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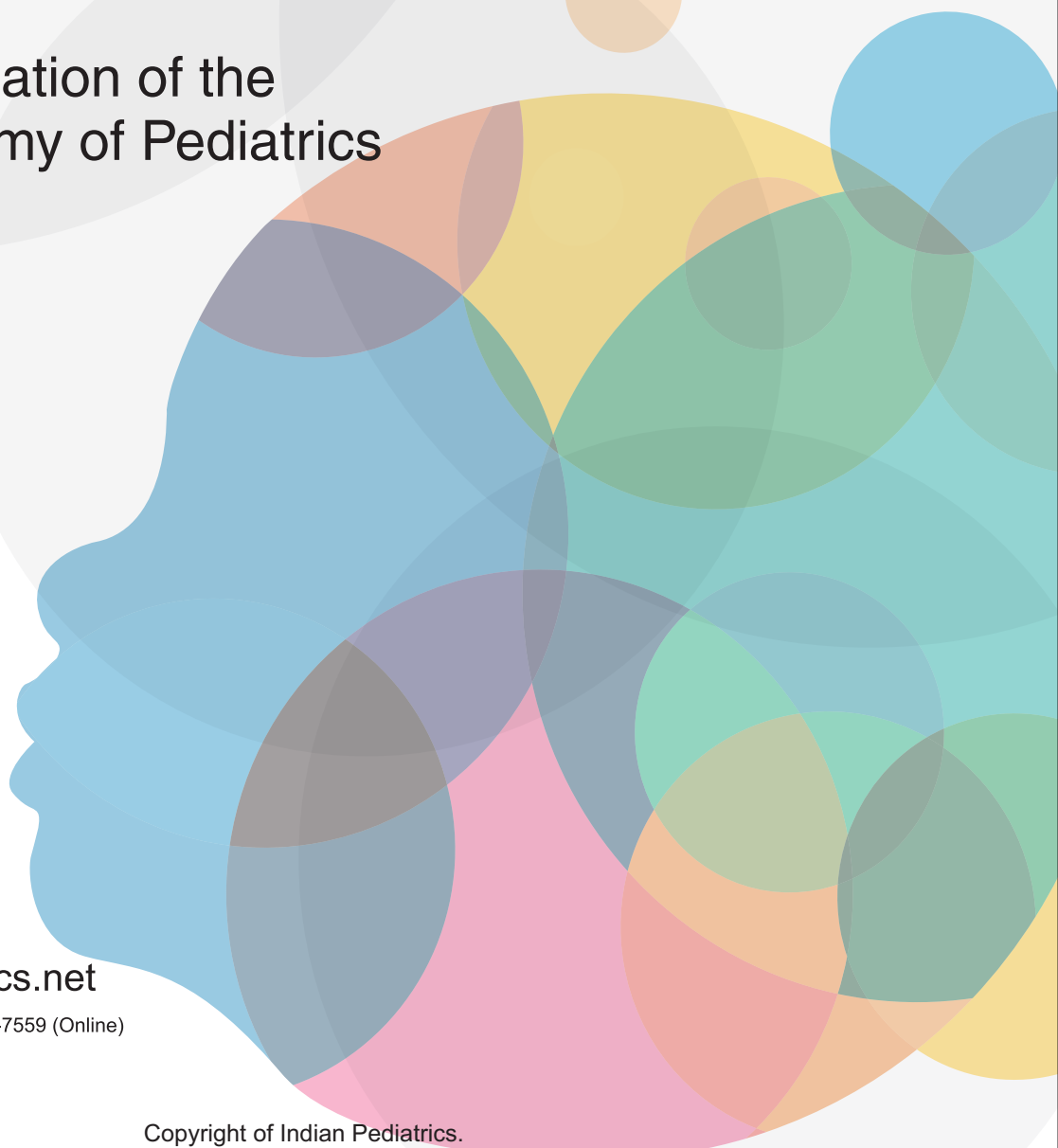
# Indian Pediatrics

Official Publication of the
Indian Academy of Pediatrics

**VOLUME 61**
**NUMBER 3**
**March 2024**



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ISSN0019-6061 (Print) | ISSN0974-7559 (Online)

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# Indian Pediatrics

March 2024 | Volume 61 | Number 3



## Contents

***Indian Pediatrics,*** the official journal of the Indian Academy of Pediatrics, is a peer-reviewed journal with monthly circulation of print/e-copies to over 40,000 pediatrician members. The journal is indexed in Current Contents/Clinical Medicine, Science Citation Index Expanded, Medline, PubMed, Indian Science Abstracts, getCITED, POPLINE, CANCERLIT, TOXLINE, Psych Line, and Dermline. The journal gives priority to reports of outstanding clinical and experimental work, as well as important contributions related to common and topical problems related to children and adolescents. Information for Authors is available on the website of the journal. *Indian Pediatrics* is available free online at *www.indianpediatrics.net*. There are no charges for publishing in the journal.



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PRESIDENT'S PAGE

# IAP ki Baat, Community ke Saath: Debuting with a Fight Against Anemia

**GV Basavaraja**
*National President, Indian Academy of Pediatrics, 2024*
*president@iapindia.org*

Dear Esteemed Members of the Indian Academy of Pediatrics (IAP),

In the contemporary era of abundant information facilitated by the internet, the dissemination of knowledge has seen unparalleled growth. However, alongside the benefits of easy access and rapid spread of information, there has been a surge in misinformation. This phenomenon has led to a widespread erosion of trust in the authenticity of online content, including news articles and social media posts.

As a response to this challenge, the initiative 'IAP ki Baat, Community ke Saath' has been launched by a consortium of esteemed colleagues of the IAP. This paper elucidates the rationale behind the inception of this program and highlights its potential to mitigate the proliferation of misinformation.

By fostering a community-driven approach towards fact-checking and promoting scientific rigor, this initiative aims to serve as a catalyst for cultivating a culture of truth and integrity in the digital landscape. Through collaborative efforts and a commitment to evidence-based communication, 'IAP ki Baat, Community ke Saath' endeavors to contribute significantly towards combating misinformation and upholding the principles of dissemination unbiased information.

## Active Participation and Collective Engagement: Mobilizing the Community Towards Truth and Integrity

In our endeavor to combat misinformation and uphold the principles of truth and integrity, active participation stands as the cornerstone of our collective effort. We call upon each member of our esteemed community, affectionately referred to as IAPians, to join hands in this noble cause.

The journey begins with a simple yet profound act of sharing our messages and spreading the word. By actively engaging in the dissemination of accurate information, we pave the way for a more informed society. We urge all IAPians to utilize their platforms and networks to amplify our message, reaching far and wide, to debunk myths and dispel falsehoods.

Furthermore, we recognize the pivotal role of parents in shaping the perspectives and knowledge base of future generations. As healthcare professionals entrusted with the well-being of children, we implore you to inform the parents of the young minds you treat. Empowering parents with reliable information not only safeguards the health and welfare of their children but also cultivates a culture of critical thinking and discernment.

While the task may seem daunting, let us not be deterred. Let us start small but aim for the sun, fueled by the unwavering belief in our collective potential. Together, we possess the strength to surmount any obstacle and transcend boundaries. It is through unity and collaboration that we will ascend to new heights of impact and influence.

On behalf of the Academy, I extend heartfelt gratitude for your unwavering support and dedication. Remember that you are not alone in this endeavor. With our combined efforts and steadfast support from our community, we are poised to effect transformative change. Join us on this journey, as together, we become architects of a brighter, more enlightened future.

## Addressing the Persistent Challenge of Anemia: Launching 'Anemia ki Baat, Community ke Saath' Program for Comprehensive Awareness and Action

Anemia stands as a pervasive health concern in India, silently sapping the vitality of our nation. Despite its manageable nature, anemia continues to afflict a significant portion of our population, particularly children and adolescent girls. This underscores the need for imperative concerted efforts to combat this debilitating condition with the launch of the 'Anemia ki Baat, Community ke Saath' Program.

The prevalence of anemia among children aged 6 months to 5 years and adolescent girls paints a stark picture of the magnitude of this health issue. With 67% of

children and 59% of adolescent girls affected, the toll of anemia on our society is undeniable [1]. However, behind these statistics lies a deeper challenge - the pervasive lack of awareness and understanding regarding the causes and management of anemia.

Central to the perpetuation of anemia is the dearth of accurate information regarding essential micronutrients and dietary practices. Misconceptions and outdated beliefs passed down through generations serve as the primary source of dietary guidance, contributing to the inadequate intake of vital nutrients. Studies have revealed a concerning trend of improper weaning practices, characterized by overcooking and dilution of weaning foods, further exacerbating the prevalence of anemia [2].

Through a multifaceted approach encompassing community outreach, capacity building, and information dissemination, the program seeks to empower individuals with the knowledge and resources necessary to address anemia effectively. By engaging with local communities, healthcare professionals, and stakeholders, 'Anemia ki Baat, Community ke Saath' endeavours to foster a culture of informed decision-making and proactive healthcare practices.

Emphasizing the importance of bi-annual deworming, we are committed to prioritizing this intervention and ensuring its consistent monitoring and implementation. Additionally, efforts will be made to enhance the capacity of ASHA workers through the launch of a Training of Trainers (TOT) program. This initiative will focus on capacity building for pediatricians, dieticians, and nutritionists, alongside the development of counseling materials, further strengthening our commitment to improving child health outcomes.

Aligned with the Anemia Mukt Bharat Program spearheaded by esteemed healthcare leaders Dr. Vinod K Paul and Dr. Pukhraj Bafna, the 'Anemia ki Baat, Community ke Saath' Program serves as a crucial ally in the national effort to eliminate anemia. By amplifying the reach and impact of government initiatives and highlighting the availability of free and affordable diagnostic and treatment facilities, the program aims to catalyze collective action towards achieving the shared goal of anemia eradication.

**REFERENCES**

1. Ministry of Health and Family Welfare, Anaemia Mukt Bharat. Posted On: Feb 04, 2022, 5:30 PM by PIB, Delhi. *https://pib.gov.in/PressReleasePage.aspx?PRID=1795421*
2. Vyas S, Kandpal SD, Semwal J, Chauhan S, Nautiyal V. Trends in weaning practices among infants and toddlers in a hilly terrain of a newly formed state of India. Int J Prev Med. 2014; 5:741-8.

# Indian Academy of Pediatrics Consensus Statement on Diagnosis and Management of Bone and Joint Infections in Children

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## ABSTRACT

**Justification:** Osteoarticular infections are fairly common in children but often these are associated with underdiagnosis, delayed diagnosis and improper management. This leads to an increased incidence of complications and poor outcomes. Given the paucity of standard protocols for the management of these children in the Indian context, Indian Academy of Pediatrics (IAP) has taken the initiative to formulate guidelines for the early diagnosis and rational management of bone and joint infections (BJIs).

**Objectives:** To critically evaluate the current evidence and formulate consensus guidelines for the diagnosis and management of BJIs in children.

**Process:** A committee comprising of eminent national faculty from different parts of the country who are experts in the field of Pediatric Infectious Diseases, Pediatric Orthopedics and Musculoskeletal Radiology was constituted and duly approved by the IAP. On Jan 16, 2021, a virtual meeting was held and a detailed discussions were carried out regarding the need to formulate these guidelines. Subsequently, the expert group defined the key questions in the first stage followed by collection and review of scientific evidences including available national and international recommendations or guidelines. This was followed by detailed deliberation among group members and presentation of their recommendations. The same were finalized in an online meeting on Aug 01, 2021, and a consensus statement was developed and adopted by the group.

**Statement**: BJIs are medical emergencies that need early diagnosis and appropriate therapy to prevent long term sequelae like limb deformities. Bacterial infections like *Staphylococcus aureus* is the most common etiological agent. Nonspecific and subtle clinical manifestations make the diagnosis of pediatric BJIs more challenging. Diagnosis of BJIs is primarily clinical, supplemented by laboratory and radiological investigations. The choice of antibiotic(s), mode of administration and duration of therapy requires individualization depending upon the severity of infection, causative organism, regional sensitivity patterns, time elapsed between onset of symptoms and the child's presentation, age, risk factors and the clinical and laboratory response to treatment. There is paucity of appropriate guidelines regarding the diagnosis and management of BJIs in children in Indian context. Hence, the need for this expert consensus guidelines in Indian settings.

**Keywords**: *Empirical antibiotics, Osteomyelitis, Septic arthritis, Staphylococcus aureus*

## BACKGROUND

Acute osteomyelitis in children is almost always a result of hematogenous (bacteremia) infection. As per available data, *Staphylococcus aureus* is the most common organism responsible for osteomyelitis which is seen in more than 50% of all culture-positive cases. Gram negative organisms are more frequent in infants compared to adults and older children [1,2]. Although data is lacking to prove *Kingella kingae* as causative agent of BJIs in children in India, 30-50% of musculoskeletal infections in children below 5 years in Europe, are due to this bacterium; isolated joint infections 65%, osteoarticular infection 30%, isolated bone infections 12% and spine

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infections 4% [3]. The prevalence of methicillin resistance in *Staphylococcus aureus* (MRSA) varies from 10-40% in different studies [4]. The incidence of *Streptococcus pneumoniae*, and *Hemophilus influenzae* type b (Hib) infections has declined with increasing immunization [5]. Multidrug resistant (MDR) and extensively drug resistant (XDR) gram negative bacilli and candida are important pathogens in neonates and critically ill children, especially those with indwelling vascular lines [6]. *Pseudomonas aeruginosa* and non-tuberculous mycobacterium are unique pathogens following penetrating injuries [6]. In patients with implants, coagulase negative Staphylococci, gram negative pathogens and fungi are encountered. Brucellosis and tuberculosis are important causes of BJIs in India, especially in cases with insidious onset. Gonorrhea is seen in sexually active adolescents [7].

## NEED FOR GUIDELINES

There is a paucity of scientific guidelines for the management of BJIs in children in India. These are intended for use by pediatricians as well as orthopedicians who take care of children with BJIs.

## OBJECTIVES

1. To critically evaluate the current evidence and formulate a consensus statement on the diagnosis and management of BJIs in children in India.
2. To provide consensus-based practice recommendations developed in a systematic manner with clinical applicability.

## TARGET AUDIENCE

These guidelines are intended for use by primary care pediatricians and orthopedic surgeons in India who manage children with BJIs.

## PROCESS FOR GUIDELINE FORMULATION

A group of experts comprising of pediatric infectious diseases specialists, pediatric orthopedicians and musculoskeletal radiologists were selected by the Indian Academy of Pediatrics (IAP) based on their experience and expertise in the respective fields. The experts are from different regions of India and comply with the policy of conflict of interest by IAP. On the Jan 16, 2021, a virtual meeting was held and detailed discussions were carried out regarding the requirements of the guidelines. Defining key questions was the first stage; it involved collecting evidence and data and conducting evaluations. The recommendations in these guidelines were developed after a review of the available literature from European Society of Pediatric Infectious Diseases (ESPID) guidelines and guidelines of the Infectional Diseases Society of America (IDSA). Special attention was given to publications made from the Indian subcontinent so as to make these recommendations applicable to local needs and clinical circumstances. All relevant papers and statements were discussed by all the expert group until a consensus was arrived at. The panel of experts based the final recommendations on the best available Indian data, global evidence, as well as the socioeconomics of healthcare. After reviewing the available scientific evidence, the committee formulated a few key questions. This was followed by detailed deliberation among group members and presentation of their recommendations. This was finalized in the meeting on Aug 02, 2021. The following Consensus Statement was adopted.

## CONSENSUS STATEMENT

### 1. CLINICAL PRESENTATIONS THAT WARRANT EVALUATION FOR BJIs:

The following clinical scenarios mandate evaluation for BJI

- A child who presents with refusal to use a limb OR restricted range of movements OR limping with / without fever
- Child has discomfort when touching or moving the joint e.g. while changing diaper
- Neonates with pseudoparalysis characterized by limited or absent limb movement without neurological involvement or excessive crying while using a limb
- Neonates with fever without a focus and irritability should have a high index of suspicion for BJIs apart from a CNS infection
- Any child with proven *Staphylococcus aureus* bacteremia
- Patients with trauma where loss of movements cannot be attributed to trauma alone
- A child with history suggestive of bleeding disorder with joint swelling associated with persistent pain with fever
- Patients with risk factors such as immuno-compromized child, known case of inflammatory joint disorder, post procedures like intraarticular injection, or arthroscopy, or prosthetic joints

Joints and long bones of the lower extremities such as tibia and femur are more frequently involved, although any bone in the body may be affected [8,9].

## 2. INITIAL INVESTIGATIONS FOR A CHILD WITH SUSPECTED BJIs

### Recommendations

- We recommend sending a complete blood count including a differential white blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum creatinine and blood culture (at least two sets to increase the yield) in all patients with suspected BJI as a part of first line investigations [10].
- Routine assessment of procalcitonin is not recommended

### Rationale

Though the diagnosis of acute osteomyelitis/ septic arthritis is usually made based on clinical findings, every effort should be made to obtain a microbiological diagnosis in order to optimize treatment. CRP is a good marker for the diagnosis and prognosis of the disease. Although ESR takes a longer time to rise and has reduced significance for this condition, the combination of both these tests (CRP and ESR) results in better sensitivity. A set of blood cultures with appropriate volume (which is 1% of circulating blood volume) should always be sent before initiating antibiotics. Blood cultures are positive in about one out of three cases [11]. Serum creatinine should be determined especially for a child who will be prescribed vancomycin or a child who needs contrast CT/ MRI [9]. There is no evidence to support the routine estimation of procalcitonin in children with BJIs [3,4].

## 3. EVALUATION OF BONE/ JOINT FLUID IN BJIs

### Recommendations

- Joint fluid evaluation is mandatory in all patients with suspected septic arthritis
- Bone /tissue/ pus evaluation whenever possible in acute osteomyelitis prior to starting antibiotics
- Non-response/ worsening while on adequate treatment
- Neonates and critically ill children with suspected BJIs

### Rationale

Synovial fluid evaluation is necessary for establishing the diagnosis of septic arthritis and for differentiation from transient synovitis and rheumatologic causes. The specimen should be sent for cell count, gram stain, aerobic culture. Inoculation of synovial fluid samples additionally into blood culture bottles instead of agar has been demonstrated in multiple studies to increase the yield [12]. If tubercular infection is suspected, then the specimen should also be sent for acid fast bacilli (AFB) stain, cartridge based nucleic acid amplification test (CBNAAT) and mycobacterial culture. In case of clinically stable patient when the diagnosis cannot be established by initial investigations, synovial aspiration/ biopsy should be attempted. In case of sick patient or rapidly progressive infection, antibiotics can be started followed by obtaining a synovial specimen as soon as possible [11].

Gram staining of bone, tissue or pus and aerobic cultures are recommended in acute osteomyelitis whenever possible since the yield is higher than blood cultures [13-16]. In neonates and immunocompromized patients, bone/pus cultures are mandatory since the etiology is diverse and often multidrug resistant. Histopathology can be helpful if tubercular osteomyelitis is suspected; mycobacterial cultures and CBNAAT of the specimen are recommended in such cases [17-23]. In 87.5% of children diagnosed with septic arthritis, PCR successfully identified the presence of a pathogen. Additionally, a lower rate of joint fluid culture positivity was observed in cases where antibiotic pretreatment occurred [24]. The yield of molecular tests is higher than cultures and these may be requested if validated and approved tests are available (e.g., Biomerieux bone and joint panel) [16].

## 4. RADIOLOGIC APPROACH

### Recommendations

- We recommend an initial plain radiograph of the involved site as a screening test.
- Ultrasonography (USG) has a high sensitivity for the diagnosis of septic arthritis [6]. Ultrasound may be performed if there is soft tissue edema or suspicion of septic arthritis.
- Imaging finding can be normal within first 24 hour of the illness. Hence, it is recommended to repeat USG or MRI in case of a high suspicion of underlying BJI [25].
- Magnetic resonance imaging (MRI) is the most reliable imaging modality for the diagnosis of BJI. MRI can be used as a confirmatory investigation for early diagnosis of osteomyelitis in cases with high clinical suspicion and also to grade the extent of disease involvement in confirmed cases [6].

### Rationale

### 4a. Plain radiographs

Plain radiography is considered as an important baseline test in all patients for comparison of disease progression/ treatment response and also to rule out other underlying conditions.

- Acute osteomyelitis: *X*-rays are frequently normal at baseline (< 2 weeks of symptom onset). Delayed

imaging may show appearance of osteolytic changes or periosteal elevation, mostly 10-21 days after onset of symptoms [6].

- Subacute osteomyelitis: *X*-ray changes can frequently be confused with malignancy; hence, MRI or histopathological correlation will be required for a definitive diagnosis.
- Septic arthritis: Limited usefulness of plain radiographs; soft tissue swelling may be seen along with blurring of fat planes, increased joint space with effusion and even joint dislocation.

### 4b. Ultrasonography

USG is most commonly indicated for septic arthritis because it has a high sensitivity for the diagnosis of joint effusion, although with a lower specificity. It should be performed in all suspected cases of septic arthritis, unless easily diagnosed by physical examination. It provides guidance for diagnostic or therapeutic aspiration and/or drainage. Doppler USG may provide early detection of a high vascular flow in the infected bone [26].

### 4c. Magnetic Resonance Imaging (MRI)

MRI is the gold standard imaging modality for acute osteomyelitis, because it can detect signs of osteomyelitis as early as within 3-5 days of disease onset. MRI provides greater details of the bone and soft tissue involvement, including the formation of abscesses, sequestra or associated pyomyositis or contiguous venous thrombosis. It is useful for appropriate preoperative planning for diagnostic and/or therapeutic purposes. MRI may not be necessary in certain situations where other clinical and diagnostic tools are strongly suggestive of the diagnosis [27,28].

- Septic arthritis: Although MRI is generally not indicated for isolated SA, it is valuable if OM associated with SA is suspected [29].
- Spondylodiscitis and vertebral OM: MRI is the most useful test for spinal infections as it provides excellent details of bone and soft tissue involvement in these complex areas. MRI aids in exclusion of other conditions such as malignancy.

Disadvantages of MRI include logistics, high cost, long scan times and need for sedation or anesthesia in young children. Presence of metallic foreign bodies, metal implants and MRI incompatible pacemakers are contraindications for performing MRI [30].

### 4d. Computerised Tomography (CT)

CT is not generally recommended in children as it is less sensitive compared with MRI in detecting early osseous lesions and exposes children to high doses of radiation [31].

- It should be reserved for settings where MRI is not feasible and USG is unremarkable with high clinical suspicion.
- Valuable for guided procedures, such as aspiration or drainage, and may not need sedation because of the short time needed.

### 4e. Bone Scintigraphy or Bone Scan Technetium Radionuclide Scan (99mTc)

It is used to identify multifocal osseous involvement and to document the site of OM when local skeletal symptoms are ill defined. It has a high sensitivity but low specificity [32] and both sensitivity and specificity are lower in neonates. It may also give false negative results in infancy and with virulent pathogens (MRSA).

## 5. REFERRAL TO ORTHOPEDIC SURGEONS

### Recommendation

- We recommend that all patients with suspected BJI be referred to orthopaedic surgeon as early as possible. The management of such children should be by the combined team of pediatrician and orthopedic surgeon.

### Rationale

All acute BJIs are emergencies need immediate and aggressive treatment. Many a times this aggressive treatment could only be empiric/appropriate broad-spectrum antibiotic/medical therapy but surgical intervention at an appropriate/early time is not only limb saving but lifesaving. A few hours of delay can mean a catastrophic outcome with permanent disability/deformity [33,34]. The decision to intervene must be made by a competent orthopedic surgeon [35,36].

## 6. EMPIRIC ANTIMICROBIAL THERAPY

### Recommendations

- We recommend intravenous (IV) cefazolin/ cefuroxime as empiric therapy in children aged 3 months to 5 years.
- We recommend IV cefazolin/cloxacillin as empiric therapy in children aged 5 years or older. Anti-MRSA therapy including vancomycin/ teicoplanin may be added in those with high suspicion for MRSA. We do not recommend linezolid as empiric therapy.
- In sick neonates and critically ill children, IV meropenem and vancomycin is recommended till culture results are available.

### Rationale

Choice of empiric therapy depends on the likely etiology and antimicrobial susceptibility and should be parenteral. In children aged 3 months - 5 years, the common culprits are *S. aureus*, *K. kingae* [7,8], *S. pneumoniae* and *H. influenzae*. The disadvantage of antistaphylococcal penicillins as empiric therapy for this age is that they do not cover for *K. kingae*, Hib or pneumococcus. In children aged 5 years and above, antistaphylococcal penicillins (cloxacillin/ flucloxacillin) or cefazolin is the drug of choice. The key decision is about initiation of anti-MRSA therapy. Empiric therapy for MRSA should be initiated if the prevalence of MRSA is more than 10-20%. The prevalence of MRSA varies in different settings, however, Indian data about the prevalence of CA-MRSA in pediatric BJIs is limited [3]. Hence, knowledge of local or institutional antibiogram is very crucial before starting MRSA therapy. Empiric therapy for MRSA may be added in very sick children, if the local experience so indicates, or if specific clinical indicators for MRSA are present such as high fever, bone abscess, multifocal involvement, fracture and deep vein thrombosis (DVT) or severe disease where either joint is involved and patient with poorly controlled comorbidity or organ damage [37,38].

It is mandatory to obtain blood and bone/ joint fluid cultures before initiating antibiotics for SA in neonates and critically ill children. Reviewing data about neonatal intensive care unit (NICU) cultures for that baby and the epidemiology of neonatal sepsis in the NICU where the baby was admitted may also help if available. Empiric therapy if indicated in a sick baby, can be initiated with a carbapenem (meropenem/ imipenem cilastatin), or a beta lactam plus beta lactamase inhibitor combination (piperacillin-tazobactam) along with vancomycin till cultures are available.

## 7. MODIFICATION OF ANTIBIOTICS BASED ON CULTURE REPORTS

### Recommendations

- The choices for definitive therapy are based on the isolate, susceptibility, availability, bone penetration, cost considerations and whether or not there is concomitant bacteremia. Parenteral therapy may be given as outpatient parenteral therapy (OPAT) in some patients.
- **Table I** and **Table II** describe the choices of antibiotics with their doses for definitive therapy of BJI [17].

### Rationale

- Methicillin sensitive *Staphyloccus aureus* (MSSA): The drug of choice for treating MSSA isolates in BJIs are either antistaphylococcal penicillins (cloxacillin/ nafcillin/flucloxacillin) or cefazolin. While the antistaphylococcal penicillins are the gold standard, disadvantages include erratic availability, four times a day dosing, thrombophlebitis and nephrotoxicity. The first-generation cephalosporin cefazolin is a good alternative with lower cost, thrice daily dosing but there is a concern about lower efficacy of cefazolin due to inoculum effect. Published data have reported similar efficacy of antistaphylococcal penicillins and cefazolin [39-41]. If the patient does not have bacteremia, other alternatives for MSSA include ceftriaxone dosed once/ twice daily or cefuroxime sodium dosed twice daily (suitable for OPAT). Preliminary studies show efficacy of cefazolin dosed twice daily also. If serious beta lactam allergy is present then daptomycin/fosfomycin can be used.
- MRSA: The drug of choice for MRSA isolates in BJIs is either vancomycin and teicoplanin. While vancomycin is the gold standard, problems include need for 3 to 4 times daily dosing, infusion-related side effects and nephrotoxicity and suboptimal tissue (bone) levels [42-44]. Teicoplanin, the other glycopeptide, has better bone levels than vancomycin, can be dosed once a day, has lesser nephrotoxicity and infusion related side effects [45-47]. A third alternative is daptomycin; availability and lack of pediatric data are limitations. Other anti-MRSA drugs such as linezolid, clindamycin and cotrimoxazole are the options for oral switchover therapy and not for initial parenteral therapy, especially, if coexistent bacteremia is present.

## 8. CHANGING FROM PARENTERAL TO ORAL ANTIMICROBIALS

### Recommendations

- This decision should be individualized.
- It should be initiated once there is resolution of symptoms and signs and improvement in the white cell count and CRP.

### Rationale

The change from parenteral to oral therapy depends on many factors including the presence/absence of bacteremia, age of the patient, severity of disease, causative pathogen, clinical and laboratory response, presence and absence of complications and availability of suitable oral option. Hence, this decision of oral switchover should be individualized for each patient. In patients with staphylococcal bacteremia, parenteral therapy for atleast 2 weeks is recommended. When this is

**Table I Definitive Antibiotic Regimens in Bone and Joint Infections Based on Etiology**

| *Organism* | *Parenteral* | | *Oral* |
|---|---|---|---|
| | *Ist line* | *Alternative* | |
| MSSA | Cloxacillin/Cefazolin | Daptomycin/Ceftriaxone/ Cefuroxime | Cephalexin/ Cloxacillin/ Clindamycin |
| MRSA | Teicoplanin/ Vancomycin | Daptomycin/ Fosfomycin | Linezolid/ Cotrimoxazole/ Clindamycin with/ without rifampicin |
| Kingella/ Pneumococcus/ Hib | Ceftriaxone | Cefuroxime/Co-amoxiclav | Cefuroxime |
| Salmonella/ susceptible Gram negative | Ceftriaxone Cotrimoxazole | Ciprofloxacin | Cefixime/ Ciprofloxacin/ |
| ESBL producing gram negative | Meropenem/ Imipenem | BL-BLI combinations (Piper-callin-Tazobactam, Cefopera-zone sulbactam)/Ertapenem | CiprofloxacinCotrimoxazole |
| Candida | Fluconazole | Amphotericin B Deoxycholate/ Liposomal Amphotericin B/ Micafungin/ Caspofungin | Fluconazole/ Voriconazole (for C. krusei) |
| Carbapenem resistant gram negatives | Polymyxins (Polymyxin B/Colistin) with tigecycline/ Fosfomycin/ Cotrimoxazole | | |
| Brucellosis | Children < 8 y: Cotrimoxazole and Rifampicin for 3 mo and Gentamicin/ Streptomycin for 7 d<br>Children older than 8 y: Doxycycline and rifampicin for 3 mo and Gentamicin/Streptomycin for 7d | | |
| Tuberculosis | Isoniazid, Rifampicin, Pyrazinamide, Ethambutol for 2 mo and then Isoniazid, Rifampicin with/ without Ethambutol for 10 mo | | |

*BL-BLI Beta-lactam and beta-lactamase inhibitor, ESBL Extended spectrum beta-lactamases, MRSA Methicillin resistant Staphylococcus aureus, MSSA Methicillin sensitive Staphyloccus aureus*

not possible due to logistic reasons, earlier switch may be considered in children who clear their bacteremia within 72 hours or serial blood culture become negative in 1-2 days of starting therapy. In patients with blood culture negative osteomyelitis, studies and meta-analysis show similar efficacy of early parenteral to oral switch versus prolonged intravenous therapy [48]. Prolonged intravenous therapy can actually be detrimental with increased drug adverse effects and infusion-related complications. Therefore, therapy should be switched to oral when the child becomes afebrile, the symptoms and signs are resolving, there are no complications, and the CRP is returning to normal, provided a suitable oral option is available and the child can take the antibiotic and if the parent/caregiver can administer the oral antibiotic to the child reliably. The cut-offs of CRP recommended to transition to oral therapy vary between 20-30 mg/L or a level 30-50% of the peak level [49-51].

Patients with MRSA infection, delayed response and complications may need prolonged parenteral therapy. Similarly, infants less than 3 months of age are best treated with parenteral therapy for the total duration of antibiotic therapy and so are patients for whom oral options are not available.

## 9. DURATION OF THERAPY

### Recommendation

- We recommend the length of total therapy should be 2-3 weeks for septic arthritis and 3-4 weeks for osteomyelitis; prolonged therapy upto 8 weeks may be needed in MRSA osteomyelitis, neonates, involvement of pelvis and spinal column.

### Rationale

Acute uncomplicated hematogenous osteomyelitis due to MSSA with good clinical response and rapid normalization of the CRP can generally be treated with 3-4 weeks of antibiotics. This recommendation is supported by prospective randomized trials in MSSA osteomyelitis where 20 days of therapy was noninferior to 30 days of treatment [48]. However, in osteomyelitis with complications (such as 2 or more bones involved with or without additional soft tissue involvement, slow response to therapy, requiring more than one surgery, persistent bacteremia after 3 or more days of therapy, complications like thrombosis, thrombophlebitis, endocarditis and pathological fracture, potential impact on bone growth) or pelvic/ spine infections, treatment for 6 weeks may be

**Table II. Doses of Commonly Used Drugs in Pediatric Bone and Joint Infections**

| *Drug* | *Route* | *Dose* | *Maximum dose/ day* |
|---|---|---|---|
| Cloxacillin | IV | 200 mg/kg/day q 6 h | 12 g |
| Cefazolin | IV | 100-150 mg/kg/day q 8 h | 6 g |
| Ceftriaxone | IV | 100 mg/kg/day q 12-24 h | 4 g |
| Cefuroxime | IV | 75 mg/kg/day q 12 h | 3 g |
| Vancomycin | IV | 45-60 mg/kg/day q 6-8 h | 3 g |
| Teicoplanin | IV | 8-12 mg/kg 12 hourly for 3 days and then 8-12 mg/kg/ day q 24 h | 1200 mg |
| Daptomycin | IV | 8-10 mg/kg/day q 24 h | 700 mg |
| Clindamycin | IV | 20-30 mg/kg/day q 8 h | 2700 mg |
| Cephalexin | IV | 100-150 mg/kg/day q 6-8 h | 4 g |
| Cefuroxime | Oral | 20 mg/kg/day q 12 h | 1 g |
| Cloxacillin | Oral | 30-50 mg/kg/day q 8 h | 3 gm |
| Clindamycin | Oral | 20 mg/kg/day 2 8 h | 1200 mg |
| Linezolid | IV, oral | 30 mg/kg/day q 8 h | 1200 mg |
| Cotrimoxazole | IV, oral | 8-12 mg/kg/day of TMP q 8-12 h | 640 mg of Trimethoprim |
| Rifampicin | Oral | 10-20 mg/kg/day q 12-24 h | 1200 mg |
| Meropenem | IV | 60-120 mg/kg/day q 8 h | 6 g |
| Imipenem | IV | 60-100 mg/kg/day q 6-8 h | 3 g |
| Ertapenem | IV | 40 mg/kg/day q 12 h | 1 g |
| Piperacillin tazobactam | IV | 300-400 mg/kg/day of piperacillin q 6-8 h | 16 g of Piperacillin |
| Cefoperazone sulbactam | IV | 100 mg/kg/day of cefoperazone q 12 h | 4 g of Cefoperazone |
| Ciprofloxacin | IV | 20-30 mg/kg/day q 12 h | 1200 mg |
| Ciprofloxacin | Oral | 30 mg/kg/day q 12 h | 1500 mg |
| Fluconazole | IV | Neonates: 25 mg/kg loading and then 12 mg/kg/day q 24 h<br>Older children: 12 mg/kg loading and then 6 mg/kg/day q 24 h | Loading 800 mg and<br>Mmaintainence 400 mg |
| Liposomal Amphotericin B | IV | 3 mg/kg/day q 24 h | None |
| Amphotericin B deoxycholate | IV | 1 mg/kg/day q 24 h | None |
| Micafungin | IV | Neonates: 10 mg/kg/day q24 h; Older children: 2-4 mg/kg/ day q24 h | 100 mg |
| Caspofungin | IV | 70 mg/m$^2$ loading and then 50 mg/m$^2$ maintenance q24h | 70 mg |
| Polymyxin B | IV | 20,000-25,000 units/kg loading and then 20000-30000 units/kg/day q 12 h | 2 million |
| Colistin | IV | 4.5 million units/kg loading and then 4.5 million units/kg/day q 8-12 h | 9-12 million units |
| Tigecycline | IV | 3 mg/kg loading and then 3 mg/kg/day maintenance q 12 h | Loading 200 mg and maintenance 200 mg |
| Fosfomycin | IV | 200-300 mg/kg/day q 6-8 h | 16 g |

needed. In MRSA osteomyelitis, treatment for up to 8 weeks may be needed. Candida osteomyelitis needs treatment for up to 6 months. In children with implant- or prosthesis-associated infections (where the implant or prosthesis has been retained), chronic suppressive therapy may need to continue for even up to 3 to 6 months, depending on the joint involvement [52-54].

In infants and children with uncomplicated septic arthritis (single joint involvement with rapid response within 3 to 5 days, resolution of bacteremia in 1-2 days, no signs of late sequelae), the treatment duration is dependent on the clinical response to therapy and the suspected organism. *S. pneumoniae*, *Hib*, *K. kingae* and *N. gonorrhoea*e are treated with appropriate antibiotics for 2-3 weeks. Infections with *S. aureus* and gram-negative organisms are treated longer for 3-4 weeks [55-59]. If there is associated osteomyelitis (complicated septic arthritis), the duration of antibiotics would be as for osteomyelitis. An MRI is the ideal imaging technique to detect coexistent osteomyelitis. However, in resource-

limited settings an *X*-ray of the affected joint to look for bony changes consistent with osteomyelitis may be done at the end of 2-3 weeks of therapy or before stopping treatment.

## 10. MANAGEMENT OF CULTURE NEGATIVE BJIs

### Recommendations

- We recommend continuing the initial empiric regimen in patients with culture negative BJI, provided there is clinical response.
- When there is no growth in culture, all efforts should be made to rule out tuberculosis and fastidious organisms as one of the possibilities.

### Rationale

Most of these BJIs respond to empirical therapy with cefazolin/ cefuroxime/cloxacillin. Duration of antibiotic therapy depends on the response to antibiotics and laboratory response using ESR and CRP. Once inflammatory markers are normal and patient has shown clinical improvement, antibiotics can be stopped [60]. In patients who are not improving with the initial regimen, repeat bone/ joint cultures should be obtained before adding an MRSA cover/ broadening therapy. When there is no growth in culture, all efforts should be made to rule out tuberculosis as one of the possibilities.

## 11. FAILURE OF THERAPY

### Recommendation

- Treatment failure should be suspected when there is absence of clinical improvement after 72 hours of antibiotic therapy, persistence of fever more than 72-96 h duration, or its reappearance (unexplained by other common causes), elevated WBC count and raised CRP even after 7 days of antibiotic therapy, or development of a pathological fracture [60,61].

Common causes of treatment failure include inappropriate drug and/or improper dose, drug resistant organisms and lack of source control.

## 12. MANAGING A PATIENT WITH SUSPECTED TREATMENT FAILURE

### Recommendations

- We recommend repeating blood/ bone/ tissue/ pus cultures, MRI imaging for assessing metastatic infection/ subperiosteal abscess, and evaluation for DVT in patients with treatment failure.
- Treatment will depend on the underlying cause of treatment failure and may include upgradation or change of antibiotics and surgical intervention.

### Rationale

A delay in the diagnosis and initiation of appropriate treatment can lead to potentially devastating morbidity including sepsis, chronic infection, disruption of longitudinal bone growth and angular deformity.

## 13. LONG-TERM FOLLOW UP OF A CHILD WITH BJIs

### Recommendations

- We recommend follow up by orthopedic surgeons and pediatricians at 2 weeks, 4-6 weeks, 3 months, and 12 months after discharge [62].
- Close monitoring of the range of motion at joint and limb length should be done.
- Pain-free normal activity is one of the important end points to consider prior to discharge from follow up.
- The need for radiological investigations during follow up should be decided by the orthopedic surgeon on a case-to-case basis.

### Rationale

Early diagnosis and appropriate treatment are associated with an excellent outcome of BJIs in children. Common sequelae include limping gait, dysmetria, chronic pain, stiffness with or without the presence of growth arrest, leg length discrepancy and deformity. Parents and care takers should be educated to look for signs such as limp, pain, deformity or leg length difference and to seek early medical attention if any concerns irrespective of scheduled appointments [63].

In the true sense, the long term follow up starts with normalization of inflammatory markers (ESR and CRP) and after cessation of antibiotics, both parenteral and oral. Clinically this is evidenced by the child walking and playing without pain and limp. In the initial period, blood investigations for inflammatory markers and radiographs should be included. Clinical examination during every visit, whilst carefully looking for sequelae is very important. If epiphyseal arrest is suspected, an MRI with or without CT scan of affected physis is recommended. Customization may be dictated by the causative organism; certain organisms such as Salmonella, MRSA or Panton-Valentine-Leucocidin (PVL) producing bacteria will need a closer follow up as they are associated with a higher rate of complications and/or sequelae like DVT [62,64].

## REFERENCES

1. Jaybhaye A, Lg S, Dash N, et al. Clinical spectrum and microbial etiology of bone and joint infections in children: a retrospective analysis from South India. Am J Trop Med Hyg. 2023;108: 936-41.

