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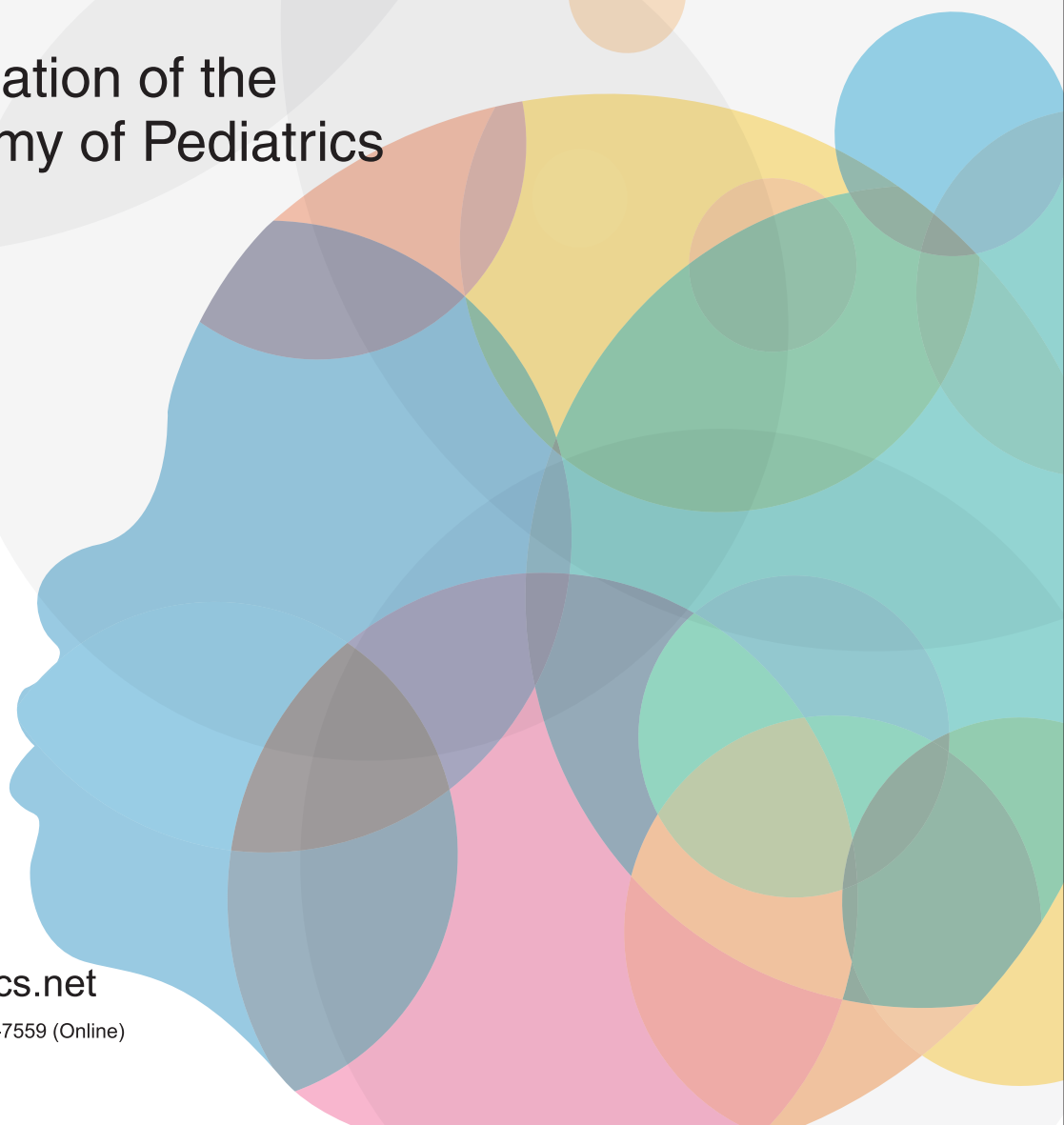

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IAP Guidelines for pediatric skincare

state that the newborn skin undergoes various structural and functional changes[1*]

Use of appropriate evidence-based skincare practices are important[2]

Protect the infant skin barrier function with safe, appropriate, and evidence-based products

Johnson's® CHOOSE gentle™

CLINICALLY mildness PROVEN®

Evidence-based skincare regimen

Cleansing regimen

As mild as pure water to maintain the skin barrier function[3,4]

Helps maintain the skin barrier function[5]

Moisturizing regimen

Improves the skin barrier integrity[6,7]

Helps enhance the skin barrier function for moisture retention[8]

*From birth to the first five years of life

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Adolescence: No Time to Sleep

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The sight of an infant enjoying blissful sleep is universally accepted as the ultimate symbol of peace, contentment and happiness. Each of us will have passed through this phase of life only to find ourselves struggling with sleep throughout the latter parts of our lives. How often do we wonder: "I wish I could sleep like that now!" For a wide variety of reasons, sleep quality declines as we age. This begins to show up as early as in adolescence, with teenagers missing sleep while loving to describe themselves as 'nigh owl's. All this, only to spend the entire weekend oversleeping lazily. Parents often overlook this issue, attributing it to teenage fancy, little realizing that this can have a lifelong impact.

So what exactly happens during teenage that makes adolescents behave this way? The triggering mechanisms for change in sleep habits may be biological in nature. Children experience a natural shift in circadian rhythm with age [1]. This makes it more difficult for them to fall asleep before 11 PM [1]. At this stage of life, several environmental and biological factors may affect both the circadian and homeostatic regulation of sleep. During the teen years, the body's internal sleep clock is reset to fall asleep later at night and wake up later in the morning. This happens as teen brains make melatonin later at night than younger children or adults. Sometimes, this delay in the sleep-wake cycle is severe enough to affect the routine daily activities [2].

THE NEED FOR SLEEP

Sleep is an essential part of everyone's routine and an indispensable part of a healthy lifestyle. It helps us to recharge and regain our energy for the day after. Humans have adapted to a system of sleeping at night and remaining active during the daytime. Disturbance in this pattern not only affects our performance potential but also makes us misfits in the performance-driven world that we live in. Sleep is a physiological necessity that we cannot afford to overlook. Lack of adequate sleep in the general population is a frequent complaint that we come across in social life.

Sleep plays a crucial role in the development of young minds. In addition to having a direct effect on happiness, research shows that sleep impacts alertness and attention, cognitive performance, mood, resiliency, vocabulary acquisition, and learning and memory. Sleep also has important effects on growth, especially in early infancy. In toddlers, napping appears to be necessary for memory consolidation, executive attention, and motor skill development [3].

While common childhood sleep disorders like night terrors and nightmares, somnambulism and bruxism, snoring, sleep apnea, and restless legs syndrome are well documented, adolescent sleep disorders have not received their due. Sleep deprivation is associated with a variety of health problems, including physical health conditions such as high blood pressure and obesity, and mental health conditions such as anxiety and depression. Among teenagers, sleep deprivation is associated with poor academic performance and increased emotional and behavioral issues. Adolescence being a particularly important period of neural development and brain maturation, insufficient sleep during this developmental period can lead to long-lasting difficulties such as cardiovascular risks.

The American Academy of Pediatrics recommends the following duration of sleep for different age groups [4]. Children 1-2 years : 11-14 hours; children 3-5 years : 10-13 hours; children 6-12 years : 9-12 hours; and teenagers 13-18 years old: 8-10 hours. Sleep problems are estimated to affect 25 to 50 percent of children and 40 percent of adolescents.

WHAT NEEDS TO BE DONE?

Sleep disorders in children, especially adolescents, may rarely get referred to the practicing pediatricians and may seem clinically irrelevant. There are also no clinical tools to address such issues. However, behavioral problems may serve as pointers to the backdrop of sleep deprivation looming behind adolescence. When confronted with such cases, the best way for the clinician to be of help would be to provide informed advice regarding the importance of sleep and provide useful suggestions to achieve the

required sleep. Some tips to recommend for better sleep:

- Keep the bedroom dark, cool, and quiet to create the ideal setting for sleep.
- Do not keep a TV or video game system in the bedroom to avoid distraction.
- About an hour before bedtime, put away homework and turn off all screens (TV, computers, and handheld devices). Turn off or silence cellphones.
- Try a relaxing bedtime routine like reading, listening to music, or meditating before going to sleep.
- Avoid caffeine (found in coffee, tea, soda, energy drinks, and chocolate) in the late afternoon and evening.
- Get regular exercise (but not too close to bedtime).
- If very tired during the day, take a short nap (less than an hour) in the early afternoon. Longer or later naps make it harder to fall asleep at night.
- Relate good sleep to benefits such as a calm mind, improved academic performance, active participation in sports and hobbies, and avoiding errors at work or accidents while driving or playing sports.
- Encourage early morning activities like breakfast, sports or being ahead of others in work or studies.

The issue of sleep is also one of the highly relevant topics that pediatricians can pick for advocacy. Pediatricians in positions of leadership or in the mass media can highlight the importance of sleep in public speeches, talks and TV discussions. The topic is simple and easy to relate for the general public, and solutions can be applied at homes by parents and children.

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INVITED COMMENTARY

Growth Faltering in Small and Sick Newborn Infants: Does it Matter?

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In an important prospective study, Joseph, et al.[1] describe the depreciation of growth (mainly weight for age *z*-scores using the Intergrowth 21 standards for preterm infants) among small and sick new-born infants [2]. These infants represented 31% of all admissions to public sector newborn care facilities in two districts of Himachal Pradesh. The authors describe growth faltering among 30% of term infants and 52.6% of preterm infants between 1-4 months of discharge from hospitals, underscoring inadequate recognition and intervention by ASHA workers in primary care settings.

These are important data on high-risk newborn outcomes and quality of care from rural settings in South Asia. However, there are also important limitations in the information that was captured. We have limited information on gestational weight gain and maternal nutrition in the cohort and sub-categories at excess risk for potential targeting [3]. Preterm infants who are also small for gestational age (SGA) represent subsets with 17-39 folds excess risk for newborn mortality [4]. These infants also have 4-5 folds higher odds for stunting, a fifth or more of which is established by 6 months of age [5]. Given the known association of early growth in infancy with maternal nutrition status prior to and during pregnancy [6], there could well be differing patterns of growth among their infants, an aspect not fully covered in the current study.

Regardless, the data provide strong evidence of growth faltering in these high-risk infants, and the need for focused attention towards their care and community follow up. The authors use the term "catch down growth" and growth faltering interchangeably, which may not be strictly correct in this setting. The term "catch down" growth has been used in the literature to account for adjustment of growth patterns in young infants to their genetically programmed growth patterns and has often been used in the context of large for dates infants and others. In the context of the average birth cohort in India, this downwards growth trajectory is neither normal nor ordained. As was underscored by the late Prof Ramalingaswami and colleagues decades ago [7], these small babies may represent the contribution of systemic disadvantage that many women face and indeed the consequence of intergenerational effects of undernutrition [8].

The subject of postnatal growth and drivers is of special interest (especially under 6 months of age), and requires attention to social determinants of growth failure in these circumstances. It is also evident that much of the long-term risks of non-communicable diseases and obesity could be determined and programmed in utero. In a recent multi-country prospective observational study of 3598 pregnant women, Villar, et al. [9] observed distinct patterns of intrauterine growth (by measurements of abdominal circumference) between 20-25 weeks gestation, metabolic signals and postnatal growth and development patterns up to 24 months of age. The group with faltering intrauterine growth pattern remained significantly small with minimal catch-up growth in the first year of life. The early catch-down growth pattern was only seen among those with the early fetal growth acceleration pattern. Importantly, in comparing maternal and cord blood samples, most metabolites associated with the faltering growth phenotype had ORs close to 1·5, indicative of an upregulation of metabolic pathways associated with impaired fetal growth. In contrast these metabolites had a reciprocal relationship with the early accelerating growth phenotype, which suggests that the same path-ways are down-regulated when fetal growth is accelerated.

The Women First Trial [6] also followed the growth trajectory of 2337 infants over the first two years of life and documented that length at birth was the best predictor of linear growth at 24 months. For infants with ultrasound-determined gestational age (n=1329), the strongest predictors of stunting were birth LAZ <-2 and <-1 to ≥ -2

with adjusted relative risk of 1.62 (95% CI: 1.39, 1.88; *P*<0.001) and 1.46 (95% CI: 1.31, 1.62; *P*<0.001), respectively.These data underscore the importance of maternal health and nutrition for child growth and the need for gestational age adjusted weight and length mea-sures at birth and thereafter; measures which are unfor-tunately lacking in large scale surveys. In a cross-sectio-nal analysis of predictors of growth among Pakistani children, maternal BMI and height were found to be independent predictors of linear growth among children suggesting that there is likely an intergenerational conse- quence of poor growth and maternal undernutrition [10].

What are the implications of these findings for public policy? This growth depreciation occurs at a period of life when there are no satisfactory alternatives to exclusive breastfeeding. Although full feeding patterns and intakes for the cohort were not described, only about half the infants were fully breastfed, which makes it quite challenging to propose nutrition solutions in this age group. Much greater emphasis must be placed on prevention of fetal growth retardation and preterm births, and optimizing maternal health and nutrition. Additionally, substantial investments are needed to support small and sick babies in the health system, not only during hospital stay but also postnatally during the follow up period. India has invested in a substantial workforce that can provide this support in primary care settings. They need to be trained for optimizing maternal health and nutrition and supporting mothers in community kangaroo care [11]. The strong evidence emerging on the role of mother newborn care units in optimizing newborn outcomes is an additional strategy worth emulating at scale [12]. India can lead the way for the region by prioritizing such investments in early child growth and human capital development [13].

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INVITED COMMENTARY

General Movement Assessment in Prediction of Neurodevelopmental Disability and Cerebral Palsy

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With the incidence of preterm births in India being 7-9%, and further rising, the associated neurodevelopmental complications have an enormous burden on the limited resources available in our country. Early diagnosis and management of these complications can mitigate the risk of adverse neurodevelopmental outcomes and improve caregiver well-being.

The article in this issue of the journal [1], a prospective cohort study with a 2-year follow-up, reiterates the universal utility and feasibility of the Prechtl General Movement Assessment (GMA) [2] for the prediction of neurodevelopmental disorders and disabilities including cerebral palsy (CP) in resource-limited settings, especially if applied at 3 to 5 months post-term age.

The GMA is a nonintrusive, highly sensitive, and reliable method to evaluate the young nervous system and has been internationally recommended as the best clinical tool to predict cerebral palsy in infants who are younger than 5 months post-term age [3]. General movements (GMs) are spontaneous entirebody movements present from early fetal life till about 5 months after term age. They are variable sequences of movements of the arm, leg, neck and trunk with changing intensity, force and speed. Essential to GM assessment is the Gestalt visual perception of movement complexity and variation [2]. GMs present distinct age specific patterns during the preterm and term periods. Prior to term age, the GMs are named Preterm GMs and from term age till two months post-term they are termed as Writhing movements. Writhing movements are typically ellipsoid movements, which creates the impression that the infant is writhing. At 6-9 weeks post-term age, these writhing movements gradually disappear and Fidgety movements (FMs) emerge, which are present until the end of the fifth month or even a bit longer. FMs are very tiny movements with variable acceleration of neck, trunk, and limbs in all directions. They are continual in the awake non-crying infant, except during focused attention [2].

If the nervous system is functionally impaired, GMs lose their variable and complex quality. Therefore, the presence of normal and variable general movements indicate normal development whereas abnormal and monotonous general movements may herald neurologic impairment. During preterm and term age, three types of abnormal GMs have been described [2]:

- *Poor repertoire GMs (PR)*: Here, the sequence of the successive movement components is monotonous and arm, leg, trunk, and head movements do not occur in the normal rich and complex sequence
- *Cramped synchronized GMs (CS)*: wherein the movements appear rigid with almost simultaneous contraction and thereafter almost simultaneous relaxation of limb and trunk muscles.
- *Chaotic GMs (Ch)*: Large amplitude abrupt movements of all limbs that occur in a chaotic order with-out any fluency or smoothness.

CS GMs have a particularly high predictive value (70% sensitivity and 97% specificity) for spastic CP [2]. CS movements that start already in the moderate to late preterm age are associated with later worse motor impairment. Infants with Ch GMs typically develop CS GMs around term and hence also have a high risk for spastic CP. PR GMs are less predictive and rather unspecific [2], as shown in the present article too [1]. However, if preterm born infants show consistently PR GMs up to 8 weeks after term, they have an increased risk for learning difficulties at school-age [4].

Fidgety movements (FMs) are judged abnormal if they are either absent (F-) i.e., FMs are never observed from ages 6 to 20 weeks post-term; or abnormal (AF), i.e., they may resemble normal FMs, but have moderately or greatly exaggerated amplitude, speed and jerkiness [2,5].

Normal FMs suggest normal neurological development while the absence of FMs at 3-5 months post-term age is the most sensitive and specific indicator of later neurological impairments [2,3,5].

Apart from the categorical GMA, further refinements in scoring of GMs have been recently developed, which include the GM optimality score (GMOS) [6] and the Motor Optimality Score-Revised (MOS-R) [5]. The MOS-R is a detailed structured assessment that is based both on standard GMA and on the assessment of postural and movement patterns co-occurring with FMs. A low motor optimality score is associated with a limited functional mobility and activity and predicts the severity of CP [5]. Recently, it has been shown that the MOS-R was highly predictive for the 12-year neurological and behavioral outcomes in children born extremely preterm [7]. Apart from utility of GMA in prediction of CP, recent evidence reveals increased occurrences of abnormal GMs in infants later diagnosed with autism spectrum disorder, various genetic disorders, as well as in infants born to mothers with viral infections during pregnancy such as HIV, Zika [5] or SARS-CoV-2. The long-term relevance of GMA for cognition and speech-language performance during puberty age or even young adulthood is also increasingly being recognized [8].

GMA requires an adequate video recording which is scored on the basis of the observer's visual Gestalt perception of normal vs. abnormal movement patterns, undisturbed by other environmental impressions. Video recording has the added advantage of playback and storing the recordings for documentation and future reference. An optimal GMA consists of at least one recording during the preterm period, one during term age and another one performed between 9-16 weeks post term [2]. As the appearance, quality and interpretation of general movements depend on the gestational age of the infant, it is imperative that the gestational age be accurately calculated, based on a confirmed last menstrual period date or a first trimester ultrasound, which is a challenge in populations without access to good quality antenatal care.

