK, Laffel LM, Weinzimer SA, Wolfsdorf JL, Schatz D. Type 1 Diabetes in Children and Adolescents: A Position Statement by the American Diabetes Association. *Diabetes Care* 2018; **41**: 2026-2044 [PMID: [30093549](https://pubmed.ncbi.nlm.nih.gov/30093549/) DOI: [10.2337/doi18-0023](https://doi.org/10.2337/doi18-0023)]
 - 65 **Bornstein SR**, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, Boehm B, Amiel S, Holt RI, Skyler JS, DeVries JH, Renard E, Eckel RH, Zimmet P, Alberti KG, Vidal J, Geloneze B, Chan JC, Ji L, Ludwig B. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol* 2020; **8**: 546-550 [PMID: [32334646](https://pubmed.ncbi.nlm.nih.gov/32334646/) DOI: [10.1016/S2213-8587\(20\)30152-2](https://doi.org/10.1016/S2213-8587(20)30152-2)]
 - 66 **Lee AA**, Piette JD, Heisler M, Rosland AM. Diabetes Distress and Glycemic Control: The Buffering Effect of Autonomy Support From Important Family Members and Friends. *Diabetes Care* 2018; **41**: 1157-1163 [PMID: [29599295](https://pubmed.ncbi.nlm.nih.gov/29599295/) DOI: [10.2337/dc17-2396](https://doi.org/10.2337/dc17-2396)]

- 67 **Bull FC**, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, Carty C, Chaput JP, Chastin S, Chou R, Dempsey PC, DiPietro L, Ekelund U, Firth J, Friedenreich CM, Garcia L, Gichu M, Jago R, Katzmarzyk PT, Lambert E, Leitzmann M, Milton K, Ortega FB, Ranasinghe C, Stamatakis E, Tiedemann A, Troiano RP, van der Ploeg HP, Wari V, Willumsen JF. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. *Br J Sports Med* 2020; **54**: 1451-1462 [PMID: [33239350](#) DOI: [10.1136/bjsports-2020-102955](#)]
- 68 **Bain SC**, Czernichow S, Bøgelund M, Madsen ME, Yssing C, McMillan AC, Hvid C, Hettiarachchige N, Panton UH. Costs of COVID-19 pandemic associated with diabetes in Europe: a health care cost model. *Curr Med Res Opin* 2021; **37**: 27-36 [PMID: [33306421](#) DOI: [10.1080/03007995.2020.1862775](#)]
- 69 **Danne T**, Limbert C, Puig Domingo M, Del Prato S, Renard E, Choudhary P, Seibold A. Telemonitoring, Telemedicine and Time in Range During the Pandemic: Paradigm Change for Diabetes Risk Management in the Post-COVID Future. *Diabetes Ther* 2021; **12**: 2289-2310 [PMID: [34338994](#) DOI: [10.1007/s13300-021-01114-x](#)]
- 70 **Castle JR**, Rocha L, Ahmann A. How COVID-19 Rapidly Transformed Clinical Practice at the Harold Schnitzer Diabetes Health Center Now and for the Future. *J Diabetes Sci Technol* 2020; **14**: 721-722 [PMID: [32443962](#) DOI: [10.1177/1932296820929368](#)]
- 71 **Espinoza J**, Shah P, Raymond J. Integrating Continuous Glucose Monitor Data Directly into the Electronic Health Record: Proof of Concept. *Diabetes Technol Ther* 2020; **22**: 570-576 [PMID: [31904260](#) DOI: [10.1089/dia.2019.0377](#)]
- 72 **Brodar KE**, Hong N, Liddle M, Hernandez L, Waks J, Sanchez J, Delamater A, Davis E. Transitioning to Telehealth Services in a Pediatric Diabetes Clinic During COVID-19: An Interdisciplinary Quality Improvement Initiative. *J Clin Psychol Med Settings* 2021 [PMID: [34708318](#) DOI: [10.1007/s10880-021-09830-z](#)]
- 73 **Choudhary P**, Wilmot EG, Owen K, Patel DC, Mills L, Rayman G, Winocour P, Ayman G, Patel R, Hambling C, Nagi DK. A roadmap to recovery: ABCD recommendations on risk stratification of adult patients with diabetes in the post-COVID-19 era. *Diabet Med* 2021; **38**: e14462 [PMID: [33230813](#) DOI: [10.1111/dme.14462](#)]
- 74 **Powell PW**, Corathers SD, Raymond J, Streisand R. New approaches to providing individualized diabetes care in the 21st century. *Curr Diabetes Rev* 2015; **11**: 222-230 [PMID: [25901504](#) DOI: [10.2174/1573399811666150421110316](#)]
- 75 **Troncone A**, Chianese A, Zanfardino A, Cascella C, Piscopo A, Borriello A, Rollato S, Casaburo F, Testa V, Iafusco D. Disordered eating behaviors in youths with type 1 diabetes during COVID-19 lockdown: an exploratory study. *J Eat Disord* 2020; **8**: 76 [PMID: [33292623](#) DOI: [10.1186/s40337-020-00353-w](#)]
- 76 **Tuomilehto J**. The emerging global epidemic of type 1 diabetes. *Curr Diab Rep* 2013; **13**: 795-804 [PMID: [24072479](#) DOI: [10.1007/s11892-013-0433-5](#)]
- 77 **Rubin RR**, Peyrot M. Psychological issues and treatments for people with diabetes. *J Clin Psychol* 2001; **57**: 457-478 [PMID: [11255202](#) DOI: [10.1002/jclp.1041](#)]

Retrospective Study

Utilization of chest tube as an esophagus stent in pediatric caustic injuries: A retrospective study

Maryam Salimi, Hamidreza Hosseinpour, Reza Shahriarirad, Samira Esfandiari, Fatemeh Pooresmaeel, Shirin Sarejloo, Hamidreza Foroutan

Specialty type: Pediatrics

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Govindarajan KK, India; Moshref RH, Saudi Arabia; Scriba MF, South Africa

Received: June 14, 2022

Peer-review started: June 14, 2022

First decision: June 27, 2022

Revised: July 17, 2022

Accepted: August 12, 2022

Article in press: August 12, 2022

Published online: September 9, 2022



Maryam Salimi, Department of Orthopaedic Surgery, Shiraz University of Medical Sciences, Shiraz 7138433608, Iran

Hamidreza Hosseinpour, Samira Esfandiari, Fatemeh Pooresmaeel, Department of Surgery, Shiraz University of Medical Sciences, Shiraz 7138433608, Iran

Reza Shahriarirad, Department of Surgery, Shiraz 7138433608, Iran

Shirin Sarejloo, Department of Cardiology, Shiraz University of Medical Sciences, Shiraz 07138433608, Iran

Hamidreza Foroutan, Department of Surgery, Shiraz Laparoscopic Research Center, Shiraz University of Medical Sciences, Shiraz 7138433608, Iran

Corresponding author: Hamidreza Foroutan, MD, Full Professor, Department of Surgery, Shiraz Laparoscopic Research Center, Shiraz University of Medical Sciences, Zand Avenue, Shiraz 7138433608, Iran. maryamsalimi9674@gmail.com

Abstract

BACKGROUND

The management of caustic esophageal burns in the pediatric population has changed over the years, while the most optimal management with regards to effectiveness, availability, and cost-beneficial stays controvertible.

AIM

To describe how to utilize a chest tube for esophageal stenting in pediatrics.

METHODS

Data regarding the etiology, treatment, and complications of caustic injury in pediatrics over 10 years was collected retrospectively. Furthermore, data regarding the patient's follow-up who underwent esophageal chest tube (ECT) were collected. The ECT was prepared by carving a narrowed section in the chest tube while maintaining the radiopaque section. The ECT will then be positioned from the cricopharyngeal and exited through the nostril and fixed on the patient's cheek.

RESULTS

During the period of our study, data from 57 patients with an average age of 2.5

years (range 1-12; SD = 1.7) were obtained. The results showed that 89% of esophageal injury was due to alkaline and 9.4% were caused by acidic agents. The treatment methods showed that 29 patients (50.8%) recovered with dilatation alone. In 16 patients (28.06%), the esophageal repair was performed by using the colon, and in 5 patients (8.7%), other surgical methods were used and in 7 patients (12.2%), the ECT stents were used. ECT was inserted in 7 cases with a mean age of 2 (range: 1.5-3) years who were classified as grade IIB or III. Grading was performed by endoscopy assessment on the first day. Antibiotics and corticosteroids were administrated as initial medical management for all patients. ECT implantation was done during the first 8 d for 5 out of 7 cases (mean: 3.8 d). For the 2 patients, ECT was used after 27 (patient 6) d and 83 (patient 7) d. The reason for late stenting in these patients was a postponed referral to our center, in which patient 7 even received 4 dilation episodes before visiting our center. ECT was removed after an average of 44 d in the first 5 patients, while in the other 2 patients (6 and 7) was 2 and 1 wk, respectively. There was no complication related to, or failure of, stent placement. It is worth mentioning that none of the 7 ECT cases required gastrostomy or jejunostomy.

CONCLUSION

The ECT method introduced in our study can be used as a broadly available, economic, and easy-use facility for esophageal stenting, particularly in developing countries and emergency departments which have limited access to modern equipment. Further multicenter studies with higher volume patients are required for further deployment of this method.

Key Words: Caustic injury; Pediatric; Esophageal stent; Facility; Emergency

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Given that caustic ingestion is one of the most common incidents in clinical practice, especially among children, we believe that our new esophageal stent is not only an accessible device but also extremely cost-benefit relative to existing Self Expandable Metallic Stents and Self-expanding Plastic Stents. We hope that this new esophageal stent, which is a modified chest tube, will help all surgeons and emergency physicians manage patients with caustic ingestion in the future, especially for those working in developing countries and areas with lower equipment accessibility.