2. Agarwal A, Aggarwal AN. Bone and joint infections in children: acute hematogenous osteomyelitis. Indian J Pediatr. 2016;83: 817-24.
3. Wong M, Williams N, Cooper C. Systematic review of Kingella kingae musculoskeletal infection in children: epidemiology, impact and management strategies. Pediatric Health Med Ther. 2020;11:73-84.
4. Thakolkaran N, Shetty AK. Acute hematogenous osteomyelitis in children. Ochsner J. 2019;19: 116-22.
5. Wahl B, O'Brien KL, Greenbaum A, et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. Lancet Glob Health. 2018;6:e744-57.
6. Saavedra-Lozano J, Falup-Pecurariu O, Faust SN, et al. Bone and joint infections. Pediatr Infect Dis J. 2017;36: 788-99.
7. Le Saux N. Diagnosis and management of acute osteoarticular infections in children. Paediatr Child Health. 2018;23:336-43.
8. Autore G, Bernardi L, Esposito S. Update on acute bone and joint infections in paediatrics: a narrative review on the most recent evidence-based recommendations and appropriate antinfective therapy. Antibiotics (Basel). 2020;9:486.
9. Saavedra-Lozano J, Mejías A, Ahmad N, et al. Changing trends in acute osteomyelitis in children. J Pediatr Orthop. 2008;28:569-75.
10. Miller JM, Binnicker MJ, Campbell S, et al. A guide to utilization of the microbiology laboratory for diagnosis of infectious diseases: 2018 update by the Infectious Diseases Society of America and the American Society for Microbiology. Clin Infect Dis. 2018;67:e1-94.
11. Woods CR, Bradley JS, Chatterjee A, et al. Clinical Practice Guideline by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America: 2021 Guideline on Diagnosis and Management of Acute Hematogenous Osteomyelitis in Pediatrics. J Pediatr Infect Dis Society. 2021;10:801-44.
12. Higgins E, Suh GA, Tande AJ. Enhancing Diagnostics in Orthopedic Infections. J Clin Microbiol. 2022;60: e0219621.
13. Branson J, Vallejo JG, Flores AR, et al. The contemporary microbiology and rates of concomitant osteomyelitis in acute septic arthritis. Pediatr Infect Dis J. 2017;36:267-73.
14. Chang WS, Chiu NC, Chi H, et al. Comparison of the characteristics of culturenegative versus culture-positive septic arthritis in children. J Microbiol Immunol Infect. 2005;38:189-93.
15. Yi J, Wood JB, Creech CB, et al. Clinical epidemiology and outcomes of pediatric musculoskeletal infections. J Pediatr. 2021;234:236-44.
16. Van den Boom M, Lennon DR, Crawford H, et al. Microbiology of septic arthritis in young Auckland children. J Paediatr Child Health. 2022;58:326-31.
17. Arnold JC, Bradley JS. Osteoarticular infections in children. Infect Dis Clin North Am. 2015;29:557-74.
18. El-Sayed AMM. Treatment of early septic arthritis of the hip in children: Comparison of results of open arthrotomy versus arthroscopic drainage. J Child Orthop. 2008;2:229-37.
19. Brown DW, Sheffer BW. Pediatric septic arthritis: an update. Orthop Clin North Am. 2019;50:461-70.
20. Givon U, Liberman B, Schindler A, Blankstein A, Ganel A. Treatment of septic arthritis of the hip joint by repeated ultrasound-guided aspirations. J Pediatr Orthop. 2004: 266-70.
21. Duman S, Camurcu Y, Ucpunar H, Çöbden A, Karahan N, Sofu H. Arthroscopic treatment of acute septic arthritis of the hip joint in pediatric patients aged 10 years or younger. Arthroscopy. Arthroscopy. 2020;36:464-72.
22. Pääkkönen M, Kallio MJ, Peltola H, Kallio PE. Pediatric septic hip with or without arthrotomy: retrospective analysis of 62 consecutive nonneonatal culture-positive cases. J Pediatr Orthop B. 2010;19:264-9.
23. Quick RD, Williams J, Fernandez M, et al. Improved diagnosis and treatment of bone and joint infections using an evidence-based treatment guideline. J Pediatr Orthopaed. 2018;38:e354-9.
24. Klosterman MM, Villani MC, Hamilton EC, Jo C, Copley LA. Primary Septic Arthritis in Children Demonstrates Presumed and Confirmed Varieties Which Require Age-specific Evaluation and Treatment Strategies. J Pediatr Orthop. 2022;42:e27-33
25. Zamzam MM. The role of ultrasound in differentiating septic arthritis from transient synovitis of the hip in children. J Pediatr Orthop B 2006;15:418-22.
26. Sabour AF, Alluri RK, Heckmann N, et al. A nation wide analysis of failed irrigation and debridement for pediatric septic arthritis of the hip. J Pediatr Orthop B. 2019;28: 470-5.
27. Mazur JM, Ross G, Cummings J, et al. Usefulness of magnetic resonance imaging for the diagnosis of acute musculoskeletal infections in children. J Pediatr Orthop. 15:144-7.
28. Courtney PM, Flynn JM, Jaramillo D, Horn BD, Calabro K, Spiegel DA. Clinical indications for repeat MRI in children with acute hematogenous osteomyelitis. J Pediatr Orthop. 2010;30:883-7.
29. Chen CE, Ko JY, Li CC, Wang CJ. Acute septic arthritis of the hip in children. Arch Orthop Trauma Surg. 2001;121:521-6.
30. Sucato DJ, Schwend RM, Gillespie R. Septic arthritis of the hip in children. J Am Acad Orthop Surg. 1997;5:249-60.
31. Sabour AF, Alluri RK, Heckmann N, Heidari KS, Rick Hatch GF 3rd, VandenBerg C. A nationwide analysis of failed irrigation and debridement for pediatric septic arthritis of the hip. J Pediatr Orthop B. 2019;28:470-5.
32. Lavy CBD, Peek AC, Manjolo G. The incidence of septic arthritis in Malawian children. Int Orthop. 2005;29:195-6.
33. Thompson RM, Gourineni P. Arthroscopic treatment of septic arthritis in very young children. J Pediatr Orthop. 2017;37:e53.
34. Gordon JE, Wolff A, Luhmann SJ, et al. Primary and delayed closure after open irrigation and debridement of septic arthritis in children. J Pediatr Orthop B. 2005;14:101-4.
35. Pääkkönen M, Peltola H. Bone and joint infections. Pediatr Clin North Am. 2013;60:425-36.
36. Arnold JC, Bradley JS. Osteoarticular infections in children. Infect Dis Clin North Am. 2015;29:557-74

37. Hollmig ST, Copley LA, Browne RH, et al. Deep venous thrombosis associated with osteomyelitis in children. J Bone Joint Surg Am. 2007;89:1517-23.
38. Hotchen AJ, Dudareva M, Ferguson JY, Sendi P, McNally MA. The BACH classification of long bone osteomyelitis. Bone & joint research. 2019;8:459-68.
39. McNeil JC, Sommer LM, Boyle M, et al. Cefazolin inoculum effect and methicillin-susceptible staphylococcus aureus osteoarticular infections in children. Antimicrob Agents Chemother. 2020;64:e00703-20.
40. Loubet P, Burdet C, Vindrios W, et al. Cefazolin versus anti-staphylococcal penicillins for treatment of methicillin-susceptible Staphylococcus aureus bacteraemia: a narrative review. Clin Microbiol Infect. 2018;24:125-32.
41. Birrell MT, Fuller A. Twice daily cefazolin is effective for treatment of serious methicillin-sensitive Staphylococcus aureus infection in an outpatient parenteral antimicrobial therapy program. Ther Adv Infect Dis. 2019;6: 2049936119882847.
42. Kini AR, Shetty V, Kumar AM, et al. Community-associated, methicillin-susceptible, and methicillin-resistant Staphylococcus aureus bone and joint infections in children. J Pediatr Orthop B. 2013;22:158-66.
43. Perlman MH, Patzakis MJ, Kumar PJ, et al. The incidence of joint involvement with adjacent osteomyelitis in pediatric patients. J Pediatr Orthop. 2000;20:40-3.
44. Hussain FM, Boyle-Vavra S, Bethel CD, et al. Current trends in community-acquired methicillin-resistant Staphylococcus aureus at a tertiary care pediatric facility. Pediatr Infect Dis J. 2000;19:1163-6.
45. Liu C, Bayer A, Cosgrove SE, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children. Clin Infect Dis. 2011;52:e18–55.
46. Matthews PC, Taylor A, Byren I, Atkins BL. Teicoplanin levels in bone and joint infections: are standard doses subtherapeutic? J Infect. 2007;55:408-13.
47. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:e1-50.
48. Faust SN, Clark J, Pallett A, Clarke NMP. Managing bone and joint infection in children. Arch Dis Child. 2012;97:545-53.
49. Zaoutis T, Localio AR, Leckerman K, et al. Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. Pediatrics 2009;123:636–42.
50. Keren R, Shah SS, Srivastava R, et al. Pediatric research in inpatient settings network. comparative effectiveness of intravenous vs oral antibiotics for post discharge treatment of acute osteomyelitis in children. JAMA Pediatr 2015;169:120-8
51. Edmonds EW, Lin C, Farnsworth CL, et al. A medial portal for hip arthroscopy in children with septic arthritis. J Pediatr Orthop. 2018;38:527-31.
52. Pääkkönen M, Kallio PE, Kallio MJ, Peltola H. Does bacteremia associated with bone and joint infections necessitate prolonged parenteral antimicrobial therapy? J Pediatric Infect Dis Soc. 2015;4:174-7.
53. Le Saux N, Howard A, Barrowman NJ, et al. Shorter courses of parenteral antibiotic therapy do not appear to influence response rates for children with acute hematogenous osteomyelitis: a systematic review. BMC Infect Dis. 2002;2:16.
54. Matthews PC, Berendt AR, McNally MA, Byren I. Diagnosis and management of prosthetic joint infection. BMJ. 2009;29:338.
55. Peltola H, Paakkonen M, Kallio P, et al. Short-versus long-term antimicrobial treatment for acute hematogenous osteomyelitis of childhood. Pediatr Infect Dis J. 2010; 29:1123-8.
56. Jagodzinski NA, Kanwar R, Graham K, et al. Prospective evaluation of a shortened regimen of treatment for acute osteomyelitis and septic arthritis in children. J Pediatr Orthop 2009;29:518–25.
57. Howard-Jones AR, Isaacs D. Systematic review of systemic antibiotic treatment for children with chronic and sub-acute pyogenic osteomyelitis. J Paediatr Child Health. 2010;46: 736-41.
58. Osmon DR, Berbari EF, Berendt AR, et al; Infectious Diseases Society of America. Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2013;56:e1-e25.
59. Peltola H, Pääkkönen M, Kallio P, et al. Osteomyelitis-Septic Arthritis (OM-SA) study group. prospective, randomized trial of 10 days versus 30 days of antimicrobial treatment, including a short-term course of parenteral therapy, for childhood septic arthritis. Clin Infect Dis 2009;48:1201-10.
60. Korean Society for Chemotherapy, Korean Society of Infectious Diseases, Korean Orthopaedic Association. Clinical Guidelines for the Antimicrobial Treatment of Bone and Joint Infections in Korea. Infect Chemother. 2014;46:125-38.
61. Dodwell ER. Osteomyelitis and septic arthritis in children. Curr Opin Pediatr. 2013;25:58-63.
62. Saavedra-Lozano J, Falup-Pecurariu O, Faust SN, et al. Bone and joint infections. The Pediatric infectious disease journal. 2017;36:788-99.
63. Atijosan O, Rischewski D, Simms V, et al. A national survey of musculoskeletal impairment in Rwanda: prevalence, causes and service implications. PLoS One. 2008;3:e2851.
64. Jones HW, Beckles VLL, Akinola B, et al. Chronic haematogenous osteomyelitis in children. J Bone Joint Surg Br. 2011;93:1005-1010.

INVITED COMMENTARY

# Minipuberty in Full-term and Preterm Asian Indian Infants: The First Glance

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Minipuberty is a transient postnatal hypothalamic-pituitary-gonadal (HPG) axis reactivation following withdrawal of the maternal estrogens. Minipuberty in male infants, promotes early penile growth, an increase in testicular size, completion of testicular descent (if not already completed at birth), and increase in growth velocity. The increased testicular size results from the lengthening of seminiferous tubules with a concomitant increase in the total numbers of germ cells and Sertoli cells. Absent or diminished minipuberty in male infants with congenital hypogonadotropic hypogonadism (CHH) is associated with reduced reproductive function during adulthood. Hence, priming of the testis during minipuberty seems crucial for future fertility [1].

Minipuberty provides a window of opportunity for the evaluation of gonadal disorders and disorders of sex development (DSD) without the need for dynamic testing [2]. In male infants with cryptorchidism, and/or micropenis, evaluation during minipuberty facilitates early diagnosis. Serum gonadotropins and testosterone levels are lower in CHH during minipuberty whereas gonadotropins are elevated in anorchia and Klinefelter syndrome [2]. Diagnosis of these disorders during infancy provides early therapeutic opportunities. In CHH, induction of minipuberty with gonadotropin therapy during infancy increases the potential for future fertility [3]. In Klinefelter syndrome, though not encouraged for routine use, testosterone therapy during infancy has positive benefits on body composition, phallic enlargement, and linear growth [4].

Interestingly, the minipubertal pattern may completely differ from the pubertal one in some conditions. For example, in complete androgen insensitivity syndrome, minipuberty is absent in contrast to elevated androgen and luteinizing hormone levels seen during puberty [2]. Besides, some common factors like prematurity may also alter minipuberty. Earlier and exaggerated minipuberty in preterm (PT) than full term (FT) infants have been well-described in Caucasians [5]. However, the data on minipuberty in Asians especially Indians, a unique and ethnically diverse population, is lacking.

In this issue of *Indian Pediatrics*, Danda et al described the patterns of minipuberty in FT and PT south-Indian infants by assessing the urinary hormonal profile and genital examination [6]. They noted an earlier and exaggerated minipuberty with faster phallic and testicular enlargement in Indian PT infants compared to those born at term gestation. Lower urinary follicle-stimulating hormone (FSH) on day 7 of life and higher luteinizing hormone (LH) and total testosterone (TT) throughout the first 4-6 months of life in PT infants were also observed [5,6]. All these observations are in a close agreement with Finnish data [5] indicating no/minimal ethnic differences in minipubertal patterns of the two populations. However, the increment in phallic length during the first month of life was noticeably different between the Indian and Finnish PT infants [5,6]. The increase in nonstretched penile length in Finnish FT infants was maximum during the first month of life with subsequent plateauing whereas it was gradually progressive till 5 months of life in PT infants. A slower increase in penile length during the first month in Finnish PT infants was associated with lower levels of urinary free prostate-specific antigen indicating an impeded androgen action [5]. In contrast, the increase in penile length in Indian PT infants was maximum during the first month of life [6]. PT infants showed a significant mean percentage increase in SPL (20% vs 13.3%; $P < 0.001$) at one month in comparison with FT infants. This observation needs further validation to verify whether this represents an ethnic-specific difference.

A study from Japan reported higher LH but lower FSH urinary concentrations in PT small for gestational age (SGA) infants than their appropriate e for gestational age (AGA) counterparts [7]. Another study from Sweden also

reported higher total testosterone at birth and 0-month corrected age in moderate and late preterm infants with birth weight < 2500 g than those with birth weight ≥ 2500 g [8]. These two studies suggest an effect of intrauterine growth retardation on minipuberty. As demonstrated in recent studies from Poland, maternal factors such as vitamin D deficiency (exaggeration) and hypothyroidism (dampening) may also affect minipuberty [9,10]. Hence, further exploration of the common factors that may alter minipuberty is warranted.

Pubertal/minipubertal testosterone level is usually noted on the first 1-2 days of postnatal life, the usual time when DSD neonates are identified with atypical genitalia [11]. This period may offer the earliest opportunity for hormonal evaluation of 46, XY DSD. However, the studies by Danda et al [6] and Kuiri-Hunninen et al [5] have not evaluated urinary gonadotropins during this period of life. A recent study from Italy has reported urinary gonadotropins and testosterone during <72 hours of life [12]. Interestingly, testosterone was higher during this period than any other period of minipuberty and this was despite relatively lower gonadotropins. More interestingly, urinary testosterone was higher in FT infants than PT infants during this period, but it reversed at ≥ 30 days of life [12]. This interesting phenomenon of contrasting trends in testosterone levels between PT and FT infants also needs further exploration.

Measurement of gonadotropins in urine, a more convenient sampling method, has been used not only to predict, diagnose, and monitor precocious puberty but also to evaluate delayed puberty [13,14]. Danda et al used the measurement of gonadotropins and testosterone in urine to evaluate minipuberty, which suggests its potential utility in the interpretation of minipuberty [6]. Most of the previous studies have used immunofluorometric or immune chemiluminescence assays whereas Danda et al have used enzyme-linked immunosorbent assay (ELISA) which is not a commonly used method for measurement of gonadotropins and testosterone [6]. Hence, future studies evaluating minipuberty in Asian Indian infants using the commonly used immunoassays with the establishment of reference ranges for urinary gonadotropins and testosterone are warranted.

*Funding*: None; *Competing interests*: None stated.

## REFERENCES

1. Busch AS, Paturlanne JM, Neuhaus N, et al. Male mini-puberty in human and non-human primates: planting the seeds of future fertility. Reproduction. 2023;166:R63-72.
2. Renault CH, Aksglaede L, Wojdemann D, Hansen AB, Jensen RB, Juul A. Minipuberty of human infancy - A window of opportunity to evaluate hypogonadism and differences of sex development? Ann Pediatr Endocrinol Metab. 2020;25:84-91.
3. Papadimitriou DT, Chrysis D, Nyktari G, et al. Replacement of male mini-puberty. J Endocr Soc. 2019;3:1275-82.
4. Davis SM, Reynolds RM, Dabelea DM, Zeitler PS, Tartaglia NR. Testosterone treatment in infants with 47,XXY: Effects on body composition. J Endocr Soc. 201;3:2276-85.
5. Kuiri-Hänninen T, Seuri R, Tyrväinen E, et al. Increased activity of the hypothalamic-pituitary-testicular axis in infancy results in increased androgen action in premature boys. J Clin Endocrinol Metab. 2011;96:98-105.
6. Danda VSR, Thaduri KR, Paidipally SR, Verpula M, Devireddy SR. Postnatal assessment of minipuberty in Indian preterm and full-term male infants. Indian Pediatr. 2024;61:221-4.
7. Nagai S, Kawai M, Myowa-Yamakoshi M, Morimoto T, Matsukura T, Heike T. Gonadotropin levels in urine during early postnatal period in small for gestational age preterm male infants with fetal growth restriction. J Perinatol. 2017;37:843-7.
8. Allvin K, Ankarberg-Lindgren C, Dahlgren J. Longitudinal sex steroid data in relation to birth weight in preterm boys. J Clin Endocrinol Metab. 2022;107:e4212-21.
9. Kowalcze K, Krysiak R, Obuchowicz A. Minipuberty in sons of women with low vitamin D status during pregnancy. Nutrients. 2023;15:4729.
10. Kowalcze K, Krysiak R, Obuchowicz A. The impact of maternal hypothyroidism during pregnancy on minipuberty in boys. J Clin Med. 2023;12:7649.
11. de Zegher F, Devlieger H, Veldhuis JD. Pulsatile and sexually dimorphic secretion of luteinizing hormone in the human infant on the day of birth. Pediatr Res. 1992;32:605-7.
12. Boncompagni A, Pietrella E, Passini E, et al. Minipuberty in male full-term neonates appropriate and small for gestational age and in preterm babies: Data from a single centre. J Clin Res Pediatr Endocrinol. 2023 Sep 26. Epub ahead of print.
13. Xu D, Zhou X, Wang J, Cao X, Liu T. The value of urinary gonadotropins in the diagnosis of central precocious puberty: a meta-analysis. BMC Pediatr. 2022;22:453.
14. Tripathy M, Baliarsinha AK, Choudhury AK, Das UK. The role of urinary LH and FSH in the diagnosis of pubertal disorders. Indian J Endocrinol Metab. 2021;25:110-20.

ORIGINAL ARTICLE

# Postnatal Assessment of Minipuberty in Indian Preterm and Full-term Male Infants

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**ABSTRACT**

**Objectives**: To study the differences in the timing and magnitude of postnatal urinary gonadotropins and testosterone secretion during minipuberty in Indian preterm (PT) and full-term (FT) male infants.

**Methods**: This prospective observational study included 30 PT and 60 FT male infants. Urinary luteinizing hormone (LH), follicular stimulating hormone (FSH), and testosterone, and stretched penile length (SPL) and testicular volume (TV) were measured on day 7, first month, second month, fourth month and at six months of age.

**Results**: The highest elevation of mean (SD) urinary LH was observed in PT infants in comparison to FT infants [12.6 (1.4) vs 4.9 (0.6) µIU/mg, respectively; $P < 0.001$] in the first month. FSH levels were lower in PT than FT infants on day 7 ($P < 0.001$). Testosterone was significantly elevated in PT than FT infants [70.8 (5.6) vs 44.6 (3.2) ng/mg; $P < 0.001$] with a greater mean percentage increase in SPL ($P < 0.001$) and TV ($P < 0.001$) by the first month.

**Conclusions**: Indian PT male infants showed a greater increase in urinary LH and testosterone, with a faster increase in SPL and TV.

**Keywords**: *Male infants, Minipuberty, Preterm, Stretched penile length, Urinary gonadotropin*

## INTRODUCTION

The hypothalamic-pituitary-gonadal (HPG) axis is transiently activated in three phases of life. The first is during the fetal period, the second is during neonatal and early infancy and the third is during puberty at adolescence [1]. At birth, the inhibitory effect of the placental estrogens on the gonadotropin-releasing hormone (GnRH) neurons is lost leading to the activation of the HPG axis during the neonatal and early infancy period [2]. This is referred to as minipuberty and was first described by Forest et al [3]. Minipuberty occurs in both sexes with peak gonadotropins between the first to third month of infancy. There is a clear sexual dimorphism, with the luteinizing hormone (LH) being higher in boys and follicle stimulating hormone (FSH) being higher in girls. LH returns to prepubertal values (<0.3 IU/L) within 6 months in both sexes. However, FSH takes 3-4 years to return to baseline in females. The surge of gonadotropins leads to an increase in testosterone in males and estradiol in females translating to penile and testicular growth in boys and breast and uterine development in females, respectively [4]. The exposure to gonadal steroids in males leads to differences in body composition with a greater fat-free mass and a higher growth velocity in comparison with females [5]. However, the importance of minipuberty in females is yet to be ascertained. Also, the consequence of HPG axis activation on future reproductive potential is not known. Minipuberty presents with a unique window of opportunity to diagnose congenital hypogonadism and disorders of sex development [6].

Data on hormonal changes in minipuberty in preterm (PT) babies are scarce. Prior studies demonstrated an exaggerated minipuberty response in PT males leading to faster penile and testicular growth [7]. Hyperandrogenism occurring as an adaptive response may adversely affect the programming during early development posing a greater risk for future cardio-metabolic disorders [5,7,8]. Minipuberty may be affected by ethnicity; studies on minipuberty from India are scant. Therefore, the main objective was to study the differences in the timing and magnitude of postnatal urinary gonadotropin and testosterone secretion in Indian PT and full-term (FT) male infants.

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Received: May 15, 2023; Initial review: June 21, 2023;
Accepted: Nov 18, 2023.

## METHODS

This prospective, observational study was conducted at a tertiary level hospital from March, 2019 to February, 2020. The procedures followed were in accordance with the ethical standards and with the Helsinki Declaration of 1964, as revised in 2013. After obtaining informed consent from their mothers, 30 PT (delivered at < 37 weeks' gestation) and 60 FT male infants were included in the study. Neonates requiring level-3 care and those with gross congenital abnormalities, ambiguous genitalia, congenital heart disease, liver disorders and renal disorders were excluded. Participants were recruited from the postnatal ward by simple random sampling and followed up for a total of five visits. Visit 1 (V1), corresponded to day 7 (D7) of life. Follow-up visit 2 (V2), visit 3 (V3), visit 4 (V4), and visit 5 (V5) were done in months 1, 2, 4, and 6, respectively. Appropriate follow-up was ensured through telephonic reminders. Basic demographic data, anthropometric measurements, and examination findings of external genitalia were collected during each visit. Measurements were taken by a trained pediatrician. Testicular volume (TV) was measured by Prader's orchidometer and stretched penile length (SPL) was measured by a transparent rigid ruler. Penis was stretched and length was measured from the pubic symphysis to the tip of the glans penis along the dorsal side of the penis to the accuracy of 1mm. The pre-pubic fat pad was pushed to the bone for accurate readings; an average of three measurements was taken.

Urinary analysis was considered for convenience as multiple samples had to be collected over a period of time. Spot urine samples were collected with the help of a condom catheter into a plastic bag and were stored at -70º C till laboratory analysis. Urine LH was measured by ELISA based kits (DRG International) with an intra-assay coefficient of variation (CV)% of 0.7% and inter-assay CV% of 9.4%. Urine FSH was measured by ELISA based kits (Calbiotech) with an intra-assay CV% of 1.4% and inter-assay CV% of 8.23%. Urine testosterone was measured by ELISA technique (Calbiotech) with an intra-assay CV% of 2.91% and inter-assay CV% of 8.65%. All the urinary samples were processed by Varioskan lux multimode plate reader for measurement of LH, FSH, and testosterone levels.

*Statistical analysis*: Data were analyzed with Microsoft Excel and Graph Pad Prism (version 7.0.4). The categorical variables were presented as frequency and percentages. Continuous data were presented as mean and standard deviation. Statistical analyses of the differences in the means between the groups and within the group were done by unpaired and paired student's *t*-test respectively. Differences were considered significant if the *P* value was < 0.05.

## RESULTS

A total of 60 FT and 30 PT male infants were recruited in the study. Out of a total of 450 visits, 23 visits were missed (17/300 in term and 6/150 in preterm) with a success rate of 94.8%. All the infants completed the study. **Table I** shows the birth characteristics of PT and FT infants at first visit. **Table II** shows the prospective and comparative levels of urinary FSH, LH, testosterone and genital findings.

The differences in mean urinary LH levels between V1-V2, V2-V3, V3-V4, and V4-V5 were +5.2, -4.2, -4.5, and -1.8 µIU/mg among PT infants in comparison to +0.7, -1.2, -2.3 and -0.8 µIU/mg among FT infants. The differences in mean urinary FSH between V1-V2, V2-V3, V3-V4, and V4-V5 were +3,-1.7,-2.1, and -0.7 µIU/mg, in PT infants in comparison to -1, -1.1, -0.3, and -0.6 µIU/mg among FT infants. Changes in the urinary testosterone values mirrored the changes in LH values with a peak at V2 which was similar in both FT and PT (**Table II**). The average change in testosterone levels between visits were +20.2, -15.2, -31, and -17.7 ng/mg in PT infants in comparison to +24.6, -20.4,-9.4, and -7.2 ng/mg among FT infants. The sequential changes in SPL in PT and FT infants are shown in **Table II**. The increment in the testicular volume was nonlinear, with a maximum increase in size seen between V1 and V2 in both groups. PT infants showed a significant mean percentage increase in SPL (20% vs 13.3%; $P < 0.001$) and TV (60% vs 30%; $P < 0.001$) at V2 in comparison with FT infants.

## DISCUSSION

This study demonstrated an earlier and exaggerated rise of urinary LH and testosterone in Indian PT male infants as

**Table I Birth Characteristics in Preterm and Term Male Infants**

| *Variables* | *Preterm (n = 30)* | *Term (n = 60)* |
|---|---|---|
| Maternal age (y) | 25.6 (3.35) | 25.8 (3.85) |
| Mode of delivery[a] | | |
| Vaginal | 20 (66.6) | 45 (75) |
| Elective cesarean section | 6 (20) | 12 (20) |
| Emergency cesarean section | 4 (13.4) | 3 (5) |
| Gestational age (week)[b,c] | 33 (32-33) | 38 (38-39) |
| APGAR score (5 min)[b,c] | 8 (7-8) | 9 (8-9) |
| Birth weight (kg)[c] | 1.5 (0.19) | 3.1 (0.19) |
| Birth length (cm)[c] | 43 (3.25) | 49.9 (1.4) |

*Data expressed as mean (SD), [a]n (%), [b]median (IQR). [c]P <0.001*

**Table II Comparison of Urinary Gonadotropins, Testosterone, and Genital Characteristics Among Preterm and Term Male Infants**

| *Visits* | *Preterm (n = 30)* | | | | | *Full-Term (n = 60)* | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *LH (μIU/mg)* | *FSH (μIU/mg)* | *Testosterone (ng/mg)* | *SPL (cm)* | *TV (mL)* | *LH (μIU/mg)* | *FSH (μIU/mg)* | *Testosterone (ng/mg)* | *SPL (cm)* | *TV (mL)* |
| Visit 1 | 7.5 (1.4)[a] | 4 (0.8) | 50.6 (6.6)[a] | 2.5 (0.1) | 1.0 (0.1)[a] | 4.3 (0.7) | 4.9 (0.5) | 20 (5.4) | 3.0 (0.2) | 1.3 (0.4) |
| Visit 2 | 12.7 (1.4)[a] | 7 (0.6)[a] | 70.8 (5.6)[a] | 3 (0.1) | 1.6 (0.4) | 5 (0.6) | 3.9 (0.5) | 44.6 (3.2) | 3.4 (0.3) | 1.7 (0.4) |
| Visit 3 | 8.5 (1.0)[a] | 5.3 (0.6)[a] | 55.6 (3.1)[a] | 3.3 (0.1) | 2 (0.4) | 3.8 (0.5) | 2.8 (0.4) | 24.2 (3.9) | 3.7 (0.3) | 2.1 (0.4) |
| Visit 4 | 4 (0.4) | 3.2 (0.4) | 24.6 (2.5) | 3.5 (0.2) | 2.3 (0.4)[a] | 1.5 (0.3) | 2.5 (0.3) | 14.8 (2.2) | 3.9 (0.3) | 2.4 (0.4) |
| Visit 5 | 2.2 (0.3) | 2.5 (0.2) | 6.9 (1.5) | 3.5 (0.1) | 2.4 (0.4) | 0.7 (0.1) | 1.9 (0.4) | 7.6 (1.4) | 3.9 (0.3) | 2.5 (0.2) |

*Data presented as mean (SD) based on 95 % completed visits. [a]P < 0.001, P > 0.05: All comparisons between PT and FT. LH Luteinizing hormone, FSH Follicle stimulating hormone, SPL Stretched penile length, TV Testicular volume*

compared to FT infants during minipuberty. There was a significant increase in SPL and TV among PT infants by the end of the first month.

Urinary gonadotropins were utilized for the assessment of minipuberty in the present study as it is non-invasive and convenient for repeated measurements. A recent Indian study demonstrated a good correlation between serum and urinary gonadotropins [9]. There was a significant elevation of LH in PT infants as early as day 7; suggesting the possibility of an earlier onset of minipuberty. The highest elevation of LH was observed by the end of first month in both groups; with the magnitude being greater in PT infants (12.7 μIU/mg vs 5 μIU/mg). An earlier Australian study established reference ranges for serum LH and serum FSH in premature newborns till 43 days after birth [10]. The mean LH levels were higher in PT infants in the present study in comparison to the earlier study [10]. Different ethnicity and assays may be the reason for this discrepancy. After the first month, there was a gradual decline in LH levels till 6 months in both the groups. However, at the end of 6 months, LH levels were in the pubertal range (i.e., > 0.3 IU/mL) in PT infants suggesting a prolonged minipuberty. Testosterone declined from first month onwards to pre-pubertal values by the end of 6 months in both groups. The results of this study conform to the earlier observations of higher testosterone levels in PT than FT infants [7]. Initial urinary FSH levels were higher in FT male infants. However, from first to third month, PT infants had significantly higher FSH levels. The mean FSH levels observed at first month were significantly higher in PT males in this study as compare to another study (5 μIU/mg vs 1.1 μIU/mg) [10]. There was a steady decline in FSH levels among FT infants reaching pre-pubertal values by six months (i.e. < 0.3 IU/mL). Postnatal HPG axis activation lays an important role in the completion of genital development, the lack of which may lead to poor penile growth and cryptorchidism.

The higher LH and testosterone levels observed in PT boys may be a mechanism to complete penile growth and testicular descent. However, the mechanisms of exaggerated minipuberty in preterms are not known. An earlier Indian study, reported gestational age-wise references for SPL and TV [11]. The mean SPL of PT infants (born at 32-33 weeks gestation) was similar to the present study at V1. The maximum mean percentage increment in SPL was observed in the first month that was greater in PT infants than to FT infants. This could be attributed to an exaggerated testosterone elevation in PT infants. The mean TV at V1 in PT infants was greater in this study as compared to the earlier Indian study [11]. The difference can be attributed to the usage of plasticine ellipsoid crafted using water displacement method with smaller volumes ranging from 0.2 mL to 0.9 mL [11]. The maximum mean percentage increase in TV occured in the first month was twice greater in PT infants in comparison with FT infants in this study as also observed in an early study [7]. As the incidence of prematurity is increasing, its association with lower reproductive rates in men and women is being investigated [12].

A study from Denmark, evaluated reproductive hormones during minipuberty in healthy infants and in those with disordered sex development [13]. In the current study, PT infants had significantly higher androgen levels in comparison to FT infants. The long-term consequences of this variation are not known. A Finnish study on minipuberty found that testosterone may have an effect on neurobehavioral development during early infancy [14]. According to the Developmental Origins of Health And Disease (DoHAD) theory, many chronic adult diseases have their origin during early development. The associa-tion of exposure to higher androgens during infancy risk of future metabolic disorders in adulthood needs to be evaluated.

There are a few limitations of our study. The sample

**WHAT THIS STUDY ADDS?**

- There is an earlier and stronger activation of the hypothalamic-pituitary-gonadal axis in preterm male infants in comparison to full-term infants.

size was small and hormonal analysis was done on urinary samples rather than serum. ELISA was used instead of newer assays for hormonal estimation. Testicular volume was measured by Prader's Orchidometer rather than ultrasonography.

To conclude, minipuberty occurred earlier with a greater magnitude, leading to a faster increase in SPL and TV in Indian PT male infants than FT infants. Further studies with a larger sample size are needed to establish the normative data in the Indian population and evaluate the association of of hyperandrogenism and future risk of metabolic disorders during adulthood in PT infants.

*Acknowledgement*: Dr. Donthamala Suchitra, Associate Professor, Department of Pediatrics and Neonatology, for her help with subject recruitment and follow-up.

*Ethics clearance*: Institutional ethics committee of Gandhi Medical College/Hospital, Hyderabad, Telangana (No: IEC/GMC/2019/2/16); dated Mar 16, 2019.

*Contributors*: VSRD: Study idea, protocol development, data collection, manuscript writing and will act as guarantor for the study; KRT: Developing protocol, data collection, analysis and manuscript writing; SRP: Developing protocol and manuscript writing; MV: Data analysis and manuscript writing; SRD: Developing protocol, data analysis and manuscript writing; VSRD, KRT, SRP: Critical appraisal and revision of manuscript. All authors approved final version of manuscript

*Funding:* None; *Competing interest*: None stated.

## REFERENCES

1. Becker M, Hesse V. Minipuberty: Why does it happen? Horm Res Paediatr. 2020;93:76.
2. Kuiri-Hänninen T, Sankilampi U, Dunkel L. Activation of the hypothalamic-pituitary-gonadal axis in infancy: minipuberty. Horm Res Paediatr. 2014;82:73-80.
3. Forest MG, Cathiard AM, Bertrand JA. Evidence of testicular activity in early infancy. J Clin Endocrinol Metab. 1973;37:148-51.
4. Bizzarri C, Cappa M. Ontogeny of hypothalamus pituitary gonadal axis and minipuberty: An on going debate? Front Endocrinol (Lausanne). 2020;11:187.
5. Davis SM, Kaar JL, Ringham BM, Hockett CW, Glueck DH, Dabelea D. Sex differences in infant body composition emerge in the first 5 months of life. J Pediatr Endocrinol Metab. 2019; 32:1235-9.
6. Renault CH, Aksglaede L, Wøjdemann D, Hansen AB, Jensen RB, Juul A. Minipuberty of human infancy - A window of opportunity to evaluate hypogonadism and differences of sex development? Ann Pediatr Endocrinol Metab. 2020;25:84-91.
7. Kuiri-Hänninen T, Seuri R, Tyrväinen E, et al. Increased activity of the hypothalamic-pituitary-testicular axis in infancy results in increased androgen action in premature boys. J Clin Endocrinol Metab. 2011;96:98-105.
8. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008;359:61-73.
9. Tripathy M, Baliarsinha AK, Choudhury AK, Das UK. The role of urinary LH and FSH in the diagnosis of pubertal disorders. Indian J Endocrinol Metab. 2021;25:110-20.
10. Greaves RF, Hunt RW, Chiriano AS, Zacharin MR. Luteinizing hormone and follicle-stimulating hormone levels in extreme prematurity: development of reference intervals. Pediatrics. 2008;121:e574-e80.
11. Mondal R, Ray S, Chatterjee K, et al. Penile length and testicular volume in newborns. Indian J Pediatr. 2016; 83: 1398-404
12. Swamy GK, Ostbye T, Skjaerven R. Association of preterm birth with long-term survival, reproduction, and next-generation preterm birth. JAMA. 2008;299:1429-36.
13. Johannsen TH, Main KM, Ljubicic ML, et al. Sex differences in reproductive hormones during mini-puberty in infants with normal and disordered sex development. J Clin Endocrinol Metab. 2018;103:3028-37.
14. Lamminmäki A, Hines M, Kuiri-Hänninen T, Kilpeläinen L, Dunkel L, Sankilampi U. Testosterone measured in infancy predicts subsequent sex-typed behavior in boys and in girls. Horm Behav. 2012;61:611-6.

ORIGINAL ARTICLE

# Physical Activity, Sedentary Behavior, Sleep and Screen Time of Healthy Under-Fives Attending Selected Immunization Clinics and Anganwadis of South Kerala, India

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## ABSTRACT

**Objective**: To estimate the proportion of healthy under-fives whose physical activity, sedentary behavior, sleep and screen time adhered to WHO 2019 recommendations and to identify risk factors for non-adherence.

**Methods**: A cross-sectional study was conducted among 480 healthy children (6 mo - 4 years) who attended 20 selected urban anganwadis or immunization clinics in South Kerala, India. Sociodemographic, anthropometric and outcome variables (duration of physical activity, sedentary behavior, sleep and screen time) were collected for all participants.

**Results**: Physical activity, sedentary behavior, sleep and screen time recommendations were adhered by 63.3%, 22.7%, 82.2% and 22.7% under-five children, respectively. Risk factors for inadequate physical activity were female sex, nuclear family, maternal education below college level, unskilled maternal occupation/housewife, unskilled paternal occupation and low monthly income. Risk factors for non-adherence to recommended sedentary behavior duration included joint family, paternal education college level/above, unskilled maternal occupation/housewife, unskilled paternal occupation and low monthly income.

**Conclusion**: Under-fives should reduce sedentary behaviors and screen time and spend more time on physical activities.

**Keywords**: *Infant, Toddler, Obesity, Preschool, Recommendation*

**Published online:** *May 20, 2022;* **PII:** *S097475591600595*

## INTRODUCTION

Being overweight and obese starts in infancy and early childhood and tracks to adolescence and adulthood. In India and Kerala, 3.4% and 4% of under-fives are overweight as per National Family Health Survey (NFHS) 5 [1,2]. World Health Organization (WHO) published recommendations in 2019 on the duration of physical activity (PA), sedentary behavior (SB), sleep time (ST) and screen time (ScrT) in a 24-hour day for under-fives [3]. Paucity of evidence on PA, SB, ST and ScrT among under-fives in Kerala, where overweight and obesity are growing concerns, was the basis for this study. Our primary objective was to estimate the proportion of healthy under-fives attending the anganwadis and immunization clinics in whom PA, SB, ST and ScrT adhered to the WHO 2019 recommendations [3]. Secondarily, risk factors of non-adherence were also identified.

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Received: June 02, 2023; Initial Review: July 19, 2023; Accepted: Feb 03, 2024

## METHODS

After approval from the Department of Women and Child Development, Government of Kerala, and Ethics Committee, a cross-sectional study was conducted from September 2021 to August 2022. Twenty anganwadis / immunization clinics of an urban integrated family health center were randomly sampled from a total of 111 centers. All healthy children between 6 months and 4 years attending these centers were included.

The estimated prevalence (24.4%) of preschoolers meeting ScrT recommendations in Canadian Health Measures Survey was utilized to calculate the sample size [4]. With an absolute precision of 5% and a design effect of 1.5, sample size was calculated as 450.

Socio-demographic characteristics (age, sex, parental education and occupation, type of family and socio-economic status as per the modified Kuppuswamy Scale 2021) and anthropometric parameters were collected. Outcome variables were defined as follows: PA- at least 30 minutes of tummy time/ floor-based play with building blocks, dolls, balls or utensils (6 mo - 1y), at least 180 minutes of moderate to vigorous activity like crawling, walking, running, jumping, pretend play, climbing in

through and over objects, dancing and riding wheeled toys (1-4 y); SB- not more than 1 hour restrained in a pram/ high chair/ carried by caregiver (6 mo-4 y) or activities like lying down, listening to music/stories, using electronic devices and coloring; ST- both night and daytime naps of at least 12-16 hours (6 mo-1 y), 11-14 hours (1-2 y) and 10-13 hours (3-4 y); ScrT- time on television, computer or mobile devices; 0 minute (6 mo-2 y), not to exceed 1 hour (2-4 y). Overweight (above +2 Z) and obesity (above +3 Z) were defined as per WHO (2006) weight-for-height Z score charts for children aged 0-5 y. Children were grouped as 6 mo–1 y, 1-2 y, 2-3 y and 3-4 y. Outcome variables were dichotomized (adhered to recommended duration or not).

Efforts were taken to address the anticipated recall bias and subjectivity of outcome variables. To elicit the time spent on different activities, a big circle depicting a 24-hour day was drawn and shown to the caregiver. ST in hours was shaded in the circle first followed by ScrT. Time spent on feeding, bathing and carrying out other basic necessities were shaded next. Play and sedentary activities were identified and shading of circle completed.

*Statistical analysis*: Descriptive statistics was used and analysis was done by using SPSS version 26. Association between proposed risk factors and outcome variables was analyzed with *Chi* square test and odds ratios with 95% confidence intervals were calculated for all such statistically significant risk factors.

## RESULTS

The study flow chart is depicted in **Fig. 1.** Baseline characteristics of 480 children of different age groups are given in **Table I**. Distribution of 480 healthy under-fives who adhered to the recommended duration of PA, SB, ST and ScrT were 304 (63.3%), 109 (22.7%), 395 (82.2%) and 109 (22.7%), respectively (**Table II**). Interactive play of infants (6 months-1 year) was mostly with mother (41.5%) followed by siblings (23.3%), grandparents (22.5%) and father (12.5%); beyond infancy, interactive play was mostly with siblings (48.1%) followed by grandparents (22.1%), mothers (21.6%) and fathers (4%).

Significant risk factors of non-adherence to recommended PA were female sex ($P$ = 0.005, OR 1.6, 95% CI 1.1-2.4), nuclear family ($P$ = 0.001, OR 2.6, 95% CI 1.3-5.0), maternal education below college level ($P$ = 0.027, OR 1.4, 95% CI 1.01-2.1), maternal occupation unskilled/nil ($P$ = 0.001, OR 2.08, 95% CI 1.3-3.3) and paternal occupation unskilled/nil ($P$ = 0.001, OR 1.8, 95% CI 1.3-2.7). Significant risk factors of non-adherence to recommended SB were joint family ($P$ = 0.001, OR 1.8, 95% CI 1.3-2.7), maternal occupation unskilled/nil ($P$ = 0.027, OR 1.7, 95% CI 1.01-3.0), paternal occupation unskilled/nil ($P$ = 0.001, OR 3.2, 95% CI 2.0-5.2) and paternal education of college level and above (OR 1.8, 95% CI 1.2-2.9). Low monthly family income was a significant risk factor for non-adherence to recommended PA ($P$ = 0.001), SB ($P$ = 0.001) and ST ($P$ = 0.006). Obesity/overweight was associated with less than recommended ST ($P$ = 0.024, OR 1.9, 95% CI 1.08-3.35) and more than recommended ScrT ($P$ = 0.009, OR 2.5, 95% CI 1.24-5.36).

## DISCUSSION

Twenty-four-hour movement and active play guidelines for early years by Canada [5], Australia [6] and New Zealand [7] and guidelines on screen time and digital wellness in infants and children by Indian Academy of Pediatrics (IAP) [8] were similar to that given by the World

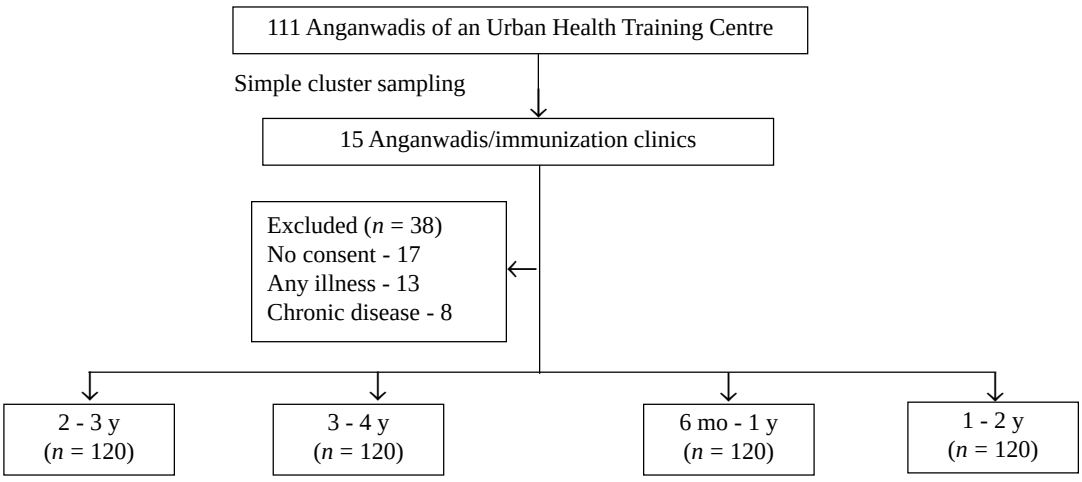


**Fig. 1** Flow chart depicting selection of participants in the study

**Table I Baseline Characteristics of Children**

| *Characteristics* | | *6 mo - 1y (n = 120)* | *1 - 2 y (n = 120)* | *2 - 3 y (n = 120)* | *3 - 4 y (n = 120)* |
|---|---|---|---|---|---|
| Sex | Male | 64 (53.3) | 69 (57.5) | 63 (52.5) | 63 (52.5) |
| Maternal Education | College | 75 (62.5) | 77 (64.1) | 67 (55.8) | 58 (48.3) |
| | School / +2 | 45 (37.5) | 43 (35.9) | 53 (44.2) | 62 (51.7) |
| Maternal Occupation | Skilled/Professional | 41 (34.2) | 28 (23.3) | 33 (27.5) | 12 (10) |
| | Unskilled/nil | 79 (65.8) | 92 (76.7) | 87 (72.5) | 108 (90) |
| Paternal Education | College | 60 (50) | 57 (47.5) | 65 (54.2) | 37 (30.8) |
| | School / +2 | 60 (50) | 63 (52.5) | 55 (45.8) | 83 (69.2) |
| Paternal Occupation | Skilled/Professional | 99 (82.5) | 64 (53.3) | 48 (40) | 41 (34.2) |
| | Unskilled/nil | 21 (17.5) | 56 (46.7) | 72 (60) | 79 (65.8) |
| Socio-economic Scale[a] | Upper | 19 (15.8) | 21 (17.5) | 18 (15) | 6 (5) |
| | Upper middle | 62 (51.6) | 54 (45) | 44 (36.6) | 50 (41.6) |
| | Lower middle | 27 (22.5) | 21 (17.5) | 30 (25) | 54 (45) |
| | Upper Lower | 12 (10) | 22 (18.3) | 26 (21.6) | 10 (8.3) |
| | Lower | 0 | 2 (1.6) | 2 (1.6) | 0 |
| Monthly income (Rupees) | > 30,000 | 111 (92.5) | 91 (75.8) | 99 (82.5) | 113 (94.1) |
| Nutritional status | Overweight | 9 (7.5) | 14 (11.6) | 28 (23.3) | 16 (13.3) |
| | Obesity | 3 (2.5) | 0 | 2 (1.6) | 7 (5.8) |

*Values expressed as n (%); [a]Modified Kuppuswamy Scale 2021*

Health Organization (WHO) in 2019. A cross-sectional study on 180 under-fives in a slum area of West Bengal showed that 69.4%, 70%, 84.4% and 63.3% had PA, SB, ST and ScrT as per the WHO guidelines [9]. Compared to this, the lower percentages of children meeting the SB and ScrT recommendations in our study might have been due to differing socioeconomic status. In SUNRISE Vietnam pilot study, among 103 preschoolers, 50.4%, 81.4%, and 44.7% had PA, ST and ScrT as per WHO (2019) [10]. When compared to our study population, children of SUNRISE study had less PA but adhered to ScrT recommendations more. A Canadian study on 151 babies aged 12-23 months found that 99.3%, 82.1% and 15.2% met PA, ST and ScrT as per Canadian guidelines [11]. In our study, 81.6%, 89.1% and 11.6% of babies aged 12-23 months met PA, ST and ScrT as per WHO guidelines. Compared to ours, all these studies had almost similar percentages adhering to ST recommendations. Though we expected infants to have less and toddlers and preschoolers to have more PA upon achievement of gross motor milestones, a fall in percentages adhering to recommended duration of PA was noted among children aged 6-12 months (100%), 1-2 years (81.6%), 2-3 years (44.1%) and 3-4 years (27.5%). A fall in percentages of PA, 1-2 years (100%), 2-3 years (60.6%) and 3-4 years (69.3%), were noted in the study conducted in West Bengal too [9]. Compared to our study, risk of inadequate PA was found to be more among under-fives without siblings in slum areas of West Bengal (OR 3.5, 95%CI 1.78, 6.9) [9]. In our study, none of the infants and only 24-34% of those aged 1-4 years adhered to recommended duration of SB. Traditional practices like carrying on arms for long hours and modern practices like restraining on chairs for long hours with electronic devices were identified as SB in our setting. In West Bengal, SB was found to be more among children without sibling (OR 4.69, 95% CI 2.35, 9.36) [9]. The SUNRISE study measured SB in 1071 preschoolers (3-5-year-olds) from 19 countries and found that 56% (7.4h) of their wake time was spent sedentary [12]. Higher country income levels and higher population density appeared to be stronger drivers of observed differences in sedentary behaviors among countries [12].