A few other precautions are necessary while recording: the infant should lie in supine position on a plain, non-distracting surface, preferably dressed in a vest and diaper, leaving arms and legs bare. Filming during prolonged episodes of fussing, crying or hiccupping must be avoided. Younger preterm infants can be recorded when bouts of activity occur, also during sleep. The duration of the recording depends on the age of the infant and doesn't need to be more than 2-5 minutes. Standardized GM recordings may be a challenge especially in home-based settings. To overcome this, a boom of technological approaches ranging from mobile-app-based recording tools to automated pose estimation through sensor based or marker less approaches have surfaced recently [9]. Apps allow parents to directly upload a video of their infant's GMs to be assessed by experts, without the need for attending an on-site appointment. However, such a procedure may not be feasible in the absence of cameras and smartphones. To counter this deficiency, community health workers or ASHAs can be trained to film the movements [10], which can be scored distantly by certified assessors with specific high-quality training.

Despite all these technicalities, GMA is much easier to be carried out than most neurodevelopmental assessments. Hence, GMA is suitable for day-to-day clinical applications, particularly in low-resource settings, where obtaining an MRI may not be practically feasible. Being entirely non-intrusive, GMA is generally accepted by caregivers with divergent social and cultural backgrounds [2,5,9]. It is imperative that the pediatrician become familiar not only with the technique of recording GMs, but also with their inter-pretation, so as to counsel the parents of high-risk infants and refer for timely intervention.

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RESEARCH PAPER

Dissimilar Associations Between Stunting and Low Ponderosity Defined Through Weight for Height (Wasting) or Body Mass Index for Age (Thinness) in Under-Five Children

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Background: Wasting and stunting commonly coexist, supposedly due to biological and social mechanisms. In under-five children, low-ponderosity is defined as <–2SD of WHO standards for either weight for height (wasted) or body mass index for age (thin) metrics. Unlike body mass index for age, weight for height ignores physiological changes in ponderosity with age, resulting in overestimation of wasting in comparison to thinness in under-5 populations with high stunting prevalence. This suggests a plausible statistical explanation for the wasting-stunting association.

Aim: To test the null hypothesis that wasting-stunting (WaSt) and thinness-stunting (ThSt) associations are similar.

Methods: Demographic Health Survey datasets (2010-2020) from South and South-East Asia (7 countries) and Sub-Saharan Africa (13 countries) were evaluated. WaSt and ThSt associations were estimated as odds ratio (OR) for individual datasets, which was pooled (random-effects meta-analysis). Stratified analyses were done for sex, age and region.

Results: Young infants (0-6 months) comprised 8-14% of under-five children, with equal representation of boys and girls. Participants, especially Asians, were mostly shorter with lower ponderosity than WHO standards. WaSt prevalence was higher than ThSt in the 6-59 months age group, but lower in young infants. Pooled WaSt estimates were not significant: Asia (OR 0.95; 95% CI 0.75-1.14), Africa (1.17; 0.95-1.40), and combined (1.09; 0.93-1.24). In contrast, pooled ThSt associations were significantly negative: Asia (0.63; 0.50-0.76), Africa (0.82; 0.68-0.96), and combined (0.75; 0.65-0.85). In girls, these associations were attenuated for WaSt (0.96; 0.8-1.1), but enhanced for ThSt (0.6; 0.5-0.7).

Conclusion: WaSt and ThSt associations are dissimilar. This suggests a primary statistical explanation for the reported wasting-stunting association, originating from ignoring physiological changes with age.

Keywords: Africa, Anthropometry, Asia, Underweight, Malnutrition.

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In the Sustainable Development Goal (SDG) 2 on Zero Hunger, stunting and wasting are listed as individual conditions. By 2025, India too is committed to achieve: *i*) a 40% reduction in the number of children under-5 who are stunted, and *ii*) reduce and maintain childhood wasting to less than 5% [1]. Recently, there has been a strong advocacy for integrated programmatic approaches for simultaneously addressing both wasting and stunting, instead of dealing with them as distinct entities. The underlying rationale is that both conditions have etiologic commonality and frequently coexist, either simultaneously or at different periods in the same child. Also, concurrently stunted and wasted children have the highest risk of near-term mortality [2,3].

A recent analysis of cross-sectional survey datasets on 1.8 million children documented a robust positive association between wasting and stunting; the pooled odds ratio was 1.40 (95% CI: 1.32, 1.49) [4]. This study, providing fuel for the intensified advocacy efforts, also recommended extension of therapeutic feeding programs to concurrently wasted-stunted cases and routine reporting of wasting-stunting prevalence in surveys [4]. To guide future investments, the Wasting-Stunting Technical Interest Group has recommended priority research topics, which predominantly focus on biological and social mechanisms of this association and policy domains [5].

Scant attention has been directed towards a statistical explanation for the wasting-stunting association. In under-five children, low-ponderosity may be defined when either weight for height or body mass index for age (BMI) are below –2SD of the respective World Health Organization (WHO) standards [6,7]. Children with low ponderosity diagnosed by weight for height metric are also referred to as wasted. Weight for height ignores the physiological changes in ponderosity with age, whereas, by construct, BMI for age accounts for such alterations [7,8]. Notwithstanding the excellent correlation (r=0.97–0.99) between these metrics,

the two definitions produce cut-offs, and hence estimates of low ponderosity, that differ with the age, sex and height of children [9]. Importantly, weight for height is associated with an overestimation of low ponderosity burden in comparison to BMI for age in under-5 populations with high stunting pre-valence, especially in children aged 6-59 months [9]. This suggests a plausible statistical explanation for the associa-tion between wasted and stunted children. For nomen-clature clarity, we subsequently refer to low ponderosity diagnosed by weight for height metric as wasted (or wasting) and that by BMI for age metric as thin (or thinness), and their co-occurrence with those stunted as wasted-stunted (WaSt) and thin-stunted (ThSt), respectively. We tested the null hypothesis that WaSt and ThSt associations are similar, to refute the statistical origin postulate. This was done in contemporary datasets from South and South-East Asia and Sub-Saharan Africa, both of which have a high prevalence of stunting.

METHODS

Ethical clearance was not required for these secondary analyses of datasets, for which informed consent of parents and ethical clearance from relevant authorities had been taken. Datasets were used from two settings: *i*) *Research*: The Meerut study was specifically designed to estimate the prevalence of severe acute malnutrition and identify midarm circumference surrogates for weight for height cutoffs. This community-based cross-sectional study was conducted between September, 2012 and October, 2013 in Meerut District, Uttar Pradesh, India [10]. This clinical research, conducted on 18,463 children between 6 and 59 months of age with quality assurance, was expected to have greater precision of measurements, *ii*) *National Surveys*: Demographic Health Survey (DHS) datasets from South- and South-East Asia and Sub-Saharan Africa, which had collected anthropometric measurements for children between 0-59 months in 2010 or later, were eligible for analysis [11]. A common set-up was constructed for the DHS datasets with the same variables, variable names, variable types, variable lengths, coding schemes, unit of measurement, and file format. These included case ID, age, sex, weight and length/height.

The WHO macro syntax for STATA was used to generate the four anthropometric indices *z*-scores from the absolute length/height, weight, age and sex, namely, length/height for age (HAZ), weight for age (WAZ), weight for height (WHZ), and body mass index for age (BMIZ) [7]. WHO criteria were followed to set the missing values (*z*-scores): HAZ <-6 or >6; WAZ <-6 or >5; WHZ <-5 or >5; and BMIZ <-5 or >5 [7,12]. In the Meerut study, we considered missing values below -7 SD for all indices, because apparently abnormal measurements had been re-verified in the field. Children with low (<-2*z* of WHO standard) anthropometric indices were labelled as follows: underweight (for weight for age), stunted (for length/height for age), wasted (for weight for height), and thin (for BMI for age). Children who were both wasted and stunted were labelled as WaSt, while those who were both thin and stunted were defined as ThSt.

Statistical analysis: The concurrent WaSt and ThSt associations (strength and direction) were evaluated by calculating the Odds Ratios (OR) for each country dataset separately. This measure of association was symmetrical because the OR for being wasted (or thin) given stunting and the OR for being stunted given wasting (or thinness) were identical [4]. The ORs from the DHS datasets were pooled using a random-effects meta-analysis [13,14], because the clinical context of the surveys was heterogeneous. Stratified analyses were also conducted for sex and age groups (mainly in two broad age groups of 0-6 months and 6-59 months, and at 6-monthly intervals from 0-1 year, and yearly intervals thereafter, in pooled estimates to explore narrower age associations). WHZ (or BMIZ) and HAZ were compared in three categories, namely, wasted (or thin) only, stunted only and WaSt (or ThSt). As these indices were not normally distributed, being right truncated at -2 *z*-scores, the data was summarized as median (IQR) and compared by nonparametric Mann-Whitney test. A non-parametric effect size measure was used to capture the changes in central tendency and data distribution shape through a user defined package (ImpactEffectsize Version: 0.6.2) [15]. Pearson correlation coefficients were computed between weight for height and BMI for age *z*-scores, and between both these metrics individually and weight (kg) and height (cm). Coefficients were also computed for the log weight regressed on log height. STATA 16.0 version (StataCorp LLC) and R software 4.0.2 version (R Core Team, 2020; *www.R-project.org/*) were used to perform the analyses.

RESULTS

Among the available online DHS datasets, twenty countries (7 from South- and South-East Asia and 13 from Sub-Saharan Africa) fulfilled the inclusion criteria. The demographic and anthropometric characteristics of the analyzed datasets are summarized in **Web Table I**. The surveys had been conducted between 2011 and 2020. Except for India (*n*=207,364), the sample size in other DHS surveys ranged from 2,318 (Nepal) to 18,279 (Kenya). Young infants (0-6 months) comprised 8-14% of under-five children. There was almost equal represen-tation of boys and girls. The participants were mostly shorter and had lower ponderosity in comparison to the WHO standards. In individual countries, the ranges for HAZ means were -0.9 to -1.6 and for their SDs 1.1 to 1.7. In South and South East

Asia, the range for WHZ means was -0.2 to -0.9 and for BMIZ means was -0.1 to -0.8. These *z*-scores were higher for Sub-Saharan Africa, ranging from +0.4 to -0.5 and +0.5 to -0.5, respectively. Their SDs in both regions ranged from 1.0 to 1.4. The 6-59 months old participants (*n*=18452) in the Meerut study from India had the maximum left shift in means of HAZ (-1.9), WHZ (-1.1) and BMIZ (-0.9).

The prevalence of anthropometric deficits in DHS datasets is summarized in **Table I**. The overall prevalence (95% CI) of those stunted, wasted, thin, WaSt and ThSt were 31% (28%, 33.9%), 7.2% (3.6%, 10.7%), 6.4% (3.2%, 9.6%), 2.3% (1.3%, 3.4%) and 1.6% (0.9%, 2.3%), respectively. All these deficits were higher in the Asian regions. India had the highest prevalence, especially pronounced for those wasted (20.1%), thin (18.3%), WaSt (6.2%) and ThSt (4.4%). In all datasets, the prevalence of WaSt was significantly higher than that of ThSt. In comparison to the 0-6 months age group, the 6-59 months age group had a higher prevalence of those stunted (**Web Tables II** and **III**). WaSt prevalence was lower than ThSt prevalence in 0-6 months age group, but the converse was true for older children. Both WaSt and ThSt prevalence were higher in boys (**Web Table IV**). The male to female ratios in individual countries in 6-59 months age group ranged from 1.05 to 2.82, except for WaSt in Ghana (0.92) and Liberia (0.99). The ratios were comparable for WaSt and ThSt (overlapping confidence intervals).

Association between stunting and wasting or thinness: In the research dataset (Meerut study), there were significant positive associations for both WaSt [OR (95% CI) 1.91 (1.8, 2.1); *P*<0.001] and ThSt [OR (95% CI) 1.11 (1.0, 1.2); *P*=0.029]. **Fig. 1** summarizes the WaSt and ThSt associations in under-five children in DHS datasets. Significant positive WaSt associations were seen in six African countries, while significant negative associations were documented in one African and two Asian countries. The pooled estimates were not significant for Asia [OR (95% CI) 0.95 (0.75, 1.14); I^2=88%], Africa [1.17 (0.95, 1.40); I^2=92%], or the combined dataset [1.09 (0.93, 1.24); I^2=92%] with considerable heterogeneity. In contrast, for ThSt, significant negative associations were documented in six Asian and seven African countries and a positive

Table I Prevalence (%) of Anthropometric Deficits in 0-59 Months Age Group in Demographic Health Survey Datasets from South and South-East Asia and Sub-Saharan Africa

Country (year)	*Number*	*Stunting (95% CI)*	*Wasting (95% CI)*	*Thinness (95% CI)*	*Wasted-stunted (95% CI)*	*Thin-stunted (95% CI)*	*P value*[a]
Demographic Health Survey Datasets: South and South-East Asia							
Bangladesh (2017-18)	7,711	31.4 (30.4, 32.5)	8.5 (7.9, 9.1)	7.3 (6.7, 7.9)	3.0 (2.6, 3.4)	2.0 (1.7, 2.3)	<0.001
Cambodia (2014)	4,289	32.8 (31.4, 34.3)	9.7 (8.8, 10.6)	8.3 (7.5, 9.2)	3.3 (2.8, 3.9)	1.9 (1.5, 2.4)	<0.001
India (2015-16)	207,364	38.1 (37.9, 38.3)	20.1 (20.0, 20.3)	18.3 (18.1, 18.4)	6.2 (6.1, 6.3)	4.4 (4.3, 4.5)	<0.001
Maldives (2016-17)	2,342	15.1 (13.7, 16.6)	9.0 (7.9, 10.2)	8.0 (7.0, 9.2)	1.6 (1.2, 2.2)	1.2 (0.8, 1.7)	0.012
Myanmar (2015-16)	4,146	30.8 (29.4, 32.2)	6.6 (5.9, 7.4)	5.8 (5.1, 6.5)	1.7 (1.3, 2.1)	1.1 (0.8, 1.4)	<0.001
Nepal (2016)	2,318	36.6 (34.7, 38.6)	9.3 (8.2, 10.5)	8.1 (7.0, 9.2)	3.5 (2.8, 4.3)	2.3 (1.8, 3.0)	<0.001
Pakistan (2017-18)	4,079	38.6 (37.1, 40.1)	7.7 (6.9, 8.5)	7.2 (6.5, 8.0)	2.8 (2.3, 3.3)	2.3 (1.8, 2.8)	0.003
Pooled SSEA	232,249	31.9 (26.4, 37.4)	10.1 (4.1, 16.1)	9.0 (3.4, 14.6)	3.2 (1.3, 5.1)	2.2 (0.8, 3.5)	
Demographic Health Survey Datasets: Sub-Saharan Africa							
Angola (2015-16)	6,268	37.6 (36.4, 38.8)	5.0 (4.5, 5.6)	4.5 (4.3, 5.3)	1.9 (1.6, 2.3)	1.5 (1.2, 1.8)	<0.001
Benin (2017-18)	11,626	32.0 (31.2, 32.9)	5.2 (4.8, 5.6)	4.7 (4.3, 5.1)	2.0 (1.7, 2.2)	1.6 (1.4, 1.8)	<0.001
Cameroon (2018)	4,435	28.1 (26.8, 29.5)	3.9 (3.4, 4.5)	4.1 (3.5, 4.7)	1.1 (0.8, 1.4)	0.9 (0.6, 1.2)	0.072
Congo (2011-12)	4,464	26.9 (25.7, 28.3)	5.4 (4.8, 6.1)	5.2 (4.5, 5.8)	1.2 (0.9, 1.6)	0.9 (0.6, 1.2)	0.003
Ethiopia (2019)	5,055	35.9 (34.6, 37.3)	8.9 (8.2, 9.7)	6.9 (6.3, 7.7)	3.5 (3.1, 4.1)	2.1 (1.7, 2.5)	<0.001
Gambia (2019-20)	3,805	18.3 (17.1, 19.6)	5.1 (4.5, 5.9)	4.3 (3.7, 5.0)	1.4 (1.1, 1.8)	0.9 (0.7, 1.3)	<0.001
Ghana (2014)	2,682	19.0 (17.5, 20.5)	4.9 (4.2, 5.8)	4.4 (3.7, 5.2)	1.4 (1.0, 1.9)	1.0 (0.7, 1.5)	0.004
Kenya (2014)	18,279	27.3 (26.6, 27.9)	5.4 (5.1, 5.8)	4.8 (4.5, 5.1)	1.7 (1.5, 1.9)	1.0 (0.8, 1.1)	<0.001
Liberia (2019-20)	2,439	32.3 (30.5, 34.2)	4.2 (3.5, 5.1)	3.5 (2.8, 4.3)	1.6 (1.2, 2.2)	1.1 (0.7, 1.6)	0.005
Malawi (2015-16)	5,110	35.5 (34.2, 36.8)	3.1 (2.6, 3.6)	2.7 (2.3, 3.1)	1.0 (0.7, 1.3)	0.7 (0.5, 1.0)	0.003
Mali (2018)	8,202	26.8 (25.8, 27.7)	9.3 (8.7, 10.0)	9.0 (8.4, 9.6)	3.0 (2.7, 3.4)	2.4 (2.1, 2.8)	<0.001
Mozambique (2011)	9,251	39.6 (38.7, 40.7)	5.2 (4.8, 5.7)	5.0 (4.6, 5.5)	1.5 (1.2, 1.7)	1.2 (1.0, 1.5)	0.005
Nigeria (2018)	11,308	36.3 (35.4, 37.1)	6.6 (6.2, 7.1)	5.9 (5.5, 6.4)	3.1 (2.8, 3.4)	2.4 (2.1, 2.7)	<0.001
Pooled SSA	92,924	30.4 (27.0, 33.8)	5.6 (4.7, 6.4)	5.0 (4.2, 5.8)	1.9 (1.5, 2.3)	1.4 (1.1, 1.7)	
Grand Pool (a+b)	325,173	31.0 (28.0, 33.9)	7.2 (3.6, 10.7)	6.4 (3.2, 9.6)	2.3 (1.3, 3.4)	1.6 (0.9, 2.3)	

P-values for the difference in WaSt and ThSt prevalence using Mc-Nemar test. Pooled SSEA: pooled estimates for South and South-East Asia. Pooled SSA: pooled estimates for Sub-Saharan Africa. Grand pool: pooled data from all the Demographic Health Survey Datasets studied.