Citation: Salimi M, Hosseinpour H, Shahriarirad R, Esfandiari S, Pooresmael F, Sarejloo S, Foroutan H. Utilization of chest tube as an esophagus stent in pediatric caustic injuries: A retrospective study. *World J Clin Pediatr* 2022; 11(5): 419-428

URL: <https://www.wjgnet.com/2219-2808/full/v11/i5/419.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v11.i5.419>

INTRODUCTION

Esophageal injury followed by caustic agent ingestion, also known as erosive material ingestion, is among the most challenging and prevalent problems, particularly in developing countries[1,2]. Complications vary from an asymptomatic effect to drastic outcomes such as esophageal stricture or perforation, which can be potentially fatal[3-5]. The severity of injury also depends on the type of ingested substance as well as the amount and time of tissue exposure[6,7]. Esophageal stricture is considered to be the most prevalent complication in these cases[8,9].

Children and pediatrics are among the most frequent caustic ingestion victims, which occur either due to accidental or unintentional ingestion of erosive materials[6]. It has also been reported to be more prevalent among males[10]. Furthermore, this problem is most common in toddlers with a prevalence peak of 2 years old[11,12].

Acids and alkalis are the two basic types of erosive materials; however, alkaline materials are considered the most common erosive agents in these cases[3,13]. Almost 25% of caustic ingestion is followed by exposure to personal care products or household chemicals, such as detergent agents and bleaches[3,12]. The high morbidity and mortality rate followed by these injuries make them a serious challenging issue that requires initial management for all of these patients, including airway assessment, hemodynamic stabilization, and electrolyte replacement, followed by prescribing corticosteroids and antibiotics[14,15].

Using esophageal stenting to prevent or reduce future stricture formation is very controversial, with no pediatric-specific esophageal stents available or clear guidelines for their use.

The idea is to avoid contact with opposing sides to decrease adherence and following stricture formation. Even though this approach has been shown to decrease the rate of stricture formation, so far it has not been accepted as a routine clinical practice[16,17].

Some authors believed that esophageal stents are an effective method for preventing esophageal stricture in the first 48 h and also eliminating esophageal stricture recurrence followed by other dilation methods. Initial reports of outcomes following esophageal stenting described the use of a Silastic tube or polytetrafluoroethylene (PTFE) rod, both secured at the nose[18-20]. More recently, the use of self-expanding stents placed either endoscopically or under fluoroscopic guidance has been described. Plastic, metal, and biodegradable self-expanding stents have been used for esophageal strictures in children; however, the effectiveness, expensiveness, accessibility, and problems that these stents cause for the patients are still challenging issues[21-23].

Therefore, in this study, we aimed to introduce a new esophageal stenting method by utilizing a chest tube as an available and accessible device in emergency departments for patients suffering from caustic injuries. We also reviewed the etiology of caustic injury pediatrics in southern west Iran and the outcome of several patients treated with this Technique.

MATERIALS AND METHODS

Study design and participant selection

In this retrospective study, hospital records during ten years of patients aged under 18 years old who were admitted due to caustic chemical ingestion at the authors' affiliated hospital, which is a referral center for pediatric injuries, were collected. Data regarding the patient's characteristics, age, cause of the burn, degree of burn, treatment with antibiotics and steroids, use of gastrostomy and jejunostomy, number of dilatations and intervals, surgeries performed, and their complications (anastomotic leakage, esophageal rupture, adhesions, other early and late complications which were in associated to burns) was also gathered.

Various endoscopic grading is available and Zargar's classification is one of the most commonly used. In his study, Zargar *et al*[24] found all patients with grade 0, I and IIA burns recovered without sequelae. The majority of grade IIB and all survivors with grade III injury developed eventual esophageal or gastric cicatrization[24].

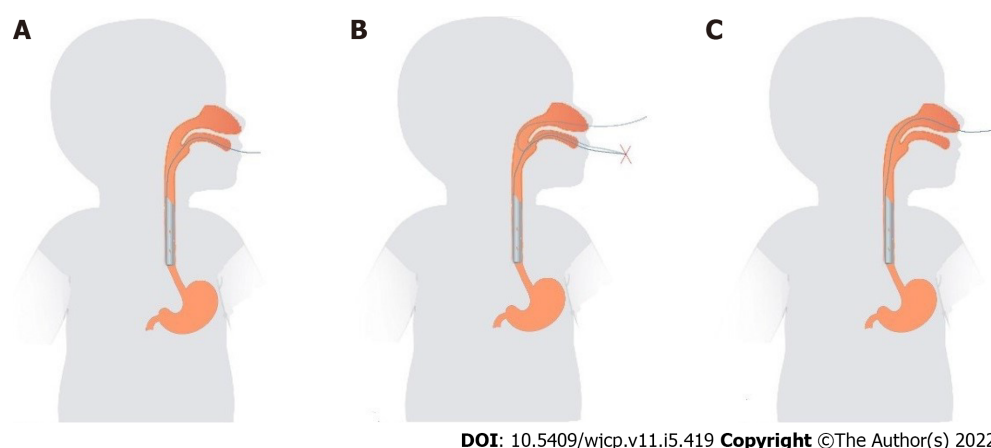
In our study esophageal stent was utilized in those with grades IIB and III.

The story and method of esophageal chest tube stenting

During several years of our clinical experiences, we found that esophageal stricture has developed frequently after caustic ingestion in those who have higher grades of corrosive injuries based on the endoscopically reports. We found that esophageal stents may prevent stricture significantly; however, the recently introduced self-expanding stents were so limited and expensive in our country; and many other low-income regions. Moreover, necrosis, ulceration, tissue hyperplasia, and fistula formation have been frequently reported by self-expandable metallic stents. After re-evaluating the patient's information, we found that esophageal stricture mostly developed in higher stages of injury (stage IIB and above). There were several recommendations from conservative management and medical therapy (such as steroids) to invasive methods; however, none of them had been proven. Therefore, we start to search for a costly and broadly available device. We consider the chest tube as an esophageal stent which may help; however, there were several concerns about it. The expected complication could be more similar to a plastic stent rather than a metal stent. Plastic stents are said to have lesser tissue hyperplasia but with a higher rate of stent migration and a lower tendency to sustain the significant radial force. Regarding the aforementioned concern, we used the radiopaque section of the chest tube to follow its place after insertion. Likewise, the external part of ECT exited the nose and fixed it to the patient's cheek using tape. Furthermore, we were afraid of the insertion procedure may lead to esophageal perforation, therefore, we placed it *via* endoscopy through a guide wire. Likewise, we didn't consider the injuries of stage IV due to its higher tendency for perforation. Moreover, we applied the anti-reflux medication and encourage the patient to elevate the head of their bed.

In this method, the esophageal chest tube (ECT) stent is inserted either in the first 48-72 h after a caustic injury or precisely after dilatation and is removed after 6-8 wk. In this technique, we utilize the ECT in three steps.

First, the chest tube's length is measured concerning age, weight, and the stature of each patient. We used different sizes of chest tubes based on the physician's preference according to the initial endoscopic evaluation. Sedative and analgesic medications were also applied. Afterward, a narrowed section is shaped by obliquely carving the chest tube and maintaining the radiopaque section, which will be positioned from the cricopharyngeal until the external section of the tube. After preparing the ECT, the tube will be inserted orally *via* endoscopy through a guide wire, with the narrow end positioned out of the mouth (Figure 1A). Following the ECT insertion, we aim to exit it through the nasal cannula, in which we use either a Nelaton or nasogastric tube. In this regard, we insert the tube through the nasal cannula so that it exits the mouth while keeping the proximal section out of the nose.



DOI: 10.5409/wjcp.v11.i5.419 Copyright ©The Author(s) 2022.

Figure 1 Utilizing a chest tube as an esophageal stent in caustic injury in pediatrics. A: Insertion of esophageal chest tube (ECT) from cricopharyngeal until lower sphincter and exiting the external part from the mouth; B: Suturing the external part of the ECT to a Nelaton or nasogastric tube which has been passed through the nostrils; C: Exiting the external part of the ECT through the nostrils.

Subsequently, the end part of the tube is sutured to the distant narrow part of the ECT (Figure 1B). Therefore, by pulling onto the proximal part of the tube, it will act as a guide for the ECT to extract it through the nasal cannula (Figure 1C). Consequently, the ECT will exit the nose and be fixed to the patient's cheek using tape. (Figure 2). Also, by preserving the radiopaque section of the ECT, monitoring the position of the tube is possible through chest radiography. (Figure 3).

Follow-up evaluation

Then patients were evaluated for early complications such as pneumonia, pneumothorax, esophageal rupture, *etc.*, or late complications such as esophageal stricture, gastroesophageal reflux, and the need for colon interposition.

RESULTS

During the period of our study, data from 57 patients with an average age of 2.5 years (range 1-12; SD = 1.7) were obtained. The results showed that 89% of esophageal injury was due to alkaline and 9.4% were caused by acidic agents. Table 1 demonstrates the etiology factors of the patients in our study.

The treatment methods showed that 29 patients (50.8%) recovered with dilatation alone. In 16 patients (28.06%), the esophageal repair was performed by using the colon, and in 5 patients (8.7%), other surgical methods were used and in 7 patients (12.2%), the ECT stents were used.

ECT was inserted in 7 cases with a mean age of 2 (range: 1.5-3) years who were classified as grade IIB or III. Grading was performed by endoscopy assessment on the first day. Antibiotics and corticosteroids were administrated as initial medical management for all patients. ECT implantation was done during the first 8 d for 5 out of 7 cases (mean: 3.8 d). For the 2 patients, ECT was used after 27 (patient 6) d and 83 (patient 7) d. The reason for late stenting in these patients was a postponed referral to our center, in which patient 7 even received 4 dilation episodes before visiting our center. ECT was removed after an average of 44 d in the first 5 patients, while in the other 2 patients (6 and 7) was 2 and 1 wk, respectively.

There was no complication related to, or failure of, stent placement. It is worth mentioning that none of the 7 ECT cases required gastrostomy or jejunostomy. Table 2 summarized information on patients managed with esophageal stenting using a chest tube.