Beyond infancy, ScrT recommendations were followed in less than 15%. An observational study conducted among 369 Indian children aged 15-18 months showed that 99.7% were exposed to screen-based media [13]. A systematic review among under-fives revealed that burden of ScrT was 21-98% in the middle-income compared to 10-93% in the high-income countries [14]. Associated factors and correlates of ScrT were explained using a socio-ecological model consisting of socio-cultural environment (neighborhood, government regulations, season), child-care media environment (access, regulation), caretaker-related and child-related

**WHAT THIS STUDY ADDS?**

- The proportion of healthy under-fives whose duration of physical activity, sedentary behavior, sleep and screen time adhered to WHO 2019 recommendations were 63.3%, 22.7%, 82.2% and 22.7% respectively.
- Infants, toddlers and preschoolers should be encouraged to reduce SB and ScrT and spend more time on moderate/vigorous PA.

**Table II Adherence of Children (age-wise) to Recommended Duration of Physical Activity, Sedentary Behavior, Sleep Time and Screen Time as per WHO Guidelines 2019**

| | *6 mo-1y (n = 120)* | *1- 2 y (n = 120)* | *2- 3 y (n = 120)* | *3- 4 y (n = 120)* |
|---|---|---|---|---|
| PA (minutes) | 150 (100, 200); 120 (100) | 255 (202, 325); 98 (81.6) | 167 (146, 240); 53 (44.1) | 130 (67, 190); 33 (27.5) |
| SB (minutes) | 180 (120, 225); 0 (0) | 105 (75, 150); 29 (24.1) | 90 (30, 127); 41 (34.1) | 90 (41, 150); 39 (32.5) |
| ST (hours) | 13 (11.6, 14); 90 (75) | 12 (12, 14); 107 (89.1) | 12 (11, 13); 105 (87.5) | 11 (10, 12); 93 (77.5) |
| ScrT (minutes) | 0 (0, 30); 63 (52.5) | 90 (30, 120); 14 (11.6) | 105 (60, 180);15 (12.5) | 120 (60, 210); 17 (14.1) |

*Values expressed as median (IQR), n (%). Physical Activity (PA), Sedentary Behavior (SB), Sleep Time (ST) and Screen Time (ScrT)*

factors (demographic, behavioral, biological) [14]. In our setting, ST recommendations were adhered by 75% of infants and 77.5-89.1% of children aged 1-4 years. A meta-analysis (including studies conducted before 2019) looked into the associations of ScrT, SB, PA with ST among under-fives and found that ScrT was negatively correlated with ST (pooled correlation coeeficient -0.09, 95% CI -0.17, -0.01; $I^2$ = 90%, $P$ = 0.04) [15]. The systematic review included original articles from North America ($n$ = 10), Europe ($n$ = 7), Australia ($n$ = 5) and Asia ($n$ = 8) [15]. The proportion of overweight among our participants (13.9%) was three times more than that from NFHS-5 (4%); burden stood highest among 2-3-year-olds. Overweight/ obesity was significantly associated with non-adherence to recommended duration of ST and ScrT; temporality could not be identified.

Our study had a few limitations. Though planned in 2019-20, we conducted the study during the post-COVID-19 lockdown phase (2021-22) after re-opening of anganwadis. Results have to be interpreted in this unique context. The global effect of COVID-19 on PA, SB, ST and ScrT among 948 preschoolers residing in 14 countries showed that PA and ScrT levels of children from low and middle-income countries have been less impacted than from high-income countries [16]. Subjective nature of parental reporting and possible recall bias were anticipated as a limitation. Hence, questions were asked in multiple ways and answers interpreted by a single interviewer logically. The strength of our study includes community setting and single interviewer.

Our results of under-fives attending urban anganwadis and immunization clinics are generalizable to similar Indian community settings. Awareness of parents, care-givers and community health care workers on recommended duration of PA, SB, ST and ScrT is a very strong felt need. Infants, toddlers and preschoolers should be encouraged to reduce SB and ScrT and spend more time on moderate/vigorous PA.

*Ethics clearance*: IEC, Human Ethics Committee, Medical College, Thiruvananthapuram, Kerala; No. 05/38/2021 MCT, dated May 19, 2021.

*Contributors*: STP: Executed the idea, substantial contribution to design, data collection, drafted the manuscript and did final approval; Questions related to the accuracy or integrity of the work were appropriately investigated and resolved; PS: Conceived the idea, devised the protocol, data analysis and approved the manuscript after revising for important intellectual content; AK: Refined the idea, approved the protocol, interpreted the data and approved for final submission.

*Funding*: None; *Competing interests*: None stated.

## REFERENCES

1. International Institute of Population Studies. National Family Health Survey- 5 2019-20 India Fact Sheet. 2020. Accessed on June 1, 2023. Available from: *http://rchiips.org/nfhs/NFHS-5_FCTS/India.pdf*
2. International Institute of Population Studies. National Family Health Survey- 5 2019-20 State Fact Sheet Kerala. 2020. Accessed on June 1, 2023. Available from: *http://rchiips.org/nfhs/NFHS-5_FCTS/Kerala.pdf*
3. World Health Organization. Guidelines on Physical Activity, Sedentary Behaviour and Sleep for children under 5 years of age. 2019. Accessed on June 1, 2023. Available from: *https://www.who.int/publications/i/item/9789241550536*

4. Chaput JP, Colley RC, Tremblay MS. Proportion of preschool children meeting the Canadian 24-hour movement guidelines and associations with adiposity: results from the Canadian Health Measures Survey. BMC Public Health. 2017;17;829.
5. Canadian Society for exercise physiology. Canadian 24-hour movement guidelines for the early years (0-4 years). 2017. Accessed on June 1, 2023. Available from: *https://csepguidelines.ca/guidelines/early-years/*
6. Okely AD, Ghersi D, Hesketh KD, et al. A Collaborative Approach to Adopting/ Adapting Guidelines - The Australian 24-hour Movement Guidelines for the Early Years (Birth to 5 years): An Integration of Physical Activity, Sedentary Behavior and Sleep. BMC Public Health. 2017;17:869.
7. Ministry of Health Wellington New Zealand. Sit Less, Move More, Sleep Well-Active Play Guidelines for Under-fives. 2017. Accessed on June 1, 2023. Available from: *https://www.health.govt.nz/system/files/documents/publications/active-play- uidelines-for-under-fives-may17.pdf*
8. Gupta P, Shah D, Bedi N, et al. Indian Academy of Pediatrics Guidelines on Screen Time and Digital Wellness in Infants, Children and Adolescents. Indian Pediatr. 2022; 59:235-44.
9. Goswami P, Chakraborty A, Das DK, et al. A cross-sectional study on physical activity, sedentary behavior and sleep among under-five children in slum areas of Burdwan municipality, West Bengal. Acta Medica Int. 2021; 8:1-6.
10. Kim TV, Pham TND, Nguyen CLD, et al. Prevalence of physical activity, screen time, and sleep, and associations with adiposity and motor development among preschool-age children in Vietnam: The SUNRISE Vietnam pilot study. Indian J Pediatr. 2022;89:148-53.
11. Lee EY, Hesketh KD, Hunter S, et al. Meeting new Canadian 24-hour movement guidelines for the early years and associations with adiposity among toddlers living in Edmonton, Canada. BMC Public Health. 2017;17:840.
12. Kariippanon KE, Chong KH, Janssen X, et al. Levels and correlates of objectively measured sedentary behavior in young children: sunrise study results from 19 countries. Med Sci Sports Exerc. 2022;54:1123-30.
13. Meena P, Gupta P, Shah D. Screen time in Indian children by 15-18 months of age. Indian Pediatr. 2020;57:1033-7.
14. Kaur N, Gupta M, Malhi P, Grover S. Screen time in under-five children. Indian Pediatr. 2019;56:773-88.
15. Janssen X, Martin A, Hughes AR, Hill CM, Kotronoulas G, Hesketh KR. Associations of screen time, sedentary time and physical activity with sleep in under 5s: A systematic review and meta-analysis. Sleep Med Rev. 2020; 49:101226.
16. Okely AD, Kariippanon KE, Guan H, et al. Global effect of COVID-19 pandemic on physical activity, sedentary behaviour and sleep among 3- to 5-year-old children: a longitudinal study of 14 countries. BMC Public Health. 2021;21:940.

ORIGINAL ARTICLE

# Effect of Companion Presence during Skin-to-Skin Contact on Maternal Anxiety: A Randomized Clinical Trial

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## ABSTRACT

**Objective**: To compare the effect of companion presence versus midwife presence during skin-to-skin contact (SSC) at birth on maternal anxiety and satisfaction, and neonatal physiological parameters.

**Methods**: A randomized controlled trial was conducted on 92 pregnant women who were randomized to provide SSC to their newly borns for one hour postpartum, in the presence of a companion (study group) or a midwife (control group). Maternal anxiety (using the Visual Analogue Scale) and the neonatal physiological parameters (including temperature, heart rate, and oxygen saturation) were assessed in four stages viz., immediately after birth, and at 30, 60 and 90 minutes after birth. Maternal satisfaction was also evaluated after transferring the mother to the postpartum ward.

**Results:** We analyzed 86 mother-infant dyads (43 per group). Having a companion significantly reduced maternal anxiety after birth as compared to having a midwife at 30, 60, and 90 minutes after birth ($P = 0.04$, $P = 0.01$, and $P = 0.04$, respectively). There was also a small to medium effect size of the presence of companion compared to midwife in terms of maternal anxiety at 30 minutes (Cohen's d = 0.45; 95% CI = 0.02, 0.87), 60 minutes (Cohen's d = 0.52; 95% CI = 0.08, 0.94) and 90 minutes after birth (Cohen's d = 0.45; 95% CI = 0.02, 0.88). However, there was no significant effect of the same on neonatal physiological parameters. Having a companion versus a midwife led to higher maternal satisfaction rates ($P = 0.02$); 65.1% of mothers in the study group and 37.2% of mothers in the control group were desirous of the same care in future ($P = 0.02$).

**Conclusion**: Companion presence during SSC leads to a significant reduction in maternal anxiety compared to midwife presence.

**Keywords:** *Kangaroo mother care, Outcome, Oximetry, Satisfaction*

**Trial registration**: IRCT20200120046200N2

## INTRODUCTION

Childbirth is a major life event, and the postpartum period plays a major role in the occurrence of maternal anxiety [1]. Incidence of serious postpartum anxiety is often higher than 17% [2,3]. The first two hours after birth is a critical period for the mother-infant dyadic interaction as it can lead to positive or negative psychological outcomes [4]. Postpartum anxiety can also have negative consequences on the mothering role, and affects the maternal attention to the baby and the successful breastfeeding [1].

Postpartum anxiety is affected by many factors, including the clinical environment surrounding childbirth. Strategies aimed at mitigating postpartum maternal anxiety include social support, psychotherapy, cognitive behavioral interventions, medications and physical exercise [5,6]. Policies like skin-to-skin contact (SSC) and companion support can reduce anxiety. SSC is one of the requirements highly recommended by the World Health Organization (WHO) in promoting the health of both mothers and neonates [7]. Furthermore, it is an important component of care, which starts immediately after birth up to at least one hour or until breastfeeding initiation [8,9]. The positive effect of SSC on maternal stress and anxiety,

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Received: Feb 03, 2023; Initial Review: March 10, 2023; Accepted: Dec 20, 2023.

physiological stability of the neonate, increasing the breastfeeding duration, the brain growth and development, and also attachment of mother and neonate has been reported in various studies [7,10,11]. Despite the increasingly robust evidence regarding the maternal and neonatal benefits of SSC, it is not implemented universally. In a systematic review, Abdulghani et al [12] found a wide range of SSC prevalence immediately after birth ranging from 1% in Tanzania to 98% in Croatia. There are many facilitators and potential solutions for ensuring implementation of promoting SSC including the use of a companion for the mother during labor or after birth, who does not necessarily have to be a highly skilled person; rather she/he can be a relative or a trusted friend with whom the mother keeps the baby during the SSC implementation [13]. In this study we compared the effect of presence of a companion versus that of a midwife during labor on maternal anxiety and satisfaction and neonatal physiological parameters during SSC.

## METHODS

This parallel group, randomized controlled trial was conducted between July and September, 2020 in Amir Al-Momenin Hospital, Zabol University of Medical Science, Sistan and Baluchestan Province, Iran. The study population consisted of mother–baby pairs admitted to the labor ward of the hospital. The study was approved by the Ethics Committee of Iran University of Medical Sciences, and the research protocol was registered in the Iranian Registry of Clinical Trials. Written consent was obtained by the investigator from all the mothers who passed the initial eligibility screening.

Sample size calculation was based on a study by Nobakht and Safdari [14] and on the assumption that the effect size of the presence of companion and midwife in the process of SSC on each of the variables of maternal anxiety, satisfaction and neonatal physiologic parameters is at least 0.5 [15]. Considering a 10% attrition rate, power of 90% and 95% confidence interval, a sample size of 46 mother–baby pairs was estimated for each group.

We included mothers aged 18-45 years with singleton pregnancy delivering at ≥ 37 weeks' gestation. Mothers with unwanted pregnancy, complications of pregnancy/ delivery (e.g., pregnancy induced hypertension, gestational diabetes), maternal illnesses (medical and/or mental), with reports of fetal anomalies in sonography, and presence of COVID-19 infection of the mother or companion were excluded. Mothers needing analgesia during delivery, delivering by cesarean section, with prolonged or arrested labor, fetal distress, grade-3 and grade-4 perineal tears, postpartum hemorrhage, requiring manual removal of placenta, neonatal birth weight less than 2500 g or more than 4500 g, one- and five-minute Apgar scores less than 7, neonates with medical problems or anomalies, and with any factors leading to discontinuation of SSC were also excluded.

After admission to the labor ward, eligible mothers were randomly assigned to either of the two groups, viz, SSC in the presence of a companion (study group) or a midwife (control group) using quadruple 1:1 web-based block (*http://www.randomization.com*). The randomiza-tion code was generated by the project statistical consultant and allocation concealment was ensured as the assignment sequence remained with this statistician. The researcher determined the group to which the mother was to be assigned through short messaging service or phone call. Although it was not possible to ensure binding of the participants or the researcher, the outcomes were assessed by a a research assistant who was unaware of the research protocol.

At the beginning of the active phase, the mothers of both groups were explained about the purpose of the study, technique of SSC and its advantages in a face-to-face session over 20-30 minutes and in simple language. Mothers were also provided related reading material and shown relevant video clips on a mobile phone. Any questions of the mothers were answered prior to enrollment, following which they were transferred to the labor ward. Additionally, in the companion group, the mother selected a female companion from among her friends or family members. The companions were explained about the danger signs in the neonates like respiratory distress, low pulse rate shown on oximeter, hypothermia (by touching), poor muscle tone, paleness, and cyanosis, need for hand washing before any contact with the neonate, technique of holding the baby during SSC, technique of assessing the neonate in prone position, and preventing fall of the baby. Both groups received usual care throughout the labor and delivery. The infants were delivered on the mothers' bare abdomen, dried, umbilical cord was clamped and cut, and breastfeeding was initiated. The infant's head was covered with a cap and was covered in a warm blanket after placing him/her on the mothers' chest with the head was placed between the mothers' breasts. SSC was started immediately under the supervision of the research team. The mothers were supported to provide uninterrupted SSC for one hour postpartum by the companion (study group) or midwife (control group).

Data collection tool was a three-part researcher-made questionnaire, including maternal demographic and obstetric characteristics and neonatal physiologic parameters.

Face and content validity were used to determine the scientific validity of the tools. To assess the validity, the

questionnaires were given to three senior members of the School of Nursing and Midwifery in order to do the necessary modifications. Anxiety was rated on a visual analog scale (VAS) of 1-10, with 10 being high anxiety and 1 being low anxiety [16]. The neonate's heart rate and oxygen saturation were recorded with a pulse oximeter (Nellcor NBP-295).

The research assistant collected information on maternal anxiety and neonatal physiologic parameters including axillary temperature, oxygen saturation and heart rate immediately, 30, 60 and 90 minutes after birth. Maternal satisfaction with the care provided and desire for the same care in future were rated on a on a scale of 1 to 5 (1: completely dissatisfied to 5: completely satisfied); responses were collected after the mother-infant dyads were transferred to the postpartum unit.

*Statistical analysis*: Data were analyzed using the SPSS software (version 21). *Chi* square test, Fisher exact test and Mann-Whitney test were used to compare qualitative variables, while independent sample *t* test was used to compare quantitative variables in two groups. Analysis of variance with repeated measures was used for the comparison of mean maternal anxiety and neonatal physiologic parameters over time. Repeated-measures ANOVA was used to compare maternal anxiety score and the neonatal physiological parameters (temperature, heart rate, and oxygen saturation) in the two groups during different times. Bonferroni test was used for making the two-by-two comparisons of means. *P* value less than 0.05 was considered statistically significant. Partial eta-square was used to calculate the effect size. Effect size (standardized mean difference) of intervention was reported based on Cohen's d (null effect = 0, trivial effect = 0 - 0.19, small effect = 0.2 = 0.49, medium effect = 0.5 – 0.79, large effect = 0.8 -1.19, very large effect = 1.2 - 2, and huge effect ≥ 2) [17].

## RESULTS

We enrolled 92 prospective mothers, of which six mothers were excluded before completing all stages of the study (**Fig.1**). The final analysis was performed on 43 mother–baby pairs in each study group. The baseline participants' characteristics are given in **Table I**.

**Table II** shows the changes in the maternal anxiety at different stages after birth. Immediately after birth, the mean score of maternal anxiety was comparable between the two groups. The companion group had lower maternal anxiety scores after birth as compared to midwife presence at 30, 60, and 90 minutes after birth ($P = 0.04$, $P = 0.01$, and $P = 0.04$, respectively). As seen in **Table II**, based on Bonferroni test, maternal anxiety in both groups in each stage had a statistically significant decrease compared to

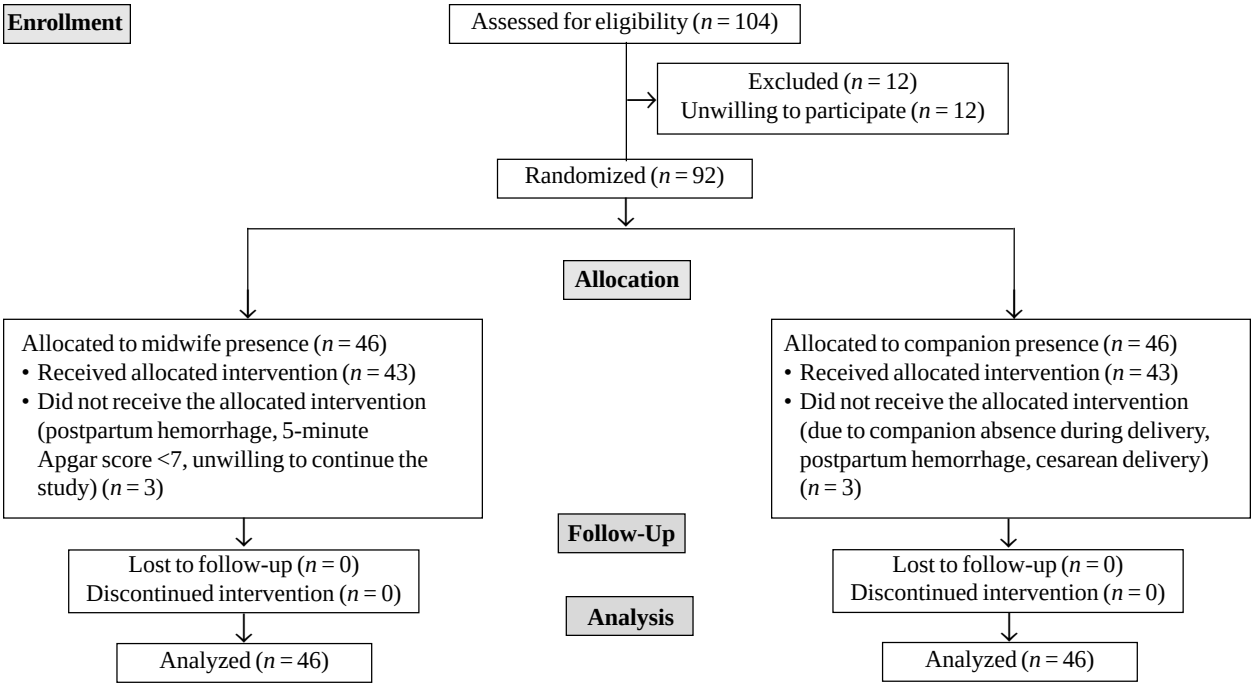


**Fig. 1** Flow of participants in the study

**Table I Baseline Characteristics of the Study Participants**

| *Characteristic* | *Companion Presence Group (n = 43)* | *Midwif Presence Group (n = 43)* |
|---|---|---|
| Maternal age (y)[a] | 28.7 (6.0) | 26.8 (6.01) |
| Paternal age (y)[a] | 33.0 (7.72) | 31.0 (8.38) |
| Maternal education | | |
| Illiterate | 2 (4.7) | 4 (9.3) |
| High school | 21 (48.8) | 20 (46.5) |
| Diploma | 15 (34.9) | 14 (32.6) |
| University | 5 (11.6) | 5 (11.6) |
| Paternal education | | |
| Illiterate | 2 (4.7) | 2 (4.7) |
| High school | 20 (46.5) | 23 (53.5) |
| Diploma | 13 (30.2) | 14 (32.5) |
| University | 8 (18.6) | 4 (9.3) |
| Financial status | | |
| Good | 6 (14) | 2 (4.6) |
| Moderate | 11 (25.6) | 10 (23.3) |
| Weak | 26 (60.4) | 31 (72.1) |
| Housewife | 40 (93) | 42 (97.7) |
| Paternal occupation | | |
| Unemployed | 4 (9.3) | 5 (11.6) |
| Worker | 11 (25.6) | 11 (25.6) |
| Employee | 5 (11.6) | 6 (14) |
| Self-employed | 23 (53.5) | 21 (48.8) |
| Urban residence | 21 (48.8) | 21 (48.8) |
| Ethnicity | | |
| Fars | 30 (69.8) | 27 (62.8) |
| Baloch | 13 (30.2) | 16 (37.2) |
| Gravida[b] | 3 (2-4) | 2 (1-4) |
| Gestational age[a] | 38.9 (0.93) | 38.9 (1.06) |
| Completed delivery time of the placenta (min)[a] | 7.81 (2.71) | 8.39 (2.41) |
| Birthweight (g)[a] | 3094.18 (384.24) | 3097.67 (366.92) |
| No previous abortion | 34 (79.1) | 36 (83.7) |
| State of perineum | | |
| Intact perineum | 25 (58.1) | 18 (41.8) |
| First-degree tear | 12 (27.9) | 10 (23.3) |
| Second degree tear | 0 | 4 (9.3) |
| Episiotomy | 6 (14) | 11 (25.6) |

*Values in n (%) or [a]mean (SD) or [b]Median (IQR)*

the previous stage ($P < 0.001$). There was no statistically significant difference between the two groups in terms of mean temperature, heart rate and oxygen saturation of neonates immediately, 30, 60, and 90 minutes after birth as shown in **Table II**.

**Table II Maternal Anxiety Scores and Neonatal Physiological Parameters in the Two Study Groups During Different Stages After Birth**

| Variable | Immediately after birth | | | 30 min after birth | | | | 60 min after birth | | | | 90 min after birth | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *CP* | *MP* | *P value* | *CP* | *MP* | *P value* | *Cohen's d (95% CI)* | *CP* | *MP* | *Cohen's d (95% CI)* | *Cohen's d; (95% CI)* | *CP* | *MP* | *P value* | *Cohen's d (95% CI)* |
| Maternal anxiety[a] | 2.76 (2.69) | 2.65 (2.14) | 0.82 | 0.48 (0.82) | 1.04 (1.55) | 0.04 | 0.45 (0.02, 0.87) | 0.09 (0.36) | 0.48 (1.008) | 0.01 | 0.52 (0.08, 0.94) | 0.02 (0.15) | 0.23 (0.64) | 0.04 | 0.45 (0.02, 0.88) |
| Neonate temperature (°C) | 36.18 (0.09) | 36.17 (0.11) | 0.84 | 36.95 (0.16) | 36.91 (0.13) | 0.16 | 0.27 (0.15, 0.7) | 37.12 (0.12) | 37.09 (0.11) | 0.17 | 0.17 (0.25, 0.6) | 37.20 (0.10) | 37.16 (0.12) | 0.10 | 0.36 (0.07, 0.78) |
| Neonatal heart rate (beats per min) | 141.19 (5.56) | 139.79 (6.28) | 0.27 | 136.60 (4.55) | 136.35 (5.52) | 0.81 | 0.05 (0.37, 0.47) | 136.14 (4.96) | 136.60 (4.78) | 0.65 | 0.09 (0.52, 0.33) | 136.28 (4.64) | 136.12 (4.40) | 0.86 | 0.05 (0.37, 0.47) |
| Neonatal oxygen saturation[a] (%) | 74.65 (1.67) | 74.25 (1.54) | 0.25 | 96.65 (0.68) | 96.51 (0.76) | 0.37 | 0.19 (0.23, 0.62) | 97.48 (0.59) | 97.39 (0.72) | 0.51 | 0.14 (0.29, 0.56) | 97.81 (0.39) | 97.74 (0.44) | 0.44 | 0.17 (0.26, 0.59) |

*All values in mean (SD). [a]P < 0.05 for difference between groups at 30 min, 60 min and 90 min after birth. CP Companion presence, MP Midwife presence*

There was also a small to medium effect size of the presence of companion compared to midwife in terms of maternal anxiety at 30, 60 and 90 minutes after birth. There was no impact on neonatal temperature, neonatal heart rate and neonatal oxygen saturation at 30, 60 and 90 mins of SSC.

A significant effect of time was noted on maternal anxiety ($\eta 2 = 0.547$, $P < 0.001$); however, the effect of group ($\eta 2 = 0.015$, $P = 0.266$) and interaction of group × time ($\eta 2 = 0.018$, $P = 0.214$) on maternal anxiety was insignificant. The effect of time, group and interaction of group × time on neonatal temperature was $\eta 2 = 0.94$, $P < 0.001$; $\eta 2 = 0.053$, $P = 0.034$; and $\eta 2 = 0.0.13$, $P = 0.35$, respectively. The effect of time, group and interaction of group × time on neonatal heart rate was $\eta 2 = 0.152$, $P < 0.001$; $\eta 2 = 0.004$, $P = 0.58$; and $\eta 2 = 0.006$, $P = 0.66$, respectively. The effect of time, group and interaction of group × time on neonatal oxygen saturation was $\eta 2 = 0.993$, $P < 0.001$; $\eta 2 = 0.036$, $P = 0.08$; and $\eta 2 = 0.0.006$, $P = 0.68$, respectively.

79.1% of the mothers in the study group were completely satisfied, and 20.9% were satisfied with the provided care compared to 55.8% and 44.2%, respectively in the control group. A significant difference was noted when comparing the maternal satisfaction between the two groups ($P = 0.02$). Regarding the mothers' desire for the same care in the future delivery, 65.1% of the mothers in the study group and 37.2% of the mothers in the control group were completely satisfied ($P = 0.008$).

## DISCUSSION

We investigated the effect of companion presence during SSC on maternal anxiety and satisfaction, and neonatal physiological parameters. Compared to a midwife, the presence of a known female companion was more effective in mitigating postpartum maternal anxiety although no significant difference was observed in the neonatal physiological parameters immediately after birth in both groups.

Although previous studies have reported that mothers engaged in SSC have lower anxiety [18,19], there is scant evidence on the impact of presence of a companion on postpartum maternal anxiety. Some researchers have investigated the role of non-specialist support by friends, relatives or spouse during labor and delivery. A study in Iran reported the effect of the presence of a companion in reducing anxiety in the late active phase of labor, although no information was provided about postpartum anxiety [20]. Salehi et al [21] conducted a clinical trial on the effect of the presence of trained husbands during labor on the anxiety level of mothers. Scores of anxiety were compared in the three study groups, viz, without companion (control), with companion (a friend or a relative), and with a trained husband. During the fourth stage of labor, the level of anxiety in the husband companionship group was significantly lower than in the companion group; it was also significantly lower in the companion group than in the control group. However, in another study, most mothers preferred to have a labor companion rather than her husband [22]. In contrast a study by Rini et al [23] reported that 27% of the mothers got more anxious when they had a companion during labor. It is true that not only the presence of a companion is important but also the manner of companionship can influence the outcome [24].

In Iran, despite the expansion of physiological childbirth, satisfaction with vaginal childbirth is low to moderate; lowest level of satisfaction is in the emotional support area [25]. Congruence between the maternal expectations and the care provided to the mothers is needed. The present study showed the presence of companion (friends or relatives) during SSC considerably improved maternal satisfaction.

The use of a companion during SSC may be limited by misconceptions and cultural or social beliefs. One of the misconceptions is that SSC implementation by a companion may have negative neonatal consequences; our findings affirm that there is no scientific basis for the same as neonatal physiological parameters were comparable between the two groups.

Our study is distinctive for it investigates the effect of companion during SSC on the neonatal physiological parameters. Other studies have focused on the effect of continuous support during labor and childbirth. Bohren et al conducted a Cochrane systematic review reported that continuous support during labor and childbirth may improve neonatal outcomes including a higher fifth-minute Apgar score [4].

One of the limitations of the study was that maternal anxiety assessment was based on VAS. We also did not account for any additive effect on anxiety due to the effect of different degrees of maternal trait anxiety. We attempted to minimize the influence of this effect by random assignment of the mother–baby pairs into groups. We did not assess qualitatively the attitudes and opinions of mothers regarding the presence of companion during SSC In this study, the presence of a companion was limited to one hour after birth; it is suggested that this intervention be repeated with the presence of a companion additionally during the labor. Also, field studies to assess the impact of SSC on hypothermia will be useful.

Given the current barriers to SSC implementation, the results of this study could encourage the use of a

**WHAT THIS STUDY ADDS?**

- Presence of a trusted or known companion after childbirth during skin-to–skin contact is effective and safe modality for reducing maternal anxiety and improving maternal satisfaction.

companion of choice in reducing maternal anxiety and promoting maternal satisfaction. They can be used by policy makers and service providers in evidence-based decision-making in the field of maternal and neonatal health. Our study can generate evidence to facilitate policy change regarding implementation of companionship programs for mothers, especially in centers with shortage of staff and high workload.

*Ethics clearance*: IEC, Iran University of Medical Sciences; No. IR.IUMS.REC.1398.1364 dated May 15, 2019.

*Contributors*: FHK, SSM, MK: Study design; FHK, HH: Data collection and analysis; FHK, SSM, MK, HH: Writing the main manuscript text. All authors contributed, designed, reviewed and approved the manuscript**.**

*Funding*: Master's thesis of Fatemeh Harati Kabir (FHK) was supported by a grant from the Student Research Committee of Iran University of Medical Sciences, Tehran, Iran.

*Competing interests*: None stated.

*Acknowledgements*: We are grateful to the postpartum women and health providers of Amir Al-Momenin Hospital, Zabol, Sistan and Baluchestan Province, Iran, that provided the background and conditions for this project. We also appreciate Mr. Ebrahim Parvin for editing and proof-reading the final manuscript.

## REFERENCES

1. Fallon V, Groves R, Halford JCG, Bennett KM, Harrold JA. Postpartum anxiety and infant-feeding outcomes: A systematic review. J Hum Lact. 2016;32:740-58.
2. Radoš SN, Tadinac M, Herman R. Anxiety during pregnancy and postpartum: course, predictors and comorbidity with postpartum depression. Acta Clin Croat. 2018; 57:39.
3. Cong S, Wang R, Fan X, et al. Skin to skin contact to improve premature mothers' anxiety and stress state: A meta analysis. Matern Child Nutr. 2021;17:e13245..
4. Bohren MA, Hofmeyr GJ, Sakala C, Fukuzawa RK, Cuthbert A. Continuous support for women during childbirth. Cochrane Database Syst Rev. 2017;7:CD003766.
5. Sockol LE, Epperson CN, Barber JP. Preventing postpartum depression: a meta-analytic review. Clinical Psychology Review. 2013;33:1205-17.
6. Liu H, Yang Y. Effects of a psychological nursing intervention on prevention of anxiety and depression in the postpartum period: a randomized controlled trial. Ann Gen Psychiatry. 2021;20:1-7.
7. Moore ER, Anderson GC, Bergman N, Dowswell T. Early skin-to-skin contact for mothers and their healthy newborn infants. Cochrane Database Syst Rev. 2012;5:CD003519. Update in: Cochrane Database Syst Rev. 2016;11: CD003519.
8. Sharma A. Efficacy of early skin-to-skin contact on the rate of exclusive breastfeeding in term neonates: A randomized controlled trial. Afr Health Sci. 2016;16:790-7.
9. Koopman I, Callaghan Koru JA, Alaofin O, et al. Early skin to skin contact for healthy full term infants after vaginal and caesarean delivery: A qualitative study on clinician perspectives. J Clin Nurs. 2016;25:1367-76.
10. Keshavarz M, Bolbol Haghighi N. Effects of kangaroo contact on some physiological parameters in term neonates and pain score in mothers with cesarean section. Koomesh. 2010;11:91-8.
11. Cooijmans KH, Beijers R, Rovers AC, de Weerth C. Effectiveness of skin-to-skin contact versus care-as-usual in mothers and their full-term infants: study protocol for a parallel-group randomized controlled trial. BMC Pediatr. 2017;17:1-16.
12. Abdulghani N, Edvardsson K, Amir LH. Worldwide prevalence of mother-infant skinto-skin contact after vaginal birth: A systematic review. PLoS One. 2018;13:e0205696.
13. Alenchery AJ, Thoppil J, Britto CD, et al. Barriers and enablers to skin-to-skin contact at birth in healthy neonates-a qualitative study. BMC Pediatr. 2018;18:1-10.
14. Nobakht F, Safdari DF, Parvin N, Rafiee VL. The effect of the presence of an attendant on anxiety and labor pain of primiparae referring to Hajar Hospital in Shahre Kurd, 2010. J Res Dev Nurs Midw. 2012;9:41-50.
15. Allen Jr JC. Sample size calculation for two independent groups: A useful rule of thumb. Proc Singapore Healthc. 2011;20:138-40.
16. Abend R, Dan O, Maoz K, et al. Reliability, validity and sensitivity of a computerized visual analog scale measuring state anxiety. J Behav Ther Exp Psychiatry. 2014;45:447-53.
17. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed., Routledge; 2013.
18. Hubbard JM, Gattman KR. Parent–infant skin-to-skin contact following birth: history, benefits, and challenges. Neonatal Netw. 2017;36:89-97.
19. Bohren MA, Hofmeyr GJ, Sakala C, et al. Continuous support for women during childbirth. Cochrane Database Syst Rev. 2017;7:C003766.
20. Toosi SZ, Mohammadinia N, Sereshti M. Effect of companionship during labor on level of anxiety of primiparous mothers and midwives points of view in Iranshahr, 2010. Journal of Mazandaran University of Medical Sciences. 2013;22.8-41:
21. Salehi A, Fahami F, Beigi M. The effect of presence of trained husbands beside their wives during childbirth on

women's anxiety. Iran J Nurs Midwifery Res. 2016;21:611.
22. Teshome M, Abdella A, Kumbi S. Partureints' need of continous labor support in labor wards. Ethiop J Health Dev. 2007;21:35-9.
23. Rini C, Schetter CD, Hobel CJ, Glynn LM, Sandman CA. Effective social support: Antecedents and consequences of partner support during pregnancy. Pers Relatsh. 2006;13: 207-29.
24. Feeney BC, Collins NL. A new look at social support: A theoretical perspective on thriving through relationships. Pers Soc Psychol Rev. 2015;19:113-47.
25. Bavil DA, Dashti S. Maternal satisfaction about delivery and its influencing factors in Iranian population: A systematic review of mixed methods. J Med Health Sci 2021;17:296-305.

ORIGINAL ARTICLE

# Color Doppler Ultrasound Indices as Predictors of Propranolol Response in Infantile Hemangioma: A Prospective Study

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## ABSTRACT

**Objective**: To evaluate the utility of color Doppler ultrasonography in assessing infantile hemangioma response to treatment with oral propranolol.

**Method**: A prospective study was conducted between January, 2016 and December, 2022, wherein children with symptomatic (ulceration, bleeding, pain and scarring) infantile hemangioma were given oral propranol (2 mg/kg per day in three divided doses) as outpatient therapy. The clinical response was assessed three months post-initiation of treatment (intermediate clinical response) and three months post-completion of treatment (final clinical response, FCR). The primary outcome measurement was a clinical and radiological response (resistivity index (RI), pulsatility index (PI) and peak systolic velocity) to treatment. The secondary outcomes assessed were the complications related to treatment.

**Result**: Out of 601 patients who were started on propranolol, 99 developed severe adverse effects and were excluded from analysis. At FCR assessment, out of 502 participants, 64.3% ($n$ = 323) showed excellent response, 17.7% ($n$ = 89) showed partial, and 17.9% ($n$ = 90) were non-responders. A significant increase in RI and PI values was noted in all children following propranolol treatment for six months. An increase > 7.5% in RI could identify responders with 92% sensitivity, 91% specificity and area under the curve (AUC) of 0.963. An increase of > 11.5% in PI could identify responders with 86% sensitivity, 91% specificity and AUC of 0.896. Patients initially showing no response but later becoming excellent responders had significantly higher RI and PI values.

**Conclusion**: Color Doppler ultrasonography is a valuable tool in predicting the treatment outcome of infantile hemangioma using propranolol.

**Keywords**: *Beta-blocker, Pulsatility index, Resistivity index, Vascular malformation*

## INTRODUCTION

Infantile hemangioma (IH), the most common soft tissue tumor in infancy, follows a distinct trajectory - emerging a few weeks post-birth, exhibiting dynamic growth, and often involuting spontaneously. By five years age, about 50% of these tumors involute, rising to 70% by the age seven years [1,2]. While many of these cases do not necessitate intervention, symptomatic lesions presenting cosmetic or functional challenges require appropriate treatment strategies, which can range from cryotherapy and sclerotherapy to the use of steroids, chemotherapeutic agents, and surgical excision [3,4].

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Received on: June 25, 2023; Initial review: Sep 15, 2023; Accepted on: Nov 25, 2023

In 2008, a breakthrough observation by Labreze et al revealed propranolol's inhibitory effect on the growth of IH in children treated for cardiac conditions [5]. This finding spurred numerous subsequent studies which validated propranolol's efficacy and safety in managing hemangiomas [6-8]. However, resistance to propranolol defined as persistent growth during the proliferative phase or a lack of size reduction during the post-proliferative phase after at least four weeks of therapy at $^{24}_{12}$ 2 mg/kg/d can pose a challenge [9,10]. Here, the reliance on clinical response as the primary outcome assessment tool can potentially lead to prolonged exposure to the drug, particularly in non-responsive patients.

Ultrasonography (USG) of IH is an inexpensive, fast and convenient diagnostic modality. USG of IH shows a well-defined mass with high vessel density and no abnormality of the surrounding fat with uniform, pulsatile, fast flow vascularity on Doppler with arterial and venous waveforms [11]. Our study seeks to explore the utility of color Doppler USG in assessing the response of IH to

propranolol treatment. Contrary to prevailing opinion, we hypothesize that color Doppler may not provide any additional advantage in assessing propranolol's treatment response for IH, nor can it accurately identify non-responders. Through this investigation, we aim to elucidate the real value of color Doppler in managing this prevalent pediatric condition, potentially influencing future approaches to IH treatment.

## METHODS

A prospective study was conducted in the Department of Pediatric Surgery in collaboration with the Department of Oral and Maxillofacial Surgery, in a tertiary centre in North India, from January, 2016 to December, 2022. Ethical approval was obtained from the Institute Review Board. Informed and written consent was taken for every participant from the parent(s).

Patients older than 1 month of age, with symptomatic hemangioma (ulceration, bleeding, pain and scarring), and without any prior treatment were considered eligible for the study. The diagnosis of IH was made on the basis of clinical examination and spectral color Doppler ultrasound. The diagnostic criterion used was lesions appearing more than 7 days after birth and absent congenitally, localized blanching of the skin and macular telangiectatic erythema with patchy expansion or subcutaneous soft tissue masses, rapid tumor growth history, and a bluish surface hue which fades away on pressing. A careful patient history, clinical examination and electrocardiography (ECG) were performed in all the patients to ascertain risk factors or contraindications pertaining to the use of propranolol. Patients with cardiovascular disorders (after cardiac evaluation and ECG), acute respiratory illness and a history of bronchial asthma were excluded from the study. Baseline hemogram, blood sugar and renal function tests were done in all patients. Participants were given oral propranolol at a dose of 2 mg/kg per day in three divided doses as outpatient therapy. Possible sequelae to treatment like refusal to feed and lethargy were explained to the parents and advised to visit the hospital at the earliest in case any of these signs appeared.

The clinical response was assessed three months post-initiation of treatment (intermediate clinical response, ICR) and three months post-completion of treatment (final clinical response, FCR). Two independent observers blinded to the outcome assessed the clinical response at each visit. Colored photographs were used for assessment and each patient was categorized as 'excellent responder' in the case of > 50% regression of the lesion, 'partial responder' in the case of 25-50% response, or 'non-responder' in the event of less than 25% response or progressive increase in size of the lesion. All patients were observed for a minimum period of 3 months after the last dose of propranolol before being considered as non-responders.

For sonographic assessment patients underwent examination with spectral Doppler ultrasound prior to treatment and 3 months after the beginning of propranolol therapy. A 7.5 MHz Doppler probe (PHILIPS IU-22) was used for assessment. The type (superficial, deep or mixed), size (major diameter, thickness and transverse diameter), morphology, internal echoes and boundaries of the hemangioma was evaluated. Volume assessment was done using the major diameter, thickness and transverse diameter of the lesion. The resistivity index (RI), pulsatility index (PI) and peak systolic velocity (PSV) were calculated as described by Chen et al [12]. For each lesion, intralesional values were calculated at multiple points, according to the size of the lesion and the possibility of sampling and then a mean value was calculated for any single lesion. The change in RI, PI, and PSV value from before to 3-months after initiation of therapy and at 3 months after completion of treatment: (value after treatment at first return visit - value before treatment)/ value before treatment and labeled as change in resistance index (DRI), change in pulsatility index (DPI), and change in peak systolic velocity (DPSV), respectively.

The primary outcome measurement was clinical and radiological response to treatment. The radiological parameters; resistivity index, pulsatility index and peak systolic velocity at time of ICR and FCR were compared. The change (from baseline/pre-treatment to 3 months) in RI, PI and PSV was compared with clinical response at 3 months and clinical response 3 months post completion of treatment. The secondary outcomes assessed were complications related to the treatment.