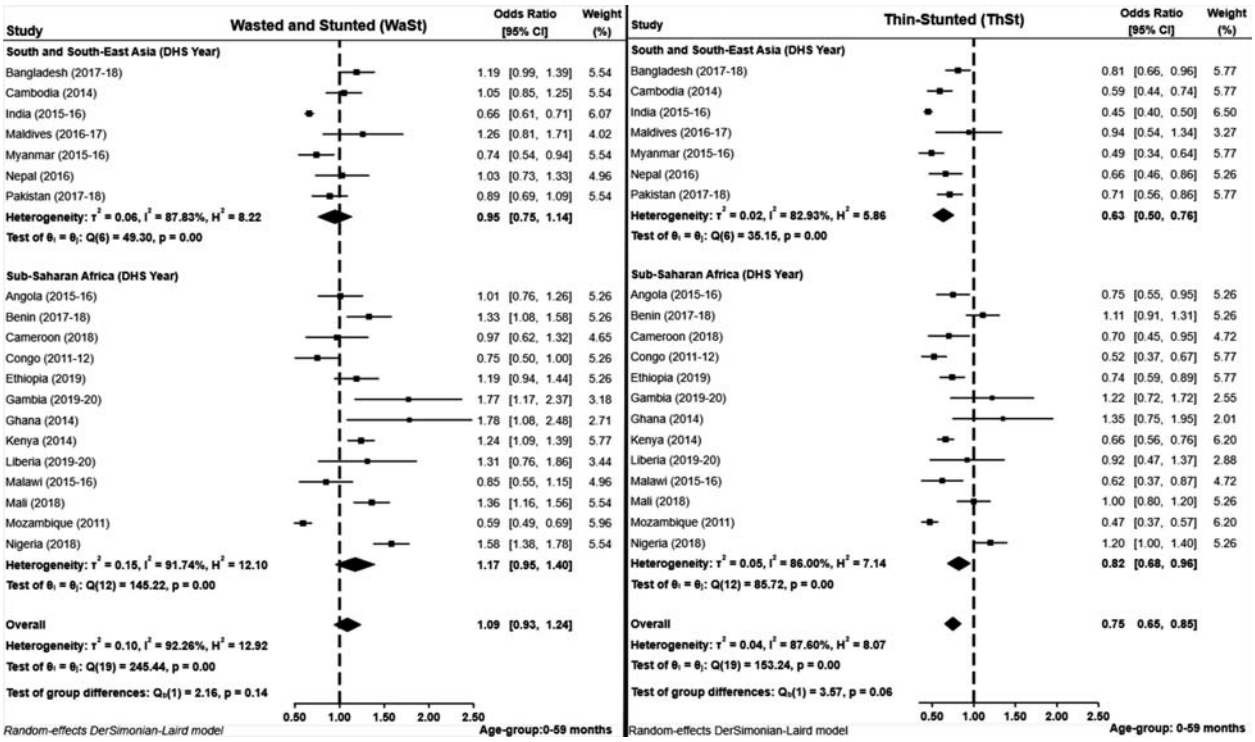

Fig. 1 Summary of wasting-stunting (WaSt) and thinness-stunting (ThSt) associations in the Demographic Health Survey datasets from South and South-East Asia and Sub-Saharan Africa for children aged 0-59 months.

association for one African country. The pooled estimates were significantly negative for Asia (0.63; 0.50, 0.76; I^2=83%), Africa (0.82; 0.68, 0.96; I^2=86%), and the combined dataset (0.75; 0.65, 0.85; I^2=88%) with considerable heterogeneity. In girls, these associations were attenuated for WaSt, but enhanced for ThSt (**Web Fig. 1**). In the combined dataset, the WaSt association for boys was 1.28 (1.09, 1.47) and for girls 0.96 (0.81, 1.10); the corresponding figures for ThSt were 0.74 (0.62, 0.85) and 0.57 (0.48, 0.67), respectively. In the combined dataset, in 0-6 months age group (**Web Fig. 2**), the WaSt association was negative (0.59; 0.40, 0.87), but the ThSt association was positive (2.0; 1.34, 3.0). The converse was documented in the 6-59 months age group (**Web Fig. 3**) for WaSt (1.18; 1.01, 1.35) and ThSt (0.69; 0.59, 0.79) associations. **Fig. 2** summarizes the comparison of WaSt and ThSt associations and their prevalence in the combined dataset in narrower age groups. The maximal contrast in these associations was evident in the 0-6 months and 12-24 months age groups.

Z-scores differences between single and combined anthropometric deficits: In 6-59 months age group, the WHZ (or BMIZ) impact difference among those only wasted (or thin) *versus* WaSt (or ThSt) was mostly null (**Web Table V**). Similarly, the HAZ impact difference (**Web Table VI**) was mostly null or small (≤0.2). However, there were large WHZ (or BMIZ) impact differences, ranging from 1.8 to 3.2, between stunted only *versus* WaSt (or ThSt). Similar findings, but of a lower magnitude, were documented for HAZ (impact differences 1.5 to 2.2). These patterns were broadly comparable for WHZ and BMIZ.

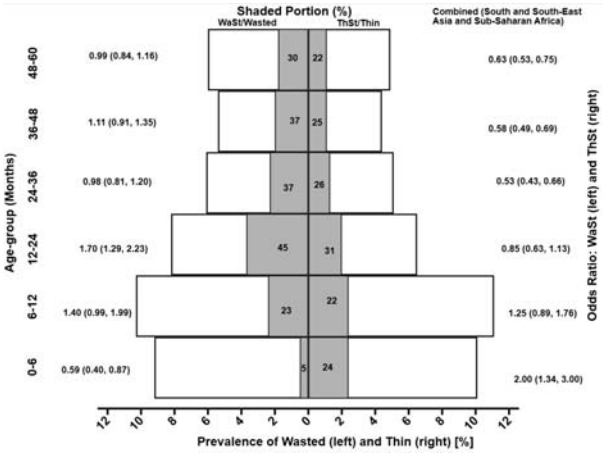

Fig. 2 Comparison of associations between wasting-stunting (WaSt) and thinness-stunting (ThSt) and their prevalence in the South and South-East Asia and Sub-Saharan Africa from the Demographic Health Survey combined datasets in stratified age groups.

Except for Nepal (r=0.92), there was almost perfect correlation (r=0.96 to 0.98) between WHZ and BMIZ in other datasets (**Web Table VII**). The beta-coefficients of log weight regressed on log height approximated 2 (1.81 to 1.95), except for Nepal (2.58). In general, both WHZ and BMIZ had comparable (non-overlapping confidence intervals) patterns of higher correlations with weight than with height.

DISCUSSION

In these analyses, the WaSt and ThSt associations were dissimilar and their directions varied with age. For the 0-59 months age group, the pooled estimates for Asia, Africa or the combined dataset were not significant for WaSt association, but were significantly negative for ThSt association. In the combined dataset, in 0-6 months age group, the WaSt association was significantly negative, but the ThSt association was significantly positive, whereas the converse was documented in 6-59 months old children. The comparison of WaSt and ThSt associations, and the descriptive epidemiology of ThSt association, from regions with high prevalence of stunting, is a novel contribution to the literature. Use of contemporary data-sets, concordance of observed patterns among various countries and regions, and alignment with earlier reports of higher WaSt prevalence in boys [4], and in comparison to ThSt [9], inspires confidence in the findings. Further, the flipover in the WaSt and ThSt associations after the age of 6 months is in consonance with the earlier findings on age differences [9].

Dissimilar, mostly opposing, associations between stunting and the two metrics of ponderosity (WHZ and BMIZ) indicate a primary statistical explanation for the reported WaSt association, which originates from ignoring physiological changes with age in the weight for height metric. Further support for this contention include: *i*) the flip-over of these associations around 6 months of age, as predicted by the curvature change in WHO BMI for age charts [7]; *ii*) almost perfect correlation between WHZ and BMIZ; *iii*) beta-coefficients of log weight regressed on log height approximated 2 (1.81 to 1.95) [16,17], providing validation for the use of BMI formula in under-five children; and *iv*) comparable patterns among both metrics of higher correlations with weight than with height.

The apparent differences from the robust positive WaSt association [OR (95% CI) 1.40 (1.32, 1.49)] in pooled analyses from 51 countries [4] merit closer scrutiny. First, these calculations excluded the 0-6 months age group, wherein the WaSt association is negative, thereby biasing the estimates upwards. Moreover, our 6-59 months pooled estimates were positive, but with a lower magnitude. Second, the earlier study's database included refugee settings and relatively dated surveys [4], with a higher probability of lower HAZ scores. In our research dataset from Meerut, with a fairly low mean (SD) HAZ of -1.9 (1.2), the WaSt association was markedly positive.

The near-term mortality in WaSt children is considerably higher than those who are either stunted only or wasted only [2-4]. In the earlier analysis [4], WaSt subjects were both more severely wasted than wasted only children, and more severely stunted than stunted only children. However, the effect sizes were small and it was hypothesised that these were probably insufficient to account for the heightened risk of mortality for WaSt and therefore, a multiplicative rather than an additive interaction between wasting and stunting is occurring. In contrast, in most datasets in this study, these effect sizes were null. But, by definition, there were large effect sizes (~2.0) in the paired anthropometric deficit; WaSt cases were both more severely stunted than wasted only children, and more severely wasted than stunted only children. Thus, the substantial conjoint effect of the two anthropometric deficits, acting either in an additive or multiplicative manner, could explain the considerably higher mortality risk in WaSt. Unfortunately, there seems to be no comparative data for the ThSt association, which merits exploration.

Governments, donors and other stakeholders should carefully examine the potential returns for investments in funding research focussing on biological and social mechanisms of WaSt association [5]. The recommended extension of routine therapeutic feeding programs to WaSt children [4] deserves careful consideration since this condition is largely a statistical phenomenon, primarily driven by severity and high prevalence of stunting. The WHO Guidelines on preventing overweight and obesity in the context of double burden of malnutrition state [18]: *"Routinely providing supplementary foods to moderately wasted infants and children presenting to primary health-care facilities is not recommended"* and *"The provision of supplementary foods for treating stunting among infants and children who present to primary health-care facilities is not recommended."* This recommendation resonates with the recent finding of 'metabolic obesity' (dysglycemia or dyslipidemia) in at least half of the children aged 5-19 years, including those who were thin or stunted, in the Comprehensive National Nutrition Survey from India [19].

The following limitations merit consideration. The DHS data across these countries were collected during different years, but within a decade. We could have analyzed all contemporary DHS datasets and also explored access to databases from refugee settings. However, their inclusion is unlikely to alter the main finding, since the analysis con-tains regions with high prevalence of stunting. A pooled analysis from exclusive research settings may have provided greater

WHAT IS ALREADY KNOWN?

- Wasting and stunting commonly coexist, supposedly due to biological and social mechanisms.
- Unlike body mass index for age, weight for height ignores physiological changes in ponderosity with age, resulting in overestimation of wasting in comparison to thinness.

WHAT THIS STUDY ADDS?

- Wasting-stunting and thinness-stunting associations are dissimilar, and mostly in opposing directions.
- This suggests a primary statistical explanation for the reported wasting-stunting association, which originates from ignoring physiological changes with age in the weight for height metric.

confidence and precision because of lower measurement errors. However, we included one such dataset, which confirmed the pattern, and also survey findings are invariably used for policy decisions.

In conclusion, WaSt and ThSt associations are dissimilar. This suggests a primary statistical explanation for the reported wasting-stunting association, which originates from ignoring physiological changes with age in weight for height metric.

Ethics clearance: Authors declare that the study procedures conform to the principles laid down in the Declaration of Helsinki.

Note: Additional matter related to this article is available with the web version at *www.indianpediatrics.net*

Contributors: HSS conceptualized the study. LNR did the primary analyses and interpretation under the supervision of MS and HSS. LNR and HSS drafted the initial manuscript. All authors provided critical inputs into revision of the article and are willing to be accountable for all aspects of the study.

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Web Table I Descriptive Characteristics of the Analysed Datasets

Country (Year)	*N (0-59 months)*	*0-6 months (% of total)*	*Boys (%)*	*HAZ: Mean (SD)*	*WHZ: Mean (SD)*	*BMIZ: Mean (SD)*
Research dataset: Meerut, Uttar Pradesh, India						
Meerut (2012-13), India[a]	18,452	NA	53.4	-1.9 (1.2)	-1.1 (0.9)	-0.9 (0.9)
Demographic Health Survey Datasets: South and South-East Asia (a)						
Bangladesh (2017-18)	7,711	11.9	52	-1.4 (1.3)	-0.5 (1.1)	-0.4 (1.1)
Cambodia (2014)	4,289	10.7	50.6	-1.4 (1.4)	-0.6 (1.2)	-0.5 (1.2)
India (2015-16)	207,364	9.9	51.7	-1.5 (1.7)	-0.9 (1.4)	-0.8 (1.4)
Maldives (2016-17)	2,342	7.6	50.9	-0.9 (1.2)	-0.4 (1.3)	-0.4 (1.3)
Myanmar (2015-16)	4,146	10.4	51.6	-1.4 (1.3)	-0.5 (1.1)	-0.3 (1.1)
Nepal (2016)	2,318	9.7	52.3	-1.6 (1.3)	-0.6 (1.1)	-0.5 (1.1)
Pakistan (2017-18)	4,079	10.4	50.5	-1.6 (1.7)	-0.2 (1.3)	-0.1 (1.3)
Pooled SSEA[b]	***232,249***	***10.0***	***51.4***	***-1.4 (1.7)***	***-0.9 (1.4)***	***-0.8 (1.4)***
Demographic Health Survey Datasets: Sub-Saharan Africa (b)						
Angola (2015-16)	6,268	12.2	49.9	-1.5 (1.5)	-0.1 (1.2)	0.0 (1.2)
Benin (2017-18)	11,626	11.6	50.5	-1.4 (1.3)	-0.3 (1.1)	-0.2 (1.1)
Cameroon (2018)	4,435	11.5	50.7	-1.1 (1.7)	0.4 (1.4)	0.5 (1.4)
Congo (2011-12)	4,464	11.9	51.0	-1.1 (1.5)	-0.2 (1.2)	-0.1 (1.2)
Ethiopia (2019)	5,055	11.0	51.2	-1.4 (1.5)	-0.5 (1.2)	-0.3 (1.2)
Gambia (2019-20)	3,805	13.8	52.4	-1.1 (1.1)	-0.4 (1.0)	-0.3 (1.0)
Ghana (2014)	2,682	12.4	51.7	-1.0 (1.3)	-0.3 (1.1)	-0.2 (1.1)
Kenya (2014)	18,279	10.2	50.6	-1.2 (1.4)	-0.1 (1.2)	0.0 (1.2)
Liberia (2019-20)	2,439	11.2	49.1	-1.4 (1.3)	0.0 (1.1)	0.2 (1.1)
Malawi (2015-16)	5,110	9.4	49.1	-1.5 (1.4)	0.1 (1.1)	0.2 (1.1)
Mali (2018)	8,202	11.4	50.8	-1.1 (1.6)	-0.5 (1.2)	-0.5 (1.2)
Mozambique (2011)	9,251	10.9	50.0	-1.6 (1.6)	0.2 (1.3)	0.4 (1.4)
Nigeria (2018)	11,308	10.4	50.7	-1.5 (1.6)	-0.3 (1.1)	-0.2 (1.2)
Pooled SSA[c]	***92,924***	***11.1***	***50.5***	***-1.3 (1.5)***	***-0.2 (1.2)***	***-0.1 (1.2)***
Grand Pool[d] (a+b)	***325,173***	***10.3***	***51.4***	***-1.4 (1.6)***	***-0.7 (1.4)***	***-0.6 (1.4)***

[a] *The Meerut study was conducted in 6-59 months old children*
[b] *Pooled SSEA: Pooled South and South-East Asia*
[c] *Pooled SSA: Pooled Sub-Saharan Africa*
[d] *Grand pool: Pooled data from all the Demographic Health Survey Datasets studied*

Web Table II Prevalence (%) of Anthropometric Deficits in 0-6 months in the Demographic Health Survey datasets

Country	*Number*	*Stunting (95% CI)*	*Wasting (95% CI)*	*Thinness (95% CI)*	*WaSt (95% CI)*	*ThSt (95% CI)*	*P-value*[a]
Demographic Health Survey Datasets: South and South-East Asia (a)							
Bangladesh	916	19.4 (17.0, 22.1)	10.0 (8.3, 12.2)	12.9 (10.9, 15.2)	1.1 (1.0, 2.0)	3.6 (2.6, 5.0)	<0.0001
Cambodia	458	16.2 (13.1, 19.8)	13.5 (10.7, 17.0)	14.4 (11.5, 17.9)	0.7 (0.2, 2.0)	2.0 (1.0, 3.7)	0.0143
India	20,582	20.3 (20.0, 20.9)	28.5 (27.9, 29.1)	29.7 (29.0, 30.3)	2.6 (2.4, 2.8)	5.4 (5.1, 5.8)	<0.0001
Maldives	177	20.9 (15.5, 27.6)	7.9 (4.7, 13.0)	8.5 (5.2, 13.6)	0.0 (0.0, 0.0)	2.3 (0.8, 5.9)	0.0455
Myanmar	430	7.2 (5.1, 10.1)	10.7 (8.1, 14.0)	10.5 (7.9, 13.7)	0.5 (0.1, 1.8)	1.4 (0.6, 3.1)	0.0455
Nepal	224	12.9 (9.1, 18.0)	13.4 (9.5, 18.5)	13.4 (9.5, 18.5)	0.9 (0.2, 3.5)	1.8 (0.7, 4.7)	0.1573
Pakistan	426	17.8 (14.5, 21.8)	11.0 (8.4, 14.4)	14.6 (11.5, 18.2)	1.6 (0.8, 3.4)	4.9 (3.2, 7.5)	0.0002
Pooled SSEA[b]	***23,213***	***16.3 (12.2, 20.4)***	***13.6 (4.7, 22.5)***	***14.9 (6.3, 23.5)***	***1.1 (0.2, 2.3)***	***3.1 (1.5, 4.7)***	
Demographic Health Survey Datasets: Sub-Saharan Africa (b)							
Angola	764	17.6 (15.1, 20.5)	5.2 (3.9, 7.1)	7.6 (5.9, 9.7)	0.3 (0.1, 1.0)	2.1 (1.3, 3.4)	0.0002
Benin	1,352	16.7 (14.8, 18.8)	6.9 (5.6, 8.4)	8.5 (7.1, 10.1)	1.3 (0.8, 2.0)	3.3 (2.5, 4.4)	<0.0001
Cameroon	509	16.5 (13.5, 20.0)	5.5 (3.8, 7.9)	6.3 (4.5, 8.8)	0.0 (0.0, 0.0)	1.6 (0.8, 3.1)	0.005
Congo	530	11.1 (8.7, 14.1)	7.0 (5.1, 9.5)	7.0 (5.1, 9.5)	0.0 (0.0, 0.0)	0.6 (0.2, 1.7)	0.0833
Ethiopia	556	16.0 (13.2, 19.3)	11.3 (8.9, 14.3)	8.6 (6.6, 11.3)	0.7 (0.3, 1.9)	1.4 (0.7, 2.9)	0.0455
Gambia	526	7.8 (5.8, 10.4)	4.2 (2.8, 6.3)	4.9 (3.4, 7.2)	0.4 (0.1, 1.5)	1.5 (0.8, 3.0)	0.0143
Ghana	332	5.7 (3.7, 8.8)	9.3 (6.6, 13)	7.8 (5.4, 11.3)	0.6 (0.2, 2.4)	0.6 (0.2, 2.4)	1.000
Kenya	1,858	11.4 (10.0, 12.9)	5.1 (4.2, 6.2)	4.7 (3.8, 5.7)	0.4 (0.2, 0.9)	0.8 (0.5, 1.3)	0.0082
Liberia	274	20.1 (15.7, 25.3)	4.4 (2.5, 7.6)	5.5 (3.3, 8.9)	0.7 (0.2, 2.9)	2.2 (1.0, 4.8)	0.0455
Malawi	482	20.9 (17.5, 24.8)	3.3 (2.0, 5.4)	3.7 (2.4, 5.9)	0.4 (0.1, 1.6)	1.5 (0.7, 3.0)	0.0253
Mali	932	12.6 (10.6, 14.8)	11.3 (9.4, 13.5)	13.5 (11.5, 15.9)	1.4 (0.8, 2.4)	3.2 (2.3, 4.6)	<0.0001
Mozambique	1,008	23.5 (21.0, 26.2)	8.4 (6.9, 10.3)	10.1 (8.4, 12.1)	1.4 (0.8, 2.3)	3.6 (2.6, 4.9)	<0.0001
Nigeria	1,174	18.0 (15.9, 20.3)	6.5 (5.2, 8.0)	9.5 (8.0, 11.4)	1.4 (0.8, 2.2)	4.1 (3.1, 5.4)	<0.0001
Pooled SSA[c]	***10,297***	***15.1 (12.4, 17.8)***	***6.7 (5.5, 7.9)***	***7.5 (6.0, 9.0)***	***0.1 (0.0, 0.1)***	***2.0 (1.3, 2.7)***	
Grand Pool (a + b)[d]	***33,510***	***15.5 (13.1, 17.9)***	***9.2 (4.1, 14.2)***	***10.1 (5.0, 15.2)***	***0.5 (0.4, 0.5)***	***2.4 (1.3, 3.3)***	