DISCUSSION

Caustic injuries are considered one of the most prevalent, as well as preventable accidental injuries. Children are among the highest groups at risk of these injuries due to their curiosity and ability to reach objects without discerning their harm and potential dangers[25,26]. In 2009, the Kids' Inpatient Database of the United States reported 807 cases of caustic injuries. Our study was conducted in southwest Iran, in which 57 pediatric hospitalized patients with caustic injuries were collected for 10 years (1994-2003), demonstrating an annual rate of 5.7 cases/year. In similar studies in our province, Honar *et al*[27] reported 75 in 2006-2011 (12.5 case/year) and Dehghani *et al*[10] reported 41 cases from 2015-2016 (20.5 cases/year). This upsurge in the number of cases shows the significance of this matter and therefore, evaluating the etiology and applied management, along with choosing the proper therapeutic option for

Table 1 Etiological features of caustic injury among pediatrics in southern west Iran

Variable	Frequency, <i>n</i> = 57	Percentage (%)
Etiology		
Caustic Soda	47	83.3
Stove-top cleaner	3	5.7
Acid	3	5.7
Hydrochloric acid	2	3.7
Boiled water	2	3.7
Medical treatment		
Antibiotic Therapy	36	66.7
Corticosteroids	22	40.7
Advanced treatment		
Dilatation	29	50.8
Stent insertion	7	12
Colon interposition	16	28
Other surgical methods	5	8.7
Surgical treatment		
Gastrostomy	19	33.3
Jejunostomy	4	7.4
Complication		
No complication	39	69.6
Pneumothorax	11	19
Esophageal rupture	6	11.4

Table 2 Caustic injury pediatrics treated with esophageal stenting using a chest tube

Variable	Patient						
	1	2	3	4	5	6	7
Age (mo)	24	24	18	36	24	30	34
Grade	III	IIB	IIB	IIB	III	IIB	IIB
Etiology	Caustic soda	Hydrochloric acid	Acid	Acid	Caustic soda	Stove cleaner	Caustic soda
Time of esophageal chest tube insertion (after injury)	1	6	8	2	1	27	83
Esophageal chest tube duration	27	35	50	90	20	16	7
Replacement (Frequency)	1:14	-	2:12 and 22	2: 30 and 60	-	1: 9	1: 4
Surgical intervention	-	-	-	-	Colon Interposition	-	-
Duration of follow-up (mo)	23	22	16	6	35	15	14
Patient Satisfaction	Satisfied	Satisfied	Satisfied	Mild esophageal stenosis	Satisfied	Satisfied	Mild esophageal stenosis

these patients is necessary.

Among the contributing factors to this increasing number of cases per year may be the increased use, easy accessibility, and low cost of detergents and bleaches, especially in developing countries. Alkaline was considered the most corrosive agent in this study with an incidence of 89% (50 out of 57 cases), while acid agents consisted of 9.4% (5 out of 57 cases) of the etiologies in our study population. In a



DOI: 10.5409/wjcp.v11.i5.419 Copyright ©The Author(s) 2022.

Figure 2 Esophageal chest tube. A: Esophageal chest tube prepared for a 6-year-old boy with a caustic injury; B: Esophageal chest tube fixed for a 6-year-old boy with a caustic injury.



DOI: 10.5409/wjcp.v11.i5.419 Copyright ©The Author(s) 2022.

Figure 3 Chest X-ray, Chest radiography demonstrating and esophageal chest tube inserted for a patient with a caustic injury.

similar study in our center, 64 hospitalized patients were reported to have had alkaline ingestion for 4 years[11]. Also, in a study conducted in Australia, 74% of caustic ingestion occurred by alkaline agents [28]. Acids, regarding their low viscosity and therefore rapid transfer to the stomach and also due to their nature cause coagulation necrosis, with eschar formation that may prevent further damage and limit the injury depth. Conversely, alkalis bind to tissue proteins and lead to liquefactive necrosis and saponification, and penetrate deeper into tissues, assisted by a higher viscosity and a longer contact time through the esophagus. On the other hand, children usually tend to swallow a larger amount of alkaline because alkalis are usually odorless and tasteless; although, acidic agents have a sour taste which makes children spit them out. Another point for our region (the south of Iran) is the excessive use of air conditioners followed by its cleaner that fundamentally and are made by NaOH which kept in beverage bottles without any warning label in addition to the low educational level of parents have led to increasing the occurrence of esophageal burn by caustic ingestion.

In caustic injury patients, a preliminary survey includes airway assessment as well as fluid and electrolyte balance[12]. We also administered antibiotics along with corticosteroids as medical management. Among the most imperative complications of esophageal burns is a stricture. Katz *et al*[9] reported esophageal stricture in more than 90% of patients with grade 3 and almost 30%-70% of grade 2B caustic injury. Malignant transformation to esophageal cancer is one of the following complications of esophageal stricture[29]. Studies have also reported that esophageal stricture is associated with hiatal hernia, reflux disease, dysphagia symptoms, and causing difficulties for esophageal reconstruction[30-32]. A study in 1992 evaluated the administration efficacy of antibiotic and systemic steroids simultaneously in caustic ingestion, which concluded that antibiotics with steroids might be useful in reducing strictures in patients with esophageal burns[33]. Controversially, a controlled randomized trial revealed the corticosteroids' ineffectiveness in preventing esophageal stricture in children with a caustic injury [34]. Therefore, novel therapeutic approaches for preventing or managing esophageal strictures that would enable a child to tolerate an oral diet in a more expeditious and less invasive manner would be highly desirable. Furthermore, the oblique cutting of the ECT facilitates feeding and also prevents unintentional aspiration.

In this report, we utilized the chest tube, as a broadly available and well-known equipment in all emergency departments, proposed as an esophageal stent for not only preventing esophageal stricture in the first 48 h but also after dilatation. Formerly, self-expanding plastic stents (SEPS) and fully covered self-expanding metal stents (FCSEMS) have been used for stenting, and each had its advantage and disadvantage. The success rate for SEPS showed 50% by Broto *et al*[21] and 75% for FCSEMS by Zhang *et al*[22].

Stent migration is another common complication that has been reported in 14% to 48% of cases, which has been related to the type of stent[35]. Metal stents that are fully covered with PTFE, polyurethane, or silicone have a higher chance of migration, compared with uncovered metal stents, which are held in place by hyper-granulation and mucosal ingrowth; nevertheless, these proliferations contribute to ulcers and struggle when removing the stent[36,37]. Self-expanding plastic stents are at greater risk of migration when compared with self-expanding metal stents, which are daunting in benign esophageal stenosis due to their high incidence of necrosis and ulceration, tissue hyperplasia, new stricture or fistula formation, and the tendency for the metal portion to embed within the esophageal wall[38,39]. Best *et al*[40] and Manfredi *et al*[39] reported high rates of mucosal ingrowth and hyper-granulation, causing difficulty in stent removal and stent-induced ulceration. Since the ECT is inserted from below the cricopharyngeal till the lower esophagus sphincter and also fixed from outside of the nose, this decreases the chance of migration compared to other methods of fixation using thread and suture. Furthermore, the stent material safeguards cell proliferation into the stent, resulting in easy removal of the ECT and less complication such as esophageal ulcers and hyper-granulation.

From an economic point of view, as one of the most important factors in management decision making particularly in developing countries, the proposed ECT can be an ideal choice due to its cost-effective aspects and in centers where other esophageal stents are unavailable.

Among the other advantages of the ECT is that the patient will be able to tolerate oral feeding with soft diets as well as liquids, so the foods are based on the inlet of the ECT, which is located in the cricopharyngeal area and allows a pathway to the stomach. However, since the ECT covers the total length of the esophagus to the lower sphincter, a risk of reflux should be considered which can be managed with proper anti-reflux medication.

Among the patients in our study, 5 were satisfied with their results, while two (patients 4 and 7) had mild esophageal stenosis. Among these two, patient 4 had ECT for 90 d. The exact duration in which stents should be used is still a matter of debate. The European Society for Gastrointestinal Endoscopy Recommendations for the Stenting of Benign Esophageal Strictures acknowledges this lack of data available and suggests the insertion of self-expanding metal and plastic stents for a minimum of 6-8 wk and no more than three mo[41]. Likewise, we recommend removing the ECT after 6-8 wk. Furthermore, patient 7 had ECT inserted 83 d after the injury, which had already caused chronic damage and stricture. It is also worth mentioning that ECT was inserted in one of the patients with grade I caustic injury, which was intended as prophylaxis for esophageal stenosis.

Endoscopic dilatation with a balloon has been the standard of treatment for benign esophageal strictures; nevertheless, the recurrence rate was reported to be 30%-40%[38]. Increasing the victims of caustic ingestion on one hand, and the high economic burden, on the other hand, made us use the ECT in early stenting, which is more economical, broadly available, and also regarding its high efficacy. In this study, we just want to report our experience in a referral center in a low-income country. Of course, there is an inevitable need to examine it during the trials. Also, we don't recommend this in the situation that another stent is available.

Limitations

Several caveats regarding our study deserve mention. First, this was a retrospective, single-institution series of esophageal stents deployed in a heterogeneous group of patients. Also, our series lack of control group and consists of a small sample size. This study was non-comparative and did not compare stenting to other therapeutic options. However, our study's main focus was utilizing an already existing device, the chest tube, as an esophageal stent for the early management of caustic injury pediatrics, especially in centers with limited equipment.

CONCLUSION

Caustic injury and its management are among the most challenging problems among pediatric surgeons. The availability, efficiency, and economic aspect of materials are important factors that should be taken into consideration in planning the therapeutic approach for these patients. In this study, we successfully report utilizing a chest tube, as an available device in almost every emergency department, as a method for esophageal stenting. This method should especially be considered in developing countries with limited utilities and also emergency departments and centers with restricted access to modern equipment.