*Statistical methods:* Statistical analysis was performed using the IBM SPSS 19.0 Statistics for Windows software. Data was tested for normality by using the Kolmogorov-Smirnov and Shapiro-Wilk test. Mann-Whitney *U* test and *t* test was used to compare the variables. The utility of change in Doppler indices (RI, PI, PSV) in terms of clinical response to the therapy was predicted by using receiver operating characteristic (ROC) Curve and Youden's J statistic. McNemar's test was used to compare the change in Doppler indices over three months. *P* value < 0.05 was considered was statistically significant at 95% confidence interval. Cohen's Kappa Coefficient was used to predict the inter-rater and intra-rater variability, values ≤0 indicated no agreement, 0.01-0.20 as none to slight, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial and 0.81-1.00 as perfect agreement [13].

## RESULTS

Over a period of 7 years, a total of 601 children with problematic IHs were evaluated, of which 99 patients (16.4%) were excluded from evaluation due to severe adverse drug reactions, and 502 children were considered eligible for analysis. The overall mean (SD) age of patients at the onset of treatment was 3.7 (2.37) months (age range 1.8 to 14 months). Out of 502 patients, 329 (65.5%) patients were female and 173 (34.5%) were male patients; female:male ratio of 3:2. A total of 13.6% patients had multifocal lesions and the rest had unifocal. Indications for treatment included cosmetic problems (29.3%), functional (19.8%), difficulty in handling (18.8%), and ulceration (17.8%). The mean (SD) size of the lesion before treatment was 2.5 (1.1) ×2.03 (0.6) cm.

At 3 months follow-up, 266 (52.9%) patients had excellent response, 74 (14.7%) had partial and 162 (32.3%) were non-responders. At FCR assessment, 323 (64.3%) patients had excellent response, 89 (17.7%) had partial, and 90 (17.9%) remained as non-responders with a mean (SD) treatment duration of 8.2 (1.8) months and a median (IQR) follow-up of 15.5 (10.5 - 18.5) mo (**Table I**). Tapering of propranolol dosage was done over a period of 2 weeks.

Doppler indices could be measured in 388 patients at baseline, 3 months and 6 months. RI and PI values of the lesions increased significantly in all children who took propranolol for 6 months irrespective of FCR (**Table II**). The mean increase in RI and PI was significantly higher among excellent responders compared to partial and non-responders (**Fig. 1a-b)**. There was no significant difference in the change in PSV among different response groups.

At 3 months, 162 patients did not respond to propranolol. However, 63 of these non-responders became excellent responders at FCR, while 90 continued to remain as non-responders. We found that RI and PI values were significantly higher in these 63 children who transitioned from an initial non-response at 3 months to excellent response at FCR, compared to those who remained as partial and non-responders at even 6 months (**Table III**).

**Table I Clinical Response to Propranolol Therapy**

| *Response* | *Intermediate clinical response (ICR)* | *Final clinical response (FCR)* |
|---|---|---|
| Excellent responder | 266 (53.0) | 323 (64.3) |
| Partial responder | 74 (14.7) | 89 (17.7) |
| Non-responder | 162 (32.3) | 90 (17.9) |
| Total | 502 (100) | 502 (100) |

*Values expressed as n (%)*

On ROC analysis of changes in Doppler indices at three months from baseline, we found that > 7.5% increase in RI could identify responders (at FCR) with a sensitivity of 92%, a specificity of 91% and area under the curve (AUC) of 0.963. Similarly, > 11.5% increase in PI could identify responders (at FCR) with a sensitivity of 86.0%, specificity of 91% and AUC of 0.896 (**Fig. 2**). We assessed the clinical response and RI, PI and PSV values at 3 months; a cut-off value of ≥ 65.5, ≥ 95.5 and < 28.5 cm/s for RI, PI and PSV, respectively, had the maximum sensitivity and specificity for predicting a positive clinical response.

A total of 21 patients (4.2%) developed refusal to feed and were diagnosed to have hypoglycemia. The dose of propranolol was tapered to 1 mg/kg for two weeks and then continued at 2 mg/kg. The other adverse reactions were excessive crying and inability to sleep (4.3%, $n$ = 22), diarrhea (2.3%, $n$ = 12), rash (2.1%, $n$ = 11) and gastro-intestinal reflux (1.7%, $n$ = 9) of patients. 4.7% children ($n$ = 24) had intolerable adverse reactions leading to discontinuation of treatment.

Adjuvant therapies used in partial responders and non-responders were intralesional steroids ($n$ = 25) and intralesional bleomycin ($n$ = 48) and surgical excision ($n$ = 15).

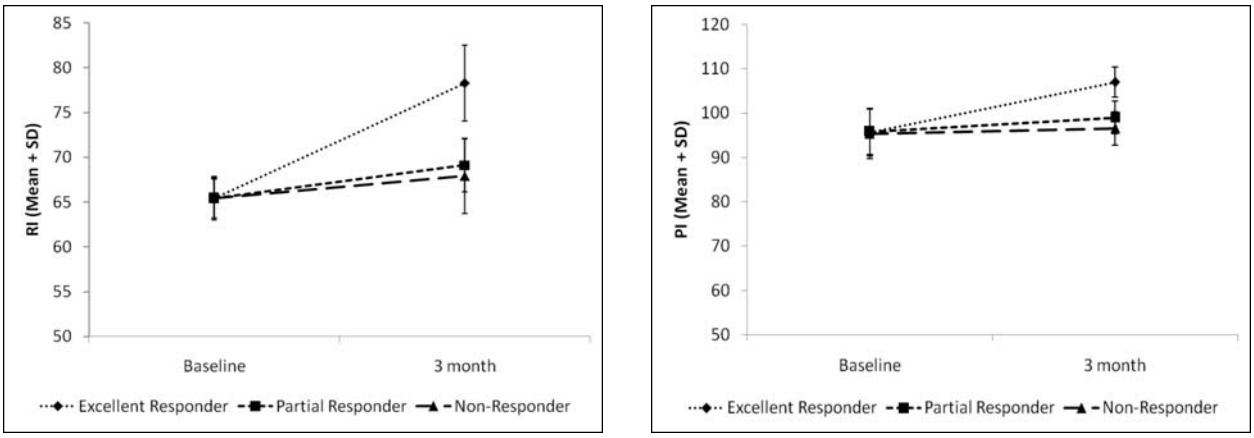
## DISCUSSION

Within our prospective cohort of 502 patients, propranolol treatment demonstrated an effective response in managing symptomatic IH in 82% of cases. Severe adverse reactions leading to discontinuation were reported in 4.7% of cases,

**Table II Change in Doppler Ultrasound Parameters after 6 months of Propranolol Amongst Different Response Groups**

| *Doppler Index* | *Excellent responders (n = 323)* | *Partial responders (n = 89)* | *Non-responders (n = 90)* |
|---|---|---|---|
| Increase in RI[a] | 12.83 (4.87) | 6.69 (3.18) | 1.50 (4.41) |
| Increase in PI[a] | 11.38 (2.77) | 5.17 (2.62) | 1.18 (2.88) |
| Decrease in PSV[b] | 4.97 (6.19) | 6.18 (6.28) | 6.02 (6.39) |

*Values expressed as mean (SD). [a]P < 0.001 for Excellent vs Partial responders, Partial Vs Non-responders, Excellent vs Non-responders; [b]P > 0.05 for all comparisons. RI Resistance index, PI Pulsatility index, PSV Peak systolic velocity*




(*a*) (*b*)

**Fig.1** a) Mean change in Resistivity index; b) Mean change in Pulsatility index

underscoring its safety. We demonstrated the utility of Doppler ultrasound indices viz, RI, PI and PSV, as early predictive markers for treatment outcomes. An increase of more than 7.5% in the RI had the potential to accurately identify responders to the treatment with a sensitivity of 92% and a specificity of 91%.

In our investigation, we identified a significant pattern of change in RI and pulsatility index (PI) at the three-month mark that played a crucial role in predicting the final response to propranolol treatment in IH, regardless of the observed clinical response at the same stage. This finding underlines the significance of Doppler ultrasound indices as early predictive markers in treatment trajectory i.e. continuing treatment in those who will show response in the future and stopping in those who will remain as non-responders.

Our study findings reaffirm that propranolol is a safe and effective treatment for IH. Previous studies have demonstrated propranolol's efficacy in as many as 88.75% of cases, positioning it as a frontline treatment for IH [5-8].

**Table III Comparative Doppler Indices at Baseline and 3 months of Treatments in Relation to Clinical Response at 6 Months**

| | *Resistivity Index (RI)* | | | | | |
|---|---|---|---|---|---|---|
| | *Baseline* | | | *3 months* | | |
| *Response (At 6 months)* | RI < 65.5 | RI ≥ 65.5 | *P* value | RI < 65.5 | RI ≥ 65.5 | *P* value |
| Excellent responder (*n* = 63) | 41 (65.07) | 22 (34.93) | < 0.001 | 0 | 63 (100) | < 0.001 |
| Partial responder (*n* = 9) | 5 (55.56) | 4 (44.44) | | 0 | 9 (100) | |
| Non-responder (*n* = 90) | 34 (37.77) | 56 (62.23) | | 31 (34.44) | 59 (65.56) | |
| | *Pulsatility Index (PI)* | | | | | |
| | *Baseline* | | | *3 months* | | |
| *Response (At 6 months)* | PI< 95.5 | PI ≥ 95.5 | *P* value | PI< 95.5 | PI ≥ 95.5 | *P* value |
| Excellent responder (*n* = 63) | 35 (55.55) | 28 (44.45) | 0.386 | 0 | 63 (100) | <0.001 |
| Partial responder (*n* = 9) | 4 (44.44) | 5 (55.56) | | 0 | 9 (100) | |
| Non-responder (*n* = 90) | 40 (44.44) | 50 (55.56) | | 23 (25.55) | 67 (74.45) | |
| | *Peak Systolic Velocity (PSV) (cm/s)* | | | | | |
| | *Baseline* | | | *3 months* | | |
| *Response (At 6 months)* | PSV < 28.5 | PSV ≥ 28.5 | *P* value | PSV < 28.5 | PSV ≥ 28.5 | *P* value |
| Excellent responder (*n* = 63) | 30 (47.62) | 33 (52.38) | 0.573 | 57 (90.47) | 6 (9.53) | 0.197 |
| Partial responder (*n* = 9) | 5 (55.56) | 4 (44.44) | | 8 (88.89) | 1 (11.11) | |
| Non-responder (*n* = 90) | 37 (41.11) | 53 (59.89) | | 72 (80.0) | 18 (20.0) | |

*Values expressed as n (%)*

**WHAT THIS STUDY ADDS?**

- Doppler USG indices, *viz*. RI and PI, can predict response to propranolol at three months in children with infantile hemangioma and this insight could potentially prevent unnecessary exposure to propranolol in non-responding patients.

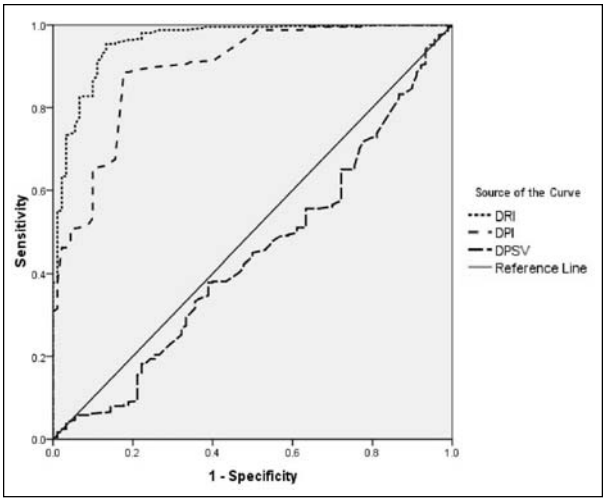



**Fig. 2** Receiver operating characteristic curve depicting sensitivity and specificity of change in resistance index (DRI), change in pulsatility index (DPI) index and change in peak systolic velocity (DPSV) for predicting the final clinical response

This is congruent with our results, where 64.3% of patients showed excellent response, and 17.7% showed a partial response at FCR.

Ginguerra et al in their study stated a high vascular density (> 5 vessels/cm2) and an arterial peak of > 2 kHz on Doppler USG as diagnostic of IH [14]. In the proliferative stage, a low RI and low resistance to blood flow are commonly observed. In the involution stage, the RI increases indicating a reduced vascular activity in the lesion [14].

Shi et al [15] studied the role of color Doppler in thirty-one patients following propranolol therapy. They found that hemangiomas' longitudinal and transverse diameter, thickness, vascular density, blood flow velocity (arterial and venous), and arterial peak systolic blood flow velocity were significantly decreased ($P = 0.05$).

The utility of Doppler ultrasound indices, namely the resistance index (RI) and pulsatility index (PI) as early outcome predictors in our study mirror the conclusions of previous investigations [16-18]. For instance, Kim et al also utilized Doppler ultrasound for response assessment and found a decrease in PSVs and an increase in RIs in patients with IH responding to propranolol [16]. We did not find PSV to be an effective index, it may be explained as it is the most operator-dependent index compared to other indices.

Color Doppler USG is a valuable tool in predicting the treatment outcome of IH using propranolol. These indices can guide the early identification of potential non-responders, helping prevent unnecessary exposure to propranolol and allowing for a timely shift toward alternative therapies

*Ethics clearance*: Institutional Ethics Committee studies, No. Dean/2015-2016/EC/75 dated May 26, 2016.

*Contributors*: PT: Conceptualization; VP: Data collection, methodology; RNB, AND: Manuscript editing and revising it for intellectual content; OPS: Critical input in the manuscript.

*Funding:* This study is the PhD work of Dr. Vaibhav Pandey with research grant support from Banaras Hindu University, Varanasi, as part of the IoE faculty incentive grant.

*Competing interest*: None stated.

## REFERENCES

1. Harter N, Mancini AJ. Diagnosis and Management of Infantile Hemangiomas in the Neonate. Vol. 66, Pediatric Clinics of North America. W.B. Saunders; 2019. p. 437-59.
2. Soliman YS, Khachemoune A. Infantile hemangiomas: our current understanding and treatment options. Dermatol Online J. 2018;24:13030/qt5jt8q9km.
3. Chinnadurai S, Fonnesbeck C, Snyder KM, et al. Pharmacologic interventions for infantile hemangioma: A meta-analysis. Pediatrics. Am Acad Pediatr. 2016;137: e20153896.
4. Cohen SR, Wang CI. Steroid treatment of hemangioma of the head and neck in children. Ann Otol Rhinol Laryngol. 1972;81:584-90.
5. Léauté-LabrèzeC, Roque ED de la, Hubiche T, Boralevi F, Thambo JB, Taýeb A. Propranolol for severe hemangiomas of infancy. N Engl J Med. 2008;358:2649-51.
6. Pandey V, Tiwari P, Gangopadhyay A, Gupta D, Sharma S, Kumar V. Propranolol for infantile haemangiomas: Experience from a tertiary center. J Cutan Aesthet Surg. 2014;7:37.
7. Yang H, Hu DL, Shu Q, Guo XD. Efficacy and adverse effects of oral propranolol in infantile hemangioma: a meta-analysis of comparative studies. World J Pediatr. 2019; 15:546-58.
8. Zhang L, Wu HW, Yuan W, Zheng JW. Propranolol therapy

for infantile hemangioma: Our experience. Drug Des Devel Ther. 2017;11:1401-8.
9. Chang L, Chen H, Yang X, Jin Y, Ma G, Lin X. Intralesional Bleomycin Injection for Propranolol-Resistant Hemangiomas. J Craniofac Surg. 2018;29:e128-e30.
10. Causse´ S, Aubert H, Saint-Jean M, et al. Propranolol-resistant infantile hemangiomas. Br J Dermatol. 2013; 169:125-9.
11. DeHart A, Richter G. Hemangioma: Recent Advances. F1000Res. 2019;8:F1000 Faculty Rev-1926.
12. Chen CY, Wu YC, Yen MS, Hung JH, Yuan CC, Chao KC. The power Doppler velocity index, pulsatility index, and resistive index can assist in making a differential diagnosis of primary ovarian carcinoma and Krukenberg tumors: A preliminary study. J Ultrasound Med. 2007;26:921-6
13. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med. 2012;22:276-82.
14. Ginguerra MA, Saito O, Fernandes JBVD, Castro DS, Matayoshi S. Clinical and Radiological Evaluation of Periocular Infantile Hemangioma Treated With Oral Propranolol: A Case Series. Am J Ophthalmol. 2018;185: 48-55.
15. Shi H, Song H, Wang J, et al. Ultrasound in Assessing the Efficacy of Propranolol Therapy for Infantile Hemangiomas. Ultrasound Med Biol. 2014;40:2622–9.
16. Kim YH, Oh JY, Song KH, Kim KH. Clinical application of color doppler ultrasound in evaluation of vascular lesions and treatment of hemangiomas. Korean J Dermatol. 2002; 40:1331-8.
17. Spierer O, Neudorfer M, Leibovitch I, Stolovitch C, Kessler A. Colour Doppler ultrasound imaging findings in paediatric periocular and orbital haemangiomas. Acta Ophthalmol. 2012;90:727-32.
18. He L, Huang G. Spectral Doppler ultrasound for predicting long-term response to topical timolol in children with infantile hemangioma. J Clin Ultrasound. 2017;45:480-7.

ORIGINAL ARTICLE

# Secondary Gains of Strategies to Prevent COVID-19 Infection in Neonatal Intensive Care Unit: Has the Frequency of Healthcare-Associated Infections Decreased?

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**ABSTRACT**

**Objective:** To compare the frequency and distribution of healthcare-associated infections (HAI) in the neonatal intensive care unit (NICU) during COVID-19 infection.

**Methods:** We compared all cases hospitalized in the NICU and diagnosed with HAIs between 1 March - 1 September 2019 (pre-COVID-19 pandemic) and 1 March - 1 September 2020 (during the COVID-19 pandemic).

**Results:** We evaluated a total of 957 babies, 427 babies in the pre-COVID-19 period and 530 babies during the COVID-19 pandemic. HAIs were determined in 47 patients (60 attacks) and 39 patients (44 attacks) in the pre-COVID-19 period and during the COVID-19 period, respectively. HAIs incidence density (per1000 hospitalization days) was found 5.43 in pre-COVID-19 period and 4.87 in COVID-19 period. During the COVID-19 period, there was a significant decrease in the HAI incidence density and bloodstream infection ($P$ = 0.009).

**Conclusions:** COVID-19 infection prevention strategies helped reduce the frequency of HAIs especially in bloodstream infection in NICU.

**Keywords:** *Bloodstream infection, Coronavirus, Nosocomial, SARS-CoV2, Sepsis*

## INRODUCTION

Healthcare-associated infection (HAI) it is an important factor that increases mortality, morbidity and treatment costs in neonatal intensive care units (NICU) [1]. The various neonatal HAIs include bloodstream infections, catheter-related infections, ventilator-associated infections, urinary tract infections, meningitis, and skin infections [2]. The incidence rates of HAIs in NICU vary globally wýth a range of 4.8 - 22 per 1000 hospitalization days [3]. The rate of compliance with HAI prevention policies is inversely proportional to the rates of developing HAIs in NICUs [4].

The outbreak of COVID-19 has been a major challenge for healthcare centers, in terms of prevention and control of nosocomial infections. A study comparing the pre- and post-COVID-19 periods, demonstrated a lower magnitude of nosocomial infections (1.75% vs 3.11%) in neonatal healthcare set-ups [5]. However, a study of the incidence of HAI in US hospitals during the COVID-19 pandemic reported a significant increase in central-line-associated bloodstream infections (CLABSI), catheter-associated urinary tract infections (CAUTI), and ventilator-associated events (VAEs) in 2020 in all hospitalized patients [6].

The COVID-19 pandemic was an era of extreme fear and led to an increased use of sanitizers and infection control measures. We assessed if the COVID-19 pandemic led to a reduction in HAIs in NICUs due to increased infection control measures.

## METHODS

The study was designed as a single-center observational study which included two study periods, pre-COVID-19 pandemic (data were obtained retrospectively) and during COVID-19 pandemic (data were obtained prospectively). The study was approved by the Ethical Committee of University of Health Sciences Sisli Hamidiye Etfal Training and Research Hospital (No:2975/2020) and the Scientific Study Group of the Ministry of Health, Turkey (No: 2020-09-03T14_25_32). The study periods were

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Received: May 12, 2023; Initial Review: May 12, 2023;
Accepted: Dec 31, 2023

between 1 March - 1 September 2019 (pre-COVID-19 pandemic) and 1 March - 1 September 2020 (during the pandemic), in NICU. All the HAIs detected during the specified periods were included. The diagnostic criteria of Centers for Disease Control and Prevention (CDC), National Hospital Infections Surveillance Network (NHISN) and Turkish Neonatology Society's for neonatal infections were used for establishing diagnosis of HAIs [1,7,8]. The diagnosis of healthcare-associated bloodstream infection (HA-BSI), CLABSIs, CAUTIs, VAEs, central nervous system (CNS) infection and necrotizing enterocolitis (NEC) were made according to the CDC recommendations [7].

Demographic characteristics, morbidity and mortality and infection foci were recorded. Prenatal and natal information included gestational age, diagnosis, sex, weight, mode of delivery, history of interventional procedures undergoing any (mechanical ventilation, placement of central or urinary catheter), and type of feeding. The use of antibiotics and antifungals, the time of detection of HAI, the focus of infection, the microorganisms grown on culture, the duration of hospital stay, mortality and early morbidity were obtained from records. In addition, we recorded the rate of compliance of healthcare professionals with the infection prevention rules and included the results of surveillance reports of our hospital's infection committee.

**Table I Comparison of Healthcare-Associated Infections Detected in Infants Before and During COVID-19 Period**

| | *Pre-COVID-19 Period Patients (n = 47) Attacks (n = 60)* | *COVID-19 Period Patients (n = 39) Attacks (n = 44)* | *P Value* |
|---|---|---|---|
| Clinical sepsis | 22 (36.6) | 23 (52.2) | 0.45 |
| Culture-proven sepsis | 38 (63.4) | 21 (47.8) | 0.47 |
| HABSI | 22 (36.6) | 6 (13.6) | 0.009 |
| CLABSI | 24 (40) | 13 (29.5) | 0.35 |
| VAE | 4 (6.6) | 6 (13.6) | 0.19 |
| CAUTI | 10 (16.6) | 8 (18.1) | 0.52 |
| Central nervous system infection | 4 (6.6) | 4 (10.2) | 0.1 |
| Necrotizing enterocolitis | 14 (23.3) | 11 (25) | 0.19 |
| Other (eye, ear, nose, throat, skin) infections | 4 (6.6) | 2 (4.5) | 0.19 |

*Data presented as n (%). CAUTI Catheter-associated urinary tract infections, CLABSI Central line-associated bloodstream infection, HABSI Healthcare-associated bloodstream infection, VAE Ventilator-associated events*

*Statistical analysis*: All data was analyzed by SPSS 22.0 for Windows. Continuous variables were expressed as mean (standard deviation) and compared using Student t test between the two periods. Categorical variables were expressed as numbers and percentages and compared using Chi square test between both periods. The risk factors for the development of HAI (duration of hospital stay, mechanical ventilation duration, umbilical catheter duration, total parenteral feeding time, fluconazole prophylaxis, etc.) were compared using Chi-square test or Student t test. $P < 0.05$ was considered significant.

## RESULTS

The study population comprised of 957 babies; 427 babies in the pre-COVID-19 period and 530 babies during the COVID-19 pandemic. Sixty HAIs occurred in 47 patients in the pre-COVID-19 period and 44 HAIs in 39 patients during the COVID-19 period. Demographic characteristics of neonates who developed HAIs in the pre-COVID-19 period and the COVID-19 period were as follows: mean (SD) gestational age 30.8 (5.5) weeks and 31.5 (4.7) weeks, birth weight 1582 (994) g and 1615 (938) g, female gender 49% and 50%, cesarean births 74% and 82%, respectively; $P > 0.05$ for all comparisons.

Among the HAIs, culture-proven sepsis was observed 63.4% of neonates in the pre-COVID-19 period, and 47.8% of neonates during COVID-19 pandemic. Details are presented in **Table I**. During the COVID-19 period, there was a significant decrease in the HAI incidence density, hospital-associated infection rate, catheter-related infection rate, and VAEs-related infection rate in the NICU

**Table II Distribution of the Density and Rates of Hospital-Acquired Infections in Infants Before and During COVID-19 Period**

| | *Pre-COVID-19 period* | *COVID-19 period* |
|---|---|---|
| HAI, attacks (*n*) | 60 | 44 |
| NICU HAI incidence density | 5.43 | 4.87 |
| NICU HAI rate | 8.43 | 5.66 |
| CLABSIs rate | 10.76 | 8.11 |
| HA-BSI rate | 11.27 | 3.74 |
| VAEs rate | 4.83 | 4.51 |

*CLABSIs Central line-associated bloodstream infections, HAI Health associated infection, HA-BSI Healthcare-associated bloodstream infection, VAEs Ventilator-associated events, HAI incidence density (Number of hospital acquired infections/hospitalization days) × 1000, HAI rate (Number of hospital acquired infections/patient number) × 100, CLABSIs rate (Catheter related bacteremia number/total catheter days) × 1000, HA-BSI rate (Number of patients with growth in blood culture/number of inpatients) × 100, VAEs rate (VAE number/ventilator days) × 1000*

unit compared to the pre-COVID-19 period. The distribution of infection rates detected in both periods is presented in **Table II**.

In the pre- and during COVID-19 period, the distribution of HAI pathogens were: 47.5% and 31.2% gram positive bacteria, 42.5% and 56.2% gram negative bacteria and 10% and 12.5% *Candida* sp, respectively. The most common pathogen isolated in blood culture in the pre-COVID-19 period was coagulase-negative staphylococcus (CONS) 32.5%, while during COVID-19 period it was *E. coli* 25%. There was no statistically significant difference in terms of the distribution of microorganisms grown between both periods. During the COVID-19 period, a total of 124 babies were subjected to repeated nasopharyngeal PCR tests due to suspicion of COVID-19. COVID-19 positivity was detected in only 8 babies.

The risk factors for HAIs are showed in **Table III.** There was no difference in mortality rates ($P > 0.05$) and only the number of days of hospitalization, and the total parenteral feeding time were significantly high in the pre-COVID-19 period ($P = 0.03$, $P = 0.04$, respectively). The hand hygiene compliance rates of the healthcare professionals working in both periods are presented in **Table IV.** There was no significant difference between the two periods.

## DISCUSSION

Hospital acquired infections are very important because they cause prolongation of hospital stay, increase in mortality, deterioration in quality of life, and increase in costs [9]. In our study, a significant decrease was found in the frequency of HAIs and culture-proven sepsis during the COVID-19 period compared to the pre-COVID-19 period.

A multicenter study in Turkey reported the HAIs in the NICU ranging from 2.6 to 17% with sepsis-related mortality rate of 24.4% [10]. In our NICU, the nosocomial infection incidence was 5.1/1000 hospitalization days (2006-2007) and 10.3/1000 hospitalization days (2008-2009) [11]. During the COVID-19 era, the incidence of HAIs has decreased. Although a decrease was detected in the mortality rates due to hospital infections during the COVID-19 period, the rates were not statistically significant.

The most common HAIs in NICUs were HA-BSI. The frequency of HA-BSI in neonatal units has been reported as 7 to 16.7% in the developed countries [12] and 12-14% in Turkey [11]. In our study, we observed that HA-BSI decreased significantly during the COVID-19 period. In a multicenter point prevalence study, clinical sepsis was 40% in NICUs [13]. We observed that was higher in the COVID-19 period; albeit these were culture negative.

In developed countries, the rate of catheter-related infection has been reported as 3.5-13% and in studies conducted in Turkey, it has been reported as 9.6-14.3% [11,14]. In our study, the rate of catheter-related infection was found to be similar to literature studies in the pre-COVID-19 period and the rate of catheter-related HAI was found to be lower in the COVID-19 period. VAE is the second most common HAI in NICUs [15] with an incidence of as 2.7-10.9 per 1000 ventilator days in developed countries [16], and 1.4-3.5% as per United States National Nosocomial Surveillance study. Our study findings were similar to this in both periods.

Turkish Neonatalogy Society reported that 45.5% of HAI were caused by gram-positive bacteria and 42.9% by gram-negative bacteria [10]. In our study, gram-positive bacteria were the most common factor in the pre-COVID-19 period, while gram-negative bacteria were found to be more common in the COVID-19 period. We attributed this due to the decreased rate of CONS in our unit.

**Table III Risk Factors for the Development of Healthcare-Associated Infections**

| | *Pre-COVID-19 period* | *COVID-19 period* | *P value* |
|---|---|---|---|
| Length of hospitalization (d)[a] | 41.2 (30.8, 13-153) | 39.2 (23.7, 14-137) | 0.03 |
| Mechanical ventilation duration (d)[a] | 21.9 (38.3, 1-150) | 28.9 (38.5, 1-130) | 0.37 |
| Umbilical catheter duration (d)[a] | 5.3 (2.2, 1-8) | 4.9 (2.9, 1-10) | 0.17 |
| Duration of peripherally inserted central catheter (d)[a] | 21.2 (13.7, 1-76) | 19.9 (15, 5-50) | 0.18 |
| Time to start breast milk (d)[a] | 2.6 (1.6, 1-8) | 2.2 (1.3, 1-7) | 0.09 |
| Transition time to full enteral feeding (d) (d)[a] | 34.7 (32.7, 1-78) | 25.7 (19.9, 1-48) | 0.09 |
| Total parenteral feeding duration (d)[a] | 38.7 (35.6, 6-135) | 20.9 (12.3, 5-48) | 0.04 |
| Fluconazole prophylaxis[b] | 27 (45) | 13 (30) | 0.08 |

*[a]Values are expressed as [a]mean (SD range), [b]n(%)*

**WHAT THIS STUDY ADDS?**

- Corona virus disease (COVID-19) infection prevention strategies reduced the frequency of hospital-acquired infections in the neonatal intensive care unit.

**Table IV Hand Hygiene Compliance Rates in the Surveillance Study of Health Professionals Working in the Neonatal Unit in Two Periods**

| *Bundle apps* | *Pre COVID-19 period (n =427)* | *COVID-19 period (n = 530)* |
|---|---|---|
| Hand hygiene compliance | 5322/5400 (98.56) | 6210/6333 (98.57) |
| Before-contact | 5591/5760 (97.06) | 6492/6720 (96.61) |
| Post-contact | 5694/5760 (98.86) | 6661/6720 (99.12) |
| Before aseptic procedures | 720/720 (100) | 1020/1020 (100) |
| After the risk of contamination from body fluids | 1220/1220 (100) | 1440/1440 (100) |
| After contact with the patient environment | 1417/1440 (98.41) | 1672/1700 (98.36) |

*Values expressed as appropriate procedures/total procedures (%); P > 0.05 for all comparisons*

Babies diagnosed with HAIs generally have a longer NICU stay [17]; two weeks longer than those who do not [18]. A recent study reported that the length of stay in the pediatric intensive care unit decreased during the COVID-19 period [5]. A similar trend was seen in our study, which probably explained the shortening of the transition time to full enteral nutrition and the reduction of total parenteral nutrition time.

It is possible that increased attention to standard infection prevention practices and the use of personal protective equipment impacted HAI rates positively [19]. Multiple factors such as training of healthcare professionals, performance feedback, use of automatic faucets, use of alcohol-based hand sanitizers are required to increase compliance with hand hygiene. In both periods of our study, the rate of hand hygiene was found to be similar. However, the awareness and compliance with hand hygiene has increased due to the COVID-19 outbreak.

The main limitation of our study was that retrospective nature of screening of patients records in the pre-COVID period. Subgroup analysis according to the gestational age and birth weight could not be performed due to inadequate number of patients. In conclusion, we found that, the rate of blood-related infections and the frequency of gram-positive pathogens decreased in our NICU during the COVID-19 pandemic.

*Ethics clearance*: The study was approved by the Ethical Committee of Sisli Hamidiye Etfal Training and Research Hospital, University of Health Sciences, Istanbul, Turkey (No:2975/2020) dated April 22, 2020, and the Scientific Study Group of the Ministry of Health (No: T14_25_32) dated Sep 03, 2020.

*Contributors*: AB, HA: Study design and methodology; AB, EKB, HSU, ETU, AD: Analysis of data and investigation; AYT, GA: Original draft preparation; AD, GA; Review and editing; EKB, ETU: Supervision. All authors read and approved the final manuscript.

*Funding*: None; *Competing interests*: None stated.

## REFERENCES

1. T.C. Ministry of Health, General Directorate of Public Health, National Health Service Associated Infections Surveillance Guide. Ankara. 2019;2-3. Accessed Dec 30, 2023. Available from: *https://hsgm.saglik.gov.tr/depo/Yayinlarimiz/Programlar/Turkiye_Saglik_Hizmeti_Ile_Iliskili_Enfeksiyonlari_Onleme_ve_Kontrol_Programi. pdf*
2. Parlak E, Kahveci H, Alay HK. Hospital infections in the neonatal intensive care unit. Current Pediatrics. 2014;1:1-8.
3. Clark R, Powers R, White R, et al. Nosocomial ýnfection in the NICU: A medical complication or unavoidable problem? J Perinatol. 2004;24:382-8.
4. Luangasanatip N, Hongsuwan M, Limmathurotsakul D, et al. Comparative efficacy of interventions to promote hand hygiene in hospital: systematic review and network meta-analysis. BMJ. 2015;351:h3728.
5. Su C, Zhang Z, Zhao X, et al. Changes in prevalence of nosocomial infection pre- and post-COVID-19 pandemic from a tertiary Hospital in China. BMC Infect Dis. 2021; 21:693.
6. Weiner-Lastinger LM, Pattabiraman V, Konnor RY, et al. The impact of coronavirus disease 2019 (COVID-19) on healthcare-associated infections in 2020: A summary of data reported to the National Healthcare Safety Network. Infect Control Hosp Epidemiol. 2022;43:12-25.
7. National Healthcare Safety Network. CDC/NHSN Surveillance Definitions for Specific Types of Infections. Accessed on Dec 30, 2023. Available from: *https://*

*www.cdc.gov/nhsn/pdfs/pscmanual/17pscnosinfdef_current.pdf*
8. Satar M, Arýsoy AE, Çelik ÝH. Turkish Neonatal Society guideline on neonatal infections-diagnosis and treatment. Turk Pediatri Ars. 2018;53:S88-S100.
9. Hooven TA, Polin RA. Healthcare-associated infections in the hospitalized neonate: a review. Early Hum Dev. 2014;90:4-6.
10. Turkish Neonatal Society; Nosocomial Infections Study Group. Nosocomial infections in neonatal units in Turkey: epidemiology, problems, unit policies and opinions of healthcare workers. Turk J Pediatr. 2010;52:50-7.
11. Bolat F, Uslu S, Bolat G, et al. Healthcare-associated infections in a Neonatal Intensive Care Unit in Turkey. Indian Pediatr. 2012;49:951-7.
12. Raymond J, Aujard Y. Nosocomial infections in pediatric patients: A European, multicenter prospective study. European Study Group. Infect Control Hosp Epidemiol. 2000;21:260-3.
13. Çaðan E, Soysal A, Bakýr M, Özek E. Prevalence of healthcare-associated blood stream ýnfections in neonatal ýntensive care units; Results of the first national point prevalence study. Çukurova Medical Journal. 2015;40: 119-28.
14. Papakyritsi D, Iosifidis E, Kalamitsou S, et al. Epidemiology and outcomes of ventilator-associated events in critically ill children: Evaluation of three different definitions. Infect Control Hosp Epidemiol. 2022;44:216-21.
15. Van der Zwet WC, Kaiser AM, van Elburg RM, et al. Nosocomial infections in a Dutch neonatal intensive care unit: surveillance study with definitions for infection specifically adapted for neonates. J Hosp Infect. 2005; 61:300-11.
16. Cernada M, Brugada M, Golombek S, Vento M. Ventilator-associated pneumonia in neonatal patients: an update. Neonatology. 2014;105:98-107.
17. Harbarth S, Pittet D, Grady L, et al. Interventional study to evaluate the impact of an alcohol-based hand gel in improving hand hygiene compliance. Pediatr Infect Dis J. 2002;21:489-95.
18. Auriti C, Maccallini A, Di Liso G, et al. Risk factors for nosocomial infections in a neonatal intensive-care unit. J Hosp Infect. 2003;53:25-30.
19. Baker MA, Sands KE, Huang SS, et al. The ýmpact of coronavirus disease 2019 (COVID-19) on healthcare-associated infections. Clin Infect Dis. 2022;74:1748-54.

ORIGINAL ARTICLE

# Time to Attain Full Enteral Feeds Among Preterm Fetal Growth Restricted Neonates With Absent/Reversed End-Diastolic Flow

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## ABSTRACT

**Objectives**: To determine the difference in time to attainment of full enteral feeds between fetal growth restricted (FGR) preterm neonates with and without absent/reversed end-diastolic flow (AREDF)**.** Secondary objectives were to compare the short-term outcomes including the incidence of necrotizing enterocolitis (NEC) and feed intolerance between the two groups and to determine the factors affecting the time to attainment of full enteral feeds (FEF) among preterm FGR neonates.

**Methods**: A prospective cohort study was conducted among consecutive preterm FGR neonates delivered at 28-36 weeks gestation admitted in level III NICU. An umbilical artery doppler ultrasound was performed antenatally for all participants to detect AREDF. FGR neonates with AREDF were taken as the study group and those without AREDF were taken as the comparison group. Time to attain FEF was defined as time taken to establish enteral feeds of 150 ml/kg/day and tolerating it for the next 3 consecutive days. Delayed attainment of FEF was taken as ≥10 days needed to attain FEF.

**Result**: The median (IQR) time to attainment of full feeds was longer among neonates with AREDF compared to those without AREDF [12 (8, 16.5) vs 8 (5, 10) days; $P < 0.001$]. Neonates with AREDF had more feed intolerance [RR, 95% CI = 1.51 (1.13 - 2.02); $P = 0.004$], higher mortality [RR, 95% CI = 2.5 (1.02 - 6.2); $P = 0.036$], prolonged time to regain birth weight [15 (11.5, 19) days, $P = 0.035$], longer NICU stay [10 (7, 15), $P < 0.001$] and longer hospital stay [33 (23, 49), $P < 0.001$]. Also, neonates with AREDF had more hypoglycemia [RR, 95% CI=2.15 (1.2-3.7); $P = 0.004$], hypoxic ischemic encephalopathy [RR, 95% CI 5.05 (1.13 - 22.4); $P = 0.016$], hypothyroidism [RR, 95% CI= 8.08 (1.02 - 63.4), $P = 0.016$], cholestasis ($P = 0.007$), prolonged parenteral nutrition requirement [10 (7, 15) days, $P < 0.001$] and oxygen requirement [4.5 (2, 8) days, $P < 0.001$]. Multivariable logistic regression showed, AREDF [aOR 95% CI 2.91 (1.49 - 5.68), $P = 0.002$], lower gestational age [aOR 95% CI 0.724 (0.604 - 0.867), $P < 0.001$] and thrombocytopenia at birth [aOR 95% CI 2.625 (1.342 - 5.136), $P = 0.005$] are significant predictors of delayed attainment of full feeds among preterm FGR neonates.

**Conclusion**: Preterm FGR neonates with AREDF are slower to attain FEF, have more feed intolerance, higher mortality, need longer time to regain birth weight, prolonged NICU stay and hospital stay. AREDF, lower gestation, sepsis and thrombocytopenia at birth are significant predictors of delayed full feed attainment among preterm FGR neonates. It is essential to devise strategies to reduce morbidity and mortality among this group of preterm neonates.

**Keywords**: *Enteral, Feed intolerance, Necrotizing enterocolitis*

***Published online:*** Jan 09, 2024; ***PII*:** S097475591600584

## INTRODUCTION

Fetal growth restriction (FGR) is a multifactorial disorder that often results in increased perinatal morbidity, mortality and poor long term neurological outcomes. Consensus based definition incorporating biometrical as well as functional parameters of placenta for FGR was first put forward in 2016 [1], and subsequently it was adopted by various organizations globally to provide a more robust diagnosis and management of pathological FGR.

Preterm FGR neonates are already undernourished at birth and optimum nutrition is essential for catch-up growth and development. The application of evidence-based perinatal management like obstetric doppler has helped in early detection of FGR and timely intervention leading to significant improvements in perinatal outcomes. A major challenge in postnatal management remains the establishment of early full enteral feeds (FEF) [2]. Early initiation of enteral feeds with slow progression generally is followed as evidence for the safe rapid advancement of

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Received: July 23, 2023; Initial Review: Aug 28, 2023;
Accepted: Dec 13, 2023

feeds (≥ 30 mL/kg/day) among preterm neonates with abnormal doppler is limited. Studies assessing the time to attain FEF, incidence of necrotizing enterocolitis (NEC) and feed intolerance among preterm FGR neonates with and without AREDF have been mostly retrospective studies with inconclusive results [3,4].

Any delay in attainment of FEF leads to a prolonged NICU stay, increased risk of sepsis, need for parenteral nutrition and its associated complications. Feeding guidelines specific to such babies are not available and the World Health Organization (WHO) recommends it as a priority research area [5]. A prospective cohort study was planned to determine the difference in time to attain FEF in FGR preterm neonates with and without AREDF. Secondary objectives were to compare the short-term outcomes including the incidence of NEC and feed intolerance between the two groups and to determine the factors affecting FEF attainment.

## METHODS

A prospective cohort study was conducted in the level III inborn neonatal intensive care unit (NICU), of a tertiary hospital between November 2021 and October 2022 after obtaining approval from the institutional ethics committee. All consecutive preterm FGR neonates delivered at 28 to 36 weeks gestation were included. An umbilical artery doppler ultrasound was performed antenatally for all participants. AREDF was identified in preterm FGR neonates with antenatal umbilical artery doppler showing absent/reversed end-diastolic flow on at least one occasion during pregnancy. FGR neonates with AREDF were taken as the study group and those without AREDF were taken as the comparison group. Those with major congenital anomalies, syndromic babies, complex congenital heart disease, twin-to-twin transfusion or missing doppler reports were excluded. The time to attain enteral feeds of 150 ml/kg/day and tolerating it for the next 3 consecutive days was regarded as "time to attain FEF'. Based on the consensus of neonatologists and results of a previous study [4], delayed attainment of FEF was taken as ≥ 10 days needed to attain FEF.

Sample size was calculated with alpha error 0.05, beta error 0.20, mean difference of FEF attainment time of 2.5 days and standard deviation 6 [3,4] requiring 90 neonates per group**.** Accounting for 10% attrition, a sample size of 100 each of preterm FGR with and without AREDF was needed.

Small for gestational age (SGA) is defined as an estimated fetal weight or birth weight below the 10th percentile for gestational age. Serial monitoring of fetus at risk for FGR was done to identify delayed intrauterine growth velocity. Diagnosis of FGR was based on a combination of measures of fetal size percentile and Doppler abnormalities [7] which was confirmed postnatally by using Fenton's revised growth charts. Our institution was following 'integrated approach to fetal growth restriction' for the timing of delivery of FGR [8]. All eligible neonates were enrolled at the time of admission to the NICU. Enteral feeds were started using 10 mL/kg/day of expressed breast milk (EBM) on day one if there were no contraindications to initiate feeds like signs of intestinal obstruction/hemodynamic instability, requiring inotropes. This was followed by slow advancement of feeds with a daily increase of 20 mL/kg/day. Breast milk was the milk of choice for feeding and if unavailable, formula feed was used. Feeding strategies were modified by the neonatologist whenever there was evidence of feed intolerance or NEC as per the standard protocol followed in the unit. NEC was diagnosed as per Modified Bells staging. Feed intolerance was defined as distended or tender abdomen, or an increase in the abdominal girth of > 2cm in 24 hour, prefeed aspirate > 50% of feed volume, hemorrhagic or bilious aspirate, >1 vomitus with yellow or green color or altered blood for which feed was discontinued for ≥ 12hrs at least for one day, or if the feeds were reduced or not increased for at least one-day duration. Blood culture positive cases were treated as sepsis. Probiotic supplements (ProGG sachet, 0.5 g, *Lactobacillus rhamnosus* 5 billion cells, half sachet twice daily) were administered dissolved in expressed breast milk, at the time of initiation of feeds for all babies <32 weeks and continued till attainment of FEF. Breast milk fortification was done if baby was not gaining weight despite a feed volume of 130-150 mL/kg/day of breast milk for 3 consecutive days. Babies were shifted to the ward once vitals were stable, without oxygen support, on full enteral feeds, weighing atleast 1.2 kg with steady weight gain and mother was confident in taking care of baby.

*Statistical analysis:* Comparison was performed by using SPSS v.26 for Windows and EpiInfo 7.2.5.0. Qualitative variables were summarized using frequency and percentages. Quantitative variables were summarized as mean (SD) or median (IQR) depending on the normality of the data. Univariate analysis was done with the t-test/ Mann-Whitney U test for continuous variables. Chi-square or Fisher's exact test was used for the association of categorical variables with delayed FEF; the strength of association was calculated with relative risk (RR) and its 95% CI. Extended Mantel-Haenzel Chi-square test was used to analyze the linear trend of time to full feeds among preterm FGR without AREDF, AEDF and REDF. Multivariable logistic regression was performed to determine factors for delayed attainment of FEF and to

adjust for potential confounders. $P < 0.05$ was considered statistically significant.