[a]*P-values calculated between the prevalence of WaSt and ThSt using Mc-Nemar test*
[b]*Pooled SSEA: Pooled estimates for South and South-East Asia;* [c]*Pooled SSA: Pooled estimates for Sub-Saharan Africa*
[d]*Grand pool: Pooled data from all the Demographic Health Survey Datasets studied*
Note: *There is no data available for 0-6 months in Meerut study*

Web Table III Prevalence (%) of Anthropometric Deficits in 6-59 Months for the Research Dataset (Meerut study) and the Demographic Health Survey datasets

Country	*Number*	*Stunting (95% CI)*	*Wasting (95% CI)*	*Thinness (95% CI)*	*WaSt (95% CI)*	*ThSt (95% CI)*	*P-value*[a]
Research dataset: Meerut district in Uttar Pradesh, India							
Meerut, India[b]	18,452	45.7 (45.0, 46.4)	16.2 (15.7, 16.8)	11.5 (11.1, 12.0)	9.6 (9.2, 10.0)	5.5 (5.2, 5.9)	<0.001
Demographic Health Survey Datasets: South and South-East Asia (a)							
Bangladesh	6,795	33.0 (31.9, 34.2)	8.3 (7.7, 9.0)	6.5 (5.9, 7.1)	3.2 (2.8, 3.7)	1.8 (1.5, 2.1)	<0.001
Cambodia	3,831	34.8 (33.3, 36.3)	9.2 (8.4, 10.2)	7.6 (6.8, 8.5)	3.6 (3.1, 4.2)	1.9 (1.5, 2.4)	<0.001
India	186,782	40.1 (39.9, 40.3)	19.2 (19.0, 19.4)	17.0 (16.8, 17.2)	6.6 (6.5, 6.7)	4.2 (4.2, 4.3)	<0.001
Maldives	2,165	14.6 (13.2, 16.2)	9.1 (8.0, 10.4)	7.9 (6.9, 9.2)	1.8 (1.3, 2.4)	1.1 (0.7, 1.6)	0.001
Myanmar	3,716	33.5 (32.0, 35.0)	6.1 (5.4, 6.9)	5.2 (4.5, 6.0)	1.8 (1.2, 2.3)	1.0 (0.7, 1.4)	<0.001
Nepal	2,094	39.2 (37.0, 41.3)	8.8 (7.7, 10.1)	7.5 (6.4, 8.7)	3.7 (3.0, 4.6)	2.3 (1.8, 3.1)	<0.001
Pakistan	3,653	41.0 (39.4, 42.6)	7.3 (6.5, 8.2)	6.4 (5.6, 7.2)	2.9 (2.4, 3.5)	1.9 (1.5, 2.4)	<0.001
Pooled SSEA[c]	***209,036***	***33.7 (27.7, 39.8)***	***9.7 (4.1, 15.3)***	***8.3 (3.2, 13.4)***	***3.4 (1.4, 5.3)***	***2.0 (0.7, 3.4)***	
Demographic Health Survey Datasets: Sub-Saharan Africa (b)							
Angola	5,504	40.4 (39.1, 41.2)	5.0 (4.5, 5.6)	4.4 (3.9, 5.0)	2.1 (1.8, 2.5)	1.4 (1.1, 1.8)	<0.001
Benin	10,274	34.0 (33.1, 35.0)	4.9 (4.5, 5.4)	4.2 (3.8, 4.6)	2.1 (1.8, 2.4)	1.4 (1.2, 1.6)	<0.001
Cameroon	3,926	29.6 (28.2, 31.1)	3.7 (3.2, 4.4)	3.8 (3.2, 4.4)	1.2 (0.9, 1.6)	0.8 (0.6, 1.1)	<0.001
Congo	3,934	29.1 (27.7, 30.1)	5.2 (4.6, 6.0)	4.9 (4.3, 5.6)	1.4 (1.0, 1.8)	0.9 (0.6, 1.2)	0.001
Ethiopia	4,499	38.4 (37.0, 39.8)	8.6 (7.8, 9.5)	6.7 (6.0, 7.5)	3.9 (3.4, 4.5)	2.1 (1.7, 2.6)	<0.001
Gambia	3,279	20.0 (18.6, 21.4)	5.3 (4.6, 6.1)	4.2 (3.6, 5.0)	1.6 (1.2, 2.1)	0.8 (0.6, 1.2)	<0.001
Ghana	2,350	20.9 (19.3, 22.5)	4.3 (3.5, 5.2)	3.9 (3.2, 4.8)	1.5 (1.1, 2.1)	1.1 (0.8, 1.6)	0.004
Kenya	16,421	29.1 (28.4, 29.8)	5.5 (5.1, 5.8)	4.8 (4.5, 5.1)	1.9 (1.7, 2.1)	1.0 (0.8, 1.1)	<0.001
Liberia	2,165	33.9 (31.9, 35.9)	4.2 (3.4, 5.1)	3.2 (3.1, 4.1)	1.7 (1.2, 2.4)	0.9 (0.6, 1.4)	<0.001
Malawi	4,628	37.0 (35.6, 38.4)	3.0 (2.6, 3.6)	2.6 (2.1, 3.0)	1.0 (0.8, 1.4)	0.6 (0.4, 0.9)	<0.001
Mali	7,270	28.6 (27.6, 29.6)	9.1 (8.4, 9.7)	8.4 (7.8, 9.1)	3.2 (2.9, 3.7)	2.3 (2.0, 2.7)	<0.001
Mozambique	8,243	41.6 (40.6, 42.7)	4.8 (4.4, 5.3)	4.4 (4.0, 4.9)	1.5 (1.2, 1.8)	0.9 (0.8, 1.2)	<0.001
Nigeria	10,134	38.4 (37.4, 39.3)	6.6 (6.1, 7.1)	5.5 (5.1, 6.0)	3.3 (2.9, 3.6)	2.2 (1.9, 2.5)	<0.001
Pooled SSA[d]	***82,627***	***32.4 (28.9, 35.3)***	***5.4 (4.6, 6.2)***	***4.7 (4.0, 5.4)***	***2.0 (1.6, 2.4)***	***1.3 (1.0, 1.5)***	
Grand Pool (a + b)[e]	***291,663***	***32.9 (29.8, 35.9)***	***6.9 (3.8, 10.0)***	***6.0 (3.3, 8.6)***	***2.5 (1.6, 3.7)***	***1.5 (0.7, 2.4)***	

[a] *P-values calculated between the prevalence of WaSt and ThSt using Mc-Nemar test*
[b] *The Meerut study was conducted in 6-59 months old children*
[c] *Pooled SSEA: Pooled estimates for South and South-East Asia*
[d] *Pooled SSA: Pooled estimates for Sub-Saharan Africa*
[e] *Grand pool: Pooled data from all the Demographic Health Survey Datasets studied*

Web Table IV Male to Female Wasting-Stunting (WaST) and Thinness-Stunting (ThSt) prevalence ratios in 6-59 months old children for Demographic Health Survey Datasets.

Country	*WaSt ratio (95% CI)*	*ThSt ratio (95% CI)*
Demographic Health Survey Datasets: South and South-East Asia		
Bangladesh	1.16 (0.9, 1.6)	1.09 (0.8, 1.6)
Cambodia	1.27 (0.9, 1.8)	1.06 (0.7, 1.7)
India	1.35 (1.3,1.4)	1.22 (1.2, 1.3)
Maldives	2.32 (1.2, 4.7)	2.68 (1.1, 6.8)
Myanmar	1.31 (0.8, 2.1)	1.17 (0.6, 2.2)
Nepal	1.29 (0.8, 2.0)	1.19 (0.7, 2.1)
Pakistan	1.52 (1.0, 2.2)	1.47 (0.9, 2.4)
Demographic Health Survey Datasets: Sub-Saharan Africa		
Angola	2.13 (1.4, 2.1)	1.86 (1.2, 3.0)
Benin	2.10 (1.6, 2.8)	1.82 (1.3, 2.6)
Cameroon	1.66 (0.9, 3.0)	1.81 (0.9, 3.8)
Congo	2.07 (1.2, 3.7)	2.82 (1.3, 6.0)
Ethiopia	2.28 (1.7, 3.1)	2.17 (1.4, 3.3)
Gambia	1.70 (1.0, 3.0)	1.13 (0.5, 2.4)
Ghana	0.92 (0.4, 1.8)	1.07 (0.5, 2.3)
Kenya	1.76 (1.4, 2.2)	1.50 (1.1, 2.1)
Liberia	0.99 (0.5, 1.9)	1.05 (0.4, 2.5)
Malawi	1.45 (0.8, 2.6)	1.38 (0.7, 2.9)
Mali	1.40 (1.1, 1.8)	1.29 (1.0, 1.7)
Mozambique	1.61 (1.1, 2.3)	1.73 (1.1, 2.8)
Nigeria	1.94 (1.5, 2.4)	2.09 (1.6, 2.8)

Web Table V Effect Size of Differences in Weight for height or BMI-for-age Z scores Between Combined and Single Anthropometric Deficits in 6-59 Months Age for Demographic Health Survey Datasets

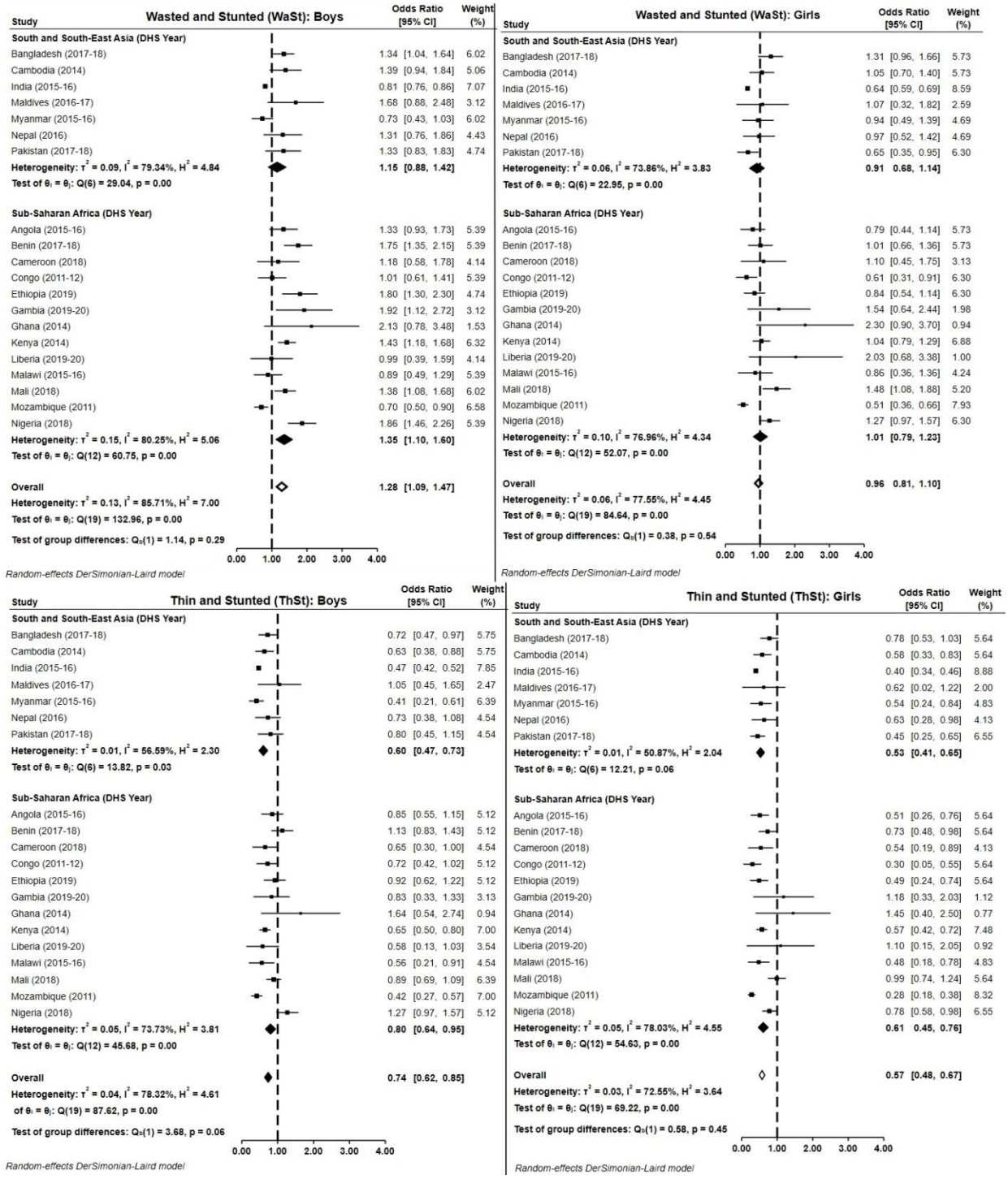
Country	*Weight for height Z-score*					*BMI-for-age Z-score*				
	Stunted only Median (Interquartile Range)	*Wasted only Median (Interquartile Range)*	*Wasted and Stunted (WaSt) Median (Interquartile Range)*	*Impact (WaSt vs Stunted only)*	*Impact (WaSt vs Wasted only)*	*Stunted only Median (Interquartile Range)*	*Thin only Median (Interquartile Range)*	*Thin and Stunted (ThSt)*	*Impact (ThSt vs Stunted only)*	*Impact (ThSt vs Thin only)*
Demographic Health Survey Datasets: South and South-East Asia										
Bangladesh	-0.6 (-1.2, 0.0)	-2.4 (-2.8, -2.2)	-2.4 (-2.6, -2.1)	2.2	0.0	-0.3 (-1.0, 0.3)	-2.4 (-2.9, -2.2)	-2.3 (-2.6, -2.1)	2.4	-0.3
Cambodia	-0.7 (-1.2, -0.1)	-2.5 (-3.3, -2.2)	-2.4 (-2.7, -2.2)	2.1	-0.4	-0.4 (-10, 0.2)	-2.5 (-3.5, -2.2)	-2.3 (-2.8, -2.1)	2.2	0.0
India	-0.6 (-1.2, 0.1)	-2.8 (-3.4, -2.3)	-2.6 (-3.1, -2.2)	-1.99	-0.24	-0.3 (-1.0, 0.4)	-2.8 (-4.3, -2.3)	-2.6 (-3.1, -2.2)	2.2	-0.3
Maldives	-0.6 (-1.3, 0.3)	-2.4 (-2.8, -2.2)	-2.4 (-2.7, -2.2)	1.8	0.0	-0.3 (-1.1, 0.5)	-2.5 (-3.0, -2.2)	-2.2 (-2.6, -2.1)	1.9	0.0
Myanmar	-0.5 (-1.0, 0.1)	-2.4 (-2.8, -2.2)	-2.4 (-2.7, -2.1)	2.4	0.0	-0.2 (-0.7, 0.5)	-2.4 (-2.9, -2.1)	-2.3 (-2.9, -2.1)	2.5	0.0
Nepal	-0.6 (-1.2, 0.0)	-2.5 (-2.8, -2.2)	-2.5 (-2.9, 2.2)	2.3	0.0	-0.3 (-0.9, 0.3)	-2.4 (-2.8, -2.2)	-2.5 (-2.8, -2.2)	2.5	0.0
Pakistan	-0.1 (-0.8, 0.6)	-2.8 (-3.3, -2.3)	-2.6 (-3.2, -2.2)	2.52	0.00	0.3 (-0.4, 1.0)	-2.9 (-3.5, -2.3)	-2.6 (-3.4, -2.3)	2.8	0.0
Demographic Health Survey Datasets: Sub-Saharan Africa										
Angola	-0.2 (-0.8, 0.5)	-2.5 (-2.8, -2.2)	-2.6 (-3.0, -2.2)	2.8	0.0	0.2 (-0.5, 0.9)	-2.5 (-3.0, -2.2)	-2.4 (-2.8, -2.2)	2.8	0.0
Benin	-0.3 (-0.9, 0.4)	-2.4 (-2.8, -2.2)	-2.5 (-2.9, -2.2)	2.6	0.0	0.1 (-0.6, 0.7)	-2.4 (-2.9, -2.2)	-2.5 (-2.8, -2.2)	2.9	0.0
Cameroon	0.5 (-0.4, 1.4)	-2.6 (-3.2, -2.2)	-2.7 (-3.1, -2.2)	2.7	0.0	0.8 (-0.1, 1.8)	-2.6 (-3.2, -2.2)	-2.8 (-3.5, -2.5)	3.0	0.0
Congo	-0.2 (-0.8, 0.5)	-2.5 (-3.0, -2.2)	-2.5 (-3.2, -2.3)	2.3	0.0	0.2 (-0.5, 0.8)	-2.6 (-3.2, -2.3)	-2.4 (-3.3, -2.1)	2.5	0.0
Ethiopia	-0.5 (-1.1, 0.2)	-2.4 (-2.8, -2.2)	-2.4 (-2.8, -2.2)	2.3	0.0	-0.2 (-0.8, 0.5)	-2.4 (-2.8, -2.2)	-2.4 (-3.0, -2.2)	2.4	0.0
Gambia	-0.6 (-1.1, 0.0)	-2.3 (-2.6, -2.1)	-2.5 (-2.9, -2.1)	2.3	0.0	-0.3 (-0.9, 0.3)	-2.3 (-2.6, -2.1)	-2.5 (-3.4, -2.4)	2.4	-0.4
Ghana	-0.3 (-0.9, 0.4)	-2.3 (-2.7, -2.1)	-2.5 (-2.9, -2.2)	2.2	0.0	0.0 (-0.6, 0.8)	-2.4 (-2.7, -2.2)	-2.5 (-2.9, -2.2)	2.5	0.0
Kenya	-0.2 (-0.9, 0.5)	-2.5 (-2.9, -2.2)	-2.4 (-2.9, -2.2)	2.5	0.0	0.2 (-0.6, 0.9)	-2.5 (-3.0, -2.2)	-2.5 (-2.9, -2.3)	2.8	0.0
Liberia	0.1 (-0.6, 0.7)	-2.4 (-2.9, -2.2)	-2.5 (-2.8, -2.2)	2.9	0.0	0.4 (-0.3, 1.0)	-2.6 (-3.3, -2.2)	-2.3 (-2.8, -2.2)	2.7	0.0
Malawi	0.1 (-0.5, 0.7)	-2.5 (-3.0, -2.2)	-2.4 (-2.7, -2.2)	2.8	0.0	0.4 (-0.3, 1.0)	-2.6 (-3.2, -2.3)	-2.4 (-2.7, -2.1)	3.2	0.0
Mali	-0.5 (-1.1, 0.3)	-2.5 (-3.0, -2.2)	-2.7 (-3.1, -2.3)	2.3	0.0	-0.1 (-0.8, 0.6)	-2.5 (-3.0, -2.2)	-2.5 (-2.9, -2.2)	2.4	0.0
Mozambique	0.4 (-0.3, 1.2)	-2.7 (-3.2, -2.3)	-2.7 (-3.2, -2.2)	2.9	0.0	0.8 (0.0, 1.6)	-2.8 (-3.4, -2.3)	-2.7 (-3.3, -2.3)	3.2	0.0
Nigeria	-0.2 (-0.9, 0.4)	-2.5 (-3.0, -2.2)	-2.5 (-3.1, -2.2)	2.6	0.0	0.2 (-0.6, 0.8)	-2.6 (-3.1, -2.3)	-2.5 (-3.0, -2.2)	2.9	0.0