ARTICLE HIGHLIGHTS

Research background

Using esophageal stenting for future stricture formation prevention is very controversial, with no clear guidelines for their use. The idea is to avoid contact with opposing sides to decrease adherence and following stricture formation. Even though this approach has been shown to decrease the rate of stricture formation.

Research Motivation

Different stents have been introduced so far, however, the effectiveness, expensiveness, accessibility, and problems that these stents cause for the patients are still challenging issues.

Research objectives

To introduce a new esophageal stenting method by utilizing a chest tube as an available and accessible device in emergency departments for patients suffering from caustic injuries.

Research methods

Collect demographic data of children with caustic injuries respectively, patients who had stage IIB and III of corrosive injuries were eligible for esophageal chest tube insertion.

Research results

Twenty-nine patients (50.8%) recovered with dilatation alone, 16 needed esophageal repair, and an esophageal chest tube (ECT) was inserted for 7 patients. None of the 7 ECT cases required gastrostomy or jejunostomy.

Research conclusions

We successfully report utilizing a chest tube, as an available device in almost every emergency department, as a method for esophageal stenting. This method is could be an alternative in developing countries with limited utilities as well as centers with restricted access to modern equipment.

Research perspectives

The chest tube has many advantages, it has a radiopaque line that could be used to monitor it, and patients could get an oral diet after stabilization. it is also costly and broadly available. By keeping the advantage and improving its problem, it could be used more efficiently. Moreover, it should be examined during different trials.

FOOTNOTES

Author contributions: Foroutan H designed and performed the research; Salimi M and Hosseinpour H designed the research and wrote the paper; Shahriarirad R designed the research and supervised the report; Esfandiari S designed the research and contributed to the analysis; Pooresmaeel F and Sarejloo S provided clinical advice.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Shiraz University of Medical Sciences.

Informed consent statement: Written informed consent was obtained from the patients' parent/guardian in our study. The purpose of this research was completely explained to the patient's parents/guardian and was assured that their information will be kept confidential by the researcher. The present study was approved by the Medical Ethics Committee of Shiraz University of Medical Sciences. Consent was obtained from the patient parent/guardian regarding the publication of this study.

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

Data sharing statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (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: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Iran

ORCID number: Maryam Salimi 0000-0001-9771-7048; Shirin Sarejloo 0000-0002-2109-0450; Hamidreza Foroutan 0000-0001-9947-6604.

S-Editor: Wang LL

L-Editor: A

P-Editor: Wang LL

REFERENCES

- 1 **Contini S**, Swarray-Deen A, Scarpignato C. Oesophageal corrosive injuries in children: a forgotten social and health challenge in developing countries. *Bull World Health Organ* 2009; **87**: 950-954 [PMID: 20454486 DOI: 10.2471/BLT.08.058065]
- 2 **Kucuk G**, Gollu G, Ates U, Cakmak ZA, Kologlu M, Yagmurlu A, Aktug T, Dindar H, Cakmak AM. Evaluation of esophageal injuries secondary to ingestion of unlabeled corrosive substances: pediatric case series. *Arch Argent Pediatr* 2017; **115**: e85-e88 [PMID: 28318189 DOI: 10.5546/aap.2017.eng.e85]
- 3 **Kurowski JA**, Kay M. Caustic Ingestions and Foreign Bodies Ingestions in Pediatric Patients. *Pediatr Clin North Am* 2017; **64**: 507-524 [PMID: 28502435 DOI: 10.16966/2381-8689.133]
- 4 **Turner A**, Robinson P. Respiratory and gastrointestinal complications of caustic ingestion in children. *Emerg Med J* 2005; **22**: 359-361 [PMID: 15843706 DOI: 10.1136/emj.2004.015610]
- 5 **Hoghoughi MA**, Kazemi T, Khojasteh A, Habibagahi R, Kalkate Z, Zarei Z, Hosseinpour H, Salimi M. The effect of intervelar veloplasty under magnification (Sommerlad's Technique) without tympanostomy on middle ear effusion in cleft palate patients. *BMC Pediatr* 2021; **21**: 377 [PMID: 34470606 DOI: 10.1186/s12887-021-02856-0]
- 6 **Watson WA**, Litovitz TL, Rodgers GC Jr, Klein-Schwartz W, Reid N, Youniss J, Flanagan A, Wruk KM. 2004 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2005; **23**: 589-666 [PMID: 16140178 DOI: 10.1016/j.ajem.2005.05.001]
- 7 **Arici MA**, Ozdemir D, Oray NC, Buyukdeligöz M, Tuncok Y, Kalkan S. Evaluation of caustics and household detergents exposures in an emergency service. *Hum Exp Toxicol* 2012; **31**: 533-538 [PMID: 21665922 DOI: 10.1177/0960327111412803]
- 8 **Siersema PD**, de Wijkerslooth LR. Dilation of refractory benign esophageal strictures. *Gastrointest Endosc* 2009; **70**: 1000-1012 [PMID: 19879408 DOI: 10.1016/j.gie.2009.07.004]
- 9 **Katz A**, Kluger Y. Caustic material ingestion injuries-paradigm shift in diagnosis and treatment. *Health Care Curr Rev* 2015; **3**: 152 [DOI: 10.4172/2375-4273.1000152]
- 10 **Dehghani SM**, Bahmanyar M, Javaherizadeh H. Caustic Ingestion in Children in South of Iran: A Two-Year Single Center Study. *Middle East J Dig Dis* 2018; **10**: 31-34 [PMID: 29682245 DOI: 10.15171/mejdd.2017.87]
- 11 **Forotan A**, Soveyd M, Banani A, Banihashemi SH, Forotan H. Esophageal burn injuries with alkali in children: A four year comprehensive analysis study. *Iran J Pediatr* 2016; **2**: 57-62 [DOI: 10.1016/j.jpedsurg.2021.09.017]
- 12 **Rafeey M**, Ghajazadeh M, Sheikhi S, Vahedi L. Caustic Ingestion in Children: a Systematic Review and Meta-Analysis. *J Caring Sci* 2016; **5**: 251-265 [PMID: 27757390 DOI: 10.15171/jcs.2016.027]
- 13 **Zargar SA**, Kochhar R, Nagi B, Mehta S, Mehta SK. Ingestion of corrosive acids. Spectrum of injury to upper gastrointestinal tract and natural history. *Gastroenterology* 1989; **97**: 702-707 [PMID: 2753330]
- 14 **Ekpe EE**, Ette V. Morbidity and mortality of caustic ingestion in rural children: experience in a new cardiothoracic surgery unit in Nigeria. *ISRN Pediatr* 2012; **2012**: 210632 [PMID: 22778986 DOI: 10.5402/2012/210632]
- 15 **Salzman M**, O'Malley RN. Updates on the evaluation and management of caustic exposures. *Emerg Med Clin North Am* 2007; **25**: 459-76; abstract x [PMID: 17482028 DOI: 10.1016/j.emc.2007.02.007]
- 16 **Berkovits RN**, Bos CE, Wijburg FA, Holzki J. Caustic injury of the oesophagus. Sixteen years experience, and introduction of a new model oesophageal stent. *J Laryngol Otol* 1996; **110**: 1041-1045 [PMID: 8944879 DOI: 10.1017/s0022215100135716]
- 17 **Wang RW**, Zhou JH, Jiang YG, Fan SZ, Gong TQ, Zhao YP, Tan QY, Lin YD. Prevention of stricture with intraluminal stenting through laparotomy after corrosive esophageal burns. *Eur J Cardiothorac Surg* 2006; **30**: 207-211 [PMID: 16829082 DOI: 10.1016/j.ejcts.2006.03.068]
- 18 **Coln D**, Chang JH. Experience with esophageal stenting for caustic burns in children. *J Pediatr Surg* 1986; **21**: 588-591 [PMID: 3090225 DOI: 10.1016/s0022-3468(86)80411-0]
- 19 **Mutaf O**. Treatment of corrosive esophageal strictures by long-term stenting. *J Pediatr Surg* 1996; **31**: 681-685 [PMID: 8861481 DOI: 10.1016/s0022-3468(96)90674-0]
- 20 **Atabek C**, Surer I, Demirbag S, Caliskan B, Ozturk H, Cetinkursun S. Increasing tendency in caustic esophageal burns and long-term polytetrafluoroethylene stenting in severe cases: 10 years experience. *J Pediatr Surg* 2007; **42**: 636-640 [PMID: 17448758 DOI: 10.1016/j.jpedsurg.2006.12.012]
- 21 **Broto J**, Asensio M, Vernet JM. Results of a new technique in the treatment of severe esophageal stenosis in children: poliflex stents. *J Pediatr Gastroenterol Nutr* 2003; **37**: 203-206 [PMID: 12883312 DOI: 10.1097/00005176-200308000-00024]
- 22 **Zhang C**, Yu JM, Fan GP, Shi CR, Yu SY, Wang HP, Ge L, Zhong WX. The use of a retrievable self-expanding stent in treating childhood benign esophageal strictures. *J Pediatr Surg* 2005; **40**: 501-504 [PMID: 15793725 DOI: 10.1016/j.jpedsurg.2004.11.041]
- 23 **Vandenplas Y**, Hauser B, Devreker T, Urbain D, Reynaert H. A biodegradable esophageal stent in the treatment of a corrosive esophageal stenosis in a child. *J Pediatr Gastroenterol Nutr* 2009; **49**: 254-257 [PMID: 19561544 DOI: 10.1097/MPG.0b013e31819de871]