## RESULTS

A total of 201 preterm FGR neonates were included in the study. Participant selection, follow-up and outcome are depicted in **Fig. 1**. Baseline characteristics of the study participants are shown in **Table I** and short-term outcomes in **Table II**.

Analysis of the trend between worsening doppler status and delayed full feed attainment showed a significant linear trend with $P = 0.00015$. Univariate analysis showed AREDF, lower birth weight, lower gestational age, lower platelet count at birth, sepsis, antenatal steroids antenatal magnesium sulphate, hypoglycemia and hemodynamically significant patent ductus arteriosus (hs-PDA) were significancly associated with delayed FEF establishment as shown in **Table III**. Univariate analysis of delayed attainment of FEF and birth weight showed a significantly lower birth weight [mean difference (95% CI) 0.14 (0.08 - 0.3)] among those with delayed FEF attainment ($P < 0.001$). Mann-Whitney U test revealed significantly lower gestational age and lower platelet count at birth were associated with delayed FEF attainment with $P < 0.001$ and $P = 0.008$, respectively. The binary logistic regression for delayed attainment of FEF performed by ENTER method showed AREDF, lower gestational age and thrombocytopenia at birth as significant independent predictors of delayed FEF attainment among preterm FGR neonates as shown in **Table IV**. **Fig. 2** depicts the attainment of feeds in both groups as a function of time. NEC accounted for 40% deaths in the AREDF group while there were no deaths attributed to NEC in the non AREDF group.

## DISCUSSION

Preterm neonates with AREDF were slower to attain FEF with a median (IQR) time to FEF attainment of 12 (8, 16.5) days. Another study reported a significant difference between two groups with median (IQR) of 8 (6, 10) days among neonates with and without AREDF [9]. A study reported mean FEF attainment of 17.7 days [3] but the mean day of feed initiation was 4.1 days. We observed a difference in FEF attainment of 4 days between neonates with and without AREDF, similar to a previous study [3]. Another study reported the median (IQR) time to attain FEF of 9 (8,12) days among REDF neonates [4]. Varying study designs, diagnostic criteria, and study populations make it difficult to compare the outcomes [4,10,11]. A retrospective cohort study [3], reported that delayed FEF attainment is not associated with AREDF. The present study is a prospective cohort study and used a standardized feeding protocol and diagnostic criteria for feed intolerance. Also, an objective primary outcome (time to attain FEF) was used instead of subjective outcomes like incidence of feed intolerance or NEC to avoid biased results. Prolongation of feed establishment is due to a significantly increased incidence of feed intolerance in this study. Those with extreme prolongation had either NEC or sepsis, which are other factors that prolong FEF attainment.

Both NEC and sepsis showed an increasing trend among neonates with AREDF which was similar to previous studies [9-11] but decreased incidence is reported by another study [12]. There were four cases of stage 3 NEC and three of them were in the AREDF group. Most of

**Table I Baseline Characteristics of Fetal Growth Restricted Neonates**

| *Characteristics* | *AREDF (n=100)* | *No AREDF (n=101)* | *P value* |
|---|---|---|---|
| Maternal age (y) | 29 (25, 33) | 27 (23.5, 30) | 0.025 |
| Primiparity[a] | 34 (34) | 50 (49.5) | 0.026 |
| Hypertension[a] | 72 (72) | 39 (38.6) | < 0.001 |
| Diabetes mellitus[a] | 33 (33) | 22 (21.7) | 0.074 |
| Infection[a] | 18 (18) | 8 (7.9) | 0.033 |
| Antenatal steroids[a] | 76 (76) | 54 (53.4) | 0.001 |
| Antenatal magnesium sulphate[a] | 62 (62) | 42 (41.5) | 0.004 |
| Birth weight (g)[b] | 1070 (220) | 1210 (220) | < 0.001 |
| *Birth weight (g)[a]* | | | |
| 500-750 g | 7 (7) | 4 (3.9) | < 0.001 |
| 751-1000 g | 48 (48) | 31 (30.7) | |
| 1001-1250 g | 28 (28) | 26 (25.7) | |
| 1251-1500 g | 15 (15) | 34 (33.7) | |
| 1501-1750 g | 2 (2) | 3 (2.9) | |
| >1750 g | 0 (0) | 3 (2.9) | |
| Gestational age (wk) | 32 (30, 33) | 33 (30, 34) | 0.025 |
| Gestational age[a] | | | |
| 28-31 wk | 48 (48) | 35 (34.6) | 0.033 |
| 32-33 wk | 35 (35) | 30 (29.8) | |
| 34-36 wk | 17 (17) | 36 (35.6) | |
| Male gender[a] | 57 (57) | 40 (39.6) | 0.014 |
| Cesarean section[a] | 99 (99) | 81 (80.1) | < 0.001 |
| Resuscitation at birth[a] | 22 (22) | 20 (19.8) | 0.702 |
| Apgar score at 5 minutes | 9 (8, 9) | 9 (8, 9) | 0.664 |
| Hemoglobin at birth (g/dL) | 17.6 (16, 18.9) | 17.9 (15.8, 19) | 0.839 |
| Platelet count at birth (x $10^9$/L) | 136 (80, 170) | 159 (120, 200) | 0.001 |

*Values are presented as median (IQR), [a]n (%) or [b]mean (SD)*

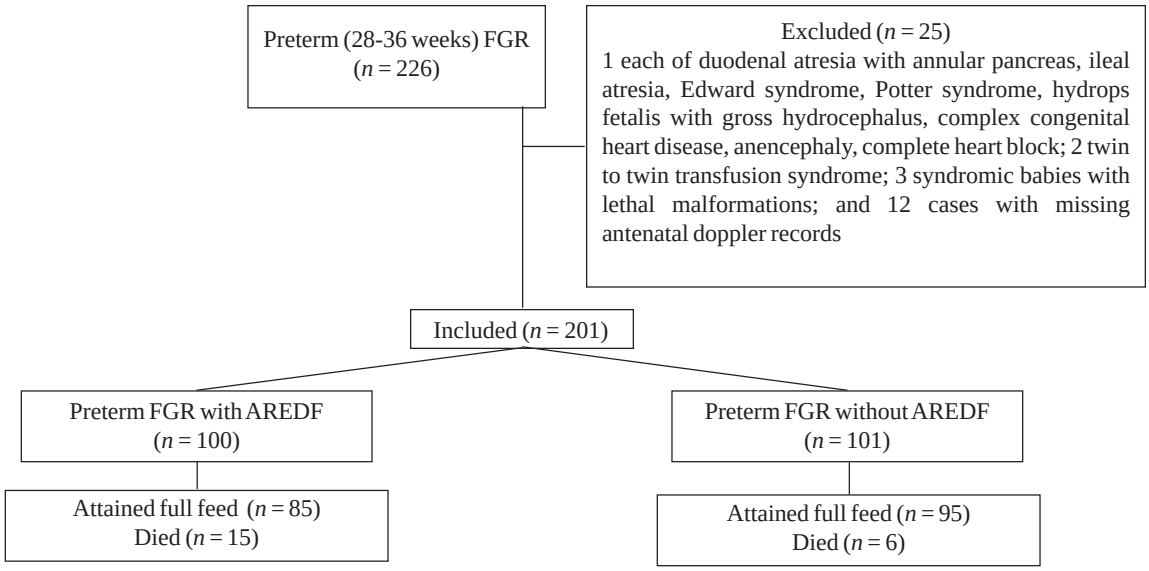


**Fig. 1** Flow chart of participants in the study

**Table II Short Term Outcomes of Fetal Growth Restricted Neonates With and Without Absent/ Reversed End-diastolic Flow**

| | *AREDF (n =100)* | *No AREDF (n =101)* | *RR (95% CI)* | *P value* |
|---|---|---|---|---|
| Time to full feeds (d) | 12 (8, 16.5) | 8 (5, 10) | - | < 0.001 |
| Feed intolerance[a] | 60 (60) | 40 (39.6) | 1.51 (1.13 - 2.02) | 0.004 |
| NEC | 18 (18) | 11 (10.8) | 1.08 (0.96 - 1.2) | 0.160 |
| Mortality, *n* (%) | 15 (15) | 6 (5.9) | 2.5 (1.02 - 6.2) | 0.036 |
| Sepsis[a] | 10 (10%) | 5 (5%) | 2.02 (0.7 - 5.7) | 0.173 |
| Time to regain birth weight (d) | 15 (11.5, 19) | 13 (9, 17.5) | - | 0.035 |
| Duration of hospital stay (d) | 33 (23, 49) | 20 (15, 34.5) | - | < 0.001 |
| Parenteral nutrition (d) | 10 (7, 15) | 7 (4, 9) | - | < 0.001 |
| Duration of ICU stay (d) | 13.5 (7, 21.5) | 8 (5, 14) | - | < 0.001 |
| Weight gain till discharge (g/kg/day) | 8.5 (6, 11.2) | 7.38 (2.9, 11.7) | - | 0.215 |
| Hypoglycemia[a] | 32 (32) | 15 (14.8) | 2.15 (1.2-3.7) | 0.004 |
| HIE[a,b] | 10 (10) | 2 (1.9) | 5.05 (1.13-22) | 0.016 |
| RDS requiring surfactant[a] | 13 (13) | 21 (20.7) | 0.62 (0.3-1.17) | 0.141 |
| Duration of oxygen (d) | 4.5 (2, 8) | 3 (1, 5) | - | < 0.001 |
| Mechanical ventilation[a] | 36 (36) | 26 (12.9) | 1.39 (0.9-2.1) | 0.115 |
| hs-PDA[a] | 12 (12) | 8 (7.9) | 1.04 (0.9-1.1) | 0.334 |
| Hypothyroidism[a,c] | 8 (8) | 1 (0.9) | 8.08 (1.02-63) | 0.016 |
| BPD[a] | 3 (3) | 2 (1.9) | 1.5 (0.25-8.8) | 0.643 |
| ROP requiring treatment [a] | 4 (4) | 1 (0.9) | 4.04 (0.46-35) | 0.212 |
| Inotrope in first 5 days[a] | 9 (9) | 6 (5.9) | 1.5 (0.56-4) | 0.409 |
| Cholestasis[a] | 7 (7) | 0 | - | 0.007 |
| Metabolic bone disease [a,d] | 11 (11) | 5 (4.9) | 1.06 (0.9-1.15) | 0.113 |
| IVH grade 3&4[a] | 4 (4) | 0 | - | 0.059 |

*Values expressed as median (IQR) or [a]n (%); [b]NICHD Neonatal Research Network Study Criteria; [c]Recommendations of the Indian Society for Pediatric and Adolescent Endocrinology (2018); [d]Serum alkaline phosphatase > 800 IU/L or serum phosphorous <4 mg/dL, BPD Bronchopulmonary dysplasia, HIE Hypoxic ischemic encephalopathy, hs-PDA Hemodynamically significant patent ductus arteriosus, IVH Intraventricular hemorrhage; RDS Respiratory distress syndrome, NEC Necrotizing enterocolitis, ROP Retinopathy of prematurity*

**Table III Predictors for Delayed Attainment of Full Feeds**

| | *Delayed FEF (n = 102, 56.6%)* | *RR (95% CI)* | *P value* |
|---|---|---|---|
| AREDF | 62 (72.9%) | 1.73 (1.32 - 2.26) | <0.001 |
| Primiparity | 43 (57.3%) | 1.02 (0.7 - 1.3) | 0.879 |
| PIH | 59 (61.5%) | 1.2 (0.9 - 1.56) | 0.165 |
| Maternal infection | 14 (58.3%) | 1.04 (0.63 - 1.73) | 0.860 |
| Incomplete course of AS | 30 (44.8%) | 0.65 (0.47 - 0.91) | 0.013 |
| Antenatal magnesium sulphate | 57 (64.8%) | 1.45 (1.02 - 2.05) | 0.032 |
| Male | 52 (61.9%) | 1.25 (0.89 - 1.77) | 0.185 |
| Feed intolerance | 50 (56.8%) | 1.01 (0.4 - 1.4) | 0.410 |
| Necrotizing enterocolitis | 14 (58.3%) | 1.41 (0.8 - 2.3) | 0.110 |
| Sepsis | 14 (100%) | - | <0.001 |
| Hypoglycemia | 28 (75.7%) | 1.9 (1.09 - 3.5) | 0.009 |
| Hypoxic ischemic encephalopathy | 5 (71.4%) | 1.53 (0.47 - 5.02) | 0.700 |
| Mechanical ventilation | 30 (68.2%) | 1.47 (0.92 - 2.36) | 0.076 |
| hs-PDA | 11 (91.7%) | 5.5 (0.8 - 36) | 0.011 |
| Inotropic support in initial 5d | 6 (66.7%) | 1.3 (0.5 - 3.3) | 0.734 |
| Hypothyroid | 7 (87.5%) | 3.5 (0.5 - 22) | 0.072 |
| IVH grade 3 & 4 | 3 (75%) | 1.45 (0.3 - 9.6) | 0.634 |
| BM + Formula | 4 (57.1%) | 1.01 (0.4 - 2.42) | 1.000 |

*AS antenatal steroid, FEF Full enteral feeds, hs-PDA Hemodynamically significant patent ductus arteriosus, IVH Intraventricular hemorrhage, BM Breast milk*

the deaths in AREDF group were due to NEC (40%) and there were no deaths due to NEC in the non AREDF group. Even though more neonates in the AREDF group received antenatal steroids, they had a higher incidence of NEC. This also indirectly shows that there is an increased risk of NEC among AREDF neonates. In this study more neonates in the AREDF group received antenatal magnesium sulphate compared to non AREDF group. The effect of antenatal magnesium sulphate on the incidence of NEC is controversial. There are reports of the protective effect of antenatal magnesium sulphate on intestinal morbidities requiring surgery in preterm infants; but one study reported antenatal magnesium sulphate is associated with death and severe NEC among extreme preterm neonates [13].

The incidence of sepsis is not significantly high in this study unlike some other studies [9,10]. Among AREDF neonates, 10% had sepsis and the reported incidence has ranged from 10-30% [9,14]. Neonates with AREDF are at increased risk of sepsis due to prolonged NICU stay for parenteral nutrition and other comorbidities. Also, fetal growth restriction affects the development and function of the immune system in neonates.

There was an increased risk of mortality among neonates with AREDF as reported before [9,12,14] and most of them are due to gastrointestinal tract complications like NEC. Among AREDF 6 (40%) deaths were attributed to NEC. An all-cause mortality of 24% is reported from a study in Ethiopia [14].

Birth weight regain day, hospital stay and NICU stay were prolonged for AREDF neonates. A higher incidence of hypoglycemia was seen among AREDF in this study compared to non-AREDF [9] and FGR is a known risk factor for hypoglycemia [15]. Increased incidence of neonatal cholestasis as a complication of prolonged parenteral nutrition was seen among 7 neonates with AREDF, but none among non-AREDF had it. One study reported parenteral nutrition associated cholestasis is earlier, prolonged and severe among FGR [16]. Metabolic bone disease, another complication of prolonged parenteral nutrition, showed an increasing trend among neonates with AREDF. Prolonged NICU stay [10] and hospital stay were seen in AREDF group similar to previous studies [3,9].

AREDF, gestational age and thrombocytopenia at birth remained as significant predictors of delayed full feed attainment [6,17] among preterm FGR neonates after adjusting for gender, inotrope use in first 5 days, hypoglycemia, formula feed, hypothyroidism, antenatal

**Table IV Predictors for Delayed Feed Attainment Determined Using Multivariable Logistic Regression**

| | *β* | *S.E* | *aOR (95% CI)* | *P value* |
|---|---|---|---|---|
| AREDF | 0.904 | 0.358 | 2.469 (1.22 - 4.98) | 0.012 |
| Gestational age | -0.322 | 0.108 | 0.725 (0.58 - 0.89) | 0.003 |
| Thrombocytopenia | 0.979 | 0.359 | 2.663 (1.31 - 5.38) | 0.006 |
| hs PDA | 1.729 | 1.128 | 5.632 (0.61 - 51.4) | 0.126 |
| Maternal magnesium sulphate | -0.289 | 0.398 | 0.749 (0.34 - 1.63) | 0.468 |
| Antenatal steroids | -0.694 | 0.371 | 0.499 (0.24 - 1.03) | 0.061 |
| Hypoglycemia | 0.719 | 0.481 | 2.053 (0.8-5.269) | 0.135 |

*AREDF Absent/reversed end-diastolic flow, aOR Adjusted odds ratio, SE Standard error*

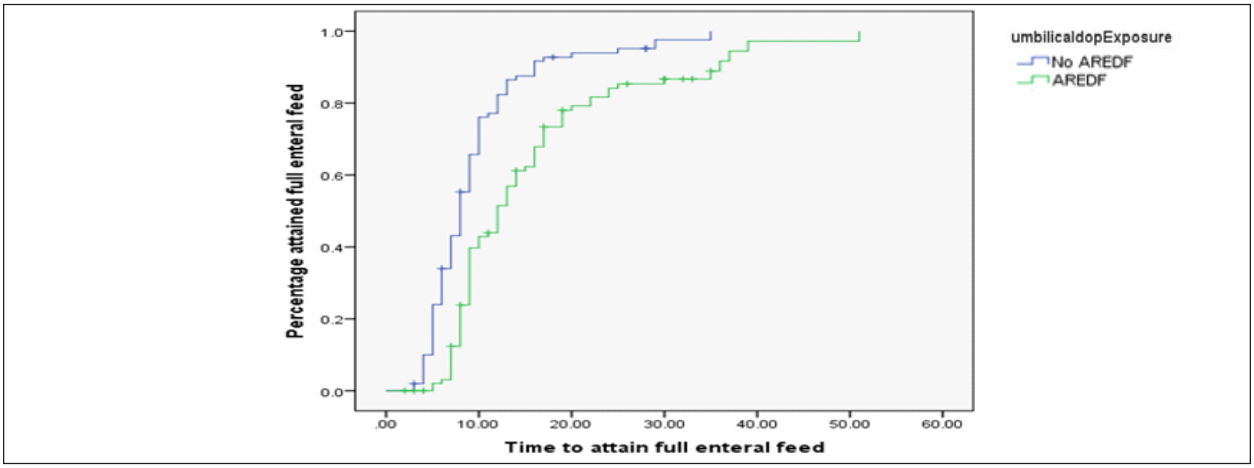


**Fig. 2** Kaplan-Meier curve showing time to attain FEF among FGR preterm with and without AREDF

magnesium sulphate/steroids and hs-PDA. Thrombocytopenia occurring in the first 72 hours of life is usually secondary to placental insufficiency and caused by reduced platelet production.

Strength of the study includes its prospective design and a reasonably larger cohort of neonates with AREDF from a level III NICU of a single tertiary care center. Standard and updated operational definitions for diagnostic criteria and standardized protocol for management were used. Appropriate inclusion and exclusion criteria were used to reduce selection bias. A good follow-up enabled reducing bias due to non-response or attrition. Unlike previous studies, an objective primary outcome was selected to avoid measurement bias instead of subjective outcomes like feed intolerance or NEC. This study is limited by the absence of data on the middle cerebral artery and post-natal splanchnic flow doppler indices to evaluate the effect of brain sparing on the tolerance of feeds.

Preterm FGR neonates with AREDF are slower to attain full enteral feed. Cautious enteral feed initiation and advancement are recommended with careful monitoring.

*Ethics clearance*: HEC NO O9/05/2021/MCT, dated Nov 12, 2021.

*Contributors*: VA: Conception, design, data collection, writing the manuscript, analysis and interpretation of data, drafting the work; GS, PS, SK: Design, analysis and interpretation of data, drafting the work; KR: Design, analysis and interpretation of data, drafting the work. All authors approved the final manuscript.

*Funding*: None. *Competing interest*: None stated.

## REFERENCES

1. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. Ultrasound Obstet Gynecol. 2016;48:333-9.
2. Leaf A, Dorling J, Kempley S, et al. Abnormal Doppler Enteral Prescription Trial Collaborative Group. Early or delayed enteral feeding for preterm growth-restricted infants: a randomized trial. Pediatrics. 2012;129: e1260-8.
3. Ahamed MF, Dar P, Vega M, Kim M, Gao Q, Havranek T.

**WHAT THIS STUDY ADDS?**

- Preterm fetal growth restricted neonates with absent/reversed end-diastolic flow in umbilical artery are slower to attain full enteral feeds and have more feed intolerance.
- Absent/reversed end diastolic flow in umbilical artery, lower gestational age, sepsis and thrombocytopenia at birth are significant predictors of delayed attainment of full feeds in preterm fetal growth restricted neonates.

Early feeding tolerance in small for gestational age infants with normal versus abnormal antenatal Doppler characteristics. J Neonatal Perinatal Med. 2017;10:43-8.
4. Aradhya AS, Mukhopadhyay K, Saini SS, Sundaram V, Dutta S, Kumar P. Feed intolerance in preterm neonates with antenatal reverse end diastolic flow (REDF) in umbilical artery: a retrospective cohort study. J Matern Fetal Neonatal Med. 2020;33:1846-52.
5. WHO Recommendations on Interventions to Improve Preterm Birth Outcomes. Geneva: World Health Organization; 2015. Accessed on September 21, 2022. Available from: *http://www.ncbi.nlm.nih.gov/books/NBK321160/*
6. Patwardhan G, Soni A, Rachwani N, Kadam S, Patole S, Pandit A. Factors associated with time to full feeds in preterm very low birth weight infants. J Trop Pediatr. 2018; 64:495-500.
7. Melamed N, Baschat A, Yinon Y, et al. FIGO (International Federation of Gynecology and Obstetrics) initiative on fetal growth: Best practice advice for screening, diagnosis, and management of fetal growth restriction. Int J Gynaecol Obstet. 2021; 152:3-57.
8. Figueras F, Gratacos E. An integrated approach to fetal growth restriction. Best Pract Res Clin Obstet Gynaecol. 2017;38:48-58
9. Lakshmi CV, Pramod G, Geeta K, et al. Outcome of very low birth weight infants with abnormal antenatal doppler flow patterns: a prospective cohort study. Indian Pediatr. 2013;50:847-52.
10. Morsing E, Brodszki J, Thuring A, Maršál K. Infant outcome after active management of early-onset fetal growth restriction with absent or reversed umbilical artery blood flow. Ultrasound Obstet Gynecol. 2021;57:931-41.
11. Gairabekova D, van Rosmalen J, Duvekot JJ. Outcome of early-onset fetal growth restriction with or without abnormal umbilical artery Doppler flow. Acta Obstet Gynecol Scand. 2021;100:1430-8.
12. Isalm ZS, Dileep D, Munim S. Prognostic value of obstetric Doppler ultrasound in fetuses with fetal growth restriction: an observational study in a tertiary care hospital. J Matern Fetal Neonatal Med. 2015;28:12-5.
13. Kamyar M, Clark EA, Yoder BA, Varner MW, Manuck TA. Antenatal magnesium sulfate, necrotizing enterocolitis, and death among neonates < 28 weeks gestation. AJP Rep. 2016;6:e148-54.
14. Tolu LB, Ararso R, Abdulkadir A, Feyissa GT, Worku Y. Perinatal outcome of growth restricted fetuses with abnormal umbilical artery doppler waveforms compared to growth restricted fetuses with normal umbilical artery doppler waveforms at a tertiary referral hospital in urban Ethiopia. PLoS One. 2020;15:e0234810.
15. Sharma A, Davis A, Shekhawat PS. Hypoglycemia in the preterm neonate: etiopathogenesis, diagnosis, management and long-term outcomes. Transl Pediatr. 2017;6:335-48.
16. Lee SM, Namgung R, Park MS, et al. Parenteral nutrition associated cholestasis is earlier, more prolonged and severe in small for gestational age compared with appropriate for gestational age very low birth weight infants. Yonsei Med J. 2013;54:839-44.
17. Corvaglia L, Fantini MP, Aceti A, et al. Emilia Romagna Perinatal Network. Predictors of full enteral feeding achievement in very low birth weight infants. PLoS One. 2014;9:e92235.

# Continuous Antibiotic Prophylaxis in Infants with Grade III, IV, or V Vesicoureteral Reflux

*Source Citation*: Morello W, Baskin E, Jankauskiene A, et al; PREDICT Study Group. Antibiotic prophylaxis in infants with grade III, IV, or V vesicoureteral reflux. N Engl J Med. 2023;389:987-97.


## SUMMARY

In this multicentric, open label, randomized trial performed across 39 European centers, the investigators randomly assigned infants 1 to 5 months of age with grade III, IV, or V vesicoureteral reflux (VUR) and no previous episode of urinary tract infection (UTI) to receive continuous antibiotic prophylaxis (prophylaxis group) or no treatment (untreated group) for 24 months. The primary outcome was the occurrence of the first UTI during the trial period. Secondary outcomes included new kidney scarring and the estimated glomerular filtration rate (GFR) at 24 months. A total of 292 participants underwent randomization (146 per group). Approximately 75% of the participants were male; the median age was 3 months, and 235 participants (80.5%) had grade IV or V VUR. In the intention-to-treat analysis, a first UTI occurred in 31 participants (21.2%) in the prophylaxis group and in 52 participants (35.6%) in the untreated group [hazard ratio 0.55; 95% confidence interval (CI) 0.35 to 0.86; $P = 0.008$]; the number needed to treat for 2 years to prevent one UTI was 7 children (95% CI 4 to 29). Among untreated participants, 64.4% had no UTI during the trial. Pseudomonas species, other non–*Escherichia coli* organisms, and antibiotic resistance were more common in UTI isolates obtained from participants in the prophylaxis group than in isolates obtained from those in the untreated group. The investigators concluded that in infants with grade III, IV, or V VUR and no previous UTIs, continuous antibiotic prophylaxis provided a small but significant benefit in preventing a first UTI despite an increased occurrence of non–*E.coli* organisms and antibiotic resistance.


## COMMENTARIES

### Evidence-based Medicine Viewpoint

This randomized controlled trial (RCT) examined the efficacy and safety of a long-term antimicrobial prophylaxis strategy among infants with high(er) grades of vesicoureteric reflux (VUR) [1]. The elements of the research question are as follows. *Population* (P): 1-5-month-old infants having VUR grades III, IV, or V (confirmed by either voiding cystourethrography or ultrasonography), with no previous episode of symptomatic urinary tract infection (UTI); *Intervention* (I): Long-term antimicrobial administration; *Comparison* (I): No long-term antimicrobial administration; *Outcomes* (O): Symptomatic UTI episodes, time to first UTI episode, new renal scarring, glomerular filtration rate (GFR), UTI organisms isolated, antimicrobial resistance pattern amongst isolated organisms, and serious adverse events; *Time-frame* of the outcome measurements (T): Two years, although the trial protocol mentioned that the infants would be followed-up for five years [2,3]; and *Study setting* (S): Multiple European institutions managing children with VUR.

In addition to the eligibility criteria described above, infants had to have gestation > 35 weeks, and GFR > 15 mL/min/1.73$^2$ surface area. Infants were excluded if they had episode(s) of previous UTI, or other conditions predisposing to VUR (and/or UTI) *viz*. neurogenic bladder, posterior urethral valves, or other obstruction at the uretero-pelvic or uretero-vesical junctions. The trial protocol additionally mentioned that the receipt of (unspecified) "experimental drugs" during the month prior to enrolment was an exclusion criterion [2,3].

The intervention was two continuous years of once-daily oral antibiotic administration. Study site investigators could choose the antimicrobial (based on the local patterns of sensitivity of *E. coli*) from one of the four options *viz*. nitrofurantoin, coamoxiclav, cefixime, or cotrimoxazole. There were criteria laid down for changing the chosen antimicrobial. Infants in the comparison arm did not receive the antimicrobial.

Follow-up visits were scheduled at 4 monthly intervals during the first year after enrolment, and 6 monthly intervals during the second year. These visits were used to confirm adherence to the prescribed regimen by reviewing diaries completed by families. The occurrence of symptomatic UTI or adverse events prompted additional visits.

*Critical appraisal*: The methods for generating the allocation sequence, and concealment of allocation, were not described in the publication [1]. As the online supplementary files and trial protocol were inaccessible, the relevant trial registries [2,3] were examined, but the information was unavailable there also. However, individual infants were randomized with stratification based on the presence of renal parenchymal damage. The randomization process appears to have been effective as there were no inter-group baseline differences in the gender distribution, age at enrolment, proportion with abnormal antenatal ultrasonography, distribution of VUR grade, prevalence of bilateral VUR, and the distribution of DMSA as well as ultrasonography scan abnormalities. In terms of renal function, blood pressure and GFR were comparable. There were also no statistically significant differences in the proportion of infants who had received antibiotic prophylaxis prior to enrolment.

The participating infants and caregivers were not blinded to the allocation. The investigators suggested that the primary outcome, did not necessitate blinding. However, this may not be true, because the outcome was 'symptomatic' UTI (and not any UTI). The trigger for parents to suspect UTI and approach the healthcare system was the presence of fever >38.0° C, unwell appearance, irritability, or loss of appetite. Therefore, a scenario can be envisaged wherein parents of infants receiving antimicrobial prophylaxis, were more confident/secure in not reporting the appearance of these symptoms, compared to those not receiving prophylaxis. In this situation, UTI could be missed, especially if infants recovered uneventfully. Therefore, ideally blinding should have been attempted in this trial.

The investigators did not report adherence to the prescribed antibiotic prophylaxis regimen. More important, they did not report whether there were deviations from the intended interventions. Thus, it is unclear whether all infants continued to receive whatever was allocated at randomization (i.e. antimicrobial or no antimicrobial). Given that almost 50% infants had taken antibiotic prophylaxis before enrolment into the trial (although the duration and interval were not specified), it is likely that infants in the comparison arm could have taken antibiotics independent of the trial (assuming that this is feasible in the trial countries). However, had this happened, we would expect to observe less difference in the outcome of symptomatic UTI between the two trial arms. This suggests that the observed reduction in UTI is a robust result.

Although a CONSORT diagram was not published [1], the attrition rate was reportedly low and comparable between the trial arms. Further, intention-to-treat analysis was undertaken. However, the dropout rates for all the outcomes were not published.

The methods for measuring the outcomes were appropriate, and there was no inter-group differences in this. All the outcomes reported were clinically relevant and most were also patient-centric. However, it is unclear why only serious adverse events were recorded, rather than all potential adverse events. Two years' oral antibiotic consumption (albeit in lower than therapeutic doses) is expected to be associated with a wide range of known side effects besides other events (difficult to classify as caused by antibiotics). However, this important information was not recorded.

The authors did not comment about selective outcome reporting. However, a glance at the trial registries [2,3] identified several outcomes that were not reported [1]. For example, hypertension and proteinuria were to be measured and reported at each of the scheduled follow-up visits. Similarly, gut microbiome evaluation was planned not only at these scheduled visits, but also annually until five years after enrolment. Even the secondary outcomes such as serum creatinine, and others like serum cystatin were to be measured annually until five years after enrolment. Similarly, body mass index was to be reported at the end of 2 and 5 years. More importantly, renal scarring was to be evaluated at the end of five years, and not two years alone. It is possible that some of these observations may appear in other publications.

It is interesting that while the publication [1] suggested that antimicrobial prophylaxis was the intervention, and 'no prophylaxis' was the comparison, the trial registries [2,3] described it the other way around; no antimicrobial prophylaxis was the experimental arm, and antimicrobial prophylaxis was the active comparator. Although this switch does not impact the interpretation of the data, it suggests that prior to the trial, antimicrobial prophylaxis use was not uncommon in the study settings, and the effort was to assess whether its omission would make a difference. However, it can be argued that in such a situation, a noninferiority trial design would be appropriate. This would have implications on the sample size calculation and data interpretation.

The trial had several methodological refinements. The main outcome, 'symptomatic UTI' was clearly defined on the basis of a combination of clinical symptoms, urinalysis findings, and quantitative bacterial culture with specimen-specific cut-offs. This fosters confidence of a low likelihood of misclassifying symptomatic UTI. However, it appears that only about 80% of those diagnosed with UTI had fever. This raises two important issues. First, there

were no UTI-specific symptoms (for want of a better term) such as crying during micturition, increased frequency, etc. Second, the symptoms were mostly non-specific for UTI. In other words, the triggers for urinalysis and culture could have missed some episodes of UTI. As there was no recording of asymptomatic UTI through serial cultures, the overall prevalence of UTI in the two groups is unclear.

The pre-trial sample size calculation necessitated 218 infants in each arm to detect a 20% difference in symptomatic UTI with 90% power. A pre-planned analysis when approximately half the sample size was enrolled, suggested the need to continue the trial (as there were no detectable benefits or harms warranting early cessation of the trial). At this point (inexplicably), power of 80% was deemed sufficient and the sample size was re-calculated, slashing it to half of the original. The stated justification of "steady accrual of 50 participants per year" is unclear. Of course, sample size calculation was undertaken only for the primary outcome, and not all the reported outcomes.

Renal scarring was identified by the observations on DMSA scans, and the abnormalities consistent with scarring were clearly defined. The DMSA scans were secured in a central database for blinded re-reporting. There was also a process for handling disagreements between the reporting of individual observers. These refinements enhance confidence in the reporting. However, this elaborate process was not standard procedure and only those images uploaded to the database were re-reported.

The investigators reported that 867 infants were screened to finally enrol the required sample size. However, the criteria for screening potentially eligible infants were not described. This information is especially important because the inclusion criteria were infants with confirmed VUR (III, IV, or V) but without prior UTI. Further, several conditions resulting in high(er) grade VUR were excluded. As the median age of enrolment was about 3 months, it appears that antenatally diagnosed urinary tract anomalies and/or early postnatal identification of this, would have been necessary. This perception is supported by the facts that over half of the screened infants already had renal scan abnormalities, and only one-third of the infants had experienced UTI. Perhaps this explains how/why over half the enrolled participants had already received antibiotic prophylaxis by the age of enrolment. This makes the enrolled cohort a carefully selected subgroup of infants with VUR, thereby limiting generalizability.

How to interpret the results of this trial? On one hand, there was an impressive relative decline in the frequency of symptomatic UTI with long-term antimicrobial prophylaxis; on the other hand, there was no impact on renal scarring, or renal function (serum creatinine, or GFR). This raises several troubling questions for physicians managing children with VUR. For example, could renal scarring be independent of UTI (at least symptomatic UTI, as this trial suggests)? If so, are previous data focusing on UTI prevalence meaningful? Should (harder to document) anatomic and/or functional renal outcomes having long-term consequences, be given precedence over the (easier to measure), shorter-term consequences of UTI episodes? Could there be a subgroup of patients wherein there may be a relationship between UTI episodes and renal scarring, within this and/or other trials? Unfortunately, there are no ready answers to these vexing questions. Since the time interval to the first episode of symptomatic UTI was not reduced with antibiotic prophylaxis, and the proportion with UTI requiring hospitalization was comparable (suggesting similar severity of episodes), the statistically significant, clinically meaningful reduction in symptomatic UTI, suggests that there could be a subgroup with better response.

Similarly, how to explain that prophylaxis was associated with fewer infants having $\leq 2$ episodes of symptomatic UTI, but more infants having $\geq 3$ episodes? Is this an artefactual finding? Or could the local microbiome be altered in such a manner that a few children were predisposed to have greater episodes of UTI? Again, in the absence of data, it is difficult to clarify these issues.

Third, it is interesting that only about one-third of infants developed symptomatic UTI over two years' follow-up, despite not receiving prophylaxis. This by itself makes a strong case to suggest that antimicrobial prophylaxis may not be required in all such infants, and that the observed reduction in symptomatic UTI is probably driven by a subgroup with better response.

The authors themselves did not focus exclusively on the beneficial effect of antibiotic prophylaxis, but weighed it against the potential harms of this approach [1]. Therefore, they unequivocally stated that their results argue against long-term antimicrobial prophylaxis. Their balanced approach is laudable. However, this evidence-based viewpoint is in divergence with the authors on a couple of subtle, but important points. The trial documented reduction in *symptomatic* (emphasis added) UTI, therefore the authors' statement that "the number needed to treat to prevent one UTI was 7" [1] is incorrect. More accurately, 7 children would need to receive prophylaxis to prevent one *additional* episode of *symptomatic* UTI. The importance of the distinction between symptomatic UTI, and UTI, has been highlighted already.

What is the impact of this study on Indian infants with this condition? First, unless there is meticulous antenatal and/or postnatal screening (with ultrasonography, radionuclide scanning, and cystourethrography), it is very difficult to identify asymptomatic infants with high grades of VUR. Second, VUR is generally detected when episode(s) of UTI are identified, with or without additional risk factors. The results of this trial are not extrapolatable to such infants. Third, continuous antibiotic consumption for two years among infants in our setting, is likely to create more harm than good, both to individual infants and also the community at large. However, the consequences of symptomatic UTI in our setting may be different from that in European countries, making a case for considering long-term antibiotic prophylaxis in some infants. Thankfully, the lack of benefit on most outcomes in this trial, with additional demonstration of harm, tips the scales against antimicrobial prophylaxis.

*Conclusion*: This elaborate RCT among young infants with pre-confirmed renal dysplasia (but no episode of UTI) demonstrated a statistically significant reduction is *symptomatic* (emphasis added) UTI, with two years of continuous oral antibiotic administration. However, there was no effect on the risk of developing new renal scars at the end of the trial period. Further, there were clinically important negative effects of antibiotic prophylaxis, notably the emergence of antimicrobial resistance amongst common organisms, appearance of other than usual organisms in urine cultures, and a three-fold higher probability of multidrug resistant organisms. Some clinically important safety outcomes such as the frequency and severity of all/any adverse events, and the impact on the gut microbiome (and its conse-quences) were not reported. Overall, the findings of this trial argue against the use of antimicrobial prophylaxis among infants conforming to those included in this study.

*Funding*: None; *Competing interests*; None stated.

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## REFERENCES

1. Morello W, Baskin E, Jankauskiene A, et al. Antibiotic prophylaxis in infants with grade III, IV, or V vesicoureteral reflux. N Engl J Med. 2023;389:987-97.
2. No authors listed. Antibiotic prophylaxis and renal damage in congenital abnormalities of the kidney and urinary tract (PREDICT). Accessed on Dec 10, 2023. Available from: *https://clinicaltrials.gov/study/NCT02021006#contacts-and-locations*
3. No authors listed. EU Clinical Trials Register. Accessed on Dec 10, 2023. Available from: *https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-000309-21/DE#P*

## Pediatric Nephrologist's Viewpoint

Primary VUR is often diagnosed following a UTI or on evaluation of antenatal hydronephrosis [1]. Low-dose antibiotic prophylaxis is the commonest strategy employed to prevent UTI in children with VUR [2]. Considering the risk of antimicrobial resistance (AMR) and modest efficacy, most international guidelines recommend its judicious use [3-5].

The role of antibiotic prophylaxis in prevention of UTI in VUR detected on evaluation of antenatal hydronephrosis is unclear. The PREDICT trial assessed the efficacy of antibiotic prophylaxis in infants with high-grade VUR (III, IV and V) prior to developing UTI [6]. Authors in this multicenter, open-label trial used four different antibiotics for prophylaxis over 24 months. There was a significant reduction in risk of symptomatic UTI (35%) on prophylaxis as compared to no therapy (21%) with no difference in efficacy between different antibiotics. However, similar to previous trials [7-9] in children with VUR, this study also failed to show a significant difference in kidney scarring and function over 24 months. Interestingly, new kidney scars developed even in children who did not have UTI which could be likely due to progression of underlying dysplasia. The study also observed higher AMR in prophylaxis group compared to untreated group [6].

This large trial reaffirms modest benefit of antibiotic prophylaxis for preventing UTI in high-grade VUR. Whereas the benefit was found in girls and not boys, the study was not powered for subgroup analysis. While we agree that only two-thirds of children had UTI, similar rates of UTI are observed in VUR detected following UTI [7]. Authors of the PREDICT trial were cautious in their conclusion about the use of antibiotic prophylaxis due to lack of difference in kidney scarring and AMR associated with this intervention [8]. However, similar to previous trials risk of serious adverse events, hospitalization, or requirement of intravenous antibiotic therapy in intervention group was not higher despite higher AMR. In recently updated evidence-based guidelines, authors have provided weak recommendations for its use to prevent UTI in high-grade VUR detected antenatally [3].

A key message for pediatricians from this study is that every child with antenatal hydronephrosis should not to be given antibiotic prophylaxis except those found to have high-grade VUR.

*Funding*: None; *Competing Interests*: None stated.

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## REFERENCES

1. Bortnick EM, Nelson CP. Vesicoureteral reflux: current care trends and future possibilities. Urol Clin North Am. 2023;50: 391-402.
2. Meena J, Hari P. Vesicoureteral reflux and recurrent urinary tract infections. Asian J Pediatric Nephrol.2019;2:61.
3. Hari P, Meena J, Kumar M, et al. Evidence-based clinical practice guideline for management of urinary tract infection and primary vesicoureteric reflux. Pediatr Nephrol. 2023 Oct 28. Epub ahead of print.
4. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. Pediatrics. 2011; 128:595-610.
5. Ammenti A, Alberici I, Brugnara M, et al. Updated Italian recommendations for the diagnosis, treatment and follow-up of the first febrile urinary tract infection in young children. Acta Paediatr. 2020;109:236-47.
6. Morello W, Baskin E, Jankauskiene A, et al. Antibiotic prophylaxis in infants with grade III, IV, or V vesicoureteral reflux. N Engl J Med. 2023;389:987-97.
7. RIVUR Trial Investigators, Hoberman A, Greenfield SP, Mattoo TK, et al. Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med. 2014;370:2367-76.
8. Craig JC, Simpson JM, Williams GJ, et al. Antibiotic prophylaxis and recurrent urinary tract infection in children. N Engl J Med. 2009;361:1748-59.
9. Hari P, Hari S, Sinha A, et al. Antibiotic prophylaxis in the management of vesicoureteric reflux: a randomized double-blind placebo-controlled trial. Pediatr Nephrol. 2015; 30:479-86.

## Pediatrician's Viewpoint

The PREDICT study group's investigation into antibiotic prophylaxis (AP) for infants with high-grade vesicoureteral reflux (VUR) sheds light on critical considerations for pediatricians. In this study continuous AP significantly reduced the risk of the first symptomatic urinary tract infection (UTI) compared to no treatment (hazard ratio 0.55). The study, conducted in 39 European centres, provides valuable insights into the potential benefits and risks of AP in this vulnerable population [1].

The benefits include a noteworthy 45% reduction in the risk of initial UTIs, potentially sparing children the pain and complications associated with these infections. Preservation of kidney function is another positive outcome, emphasizing the potential long-term advantages of prophylaxis. A landmark study, RIVUR trial, evaluated the impact of trimethoprim-sulfamethoxazole prophylaxis in this population. The study concluded that prophylaxis reduced the incidence of UTIs, but the overall clinical significance of this reduction remained a subject of debate [2].

Pediatricians who support AP argue that preventing UTIs in infants with high-grade VUR is crucial for minimizing the risk of renal scarring and long-term complications. Renal scarring can lead to hypertension and renal insufficiency later in life, making the prevention of UTIs a priority in these cases [3-5].

However, the use of AP must be carefully weighed against associated risks. Antibiotic resistance, a significant concern, may arise from overuse and impact future treatment options. Side effects, including diarrhea, nausea, and vomiting, further underscore the need for a balanced approach. Disruption of the gut microbiota, with potential downstream health implications, adds another layer of consideration [1].

Pediatricians are urged to adopt an individualized approach, considering the child's unique circumstances, risk factors, and family preferences. The decision-making process should involve collaborative discussions with parents, emphasizing the need for a nuanced evaluation of the risks and benefits of AP [6]. Various risk factors (family history, gender, laterality, age at presentation, presenting symptoms, VUR grade, duplication, and other voiding dysfunctions), early stratification help in identification of patients with potential risk of renal scarring and urinary tract infections.

The study's findings prompt a reconsideration of current guidelines, advocating for a case-to-case decision-making approach. While the reduction in UTI incidence is notable, a comprehensive evaluation of each child's risk factors is essential. Ongoing research is needed to optimize the duration and type of prophylaxis.

In conclusion, the PREDICT trial contributes valuable insights into the use of continuous antibiotic prophylaxis for infants with VUR and no prior UTIs. Pediatricians are encouraged to carefully balance the modest yet significant benefits against potential risks, fostering a thoughtful and personalized approach to care for this vulnerable population.

*Funding*: None; *Competing Interests*: None stated.