Web Table VI Effect Size of Differences in Height-for-age Z scores Between Combined and Single Anthropometric Deficits in 6-59 Months Age for Demographic Health Survey Datasets

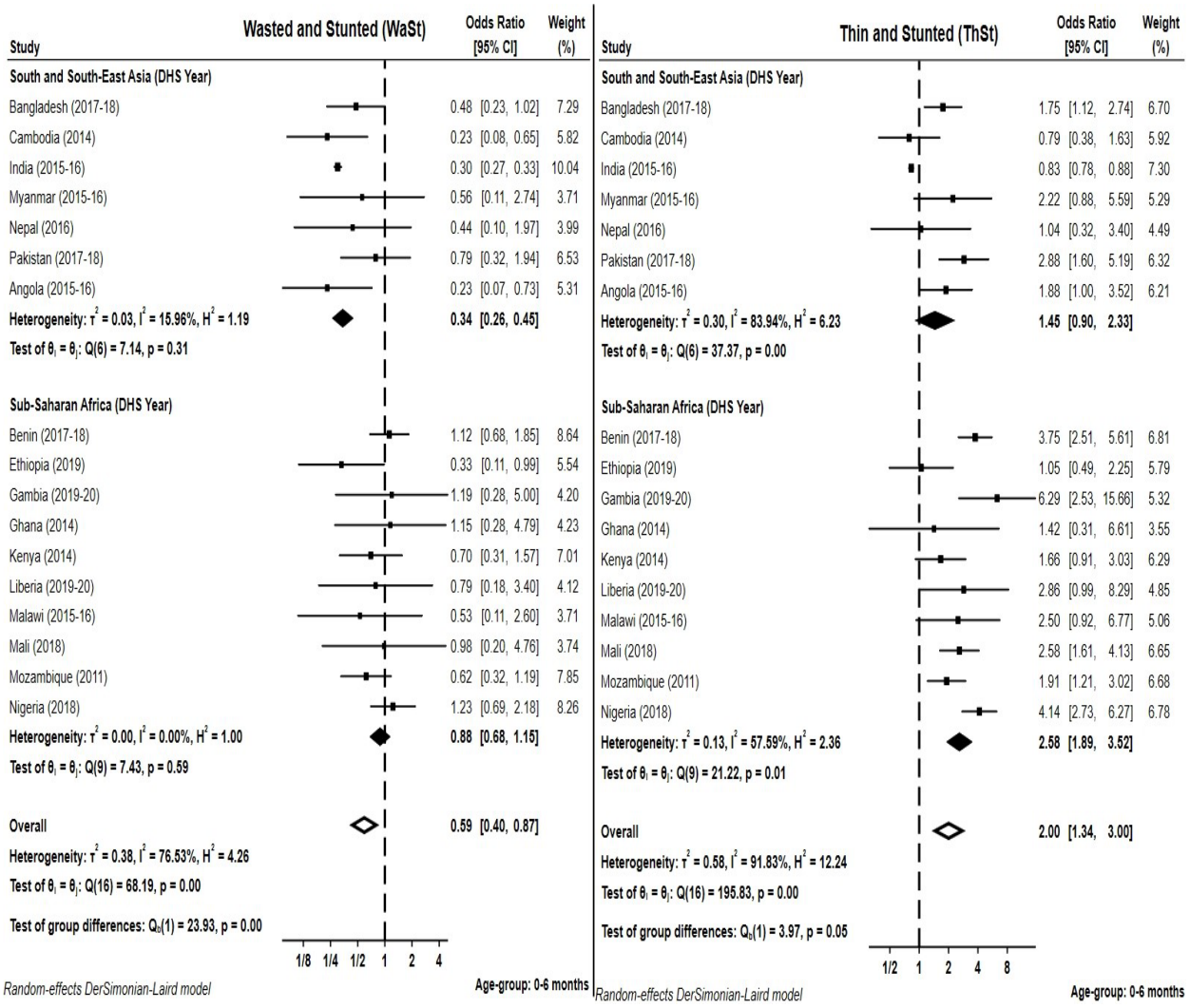
Country	*Height-for-age Z-score*								
	Stunted only Median (Interquartile Range)	*Wasted only Median (Interquartile Range)*	*Wasted and Stunted (WaSt) Median (Interquartile Range)*	*Impact (WaSt vs Stunted only)*	*Impact (WaSt vs Wasted only)*	*Thin only Median (Interquartile Range)*	*Thin and Stunted (ThSt) Median (Interquartile Range)*	*Impact (ThSt vs Stunted only)*	*Impact (ThSt vs Thin only)*
Demographic Health Survey Datasets: South and South-East Asia									
Bangladesh	-2.6 (-3.1, -2.3)	-0.9 (-1.5, -0.1)	-2.7 (-3.2, -2.4)	0.0	1.6	-0.7 (-1.4, 0.3)	-2.6 (-3.2, -2.3)	0.0	1.6
Cambodia	-2.6 (-3.1, -2.2)	-0.7 (-1.4, 0.7)	-2.7 (3.3, -2.3)	0.0	1.5	-0.4 (-1.2, 0.9)	-2.5 (-3.0, -2.2)	0.0	1.6
India	-2.8 (-3.5, -2.4)	-0.5 (-1.3, 0.7)	-2.9 (-3.5, -2.4)	0.0	1.8	-0.3 (-1.1, 0.9)	-2.8 (-3.4, -2.3)	-0.1	1.8
Maldives	-2.5 (-3.0, -2.2)	-0.9 (-1.4, 0.0)	-2.4 (-2.9, -2.1)	0.0	1.5	-0.6 (-1.3, 0.2)	-2.5 (-2.8, -2.1)	0.0	1.7
Myanmar	-2.6 (-3.1, -2.3)	-0.9 (-1.5, -0.3)	-2.6 (-3.0, -2.2)	0.0	1.5	-0.7 (-1.4, -0.1)	-2.5 (-3.1, -2.2)	0.0	1.6
Nepal	-2.7 (-3.2, -2.3)	-0.9 (-1.6, -0.2)	-2.8 (-3.2, -2.3)	0.0	2.0	-0.8 (-1.5, 0.0)	-2.8 (-3.2, -2.3)	0.0	2.1
Pakistan	-3.0 (-3.8, -2.4)	-0.6 (-1.3, 0.4)	-3.0 (-3.7, -2.4)	0.0	1.8	-0.4 (-1.2, 0.6)	-3.0 (-3.7, -2.4)	0.0	1.9
Demographic Health Survey Datasets: Sub-Saharan Africa									
Angola	-2.8 (-3.4, -2.4)	-0.7 (-1.4, 0.8)	-3.0 (-4.0, -2.3)	-0.2	1.6	-0.3 (-1.2, 1.1)	-3.0 (-3.8, -2.4)	0.0	1.7
Benin	-2.6 (-3.2, -2.3)	-1.0 (-1.5, -0.2)	-3.0 (-3.6, -2.5)	-0.2	1.7	-0.8 (-1.4, 0.0)	-2.9 (-3.6, -2.4)	-0.2	1.7
Cameroon	-2.9 (-3.6, -2.4)	-0.2 (-1.0, 0.7)	-2.8 (-3.7, -2.4)	0.0	1.8	0.0 (-0.8, 1.3)	-2.7 (-3.5, -2.4)	0.0	1.7
Congo	-2.7 (-3.3, -2.3)	-0.1 (-1.1, 1.0)	-2.9 (-3.6, -2.4)	0.0	2.0	0.2 (-0.7, 1.3)	-2.7 (-3.5, -2.3)	0.0	2.0
Ethiopia	-2.8 (-3.3, -2.3)	-0.9 (-1.4, 0.0)	-3.0 (-3.8, -2.4)	-0.2	1.8	-0.6 (-1.3, 0.5)	-2.8 (-3.3, -2.3)	0.0	1.9
Gambia	-2.5 (-2.9, -2.2)	-1.0 (-1.5, -0.5)	-2.5 (-2.9, -2.2)	0.0	2.0	-0.9 (-1.4, -0.4)	-2.5 (-3.4, -2.1)	0.0	1.1
Ghana	-2.5 (-3.0, -2.2)	-0.6 (-1.3, 0.0)	-2.8 (-3.4, -2.3)	0.0	1.8	-0.4 (-1.1, 0.3)	-2.6 (-3.5, -2.3)	0.0	1.8
Kenya	-2.6 (-3.1, -2.3)	-0.5 (-1.3, 0.5)	-2.8 (-3.4, -2.4)	-0.2	1.9	-0.3 (-1.2, 0.8)	-2.8 (-3.3, -2.4)	0.0	1.9
Liberia	-2.6 (-3.2, -2.3)	-0.5 (-1.2, 0.8)	-3.3 (-3.9, -2.8)	-0.1	1.9	-0.4 (-1.1, 0.9)	-3.2 (-3.9, -2.7)	0.0	2.0
Malawi	-2.6 (-3.1, -2.3)	-0.4 (-1.2, 1.1)	-3.0 (-3.8, -2.6)	-0.3	1.7	0.3 (-0.9, 1.3)	-2.8 (-3.5, -2.4)	0.0	2.2
Mali	-2.7 (-3.4, -2.3)	-0.6 (-1.2, 0.5)	-2.9 (-3.6, -2.4)	-0.2	1.8	-0.3 (-1.0, 0.9)	-2.9 (-3.5, -2.3)	0.0	1.9
Mozambique	-2.8 (-3.5, -2.4)	-0.1 (-1.1, 1.5)	-3.1 (-3.7, -2.5)	0.0	1.8	0.2 (-0.8, 1.6)	-3.1 (-3.7, -2.5)	0.0	2.1
Nigeria	-2.9 (-3.6, -2.4)	-0.9 (-1.5, 0.3)	-3.3 (-4.0, -2.6)	-0.2	1.8	-0.5 (-1.4, 0.8)	-3.2 (-3.9, -2.5)	-0.2	1.8

Web Table VII Correlation Coefficients for Weight for height and BMI-for-age in 0-59 Months Children for Demographic Health Survey Datasets

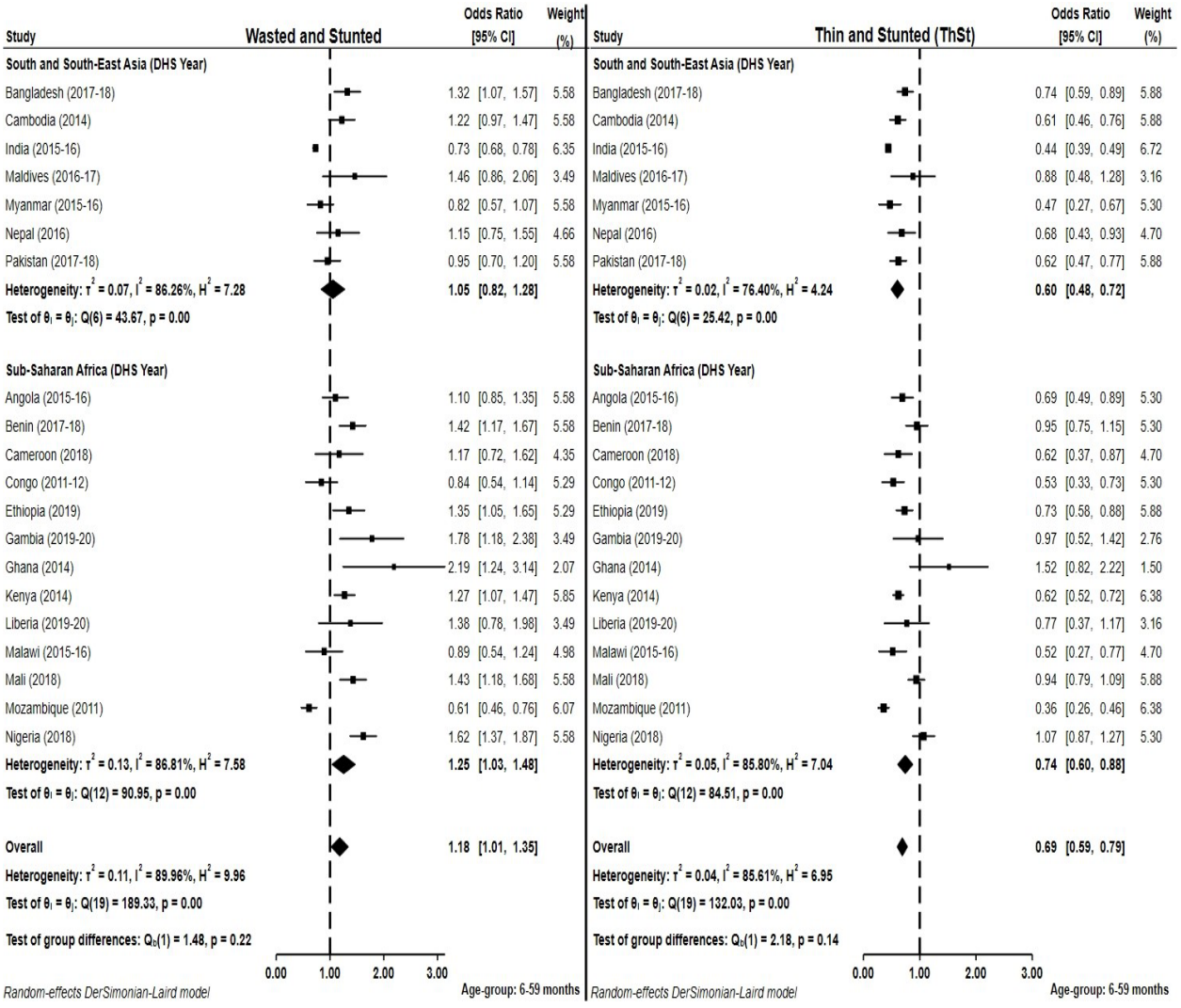
Country	*Correlation between Body mass index-for-age (z-scores) and Weight for height (z-scores) (95% CI); P*	*Coefficients of log weight regressed on log height (95% CI); P*	*Correlation between Body mass index-for-age (z-scores) and Weight (kg) (95% CI); P*	*Correlation between Weight for height (z-scores) and Weight (kg) (95% CI); P*	*Correlation between Body mass index-for-age (z-scores) and Height(cm) (95% CI); P*	*Correlation between Weight for height (z-scores) and Height (cm) (95% CI); P*
Demographic Health Survey Datasets: South and South-East Asia						
Bangladesh	0.97 (0.96, 0.97); <0.001	1.88 (1.86, 1.89); <0.001	0.23 (0.21, 0.25); <0.001	0.18 (0.16, 0.20); <0.001	-0.07 (-0.09, -0.04); <0.001	-0.12 (-0.15, -0.10); <0.001
Cambodia	0.97 (0.97, 0.97); <0.001	1.83 (1.82, 1.85); <0.001	0.23 (0.21, 0.26); <0.001	0.22 (0.17, 0.23); <0.001	-0.09 (-0.12, -0.06); <0.001	-0.12 (-0.15, -0.09); <0.001
India	0.97 (0.97, 0.97); <0.001	1.86 (1.85, 1.86); <0.001	0.33 (0.32, 0.33); <0.001	0.32 (0.31, 0.32); <0.001	-0.04 (-0.05, -0.03); <0.001	-0.06 (-0.07, -0.05); <0.001
Maldives	0.98 (0.98, 0.98); <0.001	1.81 (1.78, 1.82); <0.001	0.33 (0.28, 0.36); <0.001	0.31 (0.28, 0.35); <0.001	-0.08 (-0.12, -0.04); 0.001	-0.09 (-0.13, -0.05); <0.001
Myanmar	0.97 (0.97, 0.98); <0.001	1.82 (1.81, 1.84); <0.001	0.24 (0.21, 0.27); <0.001	0.22 (0.19, 0.25); <0.001	-0.06 (-0.09, -0.03); 0.001	-0.09 (-0.12, -0.06); <0.001
Nepal	0.92 (0.89, 0.93); <0.001	2.58 (2.4, 2.8); <0.001	0.41 (0.29, 0.51); <0.001	0.30 (0.18, 0.42); <0.001	-0.05 (-0.18, 0.08); 0.424	-0.19 (-0.31, -0.06); 0.005
Pakistan	0.97 (0.96, 0.97); <0.001	1.93 (1.91, 1.95); <0.001	0.35 (0.32, 0.38); <0.001	0.33 (0.29, 0.35); <0.001	0.04 (0.01, 0.07); 0.008	0.00 (-0.03, 0.03); 0.776
Demographic Health Survey Datasets: Sub-Saharan Africa						
Angola	0.96 (0.96, 0.96); <0.001	1.88 (1.87, 1.89); <0.001	0.27 (0.24, 0.29); <0.001	0.22 (0.20, 0.25); <0.001	-0.02 (-0.04, 0.01); 0.226	-0.07 (-0.09, -0.04); <0.001
Benin	0.96 (0.96, 0.96); <0.001	1.95 (1.94, 1.96); <0.001	0.34 (0.32, 0.35); <0.001	0.28 (0.27, 0.30); <0.001	0.09 (0.07, 0.11); <0.001	0.03 (0.01, 0.05); 0.003
Cameroon	0.97 (0.97, 0.97); <0.001	1.88 (1.86, 1.89); <0.001	0.31 (0.28, 0.33); <0.001	0.30 (0.27, 0.32); <0.001	-0.03 (-0.06, 0.0); 0.0867	-0.04 (-0.07, -0.01); 0.005
Congo	0.97 (0.97, 0.97); <0.001	1.88 (1.86, 1.90); <0.001	0.29 (0.27, 0.32); <0.001	0.27 (0.24, 0.30); <0.001	0.0 (-0.03, 0.03); 0.863	-0.03 (-0.06, 0.00); 0.052
Ethiopia	0.97 (0.96, 0.97); <0.001	1.85 (1.84, 1.87); <0.001	0.22 (0.19, 0.25); <0.001	0.21 (0.18, 0.24); <0.001	-0.08 (-0.11, -0.05); <0.001	-0.10 (-0.12, -0.07); <0.001
Gambia	0.97 (0.97, 0.97); <0.001	1.82 (1.80, 1.83); <0.001	0.09 (0.06, 0.12); <0.001	0.05 (0.02, 0.08); 0.004	-0.16 (-0.20, -0.13); <0.001	-0.21 (-0.24, -0.18); <0.001
Ghana	0.98 (0.97, 0.98); <0.001	1.94 (1.92, 1.96); <0.001	0.38 (0.34, 0.41); <0.001	0.37 (0.33, 0.40); <0.001	0.11 (0.08, 0.15); <0.001	0.10 (0.06, 0.14); <0.001
Kenya	0.98 (0.98, 0.98); <0.001	1.81 (1.80, 1.82); <0.001	0.19 (0.18, 0.21); <0.001	0.18 (0.17, 0.20); <0.001	-0.12 (-0.14, -0.11); <0.001	-0.14 (-0.15, -0.13); <0.001
Liberia	0.97 (0.96, 0.97); <0.001	1.88 (1.86, 1.91); <0.001	0.28 (0.24, 0.32); <0.001	0.23 (0.19, 0.27); <0.001	0.02 (-0.02, 0.06); 0.360	-0.04 (-0.08, 0.00); 0.064
Malawi	0.97 (0.97, 0.97); <0.001	1.81 (1.79, 1.83); <0.001	0.21 (0.18, 0.24); <0.001	0.18 (0.15, 0.20); <0.001	-0.09 (-0.12, -0.07); <0.001	-0.13 (-0.16, -0.11); <0.001
Mali	0.97 (0.97, 0.97); <0.001	1.91 (1.90, 1.92); <0.001	0.32 (0.30, 0.34); <0.001	0.31 (0.29, 0.33); <0.001	0.03 (0.01, 0.05); 0.006	0.02 (-0.01, 0.04); 0.142
Mozambique	0.97 (0.96, 0.97); <0.001	1.88 (1.87, 1.90); <0.001	0.31 (0.29, 0.32); <0.001	0.27 (0.25, 0.29); <0.001	-0.02 (-0.04, 0.00); 0.103	-0.06 (-0.08, -0.04); <0.001
Nigeria	0.96 (0.96, 0.96); <0.001	1.94 (1.93, 1.95); <0.001	0.35 (0.34, 0.37); <0.001	0.33 (0.32, 0.35); <0.001	0.10 (0.07, 0.12); <0.001	0.07 (0.05, 0.09); <0.001