- 24 **Zargar SA**, Kochhar R, Mehta S, Mehta SK. The role of fiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns. *Gastrointest Endosc* 1991; **37**: 165-169 [PMID: [2032601](#) DOI: [10.1016/s0016-5107\(91\)70678-0](#)]
- 25 **Hoghoughi MA**, Marzban MR, Shahrabaf MA, Shahriarirad R, Kamran H, Meimandi FZ, Salimi M, Hosseinpour H. Burn Injuries in People Who Used Drug, 2009-2017: A Case-Control Study in Shiraz, Southern Iran. *J Burn Care Res* 2022 [PMID: [35029683](#) DOI: [10.1093/jbcr/irac005](#)]
- 26 **Bolia R**, Sarma MS, Biradar V, Sathiyasekaran M, Srivastava A. Current practices in the management of corrosive ingestion in children: A questionnaire-based survey and recommendations. *Indian J Gastroenterol* 2021; **40**: 316-325 [PMID: [33991312](#) DOI: [10.1007/s12664-021-01153-z](#)]
- 27 **Honar N**, Haghighat M, Mahmoodi S, Javaherizadeh H, Kalvandi G, Salimi M. Caustic ingestion in children in south of Iran. Retrospective study from Shiraz - Iran. *Rev Gastroenterol Peru* 2017; **37**: 22-25 [PMID: [28489832](#)]
- 28 **Huang YC**, Ni YH, Lai HS, Chang MH. Corrosive esophagitis in children. *Pediatr Surg Int* 2004; **20**: 207-210 [PMID: [15083331](#) DOI: [10.1007/s00383-004-1153-3](#)]
- 29 **Nuutinen M**, Uhari M, Karvali T, Kouvalainen K. Consequences of caustic ingestions in children. *Acta Paediatr* 1994; **83**: 1200-1205 [PMID: [7841737](#) DOI: [10.1111/j.1651-2227.1994.tb18281.x](#)]
- 30 **Higuchi D**, Sugawa C, Shah SH, Tokioka S, Lucas CE. Etiology, treatment, and outcome of esophageal ulcers: a 10-year experience in an urban emergency hospital. *J Gastrointest Surg* 2003; **7**: 836-842 [PMID: [14592655](#) DOI: [10.1007/s11605-003-0027-7](#)]
- 31 **Zhang C**, Zhou X, Yu L, Ding J, Shi R. Endoscopic therapy in the treatment of caustic esophageal stricture: a retrospective case series study. *Dig Endosc* 2013; **25**: 490-495 [PMID: [23369028](#) DOI: [10.1111/den.12023](#)]
- 32 **Serhal L**, Gottrand F, Sfeir R, Guimber D, Devos P, Bonnevalle M, Storme L, Turck D, Michaud L. Anastomotic stricture after surgical repair of esophageal atresia: frequency, risk factors, and efficacy of esophageal bougie dilatations. *J Pediatr Surg* 2010; **45**: 1459-1462 [PMID: [20638524](#) DOI: [10.1016/j.jpedsurg.2009.11.002](#)]
- 33 **Howell JM**, Dalsey WC, Hartsell FW, Butzin CA. Steroids for the treatment of corrosive esophageal injury: a statistical analysis of past studies. *Am J Emerg Med* 1992; **10**: 421-425 [PMID: [1642705](#) DOI: [10.1016/0735-6757\(92\)90067-8](#)]
- 34 **Anderson KD**, Rouse TM, Randolph JG. A controlled trial of corticosteroids in children with corrosive injury of the esophagus. *N Engl J Med* 1990; **323**: 637-640 [PMID: [2200966](#) DOI: [10.1056/NEJM199009063231004](#)]
- 35 **Tandon S**, Burnand KM, De Coppi P, McLaren CA, Roebuck DJ, Curry JI. Self-expanding esophageal stents for the management of benign refractory esophageal strictures in children: A systematic review and review of outcomes at a single center. *J Pediatr Surg* 2019; **54**: 2479-2486 [PMID: [31522799](#) DOI: [10.1016/j.jpedsurg.2019.08.041](#)]
- 36 **Hindy P**, Hong J, Lam-Tsai Y, Gress F. A comprehensive review of esophageal stents. *Gastroenterol Hepatol (N Y)* 2012; **8**: 526-534 [PMID: [23293566](#)]
- 37 **Kaltsidis H**, Mansoor W, Park JH, Song HY, Edwards DW, Laasch HU. Oesophageal stenting: Status quo and future challenges. *Br J Radiol* 2018; **91**: 20170935 [PMID: [29888981](#) DOI: [10.1259/bjr.20170935](#)]
- 38 **De Lusong MAA**, Timbol ABG, Tuazon DJS. Management of esophageal caustic injury. *World J Gastrointest Pharmacol Ther* 2017; **8**: 90-98 [PMID: [28533917](#) DOI: [10.4292/wjgpt.v8.i2.90](#)]
- 39 **Manfredi MA**, Jennings RW, Anjum MW, Hamilton TE, Smithers CJ, Lightdale JR. Externally removable stents in the treatment of benign recalcitrant strictures and esophageal perforations in pediatric patients with esophageal atresia. *Gastrointest Endosc* 2014; **80**: 246-252 [PMID: [24650853](#) DOI: [10.1016/j.gie.2014.01.033](#)]
- 40 **Best C**, Sudel B, Foker JE, Krosch TC, Dietz C, Khan KM. Esophageal stenting in children: indications, application, effectiveness, and complications. *Gastrointest Endosc* 2009; **70**: 1248-1253 [PMID: [19836746](#) DOI: [10.1016/j.gie.2009.07.022](#)]
- 41 **Spaander MC**, Baron TH, Siersema PD, Fuccio L, Schumacher B, Escorsell À, Garcia-Pagán JC, Dumonceau JM, Conio M, de Ceglie A, Skowronek J, Nordmark M, Seufferlein T, Van Gossum A, Hassan C, Repici A, Bruno MJ. Esophageal stenting for benign and malignant disease: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2016; **48**: 939-948 [PMID: [27626318](#) DOI: [10.1055/s-0042-114210](#)]

Three novel homozygous *ITGB2* mutations among two patients with leukocyte adhesion defect type-1: Two case reports

Yiwa Suksawat, Punchama Pacharn, Nunthana Siripipattanamongkol, Boonchai Boonyawat

Specialty type: Genetics and heredity

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

Peer-review model: Single blind

Peer-review report's scientific quality classification

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

P-Reviewer: Shuang W, China; Zhao GH, China

Received: April 22, 2022

Peer-review started: April 22, 2022

First decision: May 31, 2022

Revised: June 10, 2022

Accepted: August 22, 2022

Article in press: August 22, 2022

Published online: September 9, 2022



Yiwa Suksawat, Division of Allergy and Immunology, Department of Pediatrics, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok 10400, Thailand

Punchama Pacharn, Division of Allergy and Immunology, Department of Pediatrics, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand

Nunthana Siripipattanamongkol, Division of Allergy and Immunology, Department of Pediatrics, Chiangrai Prachanukroh Regional Hospital, Chiangrai 57000, Thailand

Boonchai Boonyawat, Division of Medical Genetics, Department of Pediatrics, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok 10400, Thailand

Corresponding author: Yiwa Suksawat, MD, Doctor, Division of Allergy and Immunology, Department of Pediatrics, Phramongkutklao Hospital and Phramongkutklao College of Medicine, 315 Rajavithi Road, Ratchathewi, Bangkok 10400, Thailand.

yiwasuksawat@pcm.ac.th

Abstract

BACKGROUND

A leukocyte adhesion defect (LAD) is a rare primary immunodeficiency disorder. LAD type 1 (LAD-1) is the most common, which is caused by *ITGB2* mutation resulting in dysfunction of $\beta 2$ integrin, which impairs leukocyte adherence to the endothelium.

CASE SUMMARY

The first two cases of LAD-1 in Thailand presented with recurrent omphalitis, soft tissue infection, marked leukocytosis, and neutrophilia. One patient experienced delayed umbilical cord separation. Mutation analysis was performed by direct DNA sequencing of the *ITGB2* gene. The results revealed two novel homozygous missense mutations, c.920C>T (p.Leu307Pro) in exon 8 and c.758G>A (p.Arg-253His) in exon 7, and one novel homozygous nonsense mutation, c.262C>T (p.Gln88Ter) in exon 4, in the genomic DNA of the first and second patients, respectively. Heterozygous mutations were identified in the parents of both patients, suggesting a carrier status. The patients were administered intravenous antibiotics for infections with good clinical responses. Hematopoietic stem cell transplantation could not be performed due to the unavailability of matched donors. However, a significant decline in infections was observed after antibiotic prophylaxis. Several follow-up visits were conducted for both patients. They are currently 6 years old.

CONCLUSION

Molecular analysis is essential for definitive diagnosis, early treatment implementation, and prevention of LAD-1 in future pregnancy.

Key Words: Leukocyte adhesion defect; *ITGB2*; Omphalitis; Bacterial soft tissue infection; Molecular investigation; Case report

©The Author(s) 2022. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Leukocyte adhesion defect (LAD) is a rare autosomal recessive primary immunodeficiency disorder characterized by defects in the leukocyte recruitment cascade. LAD type 1, caused by a mutation in *ITGB2*, is the most common form. Here, we report the first two cases of LAD type 1 with a molecularly confirmed *ITGB2* mutation in Thailand. At the time of initial presentation, both patients had recurrent omphalitis, bacterial soft tissue infection, and marked leukocytosis. Molecular analysis revealed two missense variants and one nonsense mutation. Early identification of these patients by molecular analysis was proven essential for definitive diagnosis, proper antibiotic prophylaxis, and initiation of matched donor hematopoietic stem cell transplantation.