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## REFERENCES


1. Morello W, Baskin E, Jankauskiene A, et al. Antibiotic prophylaxis in infants with grade III, IV, or V vesicoureteral reflux. N Engl J Med. 2023;389:987-97.
2. RIVUR Trial Investigators, Hoberman A, Greenfield SP, Mattoo TK, et al. Antimicrobial prophylaxis for children with vesicoureteral reflux. N Engl J Med. 2014;370:2367-76.
3. Montini G, Rigon L, Zucchetta P, et al. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, non-inferiority trial. Pediatrics 2008; 122:1064-71.
4. Pennesi M, Travan L, Peratoner L, et al. Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. Pediatrics 2008;121: e1489-94.
5. Roussey-Kesler G, Gadjos V, Idres N, et al. Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. J Urol. 2008;179:674-79.
6. Peters CA, Skoog SJ, Arant BS Jr, et al. Summary of the AUA guideline on management of primary vesicoureteral reflux in children. J Urol. 2010;184:1134-44.

RESEARCH LETTER

# Smooth Roads Ahead: Lessons From our Sick Neonate Retrieval Service

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**ABSTRACT**

Strategies for free transfer of sick neonates to hospitals are in place, but reports suggest suboptimal status of the same across the country. Over 7 years, our Sick Neonate Retrieval Service (SNRS) transported 165 neonates, of whom 92.1% survived. Safe, stable transportation mandates the presence of a neonatology-trained doctor and nurse in an equipped ambulance.

**Keywords:** *Ambulance services, Neonatal transport, Newborn*

Clinical status of sick neonates who need referral for advanced care often warrants upgradation of treatment before or during the process of transport. The increased risks associated with interhospital transport of sick neonates can be minimized when the transport is being performed by trained neonatal retrieval teams. The developed world has established systems in place for the retrieval of sick neonates [1].

Free transport facilities for pregnant women and neonates by the National Ambulance Service (NAS), emergency medical training of drivers and attendants have been introduced in various states across India [2]. Clinical practice guidelines with descriptions of elements required for efficient transport of sick neonates are available in India [3]. Individual hospital-based data have also demonstrated that those infants who are accompanied by trained personnel fare better than those who come by self-arranged or unequipped means [4]. However, the literature pertaining to neonatal transport from various parts of the country reports a dismal picture [5]. This retrospective analysis aimed to systematically describe the experience of our hospital over a period of seven years (2016 to mid-2023) with the Sick Neonate Retrieval Services (SNRS) wherein the presence of a neonatology-trained doctor, nurse and patient care assistant in the equipped ambulance is mandated

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*Received: Sep 20, 2023; Initial Review: Sep 20, 2023;*
*Accepted: Jan 12, 2023*

We are a Level IIIB accredited (National Neonatology Forum, India) unit in a tertiary care facility of South Kerala, India. A written protocol is in place for the SNRS. A phone call or email or fax or text message from the referring doctor or family, documents the transport request and helps determine the history and clinical status of the infant. The daily duty-roster includes one doctor and a nurse responsible for a possible SNRS during the shift. The necessary equipment, prearranged in a ready-to-grab bag is cross-checked and the onward journey is made with the siren of the ambulance wailing and beacons flashing. When the team arrives at the pick-up destination, we follow the "stand and play method" where the baby receives treatment and stabilization on scene before transportation to the referral centre rather than "scoop and run". The return journey is pursued at a steady pace to ensure comfort of the team and control over the baby's requirements enroute. Documentation of vitals and interventions during transport are done systematically. We strive to reverse transport when clinical stability is ensured, based on the family's preferences and readiness of the referring doctor.

A sample size of 139 was calculated based on pilot data collected from our unit. We presumed that 90% of neonates who were transported by the SNRS would survive, with a precision of 5% and a type I error of 5%. Complete data was available for 7 years (2016 to mid-2023) from the electronic medical records of our unit.

Since this was a retrospective descriptive study, informed consent was not obtained, however, privacy and confidentiality of all patients is ensured. Data of 165 neonates transported by SNRS was analyzed. Demographic details, pre-referral clinical information, and outcomes are described in **Table I**. Of the 165

**Table I Demographic and Pre-Transport Clinical Characteristics of Retrieved Neonates (*n* = 165)**

| *Characteristic* | *Value* |
|---|---|
| Gestational age (wk)[a] | 37 (33, 38) (Range 25 to 40) |
| Birth weight (g)[a] | 2660 (1880, 3007) (Range 705 to 5100) |
| Male gender[b] | 99 (60) |
| Postnatal age at transport (d)[a] | 2 (0, 9) (Range 0 to 71) |
| *Primary reason for referral*[b] | |
| Respiratory distress | 90 (54.5) |
| Preterm care | 82 (49.7) |
| Very preterm | 39 (23.6) |
| Encephalopathy | 18 (10.9) |
| Shock/ heart disease | 15 (9.1) |
| Major congenital malformations and multiorgan dysfunction | 34 (20.6) |
| *Pre-referral supports already present*[b] | 33 (20) |
| Thermal control and feeds/maintenance fluids alone | 66 (40) |
| Non-invasive respiratory supportIntubation and ventilation | 66 (40) |
| Central venous line | 19 (11.6) |
| Inotrope support | 37 (22.4) |
| Hypoglycemia correction | 19 (11.7) |
| *Catchment area*[b] | |
| Within the city | 40 (24.2) |
| Within district limits | 62 (37.6) |
| Neighboring districts | 31 (18.8) |
| Neighboring states | 21 (12.7) |
| Maldives (overseas) | 11 (6.7) |
| *Therapies commenced at referring hospital by SNRS*[b] | |
| No additional supports | 115 (69.7) |
| Oxygen/ Non-invasive ventilation | 34 (20.6) |
| Hypothermia correction | 28 (16.9) |
| Intubation and ventilation | 16 (9.7) |
| Fluid bolus/ inotrope initiation for shock | 38 (23) |
| *At our unit* | |
| Outcome: Survival till discharge[b] | 152 (92.1) |
| Reverse transport after stabilization[b] | 42 (25.5) |
| Referred to other units for continuation of care[b] | 4 (2.4) |
| Duration of hospital stay (d)[a] | 6 (3, 15) (Range 2 to 97) |
| Central line insertion[b] | 48 (29.5) |
| Inotrope support[b] | 32 (19.4) |
| Hypoglycemia correction intravenous[b] | 17 (6.1) |
| Non-invasive respiratory support[b] | 58 (35.2) |
| Conventional ventilation[b] | 38 (23) |
| High frequency ventilation[b] | 17 (10.3) |
| Inhaled nitric oxide therapy[b] | 10 (6.1) |

*Value expressed as [a]median (IQR) or [b]n (%)*

neonates, 152 (92.1%) survived. It is important to emphasize that SNRS team was required to commence therapies at the referring hospital itself for 50 neonates (30.3%). None of the babies showed clinical deterioration at admission at our unit when compared to the hemodynamic status at the start of travel. Four families requested transport to other centers where they eventually expired. Five of the nine infants who expired in the unit had major congenital malformations; 3 were extreme preterm neonates who were transferred after one week of life in a moribund state; one had an intestinal perforation pre-transport and developed refractory shock. We have conducted four air transports in commercial airlines (Bengaluru and Maldives). The process involved documentation and extensive arrangements including clearance for oxygen cylinders and mechanical suctions to be made in advance.

There exist different models for institutions catering to emergency medical services (EMS) out of hospital. The Franco-German model is physician-led while the Anglo-American one is dependent on trained paramedics [6]. India has schemes based on regional circumstances like the NAS, Emergency Management and Research Institute model, Bihar model, Janani Express Scheme etc. [7]. Audits in 2013-2014, however, show that less than 20% of pregnant women use the NAS in six states [2].

In our study group, no neonate showed signs of deterioration at admission. Reports about neonatal transport from several parts of the country are not reassuring with up to 40% deaths within 24 hours of admission [8,9]. Suboptimal conditions were reported leading to 20% mortality; 76% were hypothermic at admission [10]. Multivariate analyses by Singh et al revealed that the need for immediate cardiorespiratory support on arrival, and absence of medical staff during transfer were significant predictors of mortality [4]. We wish to emphasize by our report that a robust system for retrieval of sick neonates with special emphasis on the mandatory presence of neonatology trained doctors and nurses is not only feasible, but also worthwhile and rational. Number of medical trainee seats for post-graduation in pediatrics and postdoctoral courses in neonatology are increasing across the country. With over 4000 doctors training in these subjects at any point of time, it should be prudent to earmark transport teams with specified duty rotations in every teaching hospital, both government and private. Instead of dealing with unexpected arrival of a crashing neonate to emergency rooms, an appeal needs to go out to all tertiary public and private sectors who have facilities for advanced neonatal care to consider organized retrieval of sick neonates from specific catchment areas. A model for SNRS would depend on closest available tertiary care facility, financial status of the family and distance acceptability, logistics like distance from home, accommodation facilities etc (**Fig. 1**). The design of a multimedia app (not unlike the food delivery apps) would be recommended so that the

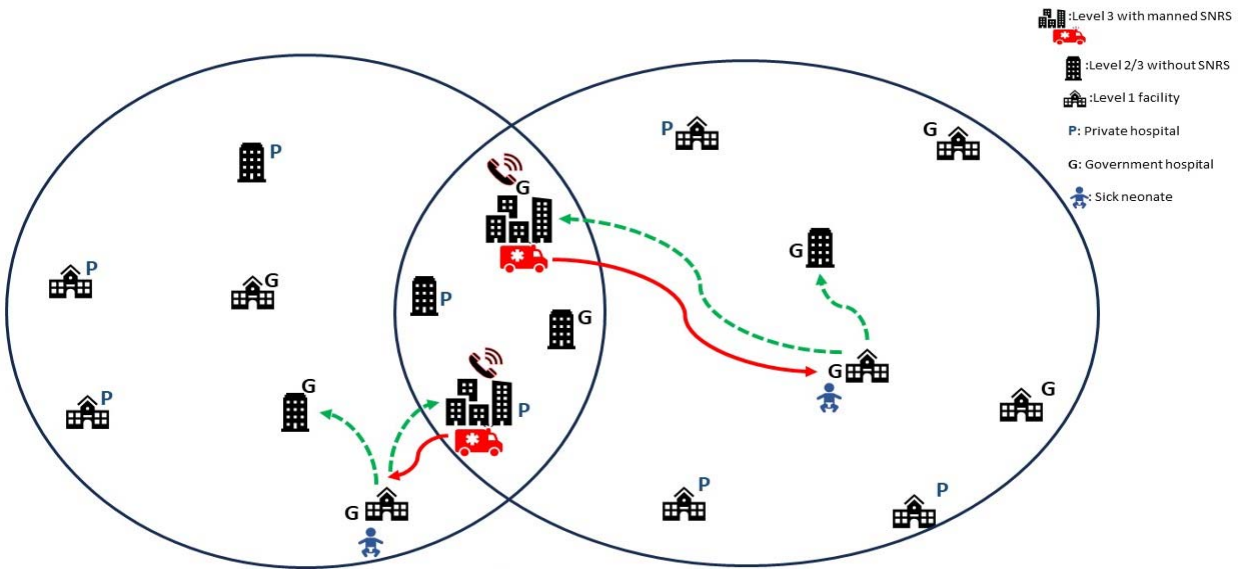


**Fig. 1** Suggested Sick Neonate Retrieval Network: Sick neonate in a Level I Government/Private facility. Transport call to the nearest Government/ Private institute with manned transport ambulance. Solid black arrow depicts rushing to retrieve sick neonate. The network can decide based on bed/ facility availability to move baby in equipped and manned ambulance to private/ government Level 2/3 facility as warranted (black dotted arrow). The choice of hospital for further care is based on multiple factors like distance, family choices, bed availability, stability for near/far transport.

referring doctor can rapidly recognize the nearest transport team available, estimated arrival time by realtime satellite maps of traffic and road conditions and closest intensive care bed/ hospital with the requisite facilities. These goals would need immense networking and collaboration amongst units to achieve one step towards equitable distribution of health services, and the target of single digit neonatal mortality rate by 2030s in India.

Private-public partnerships and use of multimedia and networking would go a long way in optimizing support for these sick neonates. There is a beacon of hope for smooth roads ahead with small strides from each of us.

*Ethics clearance:* KIMS/IHEC/Transport/04/2023 dated April 03, 2023.

*Contributors*: FP: Conceived the study, collected and analyzed data, drafted manuscript; ZAB, MMV: Collected the data; AKP, NJ: Critical inputs, will act as guarantor. All authors approved the final manuscript and are accountable.

*Funding:* None; *Competing* interests: None stated.

*Acknowledgements*: We thank Adib Shifas for designing and constructing infographics, data analysis and conceptualization of the multimedia app toward sick neonatal transport.

## REFERENCES

1. Insoft RM, Schwartz HP (Eds). Guidelines for Air and Ground Transport of Neonatal and Pediatric Patients Manual, 4th ed. American Academy of Pediatrics; 2016. Accessed on July 26, 2023. Available from: *https://doi.org/10.1542/9781581109795*
2. Kumutha J, Rao GVR, Sridhar BN, et al. The GVK EMRI maternal and neonatal transport system in India: a mega plan for a mammoth problem. Semin Fetal Neonatal Med. 2015; 20:326-34.
3. NNF Clinical Practice Guidelines. Transport of Sick Neonates. Accessed on Aug 20, 2023. Available from: *https://www.ontop-in.org/ontop-pen/Week-12-13/Transport-of-sick-NB.pdf*
4. Singh J, Dalal P, Gathwala G, et al. Transport characteristics and predictors of mortality among neonates referred to a tertiary care centre in North India: a prospective observational study. BMJ Open. 2021;11:e044625.
5. M Kumar, Dabas V, Mohta A. Neonatal transport: the long drive has not even begun. Indian J Community Med. 2017;42:244 5.
6. Dick WF. Anglo-American vs. Franco-German emergency medical services system. Prehosp Disaster Med. 2003;18:29-35
7. National Health System Resource Centre. Emergency medical service (EMS) in India: A concept paper. Accessed on Aug 31, 2023. Available from: *https://nhsrcindia.org/sites/default/files/202102/Emergency_Medical_Service_in_India_Concept_Paper.pdf.*
8. PHFI, AIIMS, and SC—State of India's Newborns (SOIN) 2014–A Report. Zodpey S, Paul VK (Eds). Public Health Foundation of India, All India Institute of Medical Sciences and Save the Children, New Delhi, India. Accessed on Aug 31, 2023. Available from: *https://www. healthynewborn network.org/hnn-content/uploads/SOIN_Report_2014.pdf*
9. Roy MP, Gupta R, Sehgal R. Neonatal transport in India: From public health perspective. Med J DY Patil Univ. 2016;9:566-9.
10. Rathod D, Adhisivam B, Bhat V. Neonatal transport in resource restricted settings: a simple clinical score at arrival and its role in predicting mortality. Int J Emerg Med. 2014;7:P2.

REVIEW ARTICLE

# Hemodynamic Management Strategies in Pediatric Septic Shock: Ten Concepts for the Bedside Practitioner

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**ABSTRACT**

The three pathophysiologic contributors to septic shock include varying combinations of hypovolemia (relative > absolute), decreased vascular tone or vasoplegia, and myocardial dysfunction. The three pillars of hemodynamic support include fluid boluses, vasopressors with or without inotrope infusions. The three end-points of hemodynamic resuscitation include an adequate cardiac output (CO), adequate mean arterial pressure (MAP) and diastolic blood pressure (DBP) for organ perfusion, and avoiding congestion (worse filling) parameters. Only 33-50% of septic patients show post-fluid bolus CO improvements; this may be sustained in ≥ 10% on account of sepsis-mediated glycocalyx injury. A pragmatic approach is to administer a small bolus (10 mL/kg over 20-30 min) and judge the response based on clinical perfusion markers, pressure elements, and congestive features. Vasoplegia marked by low DBP is a major contributor to hypotension in septic shock. Hence, a strategy of restricted fluid bolus with early low-dose norepinephrine (NE) (0.05-0.1 µg/kg/min) can be helpful. NE may also be useful in septic myocardial dysfunction (SMD) as an initial agent to maintain adequate coronary perfusion and DBP while minimizing tachycardia and providing inotropy. Severe SMD may benefit from additional inotropy (epinephrine/dobutamine). Except vasopressin, most vasoactive drugs may safely be administered via a peripheral route. The lowest MAP (5th centile for age) may be an acceptable target, provided end-organ perfusion is satisfactory. A clinical individualized approach combining the history, serial physical examination, laboratory analyses, available monitoring tools, and repeated assessment to individualize circulatory support may to lead to better outcomes than one-size-fits-all algorithms.

**Keywords**: *Fluids, Hemodynamics, Norepinephrine, Restrictive*

***Published online:*** Jan 09, 2024; ***PII*:** S097475591600586

Sepsis is a leading cause of morbidity, mortality, and hospitalization for children worldwide with > 80% of sepsis occurring in lower- and middle-income countries (LMICs) [1]. The 2020 Pediatric Surviving Sepsis Guidelines Campaign (peds-SSC) compiled evidence-based recommendations [2]. However, there was only limited evidence to guide the care in healthcare settings such as India with only few trained pediatric intensivists and level 1 and 2 pediatric intensive care units (PICUs) and fewer level 3 PICUs, vastly insufficient for the Indian pediatric population, which occupy a vast middle ground between high-income countries and health facilities where the 'Fluid Expansion as Supportive Therapy (FEAST) study' was conducted [3]. In this article we will discuss ten concepts in the hemodynamic management of pediatric septic shock that may be helpful for the bedside pediatrician.

## 1. Pathophysiology of sepsis and septic shock

Sepsis and septic shock occur because of a dysregulated host response to not just bacterial infections but also viral, fungal, and parasitic infections. The ensuing inflammatory response is a complex interaction between the inciting pathogen, the host immune response, pro- and anti-inflammatory cytokines, among others. The severity and response to treatment may be altered by host and pathogen factors such as age, genetic susceptibility, microbial load, virulence etc. A dysregulated host response may be recognized by the presence of multi-organ dysfunction, often remote from the infective focus. Cardiovascular dysfunction in the setting of sepsis, called as septic shock, represents the severest form of sepsis. Clinical features of pediatric septic shock may have a combination of 3 or more of the following: tachycardia (which is persistent and disproportion to fever), decreased peripheral perfusion, with feeble/absent or bounding peripheral pulses, low or normal mean arterial pressure (MAP), altered consciousness /irritability, capillary refill time (CRT) that is flash or prolonged > 2 seconds, mottled or cool extremities, and decreased urine output [4].

Children, like adults, may have various clinical phenotypes, of which the vasoplegic/vasodilatory phenotype of septic shock may be most common [5]. The three

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fundamental pathophysiologic contributors to septic shock include hypovolemia, decreased vascular tone (or vasoplegia), and cardiac dysfunction [5,6]. However, these may not be clinically obvious at presentation, and may dynamically progress during the initial 24-48 h.

The three main pillars of cardiovascular support include fluid bolus (FB) administration to restore adequate circulating volume, vasopressor infusions to maintain vasomotor tone, and inotropes to improve cardiac contractility.

The three end points/goals of effective hemodynamic resuscitation include an adequate cardiac output (CO); the clinical markers of which include a good extremity perfusion, and normal CRT, a sufficient MAP and diastolic blood pressure (DBP) to ensure adequate organ perfusion, and avoiding worsening of filling (respiratory) parameters, as discussed further. Furthermore, shock resuscitation must optimize both macrocirculatory variables (CO, MAP) as well as microcirculatory parameters (regional blood flow distribution), of which capillary refill time (CRT) may be a surrogate [7].

## 2. Early recognition, screening tools and initial stabilization

Most childhood infections are not associated with cardiovascular failure (septic shock) or other organ failure. Only a small minority may progress to septic shock; early recognition of this subset based on certain "Red flags" is imperative so that immediate resuscitation is instituted. Pediatricians must have age-appropriate vital parameter values (**Table I**) prominently displayed in their clinics and wards so that the frontline caregivers are able to identify those in need of urgent intervention. Implementation of a septic shock identification/screening/trigger tool [8] which combines various conditions (e.g., high-risk patient conditions, abnormal vital signs, and/or physical findings) may help prompt further evaluation or referral.

## 3. Circulating volume in septic shock and the response to fluid boluses

There are differences in hypovolemia in fluid-losing states compared to septic shock. Fluid losses in the former (e.g., diarrhea/vomiting) results in absolute hypovolemia. Here the fluid losses lead to decreased venous return (VR) and thereby decreased CO, with compensatory rise in systemic vascular resistance (SVR), recognized clinically by cold extremities with narrow pulse pressures [4]. Fluid replacement leads to improved VR, CO and normalization of the elevated SVR.

However, septic shock is not a primary fluid-losing state, and relative hypovolemia (due to redistributed blood volume) is far more common than absolute hypovolemia [8,9]. Moreover, the SVR is often low in septic shock, this is discussed further below. The response to fluid bolus (FB) is variable in septic shock. Disruptions of the inner lining of the vascular endothelium are unique to inflammatory states including sepsis [10]. Glycocalyx injury increases vascular permeability, and interstitial fluid shifts may be further potentiated when FB are rapidly administered [10]. Interestingly, while FB generally corrects hypotension in both hypovolemic states as well as septic shock, in some patients, fluid loading itself may potentiate sepsis-associated vasoplegia, and lead to lower MAP and diastolic BP [11,12]. Adverse effects of large-volume fluids may be observed in several organs, including the cardiovascular system, lungs, and brain [13]. Moreover, fluid-induced hemodilution may result in paradoxical decrease in tissue oxygen delivery [14].

The variable response to FB in septic shock suggests that, after the initial 20mL/kg bolus (provided in two aliquots of 10 mL/kg each), every subsequent bolus must be earned, rather than being automatically prescribed.

### *Fluid bolus prescriptions in septic shock*

Cautious initial fluid resuscitation using isotonic crystalloids at 10 mL/kg over 20-30 min may be safely administered, and the response carefully monitored. If there is no worsening, and the history indicates ongoing fluid losses (diarrh*Published online:* **Jan 09, 2024;** *PII*: **S097475591600584**ea ± vomiting), the FB may be repeated and titrated to match the losses [15].

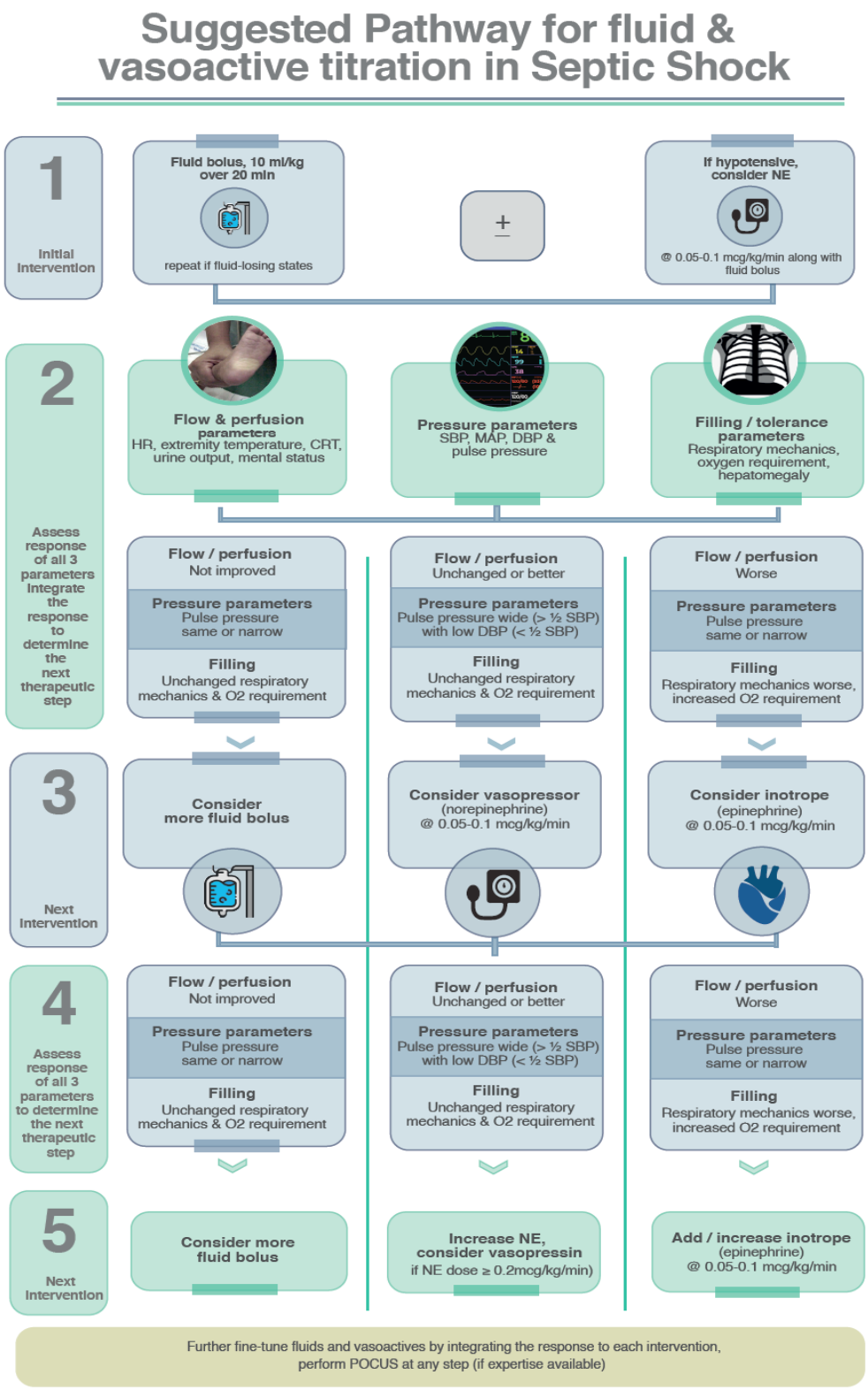
### *Fluid type*

Large volumes of normal saline may induce

**Table I Age-appropriate Vital Parameter Values**

| *Vital sign parameter* | *Age < 1 y* | *1-5 y* | *≥5-10 y* | *≥10-16 y* | *≥16 -18 y* |
|---|---|---|---|---|---|
| Heart rate (beats/min) *(Upper limit of normal)* | 180 | 140 | 120 | 100 | 90 |
| Minimum systolic blood pressures (<5th centile) (mmHg) | <70 | 70 + (age[a] × 2) | 70 + (age[a] × 2) | 90 | 90 |
| Respiratory rate (breath/min) *(Upper limit of normal)* | 60 | 40 | 30 | 30 | 16 |

[a] *age in years*




*BP Blood pressure,CO Cardiac output, CRT Capillary refill time, DBP Diastolic blood pressure, HR Heart rate, MAP Mean arterial pressure, NE Norepinephrine, POCUS Point of care ultrasound, SBP Systolic blood pressure*

**Fig. 1** Suggested pathway for fluid and vasoactive agent titration in pediatric septic shock

**Table II Ten Commandments for Fluid Bolus (FB) Administration in Septic Shock**

| | *Clinical concepts* | *Clinical considerations* | *Implications at the bedside* |
|---|---|---|---|
| 1 | Hypovolemia in fluid-losing states (e.g., vomiting, diarrhea, hemorrhage) results in absolute hypovolemia | • Absolute hypovolemia: fluid is lost from the body.<br>• Absolute hypovolemia may also occur in capillary leak states: fluid is lost from the vascular compartment.<br>• Large-volume fluid loss may result in hypotension. | • In fluid-losing states, rehydration restores circulating volume, preload, and CO.<br>• Rehydration should aim to match ongoing losses.<br>• Larger volume FB is indicated if the patient is hypotensive. |
| 2 | Hypovolemia in septic shock | • Relative > absolute hypovolemia.<br>• Fluid is re-distributed in dilated venous capacitance vessels (distributive shock).<br>• Hypotension in septic shock reflects low vascular tone rather than large volume fluid deficits. | • In septic shock, an initial fluid bolus of 10 mL /kg +10 mL/kg is reasonable as it addresses the minor element of absolute hypovolemia.<br>• Hypotension in septic shock is best addressed by low dose norepinephrine (rather than large volume FB). |
| 3 | The goal of FB in shock is to increase the CO, and thereby improve tissue O2 delivery. | • In septic shock, FB increases the CO in only ~ 50% (i.e., fluids have no benefit in the remaining half, and may harm).<br>• Even if the CO increases, the response may be sustained in < 10% by 60 min. leak. | • Disruptions in glycocalyx (which has a gate-keeper role) may explain the failure of CO rise after FB is septic shock.<br>• Each infused FB may further damage the glycocalyx, leading to further increase capillary |
| 4 | Vascular tone changes after FB | • The BP response to FB may be unpredictable.<br>• FB may improve BP parameters in most.<br>• FB may have a vasodilatory effect in some septic patients.<br>• MAP (or DBP) defines the perfusion pressure gradient in many vital regions. | • The clinician must monitor changes in pressure parameters after FB in addition to perfusion markers.<br>• If the MAP ± DBP falls after FB, further FB must be discontinued.<br>• Alternative strategies such as vasoactive infusion may be considered. |
| 5 | Monitoring the CO response to fluid bolus | Fluid-responsiveness (FR) tests aim to predict which patients will respond with increase in CO after FB. | • If the FR tests negative, unnecessary FB can be avoided in non-responders. |
| 6 | Static tests for FR | • CVP is the best-known static test for FR.<br>• CVP principally reflects myocardial function, and is around zero in patients with normal heart function. | • CVP has fallen out of favour as it is unreliable as an intra-vascular volume indicator.<br>• A significant increase in CVP after FB a should raise suspicion of myocardial dysfunction. |
| 7 | Dynamic tests for FR | • Dynamic FR tests rely on heart-lung interactions and are based on the principle of inducing brief changes in cardiac pre-load, and then observing for increase in CO.<br>• In a fluid responsive patient, CO increases by 10-15% from baseline. | • Dynamic FR tests use the respiratory variation of the arterial line waveform (pulse pressure variation or PPV). |
| 8 | Dynamic tests: limitations | • Dynamic tests require many pre-conditions that may be impractical (Invasive ventilation, no spontaneous breathing etc) | • Dynamic FR tests are not practical to perform in clinical practice.<br>• CO changes are challenging to measure.<br>• Right ventricular (RV) dysfunction may cause false a FR positive test. Here, fluid loading can be harmful. |
| 9 | Fluid overload vs fluid intolerance | • Fluid overload (FO) describes a patient who develops respiratory deterioration when too much fluid administered (hypervolemia). | • Strategies for fluid intolerance depends on the cause.<br>• In the setting of capillary leak, consider continued slow filling, colloids and (non-invasive) respiratory support. |

*contd...*

*from pre-page*

| | *Clinical concepts* | *Clinical considerations* | *Implications at the bedside* |
|---|---|---|---|
| | | • However, in severe capillary leak states (dengue shock), respiratory status deterioration may occur even when the patient is still hypovolemic. A preferred term is fluid-intolerance (FI). | |
| 10 | A restrictive fluid administration protocol + early vasoactive infusion may be beneficial for the patient | • If septic shock unresolved after FB upto 20mL/kg or if hypotension is present, early vasoactive support is recommended rather than giving more FB.<br>• In hypotensive septic shock, concurrent vasoactive (with FB) achieves rapid control of the BP and perfusion. | Restrictive fluids + early vasoactive regimen may decrease the need for PICU organ support (ventilation, dialysis). |

*BP Blood pressure, CO Cardiac output, CRT Capillary refill time, CVP Central venous pressure, DBP Diastolic blood pressure, HR Heart rate, PICU Pediatric intensive care unit, MAP Mean arterial pressure, SBP Systolic blood pressure*

hyperchloremic acidosis and increased incidence of acute kidney injury [16]. However, if lower volumes (< 20 mL/kg) are infused, these complications are unlikely, and therefore the choice of crystalloid may not matter [17].

### *Monitoring the response to FB*

During FB administration, trends in clinical perfusion markers, pressure elements, and filling (evidence or fluid overload/ fluid intolerance) must be monitored (**Fig. 1**).

**Table II** illustrates the considerations for fluid bolus in septic shock.

## 4. Decreased vascular tone or vasoplegia

A cardinal mechanism of vasodilatory/vasoplegic shock is vascular smooth muscle relaxation. The vasoplegic syndrome is encountered in many clinical scenarios, including post-cardiac bypass, after burns and trauma [18], and may be present to variable degrees in pediatric septic shock, with an Indian study reporting vasodilatory shock in more than 85% children [5]. Vasoplegia or pathologically low systemic vascular resistance (SVR) is the major contributor of hypotension in septic shock, and is recognized by low DBP with low or normal MAP, wide pulse pressures (PP) [PP > Systolic Blood Pressure (SBP) / 2] and bounding extremity pulses [5,19].

Vasoplegia must be rapidly corrected to prevent organ hypoperfusion. Organ perfusion is determined by the pressure gradient perfusing each organ, for example, cerebral perfusion pressure is determined by the difference between the MAP and intracranial pressure (ICP), and the renal perfusion pressure is the difference between MAP and central venous pressure (CVP). A low DBP is a readily available marker of low arterial tone in septic shock, however, clinicians often focus on the SBP and MAP, and overlook the DBP [20]. A low DBP may decrease coronary perfusion with co-existing tachycardia doubling the detrimental effects on the heart [21]. DBP < 50 mmHg is considered low in adults and age-appropriate pediatric DBP cut-offs have been reported in the 2020 Pediatric Advanced Life Support (PALS) Manual [4]. DBP ≥ 25 mmHg in infants and ≥ 30 mmHg children aged ≥ 1 y was associated with survival after cardiopulmonary resuscitation (CPR) [22].

The pulse pressure (PP = SBP - DBP) correlates with stroke volume (SV), and clinicians may suspect a high SV typical of a vasodilatory circulation if the pulse pressure is high. Conversely, if the PP is narrow, a low SV from either hypovolemia ± decreased cardiac function may be present.

Clinicians must be mindful that well-intended therapies that aim to correct hypotension/hypoperfusion can exacerbate vasodilatation and lead to lower BP in some patients. For example, fluid resuscitation itself may have a vasodilatory effect [23,24] possibly due to glycocalyx injury [25]. Inodilators such as milrinone may improve the CO/forward flow but can vasodilate and decrease organ perfusion pressures [26].

A low SVR is the major contributor of hypotension in septic shock [27]. While large-volume FB is often recommended in the presence of hypotension or cardiovascular collapse [2], a preferred pathophysiological strategy may be the prompt start of vasopressor such as norepinephrine concurrently with, or soon after the initial FB [10,27].

The administration of stress-dose steroids is controversial [2], but may improve vasoactive responsiveness, and is often administered if shock is unresolved despite initial fluid and vasoactive support. Intravenous

**Table III Pathophysiology and Consequences of Vasoplegia in Septic Shock**

| *Pathophysiology* | *Consequences* | *Implications for the clinician* |
|---|---|---|
| Vasodilatation is major player in septic shock | Low arterial tone leads to hypotension (low MAP[a], low DBP[b]).DBP is a useful marker of arterial tone, but rarely given importance | Low arterial tone may be recognized at presentation, or after fluid loading. Physicians must monitor MAP as well as DBP |
| Vasodilatation can affect arterial and venous capacitance vessels | Vasoplegia of venous capacitance vessels is the main cause of "relative" hypovolemia and distributive shock. Circulating volume accumulates in the expanded "unstressed" compartment, and venous return decreases | Large volume FB can improve venous return, but effects are ill-sustained.<br>Low dose pressors (NE) addresses the deranged pathophysiology and can improve venous return and CO in a sustained manner.<br>Early vasoactives can have a "fluid-sparing" effect, and decrease the need for ICU resources |
| Unintended consequences of common therapies: Vasoplegia may worsen with FB or inodilator agents | FB may potentiate vasoplegia and convert a hypodynamic to hyperdynamic circulation. Inodilators such as milrinone can also potentiate vasoplegia. | If the MAP and/or DBP falls after FB, initiate early vasoactive (NE) rather than repeated FB.<br>For myocardial dysfunction, epinephrine may be preferable to inodilators. Avoid inodilator agents, if possible, during the initial 24 h.<br>Even if dobutamine used, combination with pressor may help safeguard against hypotension. |
| Organ perfusion suffers most when upstream pressure is low (low MAP/ DBP) and downstream pressures are high (high CVP or venous congestion) | Venous congestion due to RV dysfunction may be seen in 25% of ventilated patients with pneumonia/ARDS | Therapeutic strategies to optimise organ perfusion pressure include maintaining adequate MAP/DBP with consideration for early decongestion to lower venous pressures.<br>Hypotension with low MAP and/or DBP must be corrected rapidly. |

*ARDS Acute respiratory distress syndrome, BP Blood pressure, CO Cardiac output, CVP Central venous pressure, DBP Diastolic blood pressure, FB Fluid bolus, MAP Mean arterial pressure, NE Norepinephrine, RV Right ventricular, SBP Systolic blood pressure, SVR Systemic vascular resistance*
[a]*Minimum MAP (mmHg) for age:* 1-6 mo: > 40; 7-12 mo: > 45;
MAP (5th percentile at 50th height percentile) = 1.5 × age in years + 40.
For CNS infections with raised ICP: MAP (50th percentile at 50th height percentile) = 1.5 × age in years + 55 [11,50]
[b]*Minimum DBP for age* [3]

hydrocortisone (1 mg/kg/dose q6h; max 50 mg) may be commenced when the second pressor is being started. Earlier steroid administration (within the 1st h) is helpful in chronic steroid-dependent patients.

**Table III** summarizes the pathophysiology and consequences of vasoplegia in septic shock.

## 5. Cardiac derangements in septic shock and the importance of 'loading' conditions

Septic myocardial dysfunction (SMD) may be present in 40-50% of septic shock patients [28]. Left ventricular (LV) systolic dysfunction is most commonly described, however LV diastolic dysfunction and right ventricular (RV) systolic dysfunction may also be present, both of which have higher mortality [29,30].

Myocardial dysfunction in septic shock has several important differences from typical cardiogenic shock due to viral myocarditis. Viral myocarditis presents with low CO, compensatory high SVR (manifesting as narrow pulse pressures and poor extremity perfusion), elevated filling pressures (recognized by early pulmonary edema), and low mixed venous saturations reflecting high tissue oxygen extraction. The cardiovascular support in viral myocarditis emphasizes inodilator use and diuretics.

In contrast, the manifestations of SMD (typically LV systolic dysfunction) are crucially dependent on loading conditions: preload (volume status) and more importantly the afterload or SVR [31]. This explains why at presentation, when the afterload is low, the poor LV function may not be clinically obvious. The low afterload promotes forward flow and 'masks' clinical features of SMD, which may become 'unmasked' when the low afterload is raised with pressors. Other features of SMD include normal or even elevated mixed venous saturations (due to decreased tissue oxygen extraction) [5,32] and reduced ventriculo-arterial coupling [33].

While the low SVR promotes forward flow in patients with SMD, there is a potential for coronary ischemia if the DBP is too low. In this setting, the overarching therapeutic goals are to maintain an adequate coronary perfusion/DBP,

minimize myocardial demands (tachycardia control) while providing some inotropy. Low-dose norepinephrine (NE) (0.05- 0.1 µg/kg/min) infusion may fulfil these goals in patients with mild/moderate SMD, as it has alpha-mediated vasoconstriction, minimal chronotropy, modest inotropy, and improves ventriculo-arterial coupling without imposing excess afterload [21,34]. However, in patients with severe SMD, the cardiac function may deteriorate after NE initiation, and inotropy may be indicated.

The impact of norepinephrine on cardiac function depends on the balance between the potentially beneficial effects (improved ventriculo-arterial coupling, increased coronary artery perfusion, modest inotropy) vs the higher afterload [33,35]. A safe strategy is to start with the lowest dose of norepinephrine (0.05 µg/kg/min) and carefully monitor the patient's flow/pressure and filling parameters in conjunction with serial echocardiography (**Fig. 1**) to identify patients who require additional inotropy.

Low-dose epinephrine 0.05 - 0.1 µg/kg/min, or dobutamine 5-10 µg/kg/min may be useful, while continuing norepinephrine 0.05 - 0.2 µg/kg/min for coronary perfusion; the combination may successfully restore the hemodynamics in this challenging subset with combined SMD and vasoplegia.

Inodilator use (milrinone) can be especially deleterious in the initial 24 h given its vasodilatory effect and longer-half-life (compared to catecholamines), and may be best considered after the initial 1-2 days.

## 6. Choice of initial vasoactive in pediatric septic shock

Catecholamine vasoactive agents are the most popular agents in the ER and ICU as they have a rapid onset, and more importantly, a very short offset/half-life (2-3 minutes). While life-saving, they are extremely potent, with a narrow therapeutic index and several potentially lethal complications [36]. An individualized approach considering the risk-benefit profile, using minimal effective doses to achieve precise therapeutic targets, and attempts to discontinue these agents as soon as possible is important**.**

Most vasoactives (except vasopressin) may safely be administered via a peripheral route provided a well-secured, clearly-labelled, largest bore intravenous (IV) catheter proximal to the elbow is used, and this line is dedicated only to diluted-strength vasoactive infusions [37]. Intraosseous infusions may be used until intravenous access is secured. If vasoactive infusions are required for > 6-12 h duration, a central line may be necessary, unless the circulatory parameters are clearly improving. Training of healthcare staff in the handling of vasoactives infusions whether infused via a peripheral or central line is mandatory to minimize complications.

### *Epinephrine or norepinephrine*

Epinephrine was previously considered a preferred agent in pediatric septic shock, as its powerful inotropy may address SMD, and also co-existing vasoplegia at higher doses (≥0.2µg/kg/min). However, epinephrine-induced sympathetic overstimulation often increases tachycardia, worsens markers of myocardial injury and myocardial oxygen demand [38], and has been reported to be associated with higher mortality in adults [39].

Norepinephrine with its potent $\alpha_1$-adrenergic pressor effects with mild β-agonist mediated inotropy is highly beneficial in the initial phase of resuscitation [33], and is used as a first-line agent in pediatric septic shock by many pediatric intensivists [40]. Norepinephrine can improve vascular tone (and thereby the DBP/MAP), increase venous return by reversing the distributive shock, support coronary perfusion and myocardial contractility, improve ventriculo-arterial coupling and help sustain CO and tissue perfusion [41]. Norepinephrine doses between 0.05-0.2 µg/kg/min are generally safe; higher doses can increase the blood pressure, but may worsen the cardiac function and decrease the micro-circulatory perfusion by excess vasoconstriction [35].

Myocardial depression may become clinically evident in some patients when the hypotension is corrected, and if more inotropy is considered necessary, epinephrine or dobutamine may be added depending on the BP parameters (**Fig. 1**).

If hypotension with persistent low DBP suggestive of persistent vasoplegia is observed even on norepinephrine, vasopressin infusion at 0.0005-0.002 units/kg/min may be added; stress dose steroids initiation may improve the efficacy of pressor agents [27].

## 7. Endpoints of therapy and hemodynamic monitoring

The same signs of poor perfusion that are used to recognize shock are also useful to determine the patient's response, and a combination of perfusion and pressure parameters may indicate shock reversal.

In some patients, tachycardia may persist long after other parameters have normalized. Similarly, hyperlactatemia may have causes other than tissue hypoperfusion. Moreover, lactate clearance may be delayed in sepsis [42]. Therefore, isolated tachycardia or hyperlactatemia without other signs of hypoperfusion should not be aggressively treated, but carefully observed. CRT normalization may be better than lactate as an end-point

for septic shock resuscitation [7].

A Foley's catheter must be inserted early, and hourly urine trends charted. Normal urine flow is reassuring as an indicator of adequate perfusion, unless hyperglycemia, kidney injury, or recent diuretic administration is present.

Invasive arterial monitoring is more accurate than non-invasive blood pressure (NIBP) monitoring, but may have logistic issues. The reliability of NIBP is often questioned, but may be increased by using age-appropriate arm cuffs (rather than lower limb), and taking more than one measurement [43,44]. With respect to target MAP, the lowest MAP (5th centile for age) may be accepted provided end-organ perfusion (mental status, extremity perfusion, urine output, etc) are satisfactory. While this strategy may be helpful to avoid high-dose vasoactives, a higher MAP (≥50$^{th}$ centile for age) may be necessary in the presence of raised intracranial pressure, right ventricular failure or venous congestion.

Once the end-points of shock resuscitation have been reached, it is important to expeditiously begin vasoactive weaning and discontinuation. However, given the lack of evidence, there is a variability in the practice regarding weaning and discontinuation of vasoactive support. After circulatory parameters have resolved, a rapid vasoactive taper and discontinuation over 3-6 h with careful monitoring for shock recurrence is practiced in some centres, while other centres maintain vasoactive support for 24-48 h prior to start of wearing. Any recurrence of instability during weaning should prompt re-start of vasoactive support and workup of unresolved shock described in #10 below. If vasopressin has been used, it should be weaned last [27].