Web Fig. 1 Sex differences in wasting-stunting (WaSt) and thinness-stunting (ThSt) associations in under-five children in Demographic Health Survey datasets.



Web Fig. 2 Summary of wasting-stunting (WaSt) and thinness-stunting (ThSt) associations in 0-6 months old infants in the Demographic Health Survey datasets.



Web Fig. 3 Summary of wasting-stunting (WaSt) and thinness-stunting (ThSt) associations in 6-59 months old children in the Demographic Health Survey datasets.

RESEARCH PAPER

Growth Faltering Among Discharged Babies from Inpatient Newborn Care Facilities: Learnings from Two Districts of Himachal Pradesh

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Objective: To determine the burden of early growth faltering and understand the care practices for small and sick babies discharged from newborn units in the district.

Study design: Observational and follow-up study.

Participants: 512 babies discharged from two Special Newborn Care Units (SNCUs) and four Newborn Stabilization Units (NBSUs) in two districts of Himachal Pradesh.

Methods: Anthropometric assessments, interview of mothers and Accredited Social Health Activists (ASHAs) conducted between August, 2018 and March, 2019. Change in weight-for-age *z*-score (ΔWAZ) of <-0.67SD between birth and assessment was used to define growth faltering.

Outcomes: Proportion of growth faltering (or catch-down growth) in small and sick babies discharged from SNCUs and NBSUs, and infant care practices.

Results: Growth faltering was observed in a significant proportion of both term (30%) and preterm (52.6%) babies between 1 to 4 months of age. Among babies with growth faltering (*n*=180), 73.9% received a home visit by ASHA, and only 36.7% received a follow-up visit at a facility. There were 71.3% mothers counselled at discharge (mostly informed about breast feeding). Most (96.7%) mothers did not perceive inadequate weight gain in their babies post-discharge. During home visits, ASHAs weighed 61.6% of the infants with growth faltering. Amongst infants who had growth faltering, only 49.6% of mothers had been provided information about their infant's growth and 57.1% mothers had received breastfeeding counselling.

Conclusion: Small and sick newborn infants (both term and preterm babies) discharged from special care newborn units are at increased risk of early growth faltering. Follow-up care provided to these infants is inadequate. There is a need to strengthen both facility-based and home-based follow up of small and sick newborn infants discharged from newborn care facilities.

Keywords: *Catch-down growth, Growth monitoring, Low birth weight, Preterm.*

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While there has been significant decline in neonatal mortality in India over the past few decades, bending the curve further requires greater focus on small and sick babies and addressing failure to thrive in these babies beyond survival [1,2]. Small and sick babies are newborn weighing <2500 g at birth (includes preterm, low-birth-weight (LBW) and small for gestational age (SGA) new-borns) or newborns with any medical/surgical condition [3]. These babies often require inpatient care and have the highest risk of death. Following inpatient care, small and sick survivors remain at increased nutritional and developmental risks; most of the longterm consequences are largely preventable; though, with effective follow up care [2, 4-6].

Cut-offs for defining growth faltering have varied from -0.67 to >-2 weight for age *z*-score (WAZ) in different studies [7-12]. Globally, growth faltering in pediatric population has been reported to vary from about 2% to 21% [7,13]. In India, findings from national surveys highlight high prevalence of stunting (20.1%), wasting (31.9%), and underweight (26.7%) in children under six months of age [14]. However, recent studies suggest that the cut-off of -0.67 WAZ scores defined as catch-down growth rather than growth faltering should be used to enable early detection of growth deviation, and implementation of interventions which that would prevent children from experiencing greater degrees of growth faltering [7-9,12,15].

Invited Commentary: Pages 753-54.

Several studies have assessed growth faltering in preterm or LBW babies in India; however, there is a paucity of such data among at-risk neonates discharged from district level Special Newborn Care Units (SNCUs) and Newborn Stabilization Units (NBSUs) [8,16,17]. The current

programmatic dimensions also do not adequately capture the thrive component [12]. Therefore, this study was undertaken in an attempt to fill this gap; to understand the burden of growth faltering (an important metric to assess thrive) in early infancy, and the care practices for small and sick babies.

METHODS

This was an observational and follow-up study conducted between August, 2018 and May, 2019 in two districts of Himachal Pradesh (HP). Of the 12 districts in the state, two districts (Kangra and Sirmaur), which both had a functional SNCU and NBSU, and reported a higher proportion of admissions during the financial year (2017-2018) preceding the study initiation year were included. All functional SNCUs and NBSUs in the selected districts were included. All newborn infants admitted to these facilities between April, 2018 and February, 2019 served as the potential participants for the study.

Infants were included into the study if they had been discharged alive from the identified SNCUs and NBSUs, were residents of the two identified districts, located within 150 kms of the identified facilities, and were aged between 1 and 4 months at the time of data collection.

The estimated sample size was 384 assuming prevalence of growth faltering to be 20%, with a relative precision of 20% with a confidence of 95%. Since, growth faltering data for infants aged between 1 and 4 months was not available, the reported prevalence of wasting, stunting and underweight as 21%, 38% and 36%, respectively in NFHS-4 was considered as the best proxy [1].

For the purpose of the study, change in weight for age *z*-score (WAZ) of <-0.67SD between two time points was defined as growth faltering (catch-down growth) as suggested by recent literature [7-9]. Intergrowth 21st standards were used for WAZ calculation for preterm babies and World Health Organization (WHO) Child growth standards was used for term babies [18,19]. For babies reassessed during the second follow-up visit (beyond 64 weeks postmenstrual age), *z*-scores for growth parameters were calculated using WHO child growth standards (using STATA i-growup package).

To ensure optimal recruitment to meet the estimated sample size and ensure geographical representation, planning of the route for data collection was critical, given the difficult terrain of the two districts and the intervening monsoon and winter months during the period of data collection. Data collection was planned block-wise in each district based on feasibility of travelling with each visit to a health block ranging between 3-5 days.

During the visit to the home of the identified infant, relevant demographic, maternal and infant care practice data were collected from the mother, and the infant's weight was recorded using an electronic scale with a capacity of 20 kg and a sensitivity of 5 g (Crown Scales) by trained study personnel. Birth weight was documented as per facility record. The village ASHAs were also interviewed to collect information on infant care practices followed by her. Pre-designed, pilot tested tools were used to collect data.

Standardization of weight measurement of the infant was carried out using the intergrowth 21st protocol during the Facility Based Newborn Care training sessions organized in the state and at Safdarjung Hospital, Delhi [20]. Calibration of the weighing scale was done at least twice a week. The data collected during the home visits were checked for completeness through a two-pronged check at the field site (before ending the home visit sessions) as well as by the supervisors. Amongst the infants enrolled for the study, a reassessment for validation of the growth data was conducted in a subset of 100 babies (between January, 2019 - March, 2019). In addition, periodic monitoring and onsite supervision was done by a team of specialists to ensure quality. Repeat trainings were conducted by the monitoring team, if required.

In addition to the growth assessment of infants, indepth interviews were carried out with 42 mothers/care-givers and 12 ASHAs along with non-formal interactions and group discussions using semi-structured interview guides and qualitative data analyzed using grounded theory approach (data not presented).

Ethical approval was obtained from the Institutional Ethics Committee. Written informed consent was taken from the mothers/caregivers interviewed. Administrative approvals were obtained from the state and district authorities before commencement of the study.

Statistical analysis: All statistical analyses was conducted using *STATA* version 16.1 (Stata Corp). Proportion (with 95% CI) of babies with growth faltering was estimated between birth, assessment, and reassessment. Comparisons were made between subgroups stratified by gender, birth weight and gestational age using chi-square test. Multivariate logistic regression analysis was performed considering growth faltering as dependent variable and gestational age (preterm vs term) as independent variable; covariates adjusted in the regression analysis included gender, birth order, age on assessment, mother's age, antenatal illness, number of indications for hospitalization, post discharge illness and number of follow-up visits. A probability of 5% (P<0.05) was considered statistically significant.

RESULTS

There were 2841 babies admitted to the SNCUs and

NBSUs identified for the study in the two districts of Kangra and Sirmour between April, 2018 and February, 2019. Of these 879 infants were eligible for inclusion in the study. The study enrolled 518 infants whose parents gave consent. Six babies without birth weight record were later excluded and hence 512 infants were included for analysis. **Table I** provides the baseline characteristics of the study participants. The infants at enrolment had a mean (SD) age of 74.8 (26.5) days. The mean (SD) gestational age at birth was 37.4 (2.1) weeks with a mean (SD) birth weight of 2.6 (0.6) kg.

At birth, average (SD) weight of term and preterm babies was 2.8 (0.4) kg and 2.1 (0.6) kg, respectively. At the time of assessment, the average (SD) weight was 4.9 (1.1) kg and 3.7 (1.3) kg, and the median (IQR) weight gain during the period was 2 (1.4, 2.6) kg and 1.5 (0.8, 2.3) kg in term and preterm babies, respectively. In the validation cohort reassessed at a mean (SD) age of 116.7 (15.4) days, the median (IQR) weight gain between assessment and reassessment was 1.2 (0.7, 1.7) kg and 1.5 (1.0, 2.1) kg in term and preterm babies (**Table II**).

Growth faltering (catch-down growth) was observed in 30% of 396 term babies, and 52.6% of 116 of preterm infants. **Fig. 1** depicts the magnitude of growth faltering at the ages of assessment stratified by gestation. Growth faltering was also noted in 38% of the validation cohort who were reassessed. Although the difference in growth faltering among the term and preterm babies was statistically significant ($P<0.001$), regression analysis observed that gestation could only explain about 8% of the variability in growth (**Web Table I**).

When the mother's perception of growth faltering was assessed, 96.7% of the mothers did not perceive inadequate weight gain in their infants. Around one-fourth (26%) of the mothers reported that their infants had not been visited by an ASHA post-discharge at home. Further, 66.4% of the infants had not been taken for follow-up visits

Table I Baseline Characteristics of Included Babies Discharged From Inpatient Care Facilities in Two Districts of Himachal Pradesh, 2018-19 (*N*=512)

Characteristics	*Value*
Maternal characteristics	
Household members[a]	6.7 (2.6)
Annual household income, INR[b]	1.8 Lakhs (10,000, 3 Lakhs)
Maternal age, y[a]	26.1 (4)
Maternal education status	
Higher senior secondary or graduate	305 (9.5)
Secondary or Senior secondary	136 (0.7)
Primary or literate (can read or write)	63 (12.3)
Illiterate	8 (1.5)
Maternal antenatal illness	131 (25.6)
Antenatal visits[a]	3.7 (1.2)
Neonatal characteristics	
Male	276 (53.9)
Low birth weight (<2500 g)	169 (33.0)
Preterm (<37 wk)	116 (22.7)
Birth order	1.6 (0.7)
Birth interval ≤24 mo[a]	72 (14.1)
Facility birth	500 (97.7)
Hospitalization related characteristics[c]	
Inborn admissions, (*n*=490)	358 (73.1)
Indications for hospitalization, (*n*=504)	1 (1, 2)
Age at admission, d (*n*=507)[b]	2 (0, 4)
Duration of hospital stay, d (*n*=506)[b]	3(0, 6)

Values in no. (%), [a]mean (SD) or [b]median (IQR). [c]Denominator varies for different variables based on data available from the facility records.

Table II Growth Parameters (for weight) of Small and/or Sick Babies From Birth to Assessment and Re-assessment

Growth parameters	*Birth*[b]			*Initial Assessment (1st home visit)*			*Reassessment (2nd home visit)*		
	Total (n=512)	*Preterm*[c] *(n=116)*	*Term (n=396)*	*Total (n=512)*	*Preterm*[c] *(n=116)*	*Term (n=396)*	*Total (n=100)*	*Preterm*[c] *(n=22)*	*Term (n=78)*
Age, *d*	37.4 (2.1) *wk*	34.4 (1.8) *wk*	38.3 (1.1) *wk*	74.8 (26.5)	72.5 (27.9)	75.5 (26.1)	116.7 (15.4)	116.5 (16.9)	116.8 (15.0)
Weight, kg[a]	2.6 (0.6)	2.1 (0.6)	2.8 (0.4)	4.6 (1.2)	3.7 (1.3)	4.9 (1.1)	5.65 (0.95)	5.17 (0.99)	5.78 (0.90)
Weight for age z-score[a]	-1.0 (-1.7 to -0.3)	-0.5 (-1.41 to 0.4)	-1.1 (-1.7 to -0.4)	-1.3 (-2.1 to -0.5)	-1.4 (-2.6 to -0.4)	-1.2 (-2.1 to -0.5)	-1.10 (-1.85 to -0.23)	-0.65 (-1.58 to 0.05)	-1.20 (-1.90 to -0.31)
ΔWeight, kg[a]	-	-	-	2.0 (1.2 to 2.6)	1.5 (0.8 to 2.3)	2.0 (1.4 to 2.6)	1.33 (0.82 to 1.84)	1.52 (0.95 to 2.13)	1.20 (0.71 to 1.68)
ΔWeight for age z-score[a]	-	-	-	-0.3 (-0.9 to -0.4)	-0.7 (-1.65 -0.1)	0.1 (-0.8 -to 0.45)	0.16 (-0.20 to 0.67)	0.05(-0.37 -to 0.90)	0.22(-0.17 to 0.60)

Data represented as mean (SD) or [a]median (IQR). [b]post-conceptional age in weeks. [c]Weight z-scores estimated using corrected age for preterm babies. Intergrowth and WHO standards used for z-score estimation. ΔWeight-for-age z-score is calculated.