Citation: Suksawat Y, Pacharn P, Siripipattanamongkol N, Boonyawat B. Three novel homozygous *ITGB2* mutations among two patients with leukocyte adhesion defect type-1: Two case reports. *World J Clin Pediatr* 2022; 11(5): 429-436

URL: <https://www.wjgnet.com/2219-2808/full/v11/i5/429.htm>

DOI: <https://dx.doi.org/10.5409/wjcp.v11.i5.429>

INTRODUCTION

Leukocyte adhesion defect (LAD) is a rare autosomal recessive primary immunodeficiency disorder affecting one in every 100000 individuals. A deficiency in the leukocyte adhesion cascade to the blood vessel wall is the pathogenesis of LAD and is classified into three types. LAD type 1 (LAD-1) (OMIM#116920), which is caused by a mutation in the *ITGB2* gene, is the most common form. The *ITGB2* gene (OMIM#600065) is located on 21q22.3 and encoded the common β subunit of the $\beta 2$ integrin protein (CD18). Dysfunctional $\beta 2$ integrin is the main defect in LAD-1 and is attributable to impaired neutrophil firm adhesion[1]. The hallmark characteristics are recurrent bacterial skin and soft tissue infections, omphalitis, and delayed umbilical cord separation. In addition, the absence of pus formation is a distinctive feature[2]. LAD-1 diagnosis can be confirmed by flow cytometric expression of CD18 and CD11 on leukocytes or *ITGB2* mutation analysis[2,3]. To date, more than 110 mutations have been identified[3]. Here, we report the first two cases of LAD-1 with molecularly confirmed *ITGB2* mutation in Thailand. The study protocol was approved by the Institutional Review Board of the Royal Thai Army.

CASE PRESENTATION

Chief complaints

Case 1: A 21-mo-old Burmese boy presented with prolonged fever and multiple whitish ulcers in the oropharynx (Patient #1, P1).

Case 2: A 9-d-old Thai girl presented with redness around the umbilical stump (Patient #2, P2).

History of present illness

Case 1: The patient had fever and dyspnea for 3 wk. Additionally, he had been previously treated in Myanmar and Laos; however, his clinical condition had deteriorated, and he was referred from a rural hospital near the Thai border. He was on the verge of respiratory failure due to acute upper airway obstruction. Emergency tracheostomy was performed, and pus with debris extending to the oropharynx, larynx, and epiglottis was discovered intraoperatively. *Streptococcus viridans* and *Staphylococcus epidermidis* were identified in the pus cultures. Although intravenous antibiotics were administered, healing of the wound was difficult. He was re-admitted several times with chronic wound infections around the tracheostomy site, *Pseudomonas aeruginosa* pneumonia, oral candidiasis, and cellulitis. Several organisms, including *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Pseudomonas*

aeruginosa, *Salmonella* gr.B, and carbapenem-resistant Enterobacteriaceae *Klebsiella pneumoniae* were identified in pus cultures.

Case 2: At 9 d of age, she presented with fever and abdominal distension. Physical examination revealed minimal pus with redness around the umbilical stump (Figure 1). The patient was then diagnosed with omphalitis. Intravenous cloxacillin and metronidazole were administered; however, her clinical condition worsened. Omphalitis persisted until 4 wk of age. Pus culture revealed *Staphylococcus epidermidis*, *Escherichia coli*, and extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*. The intravenous antibiotics were switched to carbapenems, with some clinical improvement. She was re-admitted because of recurrent omphalitis at 6 wk of age. After administration of intravenous antibiotics for 3 d, her symptoms subsided. At 2 mo of age, she was referred to our university hospital for assessment of recurrent omphalitis.

History of past illness

Case 1: The patient had a delayed umbilical cord detachment 30 d after birth and delayed wound healing, resulting in difficult-to-treat omphalitis.

Case 2: The patient's umbilical cord was separated 20 d after birth.

Personal and family history

Case 1: The patient was born at term with an uneventful pregnancy and delivery history. The patient completed an extended immunization program based on his age. His sister had no health issues despite being the second child of consanguineous parents.

Case 2: The patient was born at term with an uneventful pregnancy and perinatal history. Her birth weight was 2650 g. BCG and HBV vaccines were administered after birth. She was the first child of a couple who had denied consanguinity.

Physical examination

Case 1: Physical examination of P1 revealed a weight of 9.5 kg (3rd percentile) and a height of 82 cm (25th–50th percentile). Multiple whitish ulcers were present on both lips and the oral cavity, and a BCG scar was observed on the left shoulder. Mild hepatosplenomegaly was observed.

Case 2: Physical examination of P2 revealed normal growth parameters. Periumbilical redness with a lack of pus formation was observed, and a BCG scar was observed on the left shoulder.

Laboratory examinations

Case 1: Complete blood count revealed leukocytosis (WBC 94600/mm³) and neutrophil predominance (67166/mm³), while anti-HIV was negative. Bone marrow aspiration revealed no evidence of hematological malignancy. His parents were asked for permission to conduct immunologic tests, but they denied due to financial concerns.

Case 2: Complete blood count showed significant leukocytosis (65300/mm³) and neutrophilia (46800/mm³). The lymphocyte populations determined using flow cytometry, serum immunoglobulin levels, and dihydrorhodamine 123 assays were normal.

Imaging examinations

Case 1: Chest radiography showed patchy infiltration in both lower lungs. Computed tomography of the neck showed obstruction of the upper airway due to an infection involving the mucosa of the oropharynx, hypopharynx, glottic, and subglottic levels.

Case 2: Anatomical abnormalities of the umbilicus were excluded by abdominal ultrasound, which revealed neither a patent urachus nor an omphalomesenteric cyst.

The diagnosis of LAD-1 was suspected in both patients.

Further diagnostic work-up

After informed consent was obtained from the patients and their parents, genomic DNA was extracted from peripheral blood lymphocytes using commercially available kits, according to the manufacturer's protocol. Sixteen coding exons and exon-intron boundaries of the *ITGB2* gene were amplified by PCR using primers as described previously[4,5]. Each 50 µL PCR mixture contained 1.5 mmol/L MgCl₂, 200 µmol/L of each dNTP, 0.5 µmol/L of each primer, 100 to 200 ng of genomic DNA and 1.25 units of Taq DNA polymerase. The PCR conditions were as follows: Initial denaturation at 95°C for 5 min; 30 cycles of 95°C for 30 s, 62 °C to 64°C for 30 s, and 72°C for 45 s; and a final extension at 72°C for 5 min. All PCR products were purified and directly sequenced in both the forward and reverse directions. The reference sequences were NM_000211.5 and NP_000202.3 for *ITGB2* cDNA and β2 integrin amino acid positions, respectively.



DOI: 10.5409/wjcp.v11.i5.429 Copyright ©The Author(s) 2022.

Figure 1 Sign of omphalitis in Patient 2.

Results

Homozygous of two novel “likely pathogenic” missense variants, c.920T>C (p.Leu307Pro) in exon 8 and c.758G>A (p.Arg-253His) in exon 7, and homozygous of a novel nonsense mutation, c.262C>T (p.Gln88Ter) in exon 4 of the *ITGB2* gene were identified in the genomic DNA of P1 and P2, respectively. Mutations were also characterized by the heterozygous state in both parents of P1 and P2, suggesting carrier status in the parents (Figure 2). The pathogenicity predictions for these mutations are summarized in Table 1.

Clinical and laboratory information, including *ITGB2* mutation analysis results for both patients, are summarized in Table 2.

FINAL DIAGNOSIS

The final diagnosis for both patients was LAD-1 with the carrier status in the parents.

TREATMENT

Case 1

Intravenous cloxacillin, ceftazidime, and amikacin were administered for chronic wound and soft tissue infections, resulting in good clinical responses.

Case 2

The use of intravenous gentamycin and ciprofloxacin for recurrent omphalitis improved her clinical outcome. She has not presented with omphalitis since that time.

OUTCOME AND FOLLOW-UP

Currently, hematopoietic stem cell transplantation cannot be performed because of the unavailability of matched donors. Sulfamethoxazole-trimethoprim with itraconazole prophylaxis was initiated and a significant decline in infection was noted. P1 developed a soft tissue infection around the tracheostomy, and P2 had occasional gastroenteritis and chronic otitis media in response to antibiotics. Several follow-up visits were conducted for both patients. They are currently six years old.

DISCUSSION

LAD-1 was first identified in 1979[6]. To date, more than 400 LAD-1 cases have been reported with the highest prevalence in Iran, the United States, and India in over 100 publications[7,8]. Our report is the first case series of LAD-1 diagnosed in Thailand. Patients with LAD-1 usually present in infancy with delayed umbilical cord separation, omphalitis, and skin infection in both mucosal and subcutaneous

Table 1 Pathogenicity prediction of mutation/variant (s) identified in the *ITGB2* gene in Patient 1 and Patient 2

Information/computation (in silico) predictive programs	c.920T>C (p.Leu307Pro) in exon 8	c.758G>A (p.Arg253His) in exon 7	c.262C>T (p.Gln88Ter) in exon 4
Human gene mutation database (HGMD)	Not identified	Not identified	Not identified
National center for biotechnology information (NCBI): dbSNP and ClinVar	Not identified	Uncertain significance rs200423927	Not identified
Exome aggregation consortium (ExAC) and 1000 genomes project	Not identified	ExAC 0.0002817 heterozygous (only)	Not identified
Mutation taster (http://www.mutationtaster.org/)	Disease causing	Disease causing	Disease causing
PolyPhen (http://genetics.bwh.harvard.edu/pph2/)	Probably damaging	Benign	-
SIFT (http://sift.jcvi.org/)	Damaging	Damaging	-
ACMG classification (2015)	Likely pathogenic (PM2, PM3, PP2, PP3)	Likely pathogenic (PM2, PM3, PP2, PP3)	Pathogenic (PVS1, PM2, PM3, PP3)

Table 2 Clinical, laboratory and molecular information in two patients with leukocyte adhesion defect type-1

Clinical information	Patient 1	Patient 2
Age of onset	1 mo	9 d
Clinical characteristics	Omphalitis Soft tissue infection Delayed wound healing Pneumonia	Omphalitis Gastroenteritis (occasional)
Delay separation of the umbilical cord	Yes	No
Family history of consanguineous marriage	Yes	No
Organisms	<i>Streptococcus viridans</i> <i>Staphylococcus epidermidis</i> <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i> and others	<i>Staphylococcus epidermidis</i> <i>Escherichia coli</i> <i>Klebsiella pneumoniae</i> , ESBL
White blood cells (WBC)	94600/mm ³	65300/mm ³
Absolute neutrophil counts (ANC)	67166/mm ³	46800/mm ³
<i>ITGB2</i> mutation	c.920T>C (p.Leu307Pro) in exon 8 and c.758G>A (p.Arg253His) in exon 7	c.262C>T (p.Gln88Ter) in exon 4
Outcome (at present)	Alive	Alive

ESBL: Extended-spectrum beta-lactamase.

tissues. LAD-1 is classified as mild (LAD-1⁺), moderate (LAD-1⁻), or severe (LAD-1⁰) depending on CD18 expression in neutrophils. Although the CD18 expression study remains unavailable at our institution, our patients were suspected of having LAD-1⁰ due to the early age of onset[3,7-9]. Both patients experienced omphalitis at the first presentation, which was also the most common initial manifestation among patients with LAD-1⁰ in related studies[8,10,11]. However, delayed cord separation after three weeks was only observed in P1, suggesting that this clinical feature may not be an essential characteristic of LAD-1⁰[8-10,12].