## 8. Bedside approach to fluid and vasoactive titration

A clinical individualized approach combining the history, serial physical examination, laboratory analyses, available monitoring tools, and repeated assessment to individualize circulatory support may to lead to better outcomes than one-size-fits-all algorithms. The response to each therapeutic intervention (fluid/pressor/inotrope) may provide crucial information to decode the individual patient's underlying pathophysiology (**Fig.1**), even if echocardiography is unavailable. The clinician at the bedside must integrate information from changes in *"flow"* parameters (perfusion markers including CRT, limb/extremity temperature), *"pressure"* parameters (MAP, SBP, DBP, pulse pressure) and *"filling"* parameters (respiratory mechanics, oxygen requirement, hepatomegaly) in response to each intervention [6].

*a*) For example, the initial FB may be considered a *"fluid test"*, and evaluation of flow/pressure/filling parameters may help to determine the next best therapeutic step.

- If the administered FB is insufficient to match fluid losses, hypoperfusion will persist with narrow pulse pressures and unchanged lung mechanics. Those with significant myocardial dysfunction may exhibit continued poor perfusion with narrow pulse pressure but with worsened respiratory mechanics. In patients with a hyperdynamic phenotype, the FB may either lead to unchanged pressure parameters or lead to lower DBP by worsening/unmasking the vasoplegic state.
- However, if the underlying pathophysiology is unclear after the initial 10-20 mL/kg fluid, it is reasonable to start with a low dose norepinephrine infusion (0.05-0.1 µg/kg/min), given that 85% of children with septic shock are vasodilated despite a clinical "cold shock" phenotype, and about 50% have decreased myocardial function [5].

b) Norepinephrine may be initiated at 0.05-0.1 µg/kg/min as an initial vasoactive, here the norepinephrine may be considered as a *"pressor test"* and analysis of flow/pressure/filling parameters helps to determine the next therapeutic step.

- Many children, including those with mild myocardial dysfunction, improve after the combination of modest initial fluid bolus + norepinephrine infusion [34]. However, a few patients may require one or more of three additional therapies: more fluid, more pressor and/or more inotropy.
- More fluid at 10mL/kg aliquots may be provided, especially if there is history of ongoing fluid-loss.
- Additional pressor support may be required if the integrated flow/pressure/filling parameters indicate continuing vasoplegic shock (flow parameters indicating bounding pulses, pressure parameters indicate low DBP with wide pulse pressures, and filling parameters unchanged). Options include increasing norepinephrine dose to 0.2 µg/kg/min and/or adding vasopressin.
- More inotropy may be helpful in a child with low volume pulses, prolonged CRT, low/normal MAP and DBP with narrow pulses pressures, and filling parameters indicating lung congestion (worsened respiratory mechanics, increased oxygen requirement). Inotrope choice includes either epinephrine or dobutamine depending on the pressure

parameters.

c) Epinephrine at doses of 0.05-0.2 µg/kg/min may be started as the first-line vasoactive after initial fluid bolus as an "*inotrope test*", and if shock is unresolved, analysis of flow/pressure/filling parameters helps to determine the next therapeutic step. Improved perfusion as well as pressure parameters indicate that epinephrine is helping. In non-responders, worsening tachycardia ± fall in pressure parameters may warrant re-evaluation. Hypotension may occur as epinephrine's alpha-effect may be insufficient to address vasoplegia unless higher doses (> 0.2 µg/kg/min) are used. In this subset, as well in patients with complex pathophysiology, Point-of-Care Ultrasound (POCUS) performed by experienced personnel may be helpful.

### 9. Respiratory support

Similar to other life-threatening conditions in children, the physician must assess if the airway patency is satisfactory, if oxygen supplementation is required, and assess the patient's respiratory drive and work of breathing. Patients with refractory shock with/without worsening respiratory status may require additional respiratory support, and a trial of non-invasive positive pressure ventilation (NIPPV) or high-frequency nasal cannula oxygen (HFNC) support can improve oxygenation and decrease the work of breathing in some patients.

However, close patient monitoring and education of all healthcare staff is essential, as children whose cardio-respiratory status fails to improve within the initial 1-2 h of initiating NIPPV/HFNC are a high-risk subset with high mortality risk unless expert intubation and controlled ventilation is expeditiously carried out [45]. Early referral to a higher facility must be considered if the cardio-respiratory status is not improving.

Indications for intubation and positive pressure ventilation (PPV) are variable, and usually include cardio-pulmonary arrest, deteriorating mental status with a Glasgow Coma Score ≤8, inability to maintain a patent airway, and refractory shock with escalating lactate levels despite optimizing fluids and vasoactive support.

It should be understood that PPV may not always be beneficial in septic shock. The transition from spontaneous breathing to controlled PPV after intubation can worsen shock by decreasing venous return. Further, the adverse effects of sedative drugs can lead to worsening vasodilation and myocardial depression. Preserving the patient's spontaneous respiratory drive may preferable in some, unless the criteria listed above are met.

The act of intubation of the hypoxemic, shocked, acidotic patient can be fraught with complications including worsening hypoxemia, hypotension, aspiration, and cardiac arrest [46]. A high risk intubation protocol including peri intubation positive pressure/HFNC, pre-emptive vasoactive infusions/push-pressors, and low-dose ketamine may mitigate the peri-intubation risks [46]. After intubation, attempts to minimize secondary infections, and promote ventilator liberation at the earliest opportunity remain important.

### 10. Unresolved shock

Many inter-related conditions may be at play when shock is unresolved, including pre-existing morbidities, type of invading pathogen and delayed hospitalization. A comprehensive discussion is not possible, but physicians need to carefully review for correctable causes, including alternative diagnosis, inadequate source control, unrecognized additional foci of infection, inappropriate antimicrobial therapy, relief of pleural/pericardial tamponade or compartment syndromes, and need for blood transfusion and/or steroids [47].

The use of high vasoactive doses is common in refractory shock. However, catecholamine toxicity may paradoxically contribute to the circulatory instability. If the hypotension worsens as catecholamine vasoactives doses are being increased (with/without pulmonary edema), the clinician should consider whether underlying diastolic dysfunction or dynamic left ventricular output obstruction is present [48]. Improved survival has been described by the use of non-catecholamine agents (vasopressin, milrinone), slow filling, and gradual catecholamine down-titration guided by Doppler echocardiography [49]. While extra-corporeal support may be available in some centres for refractory shock, family discussions must emphasize realistic expectations (prognosis and costs).

## CONCLUSION

In order to reduce high sepsis mortality, efforts to improve early recognition and administration of the early bundle remain the key pillars of initial support. If signs of shock persist, a more individualized approach to hemodynamic resuscitation focusing on early use of vasoactives and limiting further fluid bolus therapy may be of benefit. There remains an urgent need for trials in low- and middle-income countries (LMICs) to explore the merits of an individualized approach.

*Acknowledgements*: The authors express their appreciation to our outstanding PICU consultant colleagues at Apollo Children's Hospital, including Dr Priyavarthini V, Dr Vasanth Kumar and Dr L Chidhambharam. We are also grateful to Dr Anita T, Consultant, Pediatric Emergency Department, all our enthusiastic PICU fellows and physician assistant and nurses.

We thank Mr Hariprasad G for his expertise in creation of the **Fig. 1.**

*Funding:* None; *Competing interests*: None stated

## REFERENCES

1. Fleischmann-Struzek C, Goldfarb DM, et al. The global burden of paediatric and neonatal sepsis: a systematic review. Lancet Respir Med. 2018;6:223-30.
2. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Pediatr Crit Care Med 2020;21:e52-106.
3. Maitland K, Kiguli S, Opoka R, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011;364:2483-95.
4. Duff JP, Topjian AA, Berg MD, et al. 2019 American heart association focused update on pediatric advanced life support: an update to the American heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2019;140: E904-14.
5. Ranjit S, Aram G, Kissoon N, et al. Multimodal monitoring for hemodynamic categorization and management of pediatric septic shock: A pilot observational study. Pediatr Critic Care Med. 2014;15:1-10.
6. Ranjit S, Kissoon N, Argent A, et al. Haemodynamic support for paediatric septic shock: a global perspective. Lancet Child Adolesc Health. 2023;7:588–98.
7. Zampieri FG, Damiani LP, Bakker J, et al. Effects of a resuscitation strategy targeting peripheral perfusion status versus serum lactate levels among patients with septic shock a bayesian reanalysis of the ANDROMEDA-SHOCK trial. Am J Respir Crit Care Med. 2020;201:423–9.
8. Perner A, Cecconi M, Cronhjort M, et al. Expert statement for the management of hypovolemia in sepsis. Intensive Care Med. 2018;44:791-8.
9. Hilton A, Bellomo R. A critique of fluid bolus resuscitation in severe sepsis. Crit Care. 2012;16:302.
10. Hippensteel JA, Uchimido R, Tyler PD, al. Intravenous fluid resuscitation is associated with septic endothelial glycocalyx degradation. Crit Care. 2019;23:259.
11. Ranjit S, Natraj R, Kissoon N, et al. Variability in the hemodynamic response to fluid bolus in pediatric septic shock. Pediatr Crit Care Med. 2021;22:e448-58.
12. Monge García MI, Guijo González P, Gracia Romero M, et al. Effects of fluid administration on arterial load in septic shock patients. Intensive Care Med. 2015;41:1247-55.
13. Levin M, Cunnington AJ, Wilson C, N et al. Effects of saline or albumin fluid bolus in resuscitation: evidence from re-analysis of the FEAST trial. Lancet Respir Med. 2019;7: 581-93.
14. Reuter D, Chappell D, Perel A. The dark sides of fluid administration in the critically ill patient. Intensive Care Med. 2017;44:1-3.
15. World Health Organization. Guideline: Updates on Paediatric Emergency Triage, Assessment and Treatment: Care of Critically-Ill Children. Geneva: World Health Organization; 2016. Accessed on Aug 03, 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK350528/
16. Sankar J, Muralidharan J, AV L, et al. Balanced crystalloids versus saline for initial fluid resuscitation in children with septic shock. Crit Care Med. 2020;49:17.
17. Monnet X, Lai C, Teboul JL. How I personalize fluid therapy in septic shock? Crit Care. 2023;27:123.
18. Lambden S, Creagh-Brown BC, Hunt J, et al. Definitions and pathophysiology of vasoplegic shock. Crit Care. 2018; 22:174.
19. Hernandez G, Messina A, Kattan E. Invasive arterial pressure monitoring: much more than mean arterial pressure! Intensive Care Med. 2022;48:1495-7.
20. Hamzaoui O, Shi R. Early norepinephrine use in septic shock. J Thorac Dis. 2020;2:S72-7.
21. Ospina-Tascón GA, Teboul JL, Hernandez G. et al. Diastolic shock index and clinical outcomes in patients with septic shock. Ann Intensive Care 2020;10:41.
22. Berg RA, Sutton RM, Reeder RW, et al. Association between diastolic blood pressure during pediatric in-hospital cardiopulmonary resuscitation and survival. Circulation. 2018;137:1784-95.
23. Cholley BP, Lang RM, Berger DS, et al. Alterations in systemic arterial mechanical properties during septic shock: role of fluid resuscitation. Am J Physiol. 1995;269: H375-84.
24. Ricard-Hibon A, Losser MR, Kong R, et al. Systemic pressure-flow reactivity to norepinephrine in rabbits: impact of endotoxin and fluid loading. Intensive Care Med. 1998;24:959-66.
25. Byrne L, Obonyo NG, Diab SD, et al. Unintended consequences: fluid resuscitation worsens shock in an ovine model of endotoxemia. Am J Respir Crit Care Med. 2018;198:1043-54.
26. Hollenberg SM. Vasoactive drugs in circulatory shock. Am J Respir Crit Care Med. 2011;183:847-55.
27. Hamzaoui O, Goury A, Teboul JL. The eight unanswered and answered questions about the use of vasopressors in septic shock. J Clin Med. 2023;12:4589.
28. Sanfilippo F, La Rosa V, Grasso C et al. Echocardiographic parameters and mortality in pediatric sepsis. Pediatr Crit Care Med. 2020;22:251-61.
29. Ventetuolo CE, Klinger JR. Management of acute right ventricular failure in the intensive care unit. Ann Am Thorac Soc. 2014;11:811-22.
30. Sankar J, Das R, Jain A, et al. Prevalence and outcome of diastolic dysfunction in children with fluid refractory septic shock—a prospective observational study. Pediatr Critic Care Med. 2014;15:e370-8.
31. Boissier F, Razazi K, Seemann A, et al. Left ventricular systolic dysfunction during septic shock: the role of loading conditions. Intensive Care Med. 2017;43:633–42.
32. Bouferrache K, Amiel JB, Chimot L, et al. Initial resuscitation guided by the Surviving Sepsis Campaign recommendations and early echocardiographic assessment of hemodynamics in intensive care unit septic patients. Crit Care Med. 2012;40:2821-7.
33. Foulon P, De Backer D. The hemodynamic effects of norepinephrine: far more than an increase in blood pressure! Ann Transl Med. 2018;6:S25.

34. Ranjit S, Natraj R, Kandath SK, et al. Early norepinephrine decreases fluid and ventilatory requirements in pediatric vasodilatory septic shock. Indian J Crit Care Med. 2016;20: 561-9.
35. De Backer D, Foulon P. Minimizing catecholamines and optimizing perfusion. Crit Care. 2019;23(Suppl 1):149.
36. Annane D, Ouanes-Besbes L, de Backer D, et al. A global perspective on vasoactive agents in shock. Intensive Care Med. 2018;44:833-46.
37. Owen VS, Rosgen BK, Cherak SJ, et al. Adverse events associated with administration of vasopressor medications through a peripheral intravenous catheter: a systematic review and meta-analysis. Crit Care. 2021;25:146.
38. Vorovich E. Why is epinephrine not the drug of choice in cardiogenic shock? J Shock Hemodyn. 2022;1:E20221210.
39. Tarvasmäki T, Lassus J, Varpula M, et al. Current real-life use of vasopressors and inotropes in cardiogenic shock - adrenaline use is associated with excess organ injury and mortality. Crit Care. 2016;20:208.
40. Morin L, Kneyber M, Jansen NJG, et al. Translational gap in pediatric septic shock management: an ESPNIC perspective. Ann Intensive Care. 2019;9:73.
41. De Backer D PM. Norepinephrine improves cardiac function during septic shock, but why? Br J Anaesth. 2018;120:e421-4.
42. Marik PE BR. Lactate clearance as a target of therapy in sepsis: A flawed paradigm. OA Critical Care. 2013;1:3.
43. Lehman LW, Saeed M, Talmor D, Mark R, Malhotra A. Methods of blood pressure measurement in the ICU. Crit Care Med. 2013;41:34-40.
44. Duncombe S, Voss C, Harris K. Oscillometric and auscultatory blood pressure measurement methods in children: a systematic review and meta-analysis. J Hypertens. 2016; 35:1.
45. Inglis R, Ayebale E, Schultz MJ. Optimizing respiratory management in resource-limited settings. Curr Opin Crit Care. 2019;25:45–53.
46. Heffner AC, Swords D, Kline JA, Jones AE. The frequency and significance of postintubation hypotension during emergency airway management. J Crit Care. 2012;27:417.
47. Duke T. New WHO guidelines on emergency triage assessment and treatment. Lancet. 2016;387:721-4.
48. Slama M, Tribouilloy C, Maizel J. Left ventricular outflow tract obstruction in ICU patients. Curr Opin Crit Care. 2016;22:260-6.
49. Natraj R, Ranjit S. BESTFIT-T3: A tiered monitoring approach to persistent/recurrent paediatric septic shock – a pilot conceptual report. Indian J Crit Care Med. 2022; 26:863-70.
50. Haque IU, Zaritsky AL. Analysis of the evidence for the lower limit of systolic and mean arterial pressure in children. Pediatr Crit Care Med. 2007;8:138-44.

# OBITUARY

## PADMA SHRI DR ISHWAR CHANDER VERMA

**December 25, 1936 to February 08, 2024**

It is with profound sorrow that we share the news of the demise of Dr Ishwar Chander Verma, a distinguished pediatrician and pioneer in the field of genetics. Hailed as the "Father of Genetics in India," he devoted his life to advancing medical science and providing unparalleled care to those affected by rare genetic disorders.

After his schooling from East Africa, he completed his premedical training from Elphinstone College, Mumbai. He obtained his MBBS degree from Amritsar Medical College where he was awarded the PN Chuttani Gold Medal for standing first in Clinical Medicine. After completing his residency training in Medicine, Surgery and Obstetrics from Dar es Salaam, Tanzania, he passed the MRCP (London) examination in 1966 and obtained a Diploma in Child Health from the Glasgow University. He was the first student to be awarded MNAMS by the National Academy of Medical Sciences (NAMS) by examination. Having received his academic training in genetics from several premier institutes located in Zurich, London, Edinburgh, Manchester, Boston and NIH, USA, he was instrumental in establishing two of India's premier genetic centers at All India Institute of Medical Sciences, New Delhi, and Sir Ganga Ram Hospital, New Delhi.

Born with an insatiable curiosity and a passion for bringing the best genetics diagnosis and management to patients in India, Dr. Verma's journey was nothing short of extraordinary. His initial research was focussed on the burden of genetic disorders in India. His research on the increased frequency of Down syndrome due to the low dose radiation from monazite in Kerala fetched international acclaim. His pioneering research work in the area of tribal health, especially the screening and management of sickle cell disease, is inspirational. Under his guidance, the rare disease policy was formulated. As an astute and passionate clinician, he would always be remembered by the patients and clinicians alike.

He was the Editor-in-Chief and Emeritus Editor of the Indian Journal of Pediatrics (IJP), since 1980. Under his leadership the journal achieved great heights. As the managing trustee of KC Chaudhuri Foundation which also runs the IJP, he was instrumental in providing support for health camps in rural areas, research grants for MD and DM thesis, and clinical grand rounds by senior residents, mentoring speciality training of young faculty, providing recognition to young researchers for exemplary work and felicitating deserving pediatricians with lifetime achievement awards for their dedication to child health. He played an important role in the formulation of rare disease policy in India.

He was awarded the BC Roy National Award in 1983 and the Padma Shri, the fourth-highest civilian award of the Republic of India, in 2023. Not the one to rest on these laurels, he continued to publish with the last of his over 500 scientific contributions appearing even in 2024.

In this moment of grief, we extend our heartfelt condolences to Dr. Verma's family, friends, colleagues, and the entire medical community. May his legacy continue to inspire and guide those who follow in his footsteps, ensuring that the flame of discovery and compassion in pediatrics and genetics burns ever bright.

# Child Health During War and Disasters: Building Resilience

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**ABSTRACT**

Children face unique risks resulting from disasters and conflicts. Broadly, complex emergencies create new and augment existing health risks to children. Direct, conflict-related injuries and deaths – such as those resulting from exposure to chemical weapons and blast injuries – not only have immediate impact but also have long-term impacts on the health and wellbeing of children. Lapses in vaccination coverage, changes in vector patterns, and widespread malnutrition, contribute to new and re-emerging infectious diseases among children. Understanding risks resulting from disasters and conflicts is critical for implementing timely and appropriate public health programs to reduce the negative health effects on children.

**Keywords:** *Complex emergencies, Conflict, Public health*

## BACKGROUND

Pediatric health concerns are ubiquitous across all settings but are exacerbated in disasters and conflicts. There are a range of considerations – infectious diseases, injuries, mental health impacts – that must be accounted for when assessing pediatric health outcomes in complex emergencies. Disasters and conflicts can limit or stop the provision of public health and clinical services, resulting in lapses in immunization coverage, impeded provision of other forms of preventative care [1], development of conditions prime for the spread of communicable diseases [2], and exacerbation of pre-existing or chronic conditions. Low levels of vaccination coverage, as well as high prevalences of acute malnutrition contribute to high levels of under-5 mortality, particularly for displaced children [3]. Further, poor nutrition status and associated stunting have a range of sequelae, including compromised immune function, impeded brain development and associated learning disabilities, and higher risk of chronic diseases such as metabolic syndromes later in life [4,5]. Physiological considerations such as higher risks of both short- and long-term injury-related morbidity and mortality are higher for children, due in-part to differences in metabolic rates, total blood volume, and skin permeability, compared to adults [6,7].

Adverse childhood experiences (ACEs), defined by the US Centers for Disease Control and Prevention simply as traumatic events experienced by individuals from birth to age 17 years, can have both acute and chronic negative impacts on the mental and physical wellbeing of individuals [8,9]. These effects can include, but are not limited, to the development of obesity [10], premature-onset of chronic diseases such as diabetes, cardiovascular disease and pulmonary diseases [11], and mental health conditions such as substance-use disorders, anxiety, and depression [12]. Timely and appropriate remediation efforts are needed to attenuate the negative health impacts of ACEs [13]. However, identifying and addressing ACEs is exceedingly difficult in conflict and disaster settings and is challenging even in highly resourced, stable settings [14]. Accessibility and logistical constraints in complex emergencies can impede the delivery of this aid, in effect amplifying the potential for negative downstream mental and physical health impacts.

The physiological and psychosocial principles that place children at comparatively higher risks for negative health outcomes are not unique to complex emergencies. However, these situations result in fewer resources – including, but not limited to, medical, social, and infrastructural supports – to attenuate the negative impacts of experiencing disaster or conflict events. Accordingly, it is important to consider the multitude of ways in which child health has been negatively impacted in complex emergencies. In the following sections, we discuss a few examples from recent conflicts and disasters.

## CHALLENGES AND BARRIERS

### Impact of Chemical Weapons

The Syrian Civil War officially started in March 2011,

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following widespread peaceful protests around the country against the regime of Syrian president Bashar al-Assad [15]. Chemical weapons – including the nerve agent sarin – were used by the Assad regime to deter opposition. The first suspected use of chemical weapons was reported in December 2012, but attacks have continued through 2023 [16].

Children face disproportionate impacts from exposure to chemical weapons. A retrospective case-cohort study assessing the effects of childhood exposure to chemical weapons on the prevalence of chronic disease among Iraqi Kurds found higher prevalences of chronic ocular, dermatological, respiratory, and nervous system conditions [17]. When exposed to chemical weapons, children become ill at a lower effective dose than adults, and their smaller bodies are less able to handle the stress placed on organ function and metabolism. Individuals exposed to organophosphates experience a range of negative mental health outcomes, including depression, post-traumatic stress disorder, and insomnia, among others [18-21]. Adverse childhood experiences – such as exposure to chemical warfare – have long-term effects on the mental health and wellbeing of children like those living in Syrian cities such as Ghouta, Douma, and Khan Shaykun which were targeted with organophosphates and chlorine gas.

### Impact of Air Raids and Violent Deaths

Over 17% of the estimated 145 849 Syrian civilian deaths recorded in the Violation Documentation Center due to direct violence from 18 March 2011 through 31 December 2016, were children [22]. Aerial bombardment and shelling were the two leading causes of direct deaths for both male and female children. The proportion of children among all civilian deaths increased from under 10% in 2011 to nearly 25% of all civilian violent deaths in 2016. The high levels of direct civilian deaths – and pediatric deaths, in particular – are unfortunately not uncommon in warfare defined by air offenses. Roughly 67% of excess mortality in the Yemen Civil War was attributable to direct violence [23].

Among Syrians treated for injuries in a Turkish medical facility, children were more likely to have head trauma following blasts, compared to adults who were more likely to have injuries to the torso and limbs [24]. Trauma resulted in vascular injuries at higher rates than other war-related injuries, accounting for over 60% of pediatric deaths following blasts from incendiary explosive device and suicide bombings in Pakistan [25]. In a retrospective cohort study comparing the circumstances causing and clinical presentation of burns among Syrian and Turkish pediatric burn patients, Syrian children were more likely to have fire- and blast-related burns, burns covering a greater percentage of their bodies, more intensive clinical management, and higher rates of burn-related fatalities when compared to Turkish pediatric burn patients [26]. Broadly, children are more likely than adults to have high-mortality burn injuries, and the complex nature of clinical management, reconstruction, and rehabilitation require vast medical resources that are often not available in conflict settings [27].

Beyond detrimental physical health effects, air raids and resulting blasts have negative mental health impacts for survivors. Children in Northern Ireland who were exposed to bombings were much more likely to experience post-traumatic stress disorder than their peers [28]. In a 2022 report by Save the Children, at least 80% of children in Gaza experienced symptoms of present traumatic stress syndrome due to the blockade and recurrent bombings of the Gaza Strip [29]. European countries receiving Ukrainian refugees were encouraged to develop proactive psychiatric interventions for displaced children and their families to foster resilience and address pediatric developmental needs [30].

### Lapses in Vaccination Coverage and Vaccine Preventable Diseases (VPDs)

Violence, instability, and natural hazards contribute to the spread of early-childhood, vaccine-preventable and logistically manageable diseases globally. The destabilization of the Syrian health system, as well as inaccessibility and security concerns throughout the country, resulted in limited capacity for supplemental and expanded immunization programming. From January 2015 through June 2019, there were nearly ten times as many clinically suspected measles cases ($n$ = 30241) in Syria than were recorded for the entire country in the first decade of the 21st century ($n$ = 3193) [31]. Similarly, in 2019, the Democratic Republic of the Congo reported record numbers of measles cases after large cohorts went unvaccinated due to insecurity, limited resources, flood-drought cycles, and a concurrent Ebola outbreak [32]. Yemen, which has been in a civil war since 2014 and experienced recurrent disasters from heavy rainfall and flooding, has recorded outbreaks of measles [33,34], cholera [35–38], and diphtheria [39,40].

### Malnutrition

Malnutrition contributes to the risk of infectious diseases. For example, in India, districts with a higher percentage of underweight children were more likely to have endemic malaria [41]. In areas experiencing recurrent flooding in South Sudan, malnutrition and a fertile environment for mosquitoes to breed contributed to high levels of malaria among children [42]. Other studies have found differing

relationships between malnutrition and malaria [43]. For example, a study in the Western Brazilian Amazon that found the relationship between malaria and nutritional status differed by age, where, in some cases, undernourished children had comparatively lower risk of malaria [44]. Poor nutritional status can also complicate the clinical management of infectious diseases. Nigerian children with severe acute malnutrition (SAM) under five years of age were more likely to require longer clinical management of cholera than children without SAM [45]. Both maternal-fetal and pediatric under- and malnutrition can contribute to vitamin A and zinc deficiencies that result in compromised immune function, placing children at higher risk of severe clinical manifestations of early childhood diseases such as measles [46].

## WAY FORWARD

Climate-related disasters are increasing in both frequency and severity, and geopolitical instability is affecting millions globally. Both of these circumstances create precarious environments for children around the world. In many scenarios, there are known interventions or actions that can attenuate the negative health impacts of disaster and conflict exposure on children. For example, timely linkage to mental health supports for children experiencing violence can help proactively manage stress responses and reduce the longitudinal development of more severe and persistent mental health disorders. However, the implementation and uptake of such interventions continues to be wrought with challenges. Similarly, we know that on-schedule immunization coverage greatly reduces the burden of early childhood, vaccine-preventable diseases. Again, the operationali-zation of expanded and supplemental immunization activities in disaster and conflict settings faces numerous challenges ranging from physical inaccessibility to cold chain management.

Public health balances individual and population-level health outcomes to better understand how risks operate, as well as their resulting impacts and the potential mechanisms for risk reduction. As public health practitioners, we must focus on building resilience in the face of increasingly complex environments. This requires engagement with and understanding of the persistent challenges experienced in the implementation and adoption of known risk reduction practices and post-disaster interventions. If we define resilience as "the capacity of a system to adapt successfully to challenges that threaten the function, survival, or future development of the system" [47], we have the obligation to identify population needs, listen to the experiences and perceptions of affected populations, and provide tangible supports.

*Contributors*: DGS: Conceptualization, revising and editing. SES: Drafting, revising and editing. Both authors approved the final manuscript.

*Funding*: None; *Competing interests*: None stated.

*Disclaimer*: Any opinions, findings, conclusions or recommendations expressed in this material are those of the authors.

## REFERENCES

1. Breast Screening Working Group (WG2) of the Covid-19 and Cancer Global Modelling Consortium; Figueroa JD, Gray E, Pashayan N, et al. The impact of the Covid-19 pandemic on breast cancer early detection and screening. Prev Med. 2021;151:106585.
2. de Ville de Goyet C. Stop propagating disaster myths. Prehosp Disaster Med. 1999;14:9–10.
3. Ogbu TJ, Scales SE, de Almeida MM, van Loenhout JAF, Speybroeck N, Guha-Sapir D. Predictors of exceeding emergency under-five mortality thresholds using small-scale survey data from humanitarian settings (1999 - 2020): Considerations for measles vaccination, malnutrition, and displacement status. Arch Public Health. 2022;80:160.
4. De Sanctis V, Soliman A, Alaaraj N, Ahmed S, Alyafei F, Hamed N. Early and long-term consequences of nutritional stunting: from childhood to adulthood. Acta Biomed. 2021;92:e2021168.
5. Dewey KG, Begum K. Long-term consequences of stunting in early life. Matern Child Nutr. 2011;7 Suppl 3:5-18.
6. Kong F, Galzote C, Duan Y. Change in skin properties over the first 10 years of life: a cross-sectional study. Arch Dermatol Res. 2017;309:653-8.
7. Palmieri TL. Children are not little adults: blood transfusion in children with burn injury. Burns Trauma. 2017;5: 24.
8. Centres for Disease Control and Prevention. Fast Facts: Preventing Adverse Childhood Experiences. Accessed Nov 6, 2023. Available from: *https://www.cdc.gov/violence prevention/aces/fastfact.html*
9. Dutta A, Peña F, Holcomb JM, et al. Earthquake exposure, adverse childhood experiences, and psychosocial functioning in Chilean children: A longitudinal study. J Trauma Stress. 2022;35:1177-88.
10. Schroeder K, Schuler BR, Kobulsky JM, Sarwer DB. The association between adverse childhood experiences and childhood obesity: A systematic review. Obes Rev. 2021;22:e13204.
11. Sonu S, Post S, Feinglass J. Adverse childhood experiences and the onset of chronic disease in young adulthood. Prev Med. 2019;123:163-70.
12. Bomysoad RN, Francis LA. Adverse childhood experiences and mental health conditions among adolescents. J Adolesc Health. 2020;67:868-70.
13. Bhutta ZA, Bhavnani S, Betancourt TS, Tomlinson M, Patel V. Adverse childhood experiences and lifelong health. Nat Med. 2023;29:1639-48.
14. Barnes AJ, Anthony BJ, Karatekin C, Lingras KA, Mercado R, Thompson LA. Identifying adverse childhood experiences in pediatrics to prevent chronic health conditions. Pediatr Res. 2020;87:362-70.
15. Council on Foreign Relations. Syria's Civil War: The Descent into Horror. Accessed on Nov 06, 2023. Available

from: *https://www.cfr.org/article/syrias-civil-war*
16. Arms Control Association. Timeline of Syrian Chemical Weapons Activity, 2012-2022. Accessed on Nov 03, 2023. Available from: *https://www.armscontrol.org/factsheets/Timeline-of-Syrian-Chemical-Weapons-Activity*
17. Talabani J, Ali A, Kadir A, et al. Long-term health effects of chemical warfare agents on children following a single heavy exposure. Hum Exp Toxicol. 2018;37:836-47.
18. Malekirad AA, Faghih M, Mirabdollahi M, Kiani M, Fathi A, Abdollahi M. Neurocognitive, mental health, and glucose disorders in farmers exposed to organophosphorus pesticides. Arh Hig Rada Toksikol. 2013;64:1-8.
19. Loh Y, Swanberg MM, Ingram MV, Newmark J. Case report: Long-term cognitive sequelae of sarin exposure. Neurotoxicology. 2010;31:244-6.
20. Yanagisawa N, Morita H, Nakajima T. Sarin experiences in Japan: acute toxicity and long-term effects. J Neurol Sci. 2006;249:76-85.
21. Stein BD, Tanielian TL, Eisenman DP, Keyser DJ, Burnam MA, Pincus HA. Emotional and behavioral consequences of bioterrorism: planning a public health response. Milbank Q. 2004;82:413-55.
22. Guha-Sapir D, Schlüter B, Rodriguez-Llanes JM, Lillywhite L, Hicks MH. Patterns of civilian and child deaths due to war-related violence in Syria: a comparative analysis from the Violation Documentation Center dataset, 2011-16. Lancet Glob Health. 2018;6:e103-e10.
23. Sapir DG, Ogbu JT, Scales SE, et al. Civil war and death in Yemen: Analysis of SMART survey and ACLED data, 2012–2019. PLOS Glob Pub Health. 2022;2:e0000581.
24. Er E, Çorbacýoðlu ÞK, Güler S, et al. Analyses of demographical and injury characteristics of adult and pediatric patients injured in Syrian civil war. Am J Emerg Med. 2017;35:82-6.
25. Malik MS, Afzal M, Farid A, Khan FU, Mirza B, Waheed MT. Disease status of Afghan refugees and migrants in Pakistan. Front Public Health. 2019;7:185.
26. BuyukbeseSarsu S, Budeyri A. Mortality risk factors in war-related pediatric burns: A comparative study among two distinct populations. Burns. 2018;44:1210–27.
27. Milwood Hargrave J, Pearce P, Mayhew ER, Bull A, Taylor S. Blast injuries in children: a mixed-methods narrative review. BMJ Paediatr Open. 2019;3:e000452.
28. McDermott M, Duffy M, Percy A, Fitzgerald M, Cole C. A school based study of psychological disturbance in children following the Omagh bomb. Child Adolesc Psychiatry Ment Health. 2013;7:36.
29. Save the Children International. Children's Mental Health in Gaza Pushed Beyond Breaking Point After Nearly a Month of Siege and Bombardment. Accessed on Nov 09, 2023. Available from: *https://www.savethechildren.net/news/children-s-mental-health-gaza-pushed-beyond-breaking-point-after-nearly-month-siege-and*
30. Bürgin D, Anagnostopoulos D, Board and Policy Division of ESCAP, et al. Impact of war and forced displacement on children's mental health-multilevel, needs-oriented, and trauma-informed approaches. Eur Child Adolesc Psychiatry. 2022;31:845-53.
31. Mehtar S, AlMhawish N, Shobak K, Reingold A, Guha-Sapir D, Haar RJ. Measles in conflict-affected northern Syria: results from an ongoing outbreak surveillance program. Confl Health. 2021;15:95.
32. Ducomble T, Gignoux E. Learning from a massive epidemic: measles in DRC. Lancet Infect Dis. 2020;20:542.
33. United Nations News. Yemen: Alarming Surge in Measles and Rubella Cases, Reports WHO. Accessed on Nov 07, 2023. Available from: *https://news.un.org/en/story/2023/08/1140272*
34. Qirbi N, Ismail SA. Ongoing threat of a large-scale measles outbreak in Yemen. Lancet Glob Health. 2016;4:e451.
35. Al-Sakkaf K, Bahattab A, Basaleem H. Cholera knowledge, socioeconomic and WaSH characteristics in Aden - Yemen, 2017: a community-based comparative survey. J Prev Med Hyg. 2020;61:E392–400.
36. Camacho A, Bouhenia M, Alyusfi R, et al. Cholera epidemic in Yemen, 2016–18: an analysis of surveillance data. Lancet Glob Health. 2018;6:e680–90.
37. Dureab F, Ismail O, Müller O, Jahn A. Cholera Outbreak in Yemen: Timeliness of reporting and response in the national electronic disease early warning system. Acta Inform Med. 2019;27:85–8.
38. Ng QX, De Deyn MLZQ, Loke W, Yeo WS. Yemen's Cholera Epidemic Is a One Health Issue. J Prev Med Public Health. 2020;53:289–92.
39. Badell E, Alharazi A, Criscuolo A, et al. Ongoing diphtheria outbreak in Yemen: a cross-sectional and genomic epidemiology study. Lancet Microbe. 2021;2:e386–96.
40. Dureab F, Al-Sakkaf M, Ismail O, et al. Diphtheria outbreak in Yemen: the impact of conflict on a fragile health system. Confl Health. 2019;13:19.
41. Yadav CP, Hussain SSA, Pasi S, et al. Linkages between malaria and malnutrition in co-endemic regions of India. BMJ Glob Health. 2023;8:e010781.
42. Medecins Sans Frontieres. Doctors Without Borders. South Sudan: Catastrophic Floods Cause an Escalating Humanitarian Crisis. Accessed on Nov 09, 2023. Available from: *https://www.doctorswithoutborders.org/latest/south-sudan-catastrophic-floods-cause-escalating-humanitarian-crisis-0*
43. Gebreegziabher E, Dah C, Coulibaly B, et al. The association between malnutrition and malaria infection in children under 5 years in Burkina Faso: A longitudinal study. Am J Trop Med Hyg. 2023;108:561-8.
44. Alexandre MAA, Benzecry SG, Siqueira AM, et al. The association between nutritional status and malaria in children from a rural community in the Amazonian region: a longitudinal study. PLoS Negl Trop Dis. 2015;9:e0003743.
45. Bragança Lima MV, Hinderaker SG, Ogundipe OF, Owiti PO, Kadai B, Maikere J. Association between cholera treatment outcome and nutritional status in children aged 2-4 years in Nigeria. Public Health Action. 2021;11:80-4.
46. Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet. 2013;382:427-51.
47. Masten AS, Barnes AJ. Resilience in children: Developmental perspectives. Children (Basel). 2018;5:98.

UPDATE

# Dental Caries in Children: An Update

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**ABSTRACT**

Dental caries, also known as cavities, are the most prevalent dental problem in children. The etiology is mostly multifactorial and a result of an imbalance between the constant mineralization and demineralization on the tooth surface. It is important to assess oral health risks, counsel caregivers, and encourage oral hygiene. Recent guidelines by the American Academy of Pediatrics (AAP) underscore the evolving role of the pediatrician in initiating early dental health interventions.

**Keywords**: *Cavity, Oral health, Oral hygiene, Prevention*

**Published online:** *February 26, 2024;* **PII:** *S097475591600598*

Dental caries, also known as cavities, are a common problem in children. The age-standardized prevalence worldwide of untreated caries is approximately 8% in deciduous teeth and 29% in permanent teeth [1]. Notable regional variations exist, such as in India and among South Asians, with significant implications for public health [2,3].

It is a complicated and multifactorial problem resulting from an imbalance between the dynamic processes of constant mineralization and demineralization occurring on the surface of the teeth known as the caries balance [4,5]. In a comprehensive review by Kirthinga et al wherein studies from 1981 to January 2019 were analyzed, 123 risk factors for dental caries were identified [6]. In high-income countries, the primary risk factors include dentinal caries and high levels of *Streptococcus mutans* bacteria, whereas enamel defects are more prevalent in upper-middle-income countries. Socio-economic factors such as low household income, maternal education level, mother's employment status, urban or rural residence, being raised by a single mother, and the birth order of the child can also significantly impact the prevalence of dental caries. Dietary habits, particularly the frequency of sugar consumption, quantity of sugar, and timing of meals, as well as calcium and dairy intake during pregnancy are crucial determinants of caries in children. Feeding practices in infancy, including breastfeeding and bottle feeding, are linked to specific caries patterns, and prolonged breastfeeding beyond six to seven months is associated with a higher caries risk. Oral hygiene practices, notably the use of non-fluoridated toothpaste, tooth brushing frequency, and parental supervision play a critical role in preventing caries. The composition of the oral microbiome, especially the presence of *Streptococcus mutans* and oral thrush, also contributes to caries risk. Other contributing factors include enamel hypoplasia, deep pit and fissures in teeth, and reduced salivary flow resulting from certain diseases like Sjogren's syndrome or specific medications.

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Received: May 06, 2023; Initial Review: July 10, 2023;
Accepted: Dec 18, 2023

The American Academy of Pediatrics (AAP) has recently updated several recommendations for "Maintaining and Improving the Oral Health of Young Children" in a guidance paper [7]. The guidelines were revised given the continued high prevalence of dental caries in children, and these aimed to incorporate emerging evidence on preventive strategies with the changing landscape of oral health care delivery. These recommendations are essential in guiding healthcare professionals, especially pediatricians, in the comprehensive management of oral health for young children. The key updates are as follows:

## 1. A Shift Toward Early Intervention and Preventive Strategies

One of the key updates is the advocacy for early dental visits, ideally by the age of one year or within six months after the eruption of the first tooth, to establish a foundation for lifelong oral health. This aligns with a broader shift towards early intervention in pediatric oral healthcare [8,9]. The AAP specifically recommends

brushing children's teeth before bedtime as part of their routine to effectively prevent caries. This practice is vital for removing plaque and reducing the risk of dental caries, forming an integral part of a child's daily oral health care.

Additionally, it emphasizes on the importance of using fluoride toothpaste appropriately in young children – a smear for those aged under 3-years and a pea-sized amount for children aged 3 to 6 years. This specific guidance strikes a balance between maximizing caries prevention and minimizing the risk of dental fluorosis.

This update is based on findings from numerous studies which have shown that the use of fluoride tooth-paste plays a significant role in lowering the risk of dental caries [10-12].

The study by Shekar et al. found a complex relation-ship between fluoride levels and dental caries. In areas with high fluoride concentration like Telangana/Andhra Pradesh, there was a positive correlation with dental caries, suggesting the need for region-specific fluoride usage guidelines [13]. This study highlights the impor-tance of contextual adaptation of these recommendations, especially in a diverse country like India.

### 2. Dental Home

AAP suggests the establishment of a dental home where there is frequent interaction between the dentist and patient in a comprehensive, continuously accessible, coordinated, and family-centered manner. A dental home should be established within 6 months of the eruption of the first tooth and no later than 12 months of age.

### 3. Nutritional Counseling and its Role in Caries Prevention

The report advises families to limit the consumption of sugary snacks and beverages, all of which are known to contribute to tooth decay. Instead, a diet rich in fruits, vegetables and water is recommended. The AAP also suggests avoiding the use of a bottle or sippy cup filled with sugary liquids, especially at bedtime. The paper also underscores the importance of dietary counseling aligning with WHO guidelines recommending restriction of sugar intake [14]. Nutritional counseling, thus, becomes a key component of a holistic approach to oral health care.

### 4. Expanded Role of Pediatricians in Oral Health

In line with the latest guidelines, pediatricians are encouraged to actively participate in oral health counseling, including guidance on brushing techniques, appropriate fluoride use, and the social determinants of health. By advising parents on the necessity of dental checkups, primary care providers can influence the utilization of dental services and early detection of oral health issues. This marks a significant shift, moving beyond traditional dental practice to integrate oral health more fully into general pediatric care.

The study by Goyal et al highlights a significant gap in the knowledge of pediatricians regarding oral health care in children, including the recommended age to start tooth brushing and the appropriate fluoride concentration in toothpaste [15]. This finding is critical when considering the expanded role of pediatricians in oral health, as suggested by Krol et al [7]. It underscores the need for enhanced training and awareness among pediatricians in India, a sentiment echoed by a study by Karkoutly et al which also found poor knowledge regarding dental health care among pediatricians [16]. This global trend of inadequate oral health knowledge in pediatric care providers emphasizes the necessity of integrating oral health education into pediatric training programs.

### 5. Teledentistry and Continuous Education

The guidelines also highlight the growing role of teledentistry in enhancing access to dental care and the importance of continuous education for pediatricians to remain informed about the latest oral health practices.

### 6. Increasing Focus on Behavioral and Educational Interventions

Behavioral interventions, such as modifying dietary habits and improving oral hygiene practices, are emphasized, aligning with the increasing focus on preventive care and education in the management of dental caries. A study by D'Cruz et al demonstrated that active participation of school-aged children in reinforced oral health education (OHE) can enhance their knowledge and practices regarding oral hygiene, leading to better gingival health and reduced plaque accumulation [17]. This aligns with the AAP's focus on education as a key component of oral health maintenance

### 7. Collaborative Approach in Oral Health Management

Finally, the paper advocates for a collaborative approach involving various healthcare professionals in managing oral health, emphasizing the interdisciplinary nature of modern pediatric oral healthcare. This approach recognizes the complexity of oral health issues and the need for a comprehensive, team-based strategy. By working together, healthcare providers can ensure that children receive comprehensive care that addresses all aspects of their health.