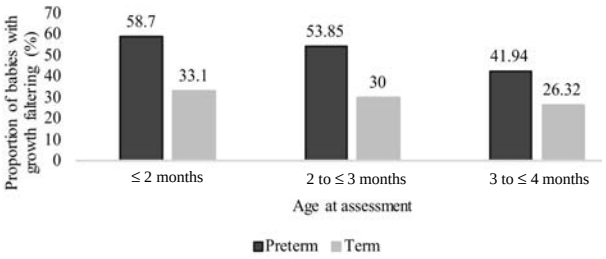

Fig. 1 Proportion of babies with growth faltering by gestation and age at assessment.

to the health facility by the family (**Table III**). Among the infants who reported having had visits by ASHA (*n*=379), infant weight had been in taken in 64.6%, breastfeeding and weight-gain related counselling had been provided in 62.5% and 55.4% respectively, and 1.6% were counselled for follow-up visits to the facility (**Table III**). Similar trends were seen in babies with and without growth faltering (weight measured in 61.6% and 66.3%, counselled for breastfeeding in 57.1% and 65.4%, counselled for weight-gain in 49.6% and 58.5%, and counselled for follow-up visits in 3.0% and 0.8%, respectively).

When assessed for mother's preparedness for follow-up care of their infants at time of discharge from the health facility, 71.3% mothers reported that counselling had been provided at the time of discharge, but many a time mother was not the primary recipient of the counselling. It was reported that the counselling was largely limited to breast-feeding the infant till six months.

Of the 193 ASHAs interviewed from the same districts, 78.7% reported to have received information about discharged babies through phone calls or visits made to the family; however, 18.2% were unaware about babies having received inpatient care. Unlike what was reported by mothers, 95.8% of the ASHAs reported that the infants are weighed during home-visits for identification of small babies (**Table III**). The post-discharge visit by ASHAs were largely limited to updating Mother-Child Protection (MCP) card and informing about immunization.

Table III Infant Care Practices Post-discharge of Small and Sick Babies as Reported by Mothers and ASHAs

Infant care practices as reported by the mothers during interview (n=512)	
Follow up visits to the facilities by caregiver/ mother	172 (33.6)
Follow up visit by ASHAs at home	379 (74.0)
Interval between discharge and 1st ASHAs visit[a], d	3 (1, 7)
Information provided to mothers by ASHAs (n=379)	
Breast feeding	237 (62.5)
Weight gain	210 (55.4)
Danger sign identification	29 (7.7)
Facility follow-up	6 (1.6)
Infant wt measured	245 (64.6)
No. of mothers provided information during home follow-up visits by ASHAs (n=193)	
Exclusive breastfeeding	187 (96.9)
Hand hygiene	172 (89.1)
Keep baby warm	152 (78.8)
Immunization	140 (72.5)
Cord care	68 (35.2)
Danger sign identification	40 (20.7)
Complementary feeding	35 (18.1)
Change in weight	78 (40.4)
Follow up care	13 (6.7)
No. of infants monitored for weight gain during home follow-up visits by ASHAs (n=193)	
Weight taken and plotted on growth chart	61 (31.6)
Only weight recorded	122 (63.2)
No weight recorded	10 (5.2)

Data represented as no. (%) or [a]median (IQR).

DISCUSSION

The present study identified a high prevalence of early growth faltering in newborn infants discharged from newborn care units in the districts of Himachal Pradesh. Follow-up home visits by ASHAs or at the facility did not lead to an early detection of growth faltering among these babies with majority of mothers being unable to perceive inadequate weight gain in their infant. During follow-up visits at home, while ASHAs recorded weight, they did not provide any information to the mothers about the infant's growth, nor were they counselled about feeding or referral to a facility in case growth failure was detected.

Previous studies for evaluating growth faltering globally and in India report varied estimates depending on the cut-offs used, birth weight, gestation, and timing of follow-up [7,8,10,13,16]. A previous study [9], involving healthy term infants reported a high proportion of babies with catch down growth (decrease in *Z*-score >0.67) during the two-year follow-up period with highest (27%) at 3.5 months from birth, which is comparable to the current study observations [9]. Likewise, growth faltering has been documented in very low birth weight neonates till one year of age (underweight, stunting, and wasting: 41%, 32%, and 27%) with *Z*-score of weight at 3 months identified as a significant risk factor for malnutrition at one year [10]. Another group reported follow-up weight gain and other key parameters among babies discharged from SNCUs for up to 6 weeks [17]. The current study is one of the first studies reporting growth faltering in these vulnerable babies up to 4 months [17]. With variations in the anthropometric criteria used, and lack of consensus on the most appropriate standard for monitoring growth in young infants, comparisons across studies is challenging [11,12]. To define growth faltering, we used WAZ score,

WHAT IS ALREADY KNOWN?

- Early growth faltering has been reported (around 20 to 60%) in India, although mostly in low birthweight babies; limited studies assess the status of small and sick babies discharged from newborn care facilities and the follow up care provided both at the facility and at home.

WHAT THIS STUDY ADDS?

- We observed growth faltering in a significant proportion of both term (30%) and preterm (52.6%) babies discharged from Special Newborn Care Units (SNCUs) and Newborn Stabilization Units (NBSUs). The potential gaps and opportunities in the follow up of these at-risk infants are highlighted.

which has been suggested as a good predictor of mortality among young infants and operationally suitable for community level assessment of at-risk infants [12,15].

A recent study [17] conducted across four states in India reported majority (97%) of babies discharged from SNCUs were followed up at the recommended time points up to 6 weeks after birth [17]. However, previous national surveys indicated irregular home-based newborn care (HBNC) services provided by ASHAs across several states including follow-up of sick newborns discharged from inpatient facilities [17, 21,22]. Likewise, the quality of services provided in the community in terms of growth monitoring/nutritional counselling have been sub-optimal, with inadequate supportive supervision and overburdening of health workers highlighted as major gaps [22-24]. Variations in self-reported and field performance of ASHAs in providing HBNC have also been reported previously [23]. Similar gaps in follow-up care provided by ASHAs or through facility visits were observed in the present study. One of the challenges for follow-up visits to SNCUs identified in the current study was the distance from these facilities, the district's hilly geographical terrain, and minimally functional NBSUs closer to home.

Growth faltering not picked by ASHAs during follow-up visits, weight not recorded in a large proportion of babies, limited number of mothers counselled, and limited number of follow-up visits made to the facility reiterate the need for strengthening follow-up care post-discharge in the community. Likewise, better preparedness of mothers/caregivers at discharge can strengthen care-seeking and newborn care practices at home. Global and national studies have demonstrated the role of community health workers in improving the child health programs and strategic actions, which at different levels of care can enable early childhood thrive [24-26].

Towards planning and prioritizing intervention strategies, various individual, household, and community level risk factors have been explored; however, causes for early growth faltering remain inadequately understood [27]. The present study attempted to explore some of the risk factors. Inability of mothers to perceive growth faltering (as documented in the study) warrants for a greater system strengthening or accountability through adequate follow-up of babies by ASHAs at home and linkage to facilities.

The strength of this study is that the infant care practices were triangulated by information provided by mothers and ASHAs. The main study limitation was the lack of standardization of birth weight measurement. The study was also not sufficiently powered to ascertain associated risk factors.

To conclude, there are limited studies in India that report growth failure in early infancy among small and sick babies discharged from SNCUs and NBSUs. The high proportion of growth faltering in these infants reiterates the need for growth monitoring of all at risk babies discharged from inpatient health facilities and strengthened HBNC in the community. Further research can help explore growth patterns and associated factors during early infancy in this vulnerable population critical to prevention of growth faltering.

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Ethics approval: Institutional Ethics Committee, Maulana Azad Medical College; No. F.1/IEC/MAMC/62/02/2018/268, dated March 30, 2018.

Note: Additional matter related to this article is available with the web version at *www.indianpediatrics.net*

Contributors: SR, HC, RDG, RMP, RG, and JJ: involved in the conceptualization of the study; SR, HC, RDG, RMP, RG along with late Dr MK Bhan: provided overall guidance across different steps involved in the study; MS: facilitated the study in the state of HP, JJ, MN, along with the research team were involved in the overall study conduct and data collection process

with inputs provided by SR, HC, RDG, JJ and RJ compiled and analyzed the data, drafted the manuscript with technical inputs from SR, HC, RDG, RMP, RG, and MS in analysis and finalizing the manuscript. All the authors have reviewed and approved the final version of the manuscript.

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RESEARCH PAPER

Preterm General Movements in Prediction of Neurodevelopmental Disability and Cerebral Palsy at Two Years: *A Prospective Cohort Study*

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Background: A neurological assessment before discharge from the NICU would enable early targeted intervention to mitigate the risk and severity of cerebral palsy (CP) and neurodevelopmental disability.

Objective: To assess the accuracy of general movements (GM) in the preterm and fidgety movement periods in predicting neurodevelopmental disability and cerebral palsy in very preterm infants (≤32 weeks gestational age) at 18-24 months corrected gestational age.

Study design: Prospective cohort study

Participants: One hundred and seventy very preterm infants, mean (SD) gestation 29.8 (1.32) weeks, and birthweight 1215 (226) g.

Outcomes: Infants underwent GM assessments in the preterm period (31-36 weeks post-conception age) and fidgety movement period (8-18 weeks post term age). Neurodevelopmental outcomes were assessed in 127 children using the Griffiths Mental Developmental Scales-2.

Results: Nine children had neurodevelopmental disability (two infants with cerebral palsy and seven with global developmental delay. The relative risk (95% CI) for neurodevelopmental disability was 1.46 (0.31-6.89) with preterm movements and 6.07 (0.97 – 38.05) with fidgety movements. Sensitivity and specificity values for the prediction of neurodevelopmental disability were 33% and 64% in the preterm period and 25% and 92% in the fidgety movement period, respectively. The sensitivity and specificity values for prediction of CP were 50% and 63% in the preterm period and 100% and 93% in the fidgety movement period, respectively.

Conclusion: Preterm movements showed lower sensitivity and specificity than fidgety movements in predicting later CP and neurodevelopmental disability in preterm infants.

Keywords: *Developmental delay, Fidgety movements, Follow up care, Prognosis.*

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Neurodevelopmental outcomes in preterm and very low birth weight infants have improved in recent decades, but they remain at risk of developing cerebral palsy (CP) as well as cognitive, language, visual perceptual, sensory, attention, and learning difficulties [1]. Early detection of these complications can mitigate the risk of adverse motor and developmental outcomes, decrease secondary complications and improve caregiver well-being [2].

General movements (GMs) are spontaneous movements that can be detected from early fetal life until 4-5 months of post-term age [3]. The general movements assessment (GMA) has a high predictive ability for neurodevelopmental disability particularly cerebral palsy in preterm and term infants with risk factors [4]. General movements are classified into three types as preterm movements (28 to 36-38 weeks post-conceptional age), writhing movements (36-38 until 46-52 weeks post-conceptional age), and fidgety movements (FMs) (46-52 till 54-58 weeks post-conceptional age) [5]. The absence of core characteristics like adequate complexity, variability, and fluency of normal GMs are associated with adverse neurological outcomes [6,7]. The predictive ability of the GMA is superior to cranial ultrasound, neurological assessment, and comparable to MRI [8]. The sensitivity and specificity of FMs is the highest, followed by writhing move- ment in predicting CP [9], but accuracy is lower for non-CP adverse outcomes [10]. Assessment of GMs beforeterm has been studied less robustly [11], with studies of preterm movements reporting low specificity values [9].

Invited Commentary: Pages 755- 56.

The follow-up rates of high-risk infants remain poor in India [12]. Reported barriers to follow-up in low and middle-income countries (LMIC) include financial constraints for transportation and perceived wellness of the infant [13].

GMA can be a useful tool for neurological assessment in resource-limited settings where expensive neuroimaging may not be easily available.

The objective of this study was to assess the sensitivity and specificity of preterm movements in predicting neurodevelopmental disability and cerebral palsy in a cohort of very preterm infants. This was compared to the sensitivity and specificity of fidgety movements in predicting neurodevelopmental disability and cerebral palsy in the same cohort. Neurodevelopmental disability was assessed using a standardized developmental assessment at 18-24 months corrected gestational age. Video recordings of the preterm movements and the fidgety movements were performed following Prechtl standards [4].

METHODS

This prospective cohort study enrolled very preterm infants (gestational age <32 weeks, calculated based on the date of the last menstrual period) admitted to the neonatal intensive care unit of a large tertiary health center in Southern India. Informed consent was obtained from either of the parents and the study was approved by the Institutional Review Board.

Very preterm infants with major congenital anomalies incompatible with survival, those whose parents were unwilling to come for follow up, and those who were on the ventilator or were sedated (could not undergo the video recordings of the GMs) were excluded. The mother's antenatal, and perinatal history and infants' details were collected from medical records. Participants for this study were recruited from September, 2013 to August, 2015; follow up assessments were done from June, 2015 to January, 2018.

The recruited infants underwent preterm movement assessment, fidgety movement assessment and neuro-developmental assessment between 18-24 months [14]. General movements were classified as normal or abnormal by the primary investigator, who had Advanced Certification by the General Movement Trust.

All infants were started on an early intervention program prior to NICU discharge. Follow up visits at the high-risk infant clinic were advised once every 3 months until 18 months corrected gestational age when the formal neurodevelopmental assessment was performed.

The neurodevelopmental assessments were performed between corrected age of 18 and 24 months using the Griffiths Mental Developmental Scales – 2nd edition (GMDS) [15] by a certified psychologist, who was blinded to the medical history and the GMA results. The GMDS has five domains: locomotor, personal and social skills, hearing and language, eye-hand coordination, and performance. A sub-quotient is obtained in each domain, the average of which is the general quotient (GQ) that is considered as the indicator of the child's overall development. Normal GQ has a mean (SD) of 100 (12); and a cut-off score of ≤76 (<-2SD) indicates neuro-developmental disability. The mean (SD) normative GQ in Indian infants aged 16-24 months was 104 (9.4) [16]. Cerebral palsy was diagnosed if the child has abnormalities in posture and tone, and was classified using the Gross Motor Function Classification System (GMFCS) by the developmental pediatrician, who was also unaware of the GMA results.

The sample size was calculated using the agreement method. With reference to a study by Mutlu, et al. [17], the agreement between general movements and neurological assessment was found to be 0.78. Assuming a sample agreement of 0.78, a population agreement of 0.50 and prevalence of severe developmental delay as 17 % [12], the sample size was calculated as 139. Estimating a 20% loss to follow up, it was decided to recruit 166 infants.

Statistical analysis: Data were analyzed using the SPSS package for Windows, version 21.0 (SPSS Inc). Fisher's exact test or Chi-square was used to compare categorical data and independent sample *t*-test was used to compare continuous data. Relative risk was calculated to predict neurodevelopmental disability. Sensitivity, specificity, and positive and negative predictive values were calculated using the Medcalc software [18].

RESULTS

The flow of the study is shown in **Fig. 1**. There were no significant differences in demographic characteristics, neonatal morbidities and prevalence of abnormal general movements between the 127 infants who completed the final neurodevelopmental assessment and the 43 infants who did not come for the assessment (**Web Table I**).

The mean (SD) gestational age of the cohort was 29.8 (1.32) weeks, and birth weight was 1215 (226) g. The mean (SD) age at preterm movement assessment was 34.4 (1.0) weeks post conceptional age and at assessment of the fidgety movements, it was 11.9 (2.1) weeks post-term age.

The mean (SD) GQ was 95 (12). 118 (93%) children had normal neurodevelopmental outcomes. Nine children (7%) had neurodevelopmental disability that included seven (5.5%) children with global developmental delay and two (1.57%) children with CP (one had GMFCS level V and the other had GMFCS level III). **Table I** shows the baseline characteristics of the 127 children who completed the final neurodevelopmental assessment.

Table II shows the sensitivity, specificity, and predictive values of GMs in two time periods for predicting

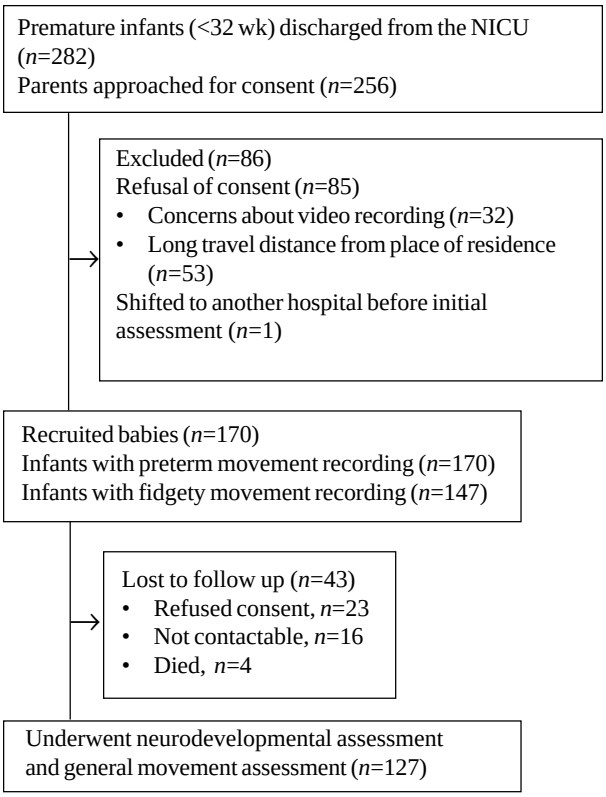

Fig. 1 Flow of the study

neurodevelopmental disability and cerebral palsy. The RR (95% CI) of preterm movements and fidgety movements for the prediction of neurodevelopmental disability was 1.45 (0.31, 6.89) (*P*=0.69), and 6.07 (0.97-38.05) (*P*=0.082), respectively. Specificity values are high during the fidgety movement period for prediction of neurodevelopmental disability and cerebral palsy. Sensitivity and specificity of preterm movements for the prediction of cerebral palsy were 50% and 63%, respectively while of fidgety movements for CP were 100% and 94%, respectively.

The index child classified as GMFCS level V had poor repertoire GMs in preterm period, followed by absent FMs; while the child with CP classified as GMFCS level III had normal preterm, but abnormal FMs.

DISCUSSION

This study looked at the value of preterm movements and fidgety movements in predicting neurodevelopmental disability (including cerebral palsy) at 18-24 months gestational age in very preterm babies. The incidence of CP was 1.57% that was consistent with results obtained from an earlier cohort from this Institution [16]. The preterm movements had poor sensitivity and specificity values for the prediction of neurodevelopmental disability and CP in this study, unlike two earlier studies [8,18]. However, longitudinal studies have shown that abnormal preterm movements normalize with brain maturation resulting in normal fidgety movements in these infants with normal neurodevelopmental outcomes. This implies that abnormal preterm movements are associated with acute perinatal complications which resolve with maturity of the central nervous system [11,19,20]. Preterm movements may have poor association with outcomes like minor neurological impairments, coordination problems, and fine manipulative disability at school age and puberty [21-23].