Other common infections that have been widely reported in related studies, including respiratory tract infection and sepsis[5-8,10], were not identified in P2, which could possibly be explained by early diagnosis and antibiotic prophylaxis in this patient. The spectra of infectious organisms in our patients were similar to those of other reported cohorts in which bacterial infections, including gram-positive cocci (*Staphylococci* or *Streptococci*) and gram-negative bacteria (*Pseudomonas aeruginosa* or *Klebsiella pneumoniae*) were predominantly identified[8,9,11]. Marked neutrophilic leukocytosis, which is the hallmark of LAD-1, was found in both patients.

The BCG vaccine is routinely prescribed for newborns as part of the national immunization program in Thailand. Vaccine-associated serious BCG infection has been reported among people with

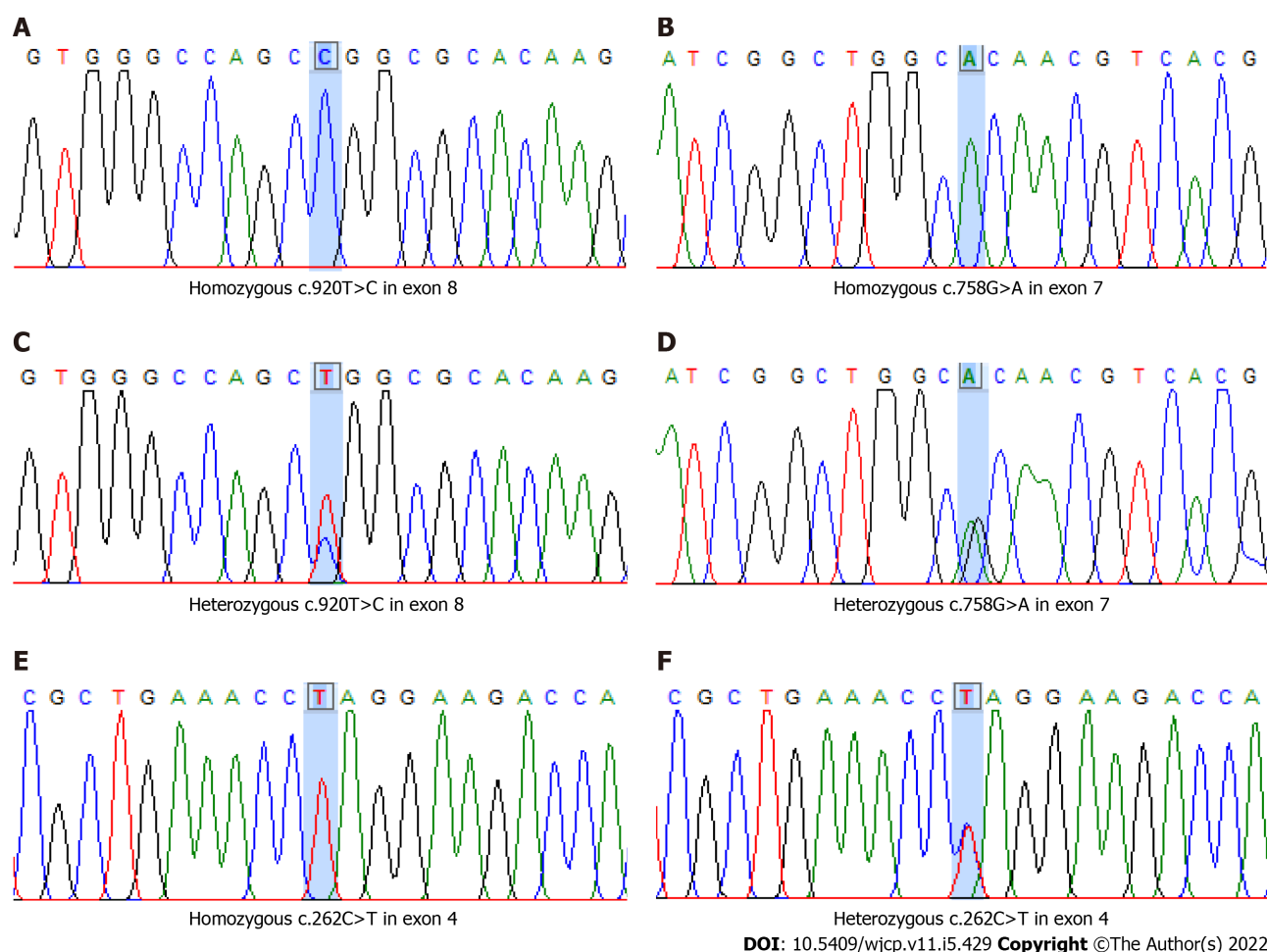


Figure 2 Direct DNA sequence analysis of the *ITGB2* gene. A and B: Homozygous c.920T>C (p.Leu307Pro) mutation in exon 8 and homozygous c.758G>A (p.Arg253His) mutation in exon 7 in the genomic DNA of Patient 1; C and D: Heterozygous c.920T>C mutation in exon 8 and heterozygous c.758G>A mutation in exon 7 of both parents in Patient 1; E: homozygous c.262C>T (p.Gln88Ter) mutation in exon 4 in the genomic DNA of Patient 2; F: heterozygous c.262C>T mutation in both paternal and maternal DNA.

immunodeficiency, particularly severe combined immunodeficiency and chronic granulomatous disease (CGD)[13]. Furthermore, we previously described a case of X-linked CGD with disseminated BCG infection[14]. According to the recent vaccination recommendations for primary immunodeficiency disease, live bacterial vaccines, such as BCG vaccine, are not recommended for patients with LAD[15]. Nevertheless, no BCG vaccine-related complications were reported among patients with LAD in the most recent systematic review[13], except for one reported Japanese girl with LAD-1 who had necrotizing ulcers after BCG vaccination[16]. This phenomenon is explained by a study in mice with abnormal integrins, CD11a and CD18, which were susceptible to *Mycobacterium tuberculosis* infection, indicating that adhesion molecules are essential for mycobacterial immunity[17]. Because BCG vaccination was administered to both patients at birth, BCG-related complications were monitored. To date, BCG-related complications have not been observed.

The diagnosis of LAD-1 is based on either the flow cytometric expression study of CD18 on leukocytes or molecular confirmation. Due to the unavailability of the CD18 expression study at our institution, molecular analysis by direct DNA sequencing of *ITGB2* was performed. Mutations in the *ITGB2* gene are heterogeneous, and missense mutations are the main cause of LAD-1 deficiency. Most mutations are located in the highly conserved domain, Von Willebrand Factor type A (VWFA), which consists of 240 amino acids encoded by exons 5 to 9 of the *ITGB2* gene. This domain is required for the enzymatic activity of the $\beta 2$ integrin (CD18). Other mutations are scattered throughout the gene[3,4,7,8,10].

This study identified three novel mutations: two likely deleterious missense mutations and one deleterious nonsense mutation. The two missense variants, c.920C>T (p.Leu307Pro) in exon 8 and c.758G>A (p.Arg253His) in exon 7, which were identified in P1, are located in the VWFA domain, which is highly conserved in the $\beta 2$ integrin protein. The c.920C>T variant has never been identified in either the Exome Aggregation Consortium (ExAC) or the 1000 Genomes Project population databases. c.758G>A is a rare variant identified in approximately 4 of 8632 individuals of East Asian ancestry according to the ExAC database and was identified only in the heterozygous state. Additionally, these

two homozygous missense mutations were not identified in the Thai Reference Exome variant database (1092 unrelated Thai individuals; T-Rex, <https://trex.nbt.or.th/>).

Most of the *in silico* analysis tools consistently predicted these two variants that may damage protein function (Table 1). Many missense pathogenic variants in nearby residues in the *ITGB2* gene have been reported to be associated with LAD-1[3]. These reasons support the possibility of “likely pathogenic” for both missense variants in Myanmar patient with LAD-1. Further *in vitro* studies may address the possible impact of amino acid substitutions on the function of $\beta 2$ integrin. Unfortunately, functional studies cannot be performed at our institution. Two mutations were detected simultaneously in some of the previously reported patients[4]. One nonsense mutation, c.262C>T (p.Gln88Ter) in exon 4, which was identified in P2, leads to a premature stop at codon 88 which normally encodes for glutamine and results in loss of both active VWFA and cysteine rich domains of $\beta 2$ integrin protein. This nonsense mutation has never been reported in the ExAC or 1000 Genomes Project databases. The VWFA domain is crucial for the structural association of a β -integrin subunits for heterodimer formation on the cell surface and functional activity. Any significant alterations in this region will definitely have a deleterious effect on the expression and function of $\beta 2$ integrin and result in the LAD-1⁰ phenotype among most patients with LAD-1[8,10]. Even though consanguineous marriage was denied by the parents of P2, consanguinity could not be excluded based on the identification of a novel nonsense mutation in the homozygous state in the patient and the heterozygous state in both parents.