## IMPLICATIONS

The National Oral Health Program and Project Punchiri in

**Table I Important Changes in the new Guidelines and Their Implications**

| *Domain* | *Recommentations* | *Implication* |
|---|---|---|
| *Emphasis on early and regular dental visits* | Highlight the importance of establishing a dental home for children by their first birthday, as opposed to the previously recommended age of 3 years | Improved early detection and prevention of dental caries |
| *Fluoride exposure and supplementation* | Provides updated recommendations on the appropriate use of fluoride toothpaste, varnish, and supplements, based on a child's age, risk of developing dental caries, and fluoride concentrations in drinking water. | Minimizes the risk of developing oral health issues. |
| *Dietary considerations* | Emphasizes the importance of a balanced diet for young children and the role of limiting sugar consumption, especially in the form of sugary drinks, | Prevention of tooth decay |
| *Anticipatory guidance and preventive counseling* | Underscores the importance of anticipatory guidance and parent education on oral hygiene practices, fluoride exposure, and the benefits of regular dental visits. | Enhanced parental awareness and education |
| *Collaboration between healthcare professionals* | Stresses the importance of interdisciplinary collaboration between pediatricians, dentists, and other healthcare professionals | Improved communication and coordination of care between pediatricians, dentists, and other healthcare professionals, ultimately resulting in better management of children's oral health. |

India represent significant efforts to integrate oral health care into the broader healthcare system [18, 19]. The National Oral Health Program aims to improve oral health determinants and reduce oral disease morbidity, while Project Punchiri focuses on addressing untreated dental caries among school-going children in Kerala. Project Punchiri is integrated with the Rashtriya Bal Swasthya Karyakram (RBSK) program, to encounter untreated dental caries among school-going children and spread awareness and adoption of practices for maintaining oral hygiene. Parents/caregivers were inter-viewed for their knowledge levels and practices regarding oral health. The specialized oral health examination was performed to check for caries, dental fluorosis, maloc-clusion, developmental anomalies, and oral hygiene status.

These initiatives exemplify the practical application of policy in improving oral health, aligning with the recommendations of Krol et al for integrated and comprehensive oral health care. AAP Guidelines highlight the need for early dental visits, the establishment of a dental home, integration of innovative approaches like teledentistry and adherence to recommended practices like appropriate fluoride use and bedtime brushing routines. They mark a significant shift towards proactive and preventive pediatric oral healthcare. The expanded role of pediatricians is pivotal in this context, encompassing risk assessment, nutritional counseling, and collaboration with dental care providers. Ultimately, these concerted efforts are crucial for improving oral health outcomes in pediatric populations, demonstrating the interplay between clinical practice, education, and preventive care in addressing the persistent challenge of dental caries in children.

*Contributors:* CMK: Conceptualized and prepared manuscript draft; SS: Reviewed literature and drafted the manuscript. CMK: Reviewed the manuscript and gave critical inputs. Both authors revised the manuscript and accorded final approval.
*Funding:* None; *Competing interest:* None stated.

## REFERENCES

1. Collaborators GOD, Bernabe E, Marcenes W, et al. Global, regional, and national levels and trends in burden of oral conditions from 1990 to 2017: a systematic analysis for the global burden of disease 2017 study. J Dental Res. 2020;99: 362-73.
2. Janakiram C, Antony B, Joseph J, Ramanarayanan V. Prevalence of dental caries in India among the WHO index age groups: a meta-analysis. J Clin Diagnos Res. 2018;12. Accessed on Jan 05, 2024. Available from: *https://www.researchgate.net/publication/326944071_Prevalence_of_Dental_Caries_in_India_among_the_WHO_Index_Age_Groups_A_Meta-Analysis*
3. Miglani S. Burden of dental caries in India: current scenario and future strategies. Int J Clin Pediatr Dentist. 2020;13:155.

4. Featherstone JD. The caries balance: the basis for caries management by risk assessment. Oral Health Prevent Dentist. 2004;2:259-64.
5. Siqueira W, Custodio W, McDonald E. New insights into the composition and functions of the acquired enamel pellicle. J Dent Res. 2012;91:1110-8.
6. Kirthiga M, Murugan M, Saikia A, et al. Risk factors for early childhood caries: a systematic review and meta-analysis of case control and cohort studies. Pediatr Dent. 2019;41:95-112.
7. Krol DM, Whelan K; Section on Oral Health. Maintaining and improving the oral health of young children. Pediatrics. 2023;151:e2022060417.
8. American Association of Public Health Dentistry. First Oral Health Assessment Policy, 2004. Accessed on Jan 06, 2024. Available from: *https://www.aaphd.org/oral-health-assessment-policy*
9. Guideline on Perinatal and Infant Oral Health Care. Pediatr Dent. 2016;38:150-54.
10. Marinho VC, Higgins JP, Sheiham A, et al. Fluoride toothpastes for preventing dental caries in children and adolescents. Cochrane Database Syst. Rev. 2003;2003: CD002278.
11. Twetman S, Dhar V. Evidence of effectiveness of current therapies to prevent and treat early childhood caries. Pediatr Dent. 2015;37:246-53.
12. American Dental Association. Fluoride: Topical and systemic supplements. Oral Health Topics Accessed on Dec 06, 2023. Available from: *https://www.ada.org/en/resources/research/science-and-research-institute/oral-health-topics/fluoride-topical-and-systemic-supplements*
13. Shekar C, Cheluvaiah MB, Namile D. Prevalence of dental caries and dental fluorosis among 12 and 15 years old school children in relation to fluoride concentration in drinking water in an endemic fluoride belt of Andhra Pradesh. Indian J Public Health. 2012;56:122-8.
14. World Health Organization. Guideline: sugars intake for adults and children: World Health Organization; 2015. Accessed on Jan 06, 2024. Available from: *https://www.who.int/publications/i/item/9789241549028*
15. Goyal A, Nishant, Morankar R, Gauba K, Jaiswal M. Awareness among pediatricians regarding oral health care in children including those with special health care needs: A cross- sectional survey. J Family Med Prim Care. 2020; 9:4151-5.
16. Karkoutly M, Kataish A, Al Kurdi S, et al. Knowledge, perceptions, and behavior regarding children's oral health among Syrian pediatricians: a cross-sectional study. BMC Oral Health. 2023;23:272.
17. D'cruz A, Aradhya S. Impact of oral health education on oral hygiene knowledge, practices, plaque control and gingival health of 13 to 15 year old school children in Bangalore city. Int J Dent Hyg. 2013;11:126-33.
18. Ministry of Health and Family Welfare, Government of India. National Oral Health Programme (NOHP): Operational Guidelines National Oral Health Programme (NOHP). Accessed on Nov 14, 2023. Available from: *https://main.mohfw.gov.in/Major-Programmes/Non-Communicable-Diseases-Injury-Trauma/Non-Communicable-Diseases1/National-Oral-Health-Programme-NOHP*
19. NitiAayog, Government of India. Project Punchiri: Oral Health Among Students in Kannur District [Internet]. Accessed on Nov 14, 2023. Available from: *https://nitidataportal.gramener.com/tag/oral-health/*

# Evolution in Management of Vesicoureteral Reflux in Children

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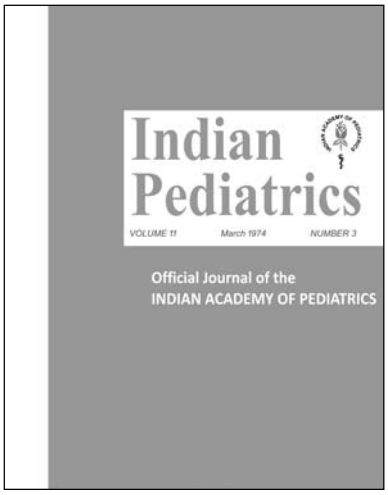
Vesicoureteral reflux (VUR) is an anatomic and/or functional disorder resulting in the retrograde flow of urine from the bladder in to the ureter with potentially serious consequences in later life [1]. Galen for the first time described the anatomy of VUR and Da Vinci postulated an antireflux mechanism to prevent urine from returning into the upper tracts [2]. Hodson and Edwards discovered the association of VUR with renal scarring due to recurrent bacterial infection [3]. Since then, several research works have demonstrated an exponential relationship between the grade of reflux and the number of urinary tract infections (UTIs) and renal scarring. Working within this concept, there was concern that uncontrolled reflux would eventually lead to reflux nephropathy and end-stage renal disease (ESRD).




Vesicoureteral reflux (VUR) affects about 1% of all children. Among infants prenatally identified to have hydronephrosis by ultrasonography (USG) and who were later screened for VUR, the prevalence of VUR was reported as 16.2% (range 7-35%) [4]. In a recent study, siblings of children with VUR had a 27.4% (range 3-51%) risk of also having VUR, whereas the offspring of parents with VUR had a still higher incidence of about 35.7% (range: 21.2-61.4%) [5].

## PAST

Before 1970s studies on VUR in India were very few. In 1974, Taneja et al published a retrospective study on children manifesting VUR [6]. In their study, the incidence of VUR was reported as 29.1% with a male preponderance (male to female ratio 9.4:1). The diagnostic modalities used to determine the cause and the degree of reflux were plain skiagram, excretory pyelography, voiding cystourethrography (VCUG) and cystourethroscopy. More than 50% of patients underwent surgical procedures whereas others were treated conservatively. Mortality was 11.2%. Similar studies in that era included diagnostic modalities like radiographic studies including plain skiagram, excretory pyelogram, voiding cystourethrogram, cystourethroscopy under general anesthesia and visual demonstration of reflux by instillation of indigo carmine into bladder by the cystoscopy [7].

In 1952, Hutch performed the first antireflux surgery which led to the investigation of relationship between VUR and upper urinary tract damage [8]. In 1958, Politano and Leadbetter introduced intravesical ureteral reimplantation, a new surgical corrective procedure for VUR [9] as an advancement over the prior surgical therapies which aimed to reduce resistance at the bladder neck. Ureteral reimplantation negated the concept that bladder outlet resistance was the major cause of reflux [10]. In 1977 Edwards et al reported high rates of spontaneous resolution of reflux (71%) on low dose continuous antibiotic prophylaxis (CAP) [11].

The routine use of prenatal imaging was brought in 1980s which made it easy to diagnose VUR early in those, who had prenatal dilatation on sonography. Prior to this, VUR was primarily identified after the onset of a febrile urinary tract infection (FUTI) episode. 1980s was also significant for the introduction of a standardized grading system by the International Reflux Study Committee [12]. VCUG became helpful for demonstration of reflux on imaging studies. The International Reflux Study proposed

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five grades of reflux based on the VCUG and discussions of management became more specific. In an attempt to bring out minimal invasive surgery in 1980s endoscopic injections for the treatment of VUR was introduced; however, the procedure gained popularity in 2001 when FDA approved dextranomer/hyaluronic acid (Deflux) [14]. Although it was initially a popular procedure, the use gradually decreased in USA because of certain discrepancies.

## PRESENT

Micturating cystourethrogram (MCU) is the gold standard to diagnose and stage VUR, which is present in approximately one-third of children with UTI. This implies that if imaging for VUR is performed in all children with UTI, two-thirds will undergo the inconvenience and hazards of imaging with negative results. Hence, the MCU study should be reserved for children with high suspicion of VUR. VUR is conventionally graded on MCU using the International Reflux Study classification [11]. Other modalities are Contrast enhanced Ultrasonography (CE-USG), direct radionuclide cystography (DRCG), indirect radionuclide cystography (IRCG), and magnetic resonance urography (MRU). Radionuclide studies such as DMSA (dimercaptosuccinic acid) scan and video urodynamic studies are important only in patients in whom secondary reflux is suspected.

Cystoscopy has a limited role in evaluating reflux except in patients with infravesical obstruction or ureteral anomalies that might influence therapy. In most patients, even high grades of VUR resolves spontaneously over a period of time. Hence, the primary focus during management of patients with primary VUR is to prevent recurrence of UTI.

*There are mainly two treatment approaches for patients with VUR*: conservative (nonsurgical) and surgical as per recent ISPN guidelines [16]. In most patients, even high grades of VUR resolve spontaneously over a period of time. Hence, the primary focus during the management of patients with primary VUR is to prevent recurrence of UTI. Surgical reimplantation be considered in patients with high-grade VUR with recurrent breakthrough febrile UTI on antibiotic prophylaxis.

The conservative approach includes watchful waiting, intermittent antibiotic prophylaxis or continuous antibiotic prophylaxis (CAP), and bladder rehabilitation in patients with lower urinary tract dysfunction [12]. Most frequently used agents for CAP are single low doses (one-third of the treatment dose) of amoxicillin and trimethoprim (patients aged < 2 mo) or trimethoprim sulfamethoxazole or nitrofurantoin (for older infants). Many clinical trials on use of CAP in VUR are available with mixed results.

Surgical treatment can be carried out by endoscopic injection of bulking agents or ureteral reimplantation. Several bulking agents have been used over the past two decades. They include polytetrafluoroethylene (PTFE, or Teflon), collagen, autologous fat, polydimethylsiloxane, silicone, chondrocytes, and more recently, a solution of dextranomer/hyaluronic acid (Deflux). The best results have been obtained with PTFE [15], but PTFE has not been approved for use in children because of concerns about particle migration [17]. Open surgical techniques share the basic principle of lengthening the intramural part of the ureter by submucosal embedding of the ureter. The most popular and reliable open procedure is the Cohen cross-trigonal reimplantation. Transperitoneal laparoscopic approaches both conventional and robot assisted include extravesical and pneumovesicoscopic intravesical ureteral reimplantation. Recent ISPN guidelines suggest open ureteric reimplantation over endoscopic correction as it has a higher success rate of resolution of VUR and a lower complication rate [16-19]. It is the preferred modality for those with Bowel Bladder Dysfunction (BBD) [20] and following failure of endoscopic correction [21]. However, it is associated with prolonged hospital stay, greater need for postoperative analgesia, and the increased risk of postoperative complications. While open reimplantation (extra- or intra-vesical approach) is the gold standard, laparoscopic or robotic-assisted laparoscopic reimplantation has a lower average length of hospital stay [22]. The disadvantages include a longer learning curve, longer operating time, and higher cost. These techniques can be considered only as alternate options based on the availability of surgical expertise and parental preference.

## FUTURE

Management of VUR continues to be a dynamic subject and varies in practice patterns between early intervention *vs* observation only. It is still a potential field with future research to further stratify VUR patients into those who are at high risk for renal damage versus those with low risk, to individualize and better management. Preventing future UTIs, renal scarring, reflux nephropathy and hypertension should be goals of managing VUR. The topdown approach with upper tract imaging (USG and radionuclide scan) and selective vesicocystourethrogram (VCUG) is a new noninvasive approach in the evaluation of children after their first FUTI. Contrast enhanced-USG may be the future imaging technique with the advantage of being free of radiation risk. Identification of the underlying genetic defects for VUR will help identifying patients with

sporadic VUR, more so in familial VUR. In addition, those at risk of developing renal failure may benefit from an analysis of genotype-phenotype correlations. Such studies would also find the association of certain mutations with reflux grade. Finally, a VUR gene may allow a biochemical understanding of VUR, and possibly add to the development of new approaches to treatment [23]. New modalities like the use of procalcitonin and urinary neutrophil gelatinase-associated lipocalin (NGAL) levels and other biomarkers can be considered as parameters in further studies for development of a universal tool [24].

*Funding*: None; *Competing interests*: None stated.

## REFERENCES

1. Fanos V, Cataldi L. Antibiotics or surgery for vesicoureteric reflux in children. Lancet. 2004;364:1720-2.
2. Schultheiss D, Grünewald V, Jonas U. Urodynamics in the anatomical work of Leonardo da Vinci (1452–1519). World J Urol. 1999;17:137-43.
3. Hodson CJ, Edwards D. Chronic pyelonephritis and vesicoureteric reflex. Clin Radiol. 1960.11:219-31.
4. Sargent MA. What is the normal prevalence of vesicoureteral reflux? Pediatr Radiol. 2000.30:587-93.
5. Skoog SJ, Peters CA, Arant Jr BS, et al. Pediatric Vesicoureteral Reflux Guidelines Panel Summary Report: Clinical Practice Guidelines for Screening Siblings of Children With Vesicoureteral Reflux and Neonates/Infants With Prenatal Hydronephrosis. J Urol. 2010; 184:1145–51.
6. Taneja et al. Vesico-ureteral reflux in children. Indian Pediatr.1974;11:189-97
7. Amar AD Demonstartion of vesicouretral reflux without radiation exposure. J Urol. 1964;92:286-8.
8. Hutch JA. Vesico-ureteral reflux in the paraplegic: cause and correction. J Urol. 1952;68:457–69.
9. Politano VA, Leadbetter WF. An operative technique for the correction of vesicoureteral reflux. 1958. J Urol. 2002;167:1415-21; discussion 1422.
10. O'Donnell B, Moloney MA, Lynch V. Vesico-ureteric reflux in infants and children: results of supervision, chemotherapy and surgery. Br JUrol 1969;41:6-13.
11. Edwards D, Normand IC, Prescod N, Smellie JM. Disappearance of vesicoureteric reflux during long-term prophylaxis of urinary tract infection in children. Br Med J. 1977;2:285-8.
12. Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Möbius TE. International system of radiographic grading of vesicoureteric reflux. International Reflux Study in Children. Pediatr Radiol. 1985;15:105-9.
13. Dias CS, Silva JM, Diniz JS, et al. Risk factors for recurrent urinary tract infections in a cohort of patients with primary vesicoureteral reflux. Pediatr Infect Dis J. 2010;29:139-44.
14. Lendvay TS, Sorensen M, Cowan C, Joyner B, Mitchell M, Grady R. The evolution of vesicoureteral reflux management in the era of dextranomer/hyaluronic acid copolymer: a pediatric health information system database study. J Urol 2006;176:1864-7.
15. Puri P, Granata C. Multicenter survey of endoscopic treatment of vesicoureteral reflux using polytetrafluoroethylene. J Urol. 1998;160:1007–11, discussion 103
16. Hari P, Meena J, Kumar M, et al; Indian Society of Pediatric Nephrology. Evidence-based clinical practice guideline for management of urinary tract infection and primary vesicoureteric reflux. Pediatr Nephrol. 2023 Oct 28. Epub ahead of print.
17. Steyaert H, Sattonnet C, Bloch C, Jaubert F, Galle P, Valla JS. Migration of PTFE paste particles to the kidney after treatment for vesico-ureteric reflux. BJU Int. 2000;85:168-9.
18. Routh JC, Inman BA, Reinberg Y. Dextranomer/hyaluronic acid for pediatric vesicoureteral reflux: systematic review. Pediatrics. 2010;125:1010-9.
19. Holmdahl G, Brandström P, Läckgren G, et al. The Swedish reflux trial in children: II. Vesicoureteral reflux outcome. J Urol. 2010;184:280-5.
20. Miyakita H, Hayashi Y, Mitsui T, et al. Guidelines for the medical management of pediatric vesicoureteral reflux. Int J Urol. 2020;27:480-90.
21. Bastos JM Netto, Rondon AV, Machado MG, et al. Brazilian consensus on vesicoureteral reflux-recommendations for clinical practice. Int Braz J Urol. 2020;46:523-37.
22. Deng T, Liu B, Luo L, Duan X, et al. Robot-assisted laparoscopic versus open ureteral reimplantation for pediatric vesicoureteral reflux: a systematic review and meta-analysis. World J Urol. 2018;36:819-28.
23. Eccles MR, Bailey RR, Abbott GD, Sullivan MJ. Unravelling the genetics of vesicoureteric reflux: a common familial disorder. Hum Mol Genet. 1996;5:1425-9.
24. Shaikh N, Borrell JL, Evron J, Leeflang MM. Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children. Cochrane Database Syst Rev. 2015;1:CD009185.

## Zinc in the Treatment of Neonatal Jaundice

We have read the paper on effects of oral Zinc supplementation on serum bilirubin levels in term neonates with hyperbilirubinemia undergoing phototherapy by Mandlecha et al with interest. We seek clarifications on two issues.

Oral zinc (Zn) therapy is hypothesized to act by inhibiting the absorption of bilirubin and increasing fecal excretion, targeting enterohepatic circulation (EHC) and lowering total serum bilirubin (TSB) [2]. Mandlecha et al enrolled term neonates with hyperbilirubinemia without risk of hemolysis or sepsis, where enhanced EHC may be one of the causal pathways. Insufficient breastfeeding causes neonatal jaundice by enhancing enterohepatic circulation, known as breastfeeding jaundice [3]. It may be clinically measured as a percentage of birth weight loss. Hence, the proportion of neonates with conventionally >10% birth weight loss present in the intervention and placebo groups needs to be informed. We noted that the proportion of exclusive breastfeeding was lower in the placebo group (43%), compared to the intervention group (66%), which is statistically significant ($P = 0.01$), but was not discussed.

Mandlecha et al used LED device with a minimum intensity of 30 μW/nm/cm$^2$ in both the intervention and placebo groups. We found that in the placebo group, the mean TSB levels (mg/dL) before the phototherapy (PT) intervention, 24 and 48 h after the PT intervention were 18.57, 17.08, and 14.62, respectively. The mean decrease in TSB with LED device appears small compared to previous published studies [3,4]. In a multicentric study from India, using single surface LED phototherapy for nonhemolytic hyperbilirubinemia in late preterm and term neonates, the rate of fall in TSB was 0.19 mg/dL/h (nearly 4.5 mg/dL over 24 hours) [3]. We also reviewed the last month of data from our unit: nine term neonates with nonhemolytic jaundice at a mean gestational age of 38.51 (0.78) wk received single-surface LED phototherapy, TSB decreased from 15.92 (1.89) to 10.59 (3.6) mg/dL after 24 h PT, mean (SD) reduction in TSB 5.32 (2.93) mg/dL.

Mandlecha et al found that oral Zn supplementation significantly reduced TSB and duration of phototherapy. However, the lack of data on inadequate milk intake, the increased rate of exclusive breastfeeding and the slower decline of TSB in the placebo group compared to published studies may have influenced the study results.

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### REFERENCES

1. Mandlecha TH, Mundada SM, Gire PK, et al. Effect of oral zinc supplementation on serum bilirubin levels in term neonates with hyperbilirubinemia undergoing phototherapy: a double-blind randomized controlled trial. Indian Pediatr. 2023;60:991-5.
2. Méndez-Sánchez N, Martínez M, González V, et al. Zinc sulfate inhibits the enterohepatic cycling of unconjugated bilirubin in subjects with Gilbert's syndrome. Ann Hepatol. 2002;1:40-3.
3. Kumar P, Murki S, Malik GK, et al. Light emitting diodes versus compact fluorescent tubes for phototherapy in neonatal jaundice: a multi-center randomized controlled trial. Indian Pediatr. 2010;47:131-7.
4. Seidman DS, Moise J, Ergaz Z, et al. A new blue light-emitting phototherapy device: a prospective randomized controlled study. J Pediatr. 2000;136:771-4.

### AUTHORS' REPLY

We agree that insufficient breastfeeding can lead to weight loss and potentially influence enterohepatic circulation (EHC). In our study, all participants were closely monitored to maintain hydration. The inclusion criteria ensured all infants were term neonates with comparable birth weights. All neonates received standardized feeding protocols regardless of group allocation, and we maintained a randomized controlled trial design and double-blinding, minimizing potential bias due to feeding practices. We acknowledge that comparing weight loss between the zinc and placebo groups could have provided valuable data. We regret this omission and recommend including such analyses in future studies.

The rate of decline of total serum bilirubin level during phototherapy depends on several factors: type of phototherapy, type of light, irradiance level, surface area covered, initial total serum bilirubin level and in the timing of TSB measurements post-intervention. While the observed TSB decrease in our study may appear small, the following are a few studies with results more closely aligned with our findings. A study compared the efficacy a single-surface LED and a conventional blue fluorescent lamp, on nonhemolytic hyperbilirubinemia in term

neonates wherein the mean TSB decline within 24 hours for the single-surface LED group was 2.41 (1.57) mg/dL [1], similar to our study. Another study reported a mean decline in TSB of 1.06 (0.20) mg/dL at 24 hours after PT in control group [2], similar to in our study. These studies affirm that the decrease in TSB while seemingly lower than some findings, fall within the range of documented efficacy for single-surface LED phototherapy in term neonates with nonhemolytic hyperbilirubinemia. It is important to consider the specific context of each study, including baseline TSB levels, treatment protocols, and patient populations, when drawing comparisons. Different studies may use different phototherapy protocols, including phototherapy parameters such as light intensity, wavelength, treatment duration, and device type. This may explain the skewed results. The method employed to evaluate bilirubin, the precision and timing of bilirubin measurement, and different inclusion and exclusion criteria among studies can also contribute to variations in study results.

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## REFERENCES

1. Aiyappa GKC, Shriyan A, Raj B. Cord blood albumin as a predictor of neonatal hyperbilirubinemia in healthy neonates. Int J Contemp Pediatr. 2017;4:503-6.
2. Awad MH, Amer S, Hafez M, et al. Feno fibrate as an adjuvant to phototherapy in pathological unconjugated hyperbilirubinemia in neonates: a randomized control trial. J Perinatol. 2021;41:865-72.

# WHO Growth Charts Should be Used to Make Indian Children Reach Their Highest Growth Potential

We offer comments on a research article by Ghosh et al published in Indian Pediatrics [1]. We strongly recommend that the WHO growth charts should be used to make Indian children reach their highest growth potential [2]. In 2006, the WHO released growth standard charts (Multicentre Growth Reference Study, MGRS) for children which are thus normative, prescriptive and on children under ideal physiologic circumstances [3]. Using these growth charts, National Family Health Survey (NFHS)-3 (2005-2006), NFHS-4 (2015-2016) and NFHS-5 (2019-2021) have reported the prevalence of stunting as 48%, 38.4% and 35.5% respectively, wasting as 19.8%, 21%, and 19.3%, respectively, and that of underweight as 42.5%, 35.8%, and 32.1% respectively. The reduction in burden from NFHS-4 to NFHS-5 has been marginal [4]. Ghosh et al argued statistically that the WHO growth standards require contextual customization and have shown that with such arithmetical derivatives, the levels of stunting, wasting, underweight are nearly halved [1]. We feel that using lower standards is liking drawing the poverty line lower to decrease the number of poor people in a country. Their first argument that the impact of nutrition program from 2015 to 2020 (NFHS-4 to NFHS-5) is not felt and therefore needs contextualization, itself seems biased. The definition of healthy children in Ghosh's paper is not explicitly mentioned and clarity on sampling is needed. The assumption that that z scores should be unit normal in a healthy population may not hold true universally. WHO data was normalized using least-mean-squares (LMS). Ghosh et al could have used normalization, when the lower mean that they got would have got corrected. In WHO data, intercountry differences were noted and these were ironed out. Difference between NFSH 4, and NFHS-5 and that between NFHS-3 and NFHS-4 may not be comparable as the number of years difference is 5 and 10 years respectively. Authors used age-specific correction. It may be highlighted that weight for height is age-independent. By reducing the cut-offs, we are down playing the optimal opportunity for any child to grow to its full potential, especially from the poorest communities. Therefore, it is scientifically inappropriate that we give less opportunity to Indian children. This problem will not arise if the mean is not altered. Calculation of a new term excess mean risk of growth faltering (EMRGF), which has not been validated, will not be needed. Wasting which is the most important parameter, is thus not shown.

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## REFERENCES

1. Ghosh S, Majumder R, Sachdev HS, Kurpad AV, Thomas T. Customization of WHO Under-five Growth Standards for an Appropriate Quantification of Public Health Burden of Growth Faltering in India. Indian Pediatr. 2023;60:804-10.
2. World Health Organization. Investing in our future: a comprehensive agenda for the health and well-being of children and adolescents. Accessed on Dec 20, 2023. Available from: *https://www.who.int/health-topics/child-growth*
3. de Onis M, Onyango A, Borghi E, Siyam A, Blössner M, Lutter C; WHO Multicentre Growth Reference Study Group. Worldwide implementation of the WHO Child Growth Standards. Public Health Nutr. 2012;15:1603-10.
4. Vir SC, Suri S. The 5th National Family Health Survey of India: a sub-national analysis of child nutrition. ORF Occasional Paper. 2021 May 18; 315. Accessed on Dec 07, 2023. Available from: *https://www.orfonline.org/wp-content/uploads/2021/05/ORF_OccasionalPaper_315_NFHS5- ChildNutrition.pdf*

## AUTHOR'S REPLY

We would like to provide our response to the critique on our statistical approach to customize the WHO Growth standards for the Indian context [1]. The main argument proposed in the critique is that the WHO MGRS study which was used to develop WHO global growth standards followed the best methods and therefore provides aspirational standards for children globally. However, there are contradictions in the way the WHO standards have been considered because these are referred to as both 'prescriptive' and 'normative'. Firstly, prescriptive standards are used in a clinical setting with continuous monitoring of child growth, but we feel that such standards should not be used to arrive at national undernutrition estimates wherein average values or the prevalence of undernutrition are used to formulate public health nutrition policies. Secondly, the WHO Growth standards are certainly not normative. Normative data are generated from representative samples of the population which was not the case with the WHO MGRS study. The WHO MGRS explicitly generated data to develop the WHO growth standards which essentially describe how healthy children would grow when they have had the best potential for growth, and the best environment.

Our motivation for seeking a better growth standard for Indian children was the non-improvement of the massive burden of undernutrition across multiple national surveys based on the prevailing WHO standards. We were explicit in our paper that one of the many (amongst others) possible reasons for an inflated undernutrition burden was the use of the WHO growth standards which may have been inappropriate [1]. We also feel that with a lower 'true' undernutrition burden, the population growth response to remedial measures like supplementary feeding will progressively become lower and slower as normalcy is reached.

Further, we relied on the NFHS data due to the absence of any other national survey specifically in healthy Indian children, while taking care to choose a sample of 'healthy' children from the NFHS and the Comprehensive National Nutrition Survey (CNNS), who would be most similar in social and health characteristics to the children in the WHO MGRS survey. The entire exercise was based on that selected healthy subsample only, and not on the entire survey data. According to the WHO standards, the distribution of z-scores of all three metrics in a healthy population must be standard normal. Then, according to this assumption, z-scores within the healthy subsample extracted from multiple national surveys should also have standard normal distribution which is independent of age. If there is deviation from this assumption in that healthy subsample of children, including dependency on age, it must point either to the growth standard being inappropriate for Indian children, or to the inadequacy of the inclusion criteria used to extract the healthy sample of children from the surveys. Since the definition of healthy was mostly adopted to match the WHO MGRS survey, the second possibility can be ruled out. Then, the inappropriateness of the growth standard for Indian children appears more logical.

In response to the suggestion for 'normalization by LMS', we would like to emphasize that we only suggested customization on normalized z-scores derived by WHO recommended LMS values of respective metrics to estimate a more accurate prevalence of undernutrition among Indian children. The correction factors being age-dependent, forces z-scores of all metrics, including weight for height, to be standard normal distribution for healthy Indian children. We further clarify that our recommended correction will not alter the temporal trend of undernutrition estimates in Indian national surveys. It will only remove a constant bias from prevalence estimates across surveys over time.

We also wish to emphasize that the proposed term 'Excess Mean Risk of Growth Faltering (EMGRF)' as an alternative objective measure of prevalence/probability/risk of undernutrition, akin to standard terms like stunting, underweight and wasting. The major limitation of the subjective cut-off based undernutrition diagnostic is the drawing of an arbitrary line between normal and abnormal, ignoring the fact that those who lie in the neighborhood of the diagnostic cut-off must share quite similar characteristics. For example, a child with HAZ -1.9 is not very different from a child with HAZ -2.1, yet, based on a

binary classification, these will be normal height and stunted respectively. Further, regarding the concern that we have missed the weight-for-height metric, we draw the attention to the 7.1% EMGRF estimate in Table 1.

We assert that the continued application of the present WHO standards creates inflated and never-changing measures of pervasive undernutrition in Indian children, which results in unnecessary shaming, and in knee-jerk excessive nutritional policy reactions of 'feeding more'. In turn, simply feeding more (quantity), with little attention to the biological framework and antecedents of growth and its composition in Indian children, the precision of actual gaps in nutrient intakes and requirements, and of diversity in food intake and quality, is more than likely to create overnutrition, with all its consequences, in Indian children. There is already proof of this, as the recent CNNS survey in India [2] found that 1 out of 2 children, whether anthropometrically normal or undernourished, had dysglycemia or dyslipidemia.

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*Funding*: SERB Power Grant No. SPG/2021/003012

## REFERENCES

1. Ghosh S, Majumder R, Sachdev HS, Kurpad AV, Thomas T. Customization of WHO under-five growth standards for an appropriate quantification of public health burden of growth faltering in India Indian Pediatr. 2023;60:804-10.
2. Sachdev HS, Porwal A, Sarna A, et al. Intraindividual double-burden of anthropometric undernutrition and "metabolic obesity" in Indian children: a paradox that needs action. Eur J Clin Nutr. 2021;75:1205-17.

# CLIPPINGS: PEDIATRIC RHEUMATOLOGY

**Clinical and laboratory differences between leukemic arthritis and juvenile idiopathic arthritis** (*Pediatr Rheumatol Online J. 2023;21:50*)

Musculo-skeletal complaints such as joint pain and swelling is the one of the common presentations in both lympho-proliferative and rheumatological conditions. This retrospective study was conducted to determine the clinical differences between leukemic arthritis (LA) and juvenile idiopathic arthritis (JIA). A total 76 patients were analyzed, 14 with LA and 62 with JIA. Female gender predominated in JIA compared to LA (79% vs 50%) and mean (range) age in LA was 8.1 (3-14) y and 10.3 (2-15) y in JIA. Arthritis pattern observed in LA was predominantly oligoarticular (50%), 71% were migratory in nature, followed by polyarticular in 43%, whereas in JIA 85% were polyarticular. The onset of symptoms was much earlier in LA (4.2 mo) compared to JIA (9.1 mo), $P$ = 0.017. Severity of pain was significantly greater in LA compared to JIA. In LA group, 64% had fever and 86% had significant weight loss. The presence of nocturnal pain, poor response to analgesics, and hepatosplenomegaly were significant findings to differentiate LA from JIA. There was significant anemia, leucopenia, thrombocytopenia and neutropenia in the LA group. Inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate showed no difference between the two groups.

**Pediatric onset Takayasu arteritis is associated with greater risk of mortality than adult onset Takayasu arteritis** (*Semin Arthritis Rheum. 2024.65:152355*)

This systematic review and meta-analysis analyzed the risk of mortality in pediatric-onset Takayasu arteritis (TAK) (<18 years) compared to adult-onset TAK. Five studies (single center 4; multicentric 1) were analyzed; pediatric onset TAK ($n$ =151; 112 girls, 39 boys) and adult-onset TAK ($n$ = 499, 437 women, 62 men). Cardiovascular disease (stroke, heart failure and myocardial infarction) and infections were the major cause of death in either pediatric-onset or adult-onset TAK. Increased mortality was observed in pediatric-onset TAK secondary to more frequent severe organ dysfunction leading to heart failure and renal failure. The pooled risk ratio (95% confidence interval) of 2.27 (1.05-4.85, $I^2$ 0%) for death was observed in pediatric-onset TAK, much higher than that in adult-onset TAK. However, meta-regression did not reveal a significant influence of differences in sex distribution or the age proportion of patients with pediatric TAK or adult-onset TAK on the pooled mortality risk.

**Barcitinib in Juvenile idiopathic arthritis** (*Lancet. 2023;402:555-70*)

Juvenile idiopathic arthritis (JIA) is sometimes refractory to all treatment regimens, hence new medications are needed to treat this population. JUVE-BASIS, a phase 3, randomized, double-blind, placebo-controlled, withdrawal, efficacy and safety trial, was conducted in 75 centers from 20 countries. Patients aged 2-18y with rheumatoid factor positive or negative polyarticular JIA, extended oligoarticular JIA, enthesitis related arthritis or juvenile psoriatic arthritis who had an inadequate response (after ≥ 12 weeks of treatment) or intolerance to one or more conventional synthetic or biologic disease-modifying anti-rheumatic drugs (DMARDs) were enrolled. It consisted of a 2-week safety and pharmacokinetic assessment subcohort, a 12-week open-label lead in period and up to 32-week placebo controlled double-blind withdrawal period, wherein those who completed 2-week safety and pharmacokinetic assessment proceeded to the open label lead in period for 10 weeks. Once a dose was confirmed for an age group in the pharmacokinetic and safety period, patients received a once daily 4 mg adult-equivalent doses of Baricitinib in the open label lead in period. Patients meeting Juvenile Idiopathic Arthritis-American College of Rheumatology (JIA-ACR) 30 criteria (JIA-ACR30 responders) at the end of the open-label lead-in (week 12) were eligible for random assignment (1:1) to receive placebo or continue receiving Baricitinib, and remained in the double-blind withdrawal period until disease flare or up to the end of the double-blind withdrawal period (week 44). The primary end point was time to disease flare during the double-blind withdrawal period. 220 patients were enrolled between Dec 17, 2018 and Mar 3, 2021, and received at least one dose of Baricitinib. 219 patients received Baricitinib and one patient was excluded from safety and pharmacokinetic period due to untreated latent tuberculosis. At the end of open label lead in period (week 12), 74% had at least a JIA ACR 30 response and randomly assigned in double-blind withdrawal period; placebo 81 and Baricitinib 82. Time to JIA flare was significantly shorter in the placebo group than in Baricitinib group in double-blind withdrawal period. Disease flare rate during the double-blind withdrawal period was significantly lower in the Baricitinib group (14 of 82 patients) than in placebo group (41 of 81 patients). At the end of double-blind withdrawal period (week 44) JIA-ACR 30, 50 and 70 response rate in Baricitinib group ($n$ = 82) was 67%, 63% and 54% respectively, as compared to 38%, 37% and 36% in the placebo group ($n$ = 81). Serious adverse events were seen in 6 out of 220 patients in the safety and pharmacokinetic period/ open-label lead in period. In the double-blind withdrawal period, serious adverse events were reported in 4/82 (5%) patients (incidence rate [IR] 9·7 [95% CI 2·7–24·9] per 100 patient-years at risk) in the Baricitinib group and 3/81 (4%) (IR 10·2 [2·1–29·7]) in the placebo group. No deaths were reported. Baricitinib was reported as an efficacious, once daily oral therapeutic alternative for patients with JIA who showed inadequate response or intolerance to standard therapy.

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### India's Drug Controller Bans FDC Cough Syrups Below 4 Years

Fixed drug combinations (FDCs) containing chlorpheniramine maleate and phenylepherine have been banned for use in children below 4 years in India. The Central Drugs Standard Control Organization (CDSCO) of India has ordered that pharmaceutical companies must mention this on the package insert and labels. Indian pharmaceutical industry has been under the spot light after childhood deaths were reported in children in Gambia, Uzbekistan and Kashmir after the use of certain cough syrups. The toxicity was linked to unacceptably high concentrations of diethyl glycol and ethylene glycol which is a contaminant of the preservative glycerine. A look at the laws in the United States and Canada also shows that over-the-counter FDCs used as cough syrups have been banned in children below 4 years since 2008. Cough syrups generally have a combination of antihistaminics, decongestants, antitussives and expectorants. Chlorpheniramine is a common first generation antihistaminic which helps in nasal and ocular itching, sneezing and rhinorrhea. The commonest side effects are drowsiness, dizziness and dry mouth. Second generation antihistaminics have lesser side effects and include cetirizine which is approved for use in children above 6 months of age and loratadine which is approved for those above 2 years of age. Phenylepherine is a decongestant which acts on alpha-1 receptors and causes vasoconstriction in the nasal mucosa. Side effects include tachycardia, arrhythmias, hypertension and anxiety. Cochrane Collaboration has three reviews looking at the efficacy of OTC cough cold medications and found none had a significantly higher reduction of common symptoms. In contrast the US National Adverse Drug Surveillance program found that 6% of emergency visits in a year were due to complications of these OTC cough formulations. Pitetti et al have reported that 5% of apparent life-threatening events were related to OTC cough formulations. Other studies have noted that factors associated with the fatalities included age younger than 2 years, use of the medication for sedation, use in a day care setting, combining two or more medications containing the same ingredient, failure to use a measuring device, product misidentification, and use of products intended for adults. (*The Hindu, Dec 20, 2023; Shefrin AE, Goldman RD. Use of over-the-counter cough and cold medications in children. Can Fam Physician. 2009;55:1081-3*.)

### FDA Approves Two Gene Editing Therapies for Sickle Cell Anemia

Casgevy (exagamglogene autotemcel) is a cell-based treatment which uses CRISPR/Cas9 based technology which results in increased fetal hemoglobin (HbF) in patients with sickle cell anemia. Stem cells from the patient are collected and the patient then undergoes myeloablative therapy to destroy their own stem cells. The extracted stem cells are modified using CRISPR/Cas9 to deactivate a gene called *BCL11A* which normally represses HbF production. The modified stem cells when reintroduced into the patient result in increased HbF production. Of the 30 patients with sickle cell anemia who underwent this treatment, 29 no longer had any of the severe vaso-occlusive crises they had previously suffered from. It was also used in 42 patients with beta-thalassemia of whom 39 no longer required blood transfusions or bone marrow transplantation. The second gene-based therapy is Lyfgenia which works slightly differently. Here, the patient's stem cells are modified to produce a new kind of hemoglobin $HbA^{T87Q}$. This is introduced into the patient using a lentiviral vector. This modified HbA has lower tendency to sickle or occlude blood flow. The United States Food and Drug Administration (US FDA) has recently approved both the therapies on December 08, 2023 and it becomes the second country after United Kingdom to do so. Currently hematopoietic stem cell transplant (HSCT) is a good option only for patients with sickle cell anemia having matched donors while the new gene editing therapies are theoretically possible for all patients. However, the prohibitive costs of nearly $2 million per patient is the major stumbling block. *(FDA News Release, Dec 08, 2023, https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapies-treat-patients-sickle-cell-disease*)

### Children in Gaza

The UNICEF has called for immediate ceasefire and sustained and unimpeded access to humanitarian access in the Gaza Strip which has been witness to unprecedented violence. About 160 children are dying daily here which amounts to one child every 10 minutes according to Christian Lindmeier, spokesperson for UN World Health Organization (WHO). Destruction of water treatment plants and distribution systems have resulted in severe water shortages and use of unportable water by vulnerable populations. Cases of diarrhea increased from 48,000 to 71,000 in a single week starting December 17, 2023. This accounts for 3200 cases/day whereas it had been 2000 cases/month prior to hostilities. There have been 304 attacks on healthcare facilities between October 07, 2023 and January 05, 2024. About 140 staff workers of the UN Relief and Works Agency have been killed in the hostilities in the past 3 months. "The killing and maiming of children, abduction of children, attacks on hospitals and schools, and the denial of humanitarian access constitute grave violations of children's rights," said Adele Khodr, UNICEF Regional Director for the Middle East and North Africa. "UNICEF urgently appeals on all parties to agree to a ceasefire, allow humanitarian access and release all hostages. Even wars have rules. Civilians must be protected – children particularly – and all efforts must be made to spare them in all circumstances." (*UNICEF Press Centre, Oct 24, 2023, https://www.unicef.org/press-releases/child-casualties-gaza-growing-stain-our-collective-conscience; UN News, Jan 05, 2024, https://news.un.org/en/story/2024/01/1145317; UN Tûrkiye, Nov 22, 2023,https://turkiye.un.org/en/253479-gaza-crisis-aid-agencies-warn-%E2%80%98tragic-avoidable-surge%E2%80%99-child-deaths*)

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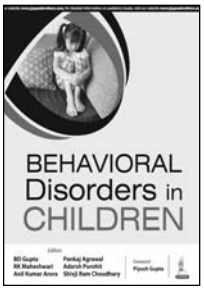
## BOOK REVIEW




**Behavioral Disorders in Children**

**Editors: BD Gupta, RK Maheshwari, AK Arora, P Agrawal, A Purohit, SR Choudhary**

*Jaypee Brothers Medical Publishers, 2024*
*ISBN 9789356968585*
*Pages: 270; Rs. 1195/-.*

There has been a progressive increase in behavioral disorders in children and adolescents in the last decade. There is a strong felt need for clinicians to attain competency in the requisite cognitive, clinical, communication, and attitudinal skills to effectively manage these children and their families. A pediatrician should be able to screen for behavioral disorders, as well as evaluate and make a clinical diagnosis in children presenting with atypical behavior. It is important to be able to discern typical developmental variations from transient atypical behavior triggered by stressors encountered while growing up; and significant pathological atypical behavior. For this, one must possess an in-depth knowledge of all the heterogeneous conditions that constitute behavioral disorders. This book comprises of 30 chapters covering most of these. It is multi-authored with 47 contributors predominantly hailing from Rajasthan. Starting with an introduction that includes neurobiology and classification, the rest of the book covers conditions that one commonly encounters in infancy, early childhood, school age, and adolescence. This includes disorders that are genetic, acquired (addictive substances, electronic gadgets, and social media) or epigenetic in origin. The format is fairly uniform covering scientific theory, manifestations enabling recognition of behavioral phenotype, establishing diagnosis, planning investigations, and management including non-pharmacological modalities and counselling.

I congratulate all concerned for their vision and hard work to have brought out this book and I wish them success. Though there is some overlap in topics and the content is more theoretical than clinically oriented, it is nonetheless multi-dimensional in nature. Taking a cue from the preface that invites constructive critique, my suggestions for the second edition would be to make it more operational for the readers by adding case scenarios, algorithms, and highlighting the key points.

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Printed and published by Dr Devendra Mishra on behalf of Indian Academy of Pediatrics and printed at Cambridge Press, Kashmere Gate, Delhi-110006 and published at 115/4, Ground Floor, Gautam Nagar, New Delhi 110 049. Editor: Dr Pooja Dewan

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