LAD-1⁰ has an extremely poor prognosis, with the majority of patients dying within two years of life [7,12]. Early hematopoietic stem cell transplantation remains the treatment of choice, but this is unavailable for the majority of affected children in developing countries, including our patients. Thus, antibiotics used for prophylaxis and treatment of infections are the mainstay of treatment, while waiting for matched donors.

CONCLUSION

Herein, we report two classic cases of severe LAD-1. Early onset and recurrent omphalitis were common pathognomonic signs in our patients. A significant increase in white blood cell counts combined with neutrophilia should increase the awareness of LAD-1. Mutation analysis of the *ITGB2* gene remains the gold standard for the diagnosis of LAD-1. Three novel homozygous *ITGB2* mutations were identified in these patients. Molecular investigation is essential for definitive diagnosis, early treatment implementation, and prenatal diagnosis in future pregnancies.

ACKNOWLEDGEMENTS

The authors express their gratitude to the patients and their families who participated in this study. This study was supported by Phramongkutklao College of Medicine.

FOOTNOTES

Author contributions: Suksawat Y, Siripipattanamongkol N and Boonyawat B contributed to the drafting and writing of the case report manuscript and were involved in the clinical care of the patients; Boonyawat B extracted genomic DNA and performed genetic studies; Pacharn P supervised and edited the manuscript; all authors approved the final draft of the manuscript.

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

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

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (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: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: Thailand

ORCID number: Yiwa Suksawat 0000-0002-3083-743X; Punchama Pacharn 0000-0002-2507-2057; Nunthana

Siripipattanamongkol 0000-0001-8590-9085; Boonchai Boonyawat 0000-0002-2968-5467.

S-Editor: Gong ZM

L-Editor: A

P-Editor: Gong ZM

REFERENCES

- 1 **Hanna S**, Etzioni A. Leukocyte adhesion deficiencies. *Ann N Y Acad Sci* 2012; **1250**: 50-55 [PMID: [22276660](#) DOI: [10.1111/j.1749-6632.2011.06389.x](#)]
- 2 **van de Vijver E**, van den Berg TK, Kuijpers TW. Leukocyte adhesion deficiencies. *Hematol Oncol Clin North Am* 2013; **27**: 101-116, viii [PMID: [23351991](#) DOI: [10.1016/j.hoc.2012.10.001](#)]
- 3 **van de Vijver E**, Maddalena A, Sanal Ö, Holland SM, Uzel G, Madkaikar M, de Boer M, van Leeuwen K, Köker MY, Parvaneh N, Fischer A, Law SK, Klein N, Tezcan FI, Unal E, Patrioglu T, Belohradsky BH, Schwartz K, Somech R, Kuijpers TW, Roos D. Hematologically important mutations: leukocyte adhesion deficiency (first update). *Blood Cells Mol Dis* 2012; **48**: 53-61 [PMID: [22134107](#) DOI: [10.1016/j.bcmd.2011.10.004](#)]
- 4 **Yassaee VR**, Hashemi-Gorji F, Boosaliki S, Parvaneh N. Mutation spectra of the ITGB2 gene in Iranian families with leukocyte adhesion deficiency type 1. *Hum Immunol* 2016; **77**: 191-195 [PMID: [26639818](#) DOI: [10.1016/j.humimm.2015.11.019](#)]
- 5 **Taghizade Mortezaee F**, Esmaeli B, Badalzadeh M, Ghadami M, Fazlollahi MR, Alizade Z, Hamidieh AA, Chavoshzadeh Z, Movahedi M, Heydarzadeh M, Sadeghi Shabestari M, Tavassoli M, Nabavi M, Nasiri Kalmarzi R, Pourpak Z. Investigation of ITGB2 gene in 12 new cases of leukocyte adhesion deficiency-type I revealed four novel mutations from Iran. *Arch Iran Med* 2015; **18**: 760-764 [PMID: [26497373](#)]
- 6 **Hayward AR**, Harvey BA, Leonard J, Greenwood MC, Wood CB, Soothill JF. Delayed separation of the umbilical cord, widespread infections, and defective neutrophil mobility. *Lancet* 1979; **1**: 1099-1101 [PMID: [86829](#) DOI: [10.1016/s0140-6736\(79\)91786-0](#)]
- 7 **Almarza Novoa E**, Kasbekar S, Thrasher AJ, Kohn DB, Sevilla J, Nguyen T, Schwartz JD, Bueren JA. Leukocyte adhesion deficiency-I: A comprehensive review of all published cases. *J Allergy Clin Immunol Pract* 2018; **6**: 1418-1420.e10 [PMID: [29371071](#) DOI: [10.1016/j.jaip.2017.12.008](#)]
- 8 **Kambli PM**, Bargir UA, Yadav RM, Gupta MR, Dalvi AD, Hule G, Kelkar M, Sawant-Desai S, Setia P, Jodhawat N, Nambiar N, Dhawale A, Gaikwad P, Shinde S, Taur P, Gowri V, Pandrowala A, Gupta A, Joshi V, Sharma M, Arora K, Pilania RK, Chaudhary H, Agarwal A, Katiyar S, Bhattad S, Ramprakash S, Cp R, Jayaram A, Gornale V, Raj R, Uppuluri R, Sivasankaran M, Munirathnam D, Lashkari HP, Kalra M, Sachdeva A, Sharma A, Balaji S, Govindraj GM, Karande S, Nanavati R, Manglani M, Subramanyam G, Sampagar A, Ck I, Gutha P, Kanakia S, Mundada SP, Krishna V, Nampoothiri S, Nemani S, Rawat A, Desai M, Madkaikar M. Clinical and Genetic Spectrum of a Large Cohort of Patients With Leukocyte Adhesion Deficiency Type 1 and 3: A Multicentric Study From India. *Front Immunol* 2020; **11**: 612703 [PMID: [33391282](#) DOI: [10.3389/fimmu.2020.612703](#)]
- 9 **Shaw JM**, Al-Shamkhani A, Boxer LA, Buckley CD, Dodds AW, Klein N, Nolan SM, Roberts I, Roos D, Scarth SL, Simmons DL, Tan SM, Law SK. Characterization of four CD18 mutants in leukocyte adhesion deficient (LAD) patients with differential capacities to support expression and function of the CD11/CD18 integrins LFA-1, Mac-1 and p150,95. *Clin Exp Immunol* 2001; **126**: 311-318 [PMID: [11703376](#) DOI: [10.1046/j.1365-2249.2001.01661.x](#)]
- 10 **Madkaikar M**, Italia K, Gupta M, Chavan S, Mishra A, Rao M, Mhatre S, Desai M, Manglani M, Singh S, Suri D, Agrawal A, Ghosh K. Molecular characterization of leukocyte adhesion deficiency-I in Indian patients: identification of 9 novel mutations. *Blood Cells Mol Dis* 2015; **54**: 217-223 [PMID: [25703682](#) DOI: [10.1016/j.bcmd.2015.01.012](#)]
- 11 **Parvaneh N**, Mamishi S, Rezaei A, Rezaei N, Tamizifar B, Parvaneh L, Sherkat R, Ghalehbaghi B, Kashef S, Chavoshzadeh Z, Isaiean A, Ashrafi F, Aghamohammadi A. Characterization of 11 new cases of leukocyte adhesion deficiency type 1 with seven novel mutations in the ITGB2 gene. *J Clin Immunol* 2010; **30**: 756-760 [PMID: [20549317](#) DOI: [10.1007/s10875-010-9433-2](#)]
- 12 **Wolach B**, Gavrieli R, Wolach O, Stauber T, Abuzaitoun O, Kuperman A, Amir Y, Stepensky P, Somech R, Etzioni A. Leukocyte adhesion deficiency-A multicentre national experience. *Eur J Clin Invest* 2019; **49**: e13047 [PMID: [30412664](#) DOI: [10.1111/eci.13047](#)]
- 13 **Fekrvand S**, Yazdani R, Olbrich P, Gennery A, Rosenzweig SD, Condino-Neto A, Azizi G, Rafiemanesh H, Hassanpour G, Rezaei N, Abolhassani H, Aghamohammadi A. Primary Immunodeficiency Diseases and Bacillus Calmette-Guérin (BCG)-Vaccine-Derived Complications: A Systematic Review. *J Allergy Clin Immunol Pract* 2020; **8**: 1371-1386 [PMID: [32006723](#) DOI: [10.1016/j.jaip.2020.01.038](#)]
- 14 **Boonyawat B**, Suksawat Y, Pacharn P, Suwanpakdee P, Traivaree C. X-Linked Chronic Granulomatous Disease: Initial Presentation with Intracranial Hemorrhage from Vitamin K Deficiency in Infant. *Case Rep Pediatr* 2018; **2018**: 7041204 [PMID: [30034904](#) DOI: [10.1155/2018/7041204](#)]
- 15 **Sobh A**, Bonilla FA. Vaccination in Primary Immunodeficiency Disorders. *J Allergy Clin Immunol Pract* 2016; **4**: 1066-1075 [PMID: [27836056](#) DOI: [10.1016/j.jaip.2016.09.012](#)]
- 16 **Kurosawa H**, Mizukami T, Nunoi H, Kato M, Sato Y, Okuya M, Fukushima K, Katsuyama Y, Arisaka O. Necrotizing Ulcer After BCG Vaccination in a Girl With Leukocyte-adhesion Deficiency Type 1. *J Pediatr Hematol Oncol* 2018; **40**: 63-66 [PMID: [28538512](#) DOI: [10.1097/MPH.0000000000000853](#)]
- 17 **Ghosh S**, Chackerian AA, Parker CM, Ballantyne CM, Behar SM. The LFA-1 adhesion molecule is required for protective immunity during pulmonary Mycobacterium tuberculosis infection. *J Immunol* 2006; **176**: 4914-4922 [PMID: [16585587](#) DOI: [10.4049/jimmunol.176.8.4914](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