This study reiterated the strong psychometric properties of fidgety movements for the prediction of CP, in concurrence with published literature [6,7,24], that illustrate its usefulness in predicting CP.

While CP, a motor disorder, was predicted accurately by GMA, neurodevelopmental disability was less accurately predicted. This may be accounted for by the general quotient

Table I Association of Antenatal and Neonatal Complications With Neurodevelopmental Outcomes

Complications	*Neurodevelopmental outcome*	
	Normal (n=118)	*Abnormal (n= 9)*
Female	48 (40)	3 (33)
Gestational age, wk[a]	29.9 (1.29)	29.38 (1.67)
Birth weight, g[a]	1219 (229)	1157 (179)
Birth weight *z*-score <-2SD	1(0.8)	0
Length *z*-score <-2SD	15 (13)	0
Head circumference *z*-score <-2SD	8 (7)	0
Normal delivery	41 (35)	5 (56)
Multifetal pregnancy	37 (31)	6 (67)
PIHP	32 (27)	5 (55)
No antepartum steroids (*n*=121)	16 (14)	1 (11)
Perinatal asphyxia	4 (3)	0
Pneumonia	5 (5)	0
Bronchopulmonary dysplasia	19 (16)	0
Hyaline membrane disease[b]	41 (35)	7 (78)
Invasive ventilation	20 (17)	0
Septicemia	10 (8)	0
Necrotizing enterocolitis	2 (2)	0
Early major brain lesion[c] (*n*=120)	4 (4)	0
Late major brain lesion[c] (*n*= 122)	12 (10)	3 (37)

Data expressed as n (%) or [a]mean (SD). PIHP- pregnancy induced hypertension. [b]P=0.026. [c]Major brain lesion was defined as Grade 3 or 4 IVH or PVL using Papile grading using ultrasound findings for intraventricular hemorrhage, and de Vries classification using ultrasound findings for periventricular leukomalacia. Early cranial ultrasound was done between day 1 to day 20 of life [mean (SD) 6(13) days]; late cranial ultrasound was done between day 21 to day 80 of life [mean (SD) 44 (11) days].

WHAT IS ALREADY KNOWN?

- Fidgety movements have superior psychometric properties for prediction of cerebral palsy.

WHAT THIS STUDY ADDS?

- Preterm general movement assessment had limited utility in predicting neurodevelopmental disability or cerebral palsy.
- The utility of fidgety movements was predominantly in predicting cerebral palsy.

Table II Accuracy of General Movements During Preterm and Fidgety Movement Age for the Prediction of Neurodevelopmental Disability and Cerebral Palsy

	Preterm general Movements (n=127)	*Fidgety movements (n=118)*
Neurodevelopmental disability		
Sensitivity	33.33 (7.49-70.07)	25.00 (3.19- 65.09)
Specificity	64.41 (55.07- 73.00)	92.73 (86.17- 96.81)
PPV	5.83 (2.33- 13.86)	18.51 (5.44- 47.29)
NPV	93.60 (90.03- 95.94)	94.93 (92.59- 96.55)
Cerebral palsy		
Sensitivity	50 (1.26- 98.74)	100 (15.81- 100)
Specificity	63.69 (55.93- 70.96)	93.79 (88.54-97.12)
PPV	1.60 (0.40- 6.20)	16.02 (9.20- 26.42)
NPV	99.08 (96.40-99.77)	100

Data expressed as value (95% CI). PPV-positive predictive values; NPV-negative predictive value.

of the Griffith scale that is a composite of the child's abilities domains that include language, eye-hand coordination and personal social skills. A child with poor language or personal-social abilities (to which the environ- ment is a major contributor), but good motor abilities, would be classified as having a neurodevelopmental disability, but may have had normal fidgety movements.

The assessors of the neurodevelopmental outcomes were blinded to the infants' GM results which reduced the chance for bias. This study showed that abnormal fidgety movements were highly predictive of CP. This makes it a very useful and single tool to predict neurodevelopmental outcomes by trained assessors. Moreover, since parents are likely to stop bringing infants for follow up after the first few months; assessment of infants using GMs can be a very useful tool in the NICU for counseling parents.

There were a few limitations in this study. As the study was done in a tertiary institution with adequate facilities for assessment and follow up, generalizability of results to the community should be done with caution. The scoring for GMs in this study was done by a single observer, as there was no other trained assessor limiting the measurement of interrater reliability for assessment. There was a significant drop-out of about 25% (43 of 170 infants) who despite our best efforts did not complete the follow up which could have influenced the final results.

To conclude, this paper reiterates the utility of fidgety movements in the prediction of CP, while preterm movement assessments have limited use in prediction of neurodevelopmental disability or CP.

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Ethics clearance: IEC, Christian Medical College, Vellore; No. 8390, dated Sept 09, 2013.

Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

Contributors: HB: conceptualized and designed the study, was involved in data collection and analysis, interpretation and conclusion, prepared and revised the manuscript; SPO, RS, LA: involved in study design, supervised data acquisition and analysis, interpretation of data and critical revision of the manuscript; STO: involved in data collection and critical revision of the manuscript. MK: involved in data acquisition and interpretation, guided and critically revised the final manuscript.

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RESEARCH PAPER

Pediatric Appendicitis Score for Identifying Acute Appendicitis in Children Presenting With Acute Abdominal Pain to the Emergency Department

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Objective: To determine the diagnostic accuracy of Pediatric Appendicitis Score (PAS) in predicting appendicitis in children presenting with acute abdominal pain to the Emergency Department (ED) of a private hospital in Pakistan. **Methods**: This validation study was through retrospective chart review of children between 4-18 years of age with clinical suspicion of acute appendicitis, presenting to the pediatric ED. Diagnostic accuracy was determined using sensitivity, specificity, predictive values, and area under the curve (AUC). **Results**: 104 children (76% boys) with mean (SD) age of 10.9 (3.5) years met the eligibility criteria. 91% (*n*=95) patients had moderate to high PAS (score ≥4), and 95% (*n*=99) had biopsy-proven appendicitis. The likelihood ratio calculated for low, equivocal and high-risk PAS was 0.10, 2.17 and 2.53, respectively. An equivocal PAS (score 4-6) showed a sensitivity of 96.8%, specificity of 80%, positive predictive value of 98.9% and AUC of 0.84 for predicting acute appendicitis. **Conclusion**: PAS showed good diagnostic accuracy in predicting acute appendicitis in children presenting to the ED.

Keywords: *Diagnosis, Management, Perforation, Right quadrant pain, Surgery*.

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Appendicitis is one of the leading causes of abdominal pain in the pediatric population, and it usually requires immediate surgical intervention [1]. Timely diagnosis of a child with appendicitis is extremely important [2], as there is a risk of perforation in 12.5-30% of cases [3-5]. There is a high chance of misdiagnosis and it has been reported that approximately 28-57% of children of school going age are misdiagnosed [4].

To limit exposure to ionizing radiations during computerized tomography (CT) [4], and to overcome the subjective nature of USG [6], in children, different scoring systems have been used for the diagnosis of appendicitis. Two of the most common scoring systems are the Alvarado scoring system [3] and the Pediatric appendicitis score (PAS) [7]. Both scoring systems assign point values to data collected from patient history, physical examination and laboratory tests, and determine cut-offs to predict presence of appendicitis. There is conflicting evidence in the literature regarding the utility of these two scores in diagnosing acute appendicitis in children [8,9].

The scores may be particularly beneficial for developing countries, due to the limited access to diagnostic modalities in many health centers. Thus, our primary objective was to validate PAS in predicting appendicitis in children presenting with acute abdominal pain to the Emergency Department (ED) of a private hospital, and also to study the association of PAS with the gold standard (histopathology), and with ultrasound imaging.

METHODS

This was a retrospective chart review conducted by accessing records of children aged 4 to 18 years, brought to the pediatric ED from January 1, 2010 to December 31, 2012.

The ED of Aga Khan University Hospital (AKUH), a large urban tertiary care hospital, is a 62-bed facility receiving an average of 170 patients daily (around 1/3rd <18 years old). Pediatric patients receive initial management in the ED and those who are clinically stable get discharged, while remaining are then transferred to the pediatric inpatient wards, Pediatric intensive care unit (PICU) or the special care unit (SCU) for further management.

Ethical approval for this study was obtained from Ethics Review Committee of Aga Khan University Hospital, due to the nature of the study (retrospective chart review), consent was not deemed necessary.

We included children of either gender between 4-18 years of age who presented with acute abdominal pain (up

to 24 hours) of varying severity to the pediatric ED. Patients were excluded if they had ectopic pregnancy, lymphoproliferative disorder, abdominal trauma, or were referred for pre-diagnosed appendicitis.

Data were collected via review of files and the Patient Care Inquiry software, and included demographics, clinical signs and symptoms, laboratory and histopathology results. The data retrieved had initially been recorded in the patients' clinical file by a pediatric resident, senior medical officer and/or faculty. The initial clinical findings had been reviewed by the pediatric surgery team. We calculated the PAS of patients diagnosed clinically with acute appendicitis using the information provided at initial clinical presentation. Appendicitis was defined as appendectomy with positive histopathology results (gold standard). We then sought associations between the PAS score and histopathology results of those patients.

Sample size calculation was based on surveillance showing 19% of children who came to the hospital with complaint of acute abdominal pain would have acute appendicitis [10]. Assuming that PAS has a sensitivity of 92% and specificity of 88% for acute appendicitis [9,10], the estimated sample size calculated for this study was 104 children (with 95% confidence) at α=5% and power of 0.8.

Statistical analysis: Data were entered and analyzed using SPSS v21. PAS was calculated as a continuous variable (0-10) and then categorized as low (<4), equivocal (4-6) and high risk (>6) for acute appendicitis. Frequencies and percentages were derived for categorical variables, and mean and standard deviations for normally distributed continuous variables. Predictive values and area under the curve (AUC) were calculated to determine the diagnostic performance of PAS. Associations between the PAS and clinical outcomes were made, including comparison between PAS and ultrasound, CT scan and histopathology results.

RESULTS

For the study period, data on a total of 104 patients (76% boys) with clinical suspicion of acute appendicitis was analyzed. The mean (SD) age of the patients enrolled was 10.9 (3.5) years. The clinical parameters for the PAS are given in **Table I**. Although, 76% (*n*=79) of patients presented with right lower abdominal pain, 23% had umbilical pain. The mean (SD) PAS was 6.3 (1.6), with the maximum score being 10 in one child. Low risk probability PAS (score <4) was seen in 8.7% children; however, 43% had equivocal PAS (score 4-6) and 49% had high-risk PAS (score >6) probability. The likelihood ratio calculated for low, equivocal and high risk PAS was 0.10, 2.17 and 2.53, respectively (**Table I**).

Table I Clinical Characteristics of Children With Suspected Acute Appendicitis (*N*=104)

Characteristics	*Value*
Age[a]	10.9 (3.5)
Male	79 (76)
Right lower abdomen pain	79 (76)
Migration of pain	68 (65.4)
Anorexia	40 (38.5)
Nausea/vomiting	89 (85.6)
Right lower quadrant tenderness	95 (91.3)
Coughing/hopping/percussion pain	23 (22.1)
Fever	48 (46.2)
Leukocytosis	85 (81.7)
Left shift on WBC differential	91 (87.5)

Values in no. (%) or [a]mean (SD). WBC-white blood cells.

Majority of patients underwent imaging (88.5%), and ultrasound abdomen was the preferred imaging modality (64.4%) in these children. However, four patients (3.8%), in whom ultrasound abdomen was not suggestive of appendicitis, had to go through focused (unenhanced) abdominal CT scan, before surgery was opted.

Surgical intervention was performed by the pediatric surgery team in all 104 patient, of which, 99 patients (95.2%) had biopsy proven appendicitis; biopsy being positive in 6 (66.6%), 43 (97.7%) and 50 (98%) children with low-risk, equivocal and high-risk PAS, respectively.

Table II Diagnostic Performance of Pediatric Appendicitis Score (PAS) at Various Cutoff Points

	PAS <4	*PAS 4-6*	*PAS >6*
Sensitivity	93.94 (87.27-97.74)	96.81 (90.96-99.34)	74.75 (65.02-82.94)
Specificity	60 (14.66-94.73)	80 (28.36-99.49)	80 (28.36-99.49)
Positive predictive value	97.89 (94.07-99.27)	98.91 (94.03-99.81)	98.67 (92.74-99.77)
Negative predictive value	33.3 (14.82-58.96)	57.14 (28.72-81.52)	13.79 (8.42-21.78)
Accuracy	92.3 (85.4-96.62)	95.96 (89.98-98.89)	75 (65.55-82.97)

Values in point estimate (95% CI).

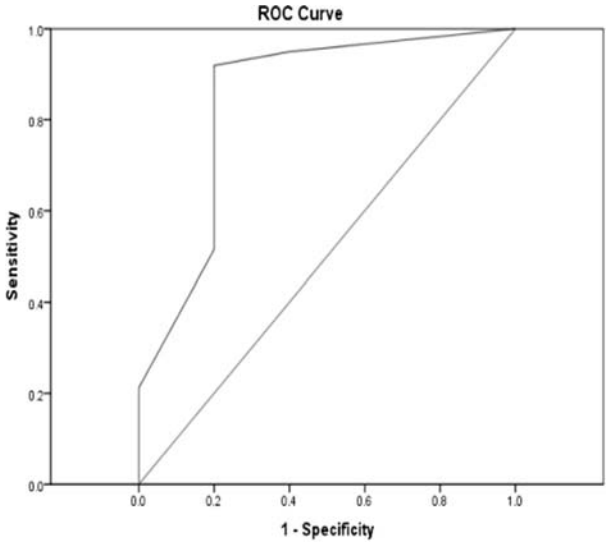

Fig. 1 Receiver operating characteristic curve for pediatric appendicitis score (PAS).

The PAS was compared for low, equivocal and high-risk and for each probability, sensitivity, specificity, PPV and NPV along with accuracy were calculated (**Table II**). PAS was similarly compared with ultrasound, and histopathology results (**Web Table I**). Diagnostic accuracy (95% CI) of an equivocal PAS (score 4-6) in predicting acute appendicitis in our patients showed sensitivity of 96.8% (90.9-99.3%), specificity of 80% (28.4-99.5%), PPV of 98.9% (94.3-99.8%), and Area under the curve, AUC (r= 0.84) (**Fig. 1**).

DISCUSSION

We studied PAS utilized in the pediatric ED of a hospital in a developing country. We used two cut-off points as opposed to Samuel, et al. [7] in his derivation study, where he used a single cut-off point of 5; the rationale for this was to compare amongst groups based on severity, as per the PAS. Another prospective cohort study [11] conducted at a pediatric ED revealed that using two cut-off points for the PAS improves its performance significantly. They set a PAS ≤4 as low risk for having appendicitis; patients with a score within that margin could be safely discharged (sensitivity of 97.6% and NPV of 97.7%) [11]. They also noticed that a single cut-off point for the PAS overestimated appendicitis and resulted in a negative appendectomy rate of 37.6% [11].

In our study, as a consequence, the low negative appendectomy rates, the negative predictive value and specificity of PAS cannot be assessed properly – the specificity and NPV of PAS is low compared to ultrasound and against gold standards. A similar trend was seen in various other validation studies for the PAS. Goldman, et al. [9] achieved similar results, at a pediatric ED, when they validated PAS with cut-offs of ≤2 and ≥7 for low and high-risk patients with a total AUC of 0.948 in 849 children. A retrospective study [12] at the ED of a community hospital concluded that the diagnostic performance of the PAS in 285 children with PAS ≥7 had good diagnostic performance, which was comparable to that of abdominal CT imaging, which is the best imaging tool for diagnosis of appendicitis in children. In a prospective study [13] of 140 children in an inpatient setting, a single PAS cutoff of ≥5 performed better than abdominal ultrasound as a screening tool. Other studies have also reported good performance of PAS in children [10].

Kulik, et al. [8] conducted a systematic review of 12 studies, none of which were in low-to-middle income countries, deriving and validating six different clinical prediction rules (CPR) including the PAS and Alvarado scores using a rigorous 17-item checklist for inclusion. They found that the PAS had been more broadly validated in a variety of settings as compared to the Alvarado score. These included inadequate description of predictor variables and absence of reproducibility testing of predictor variables.

In contrast, Ebell and Shinholser's [14] meta- analysis of 29 studies validating the PAS and Alvarado scores showed that although the latter was able to rule out acute appendicitis in children with a pretest probability <60% and a score ≤4, PAS failed to demonstrate clinically useful high (>85% probability) or low (<3%) risk groups for any pretest probability.

In his derivation set, Samuel, et al. [7] did not set concrete definitions for the parameters of the PAS. For instance, recording of "pain on coughing/hopping/ percussion" is subject to the level of training of the healthcare provider obtaining the history and performing the physical exami-nation, and upon time constraints witnessed at a fast-paced site such as the ED. In a retrospective design such as ours, this cannot be accounted for. Cut-offs for pyrexia and neutrophilia are also subject to varying thresholds set by different hospitals and laboratories across the globe.

Further studies are required to validate the PAS in a pediatric population presenting to the ED of a tertiary care center in a developing country, especially taking into account the above-mentioned factors. Our study was a retrospective chart review conducted at a single center, and it had a relatively small sample size. We included patients who presented within 24-hour of onset of acute abdominal pain. In future iteration; however, children with abdominal pain for up to 72 hours should be considered. Inter-observer variability could have been observed due

WHAT THIS STUDY ADDS?

- The pediatric appendicitis score (PAS) showed good diagnostic accuracy in predicting acute appendicitis in children presenting to the emergency department in a low- and middle-income county.

to patient assessment at the ED by residents of different training levels. Our study center is a large tertiary care hospital that caters to patients from a wide socioeconomic background; hence, under reporting may also have occurred.

In this study we found an equivocal PAS (4-6) to be fairly accurate in predicting acute appendicitis in children presenting to the pediatric ED of a developing country. Thus, potential exists to incorporate the PAS into evidence- based, patient-centric, quality and safety initiatives in the resource-limited pediatric ED, as it has good diagnostic accuracy.

Ethics clearance: IEC, Aga Khan University; No.: 4433-EM ERC-16 dated Sept 9, 2016.
Note: Additional matter related to this article is available with the web version at *www.indianpediatrics.net*
Contributors: MS, AIM: helped in conceptualization of the study, devised methodology, developed tool for the study, contributed in training the research assistant for data collection, gave supervision in data collection, input in data analysis, manuscript writing and critically reviewed the manuscript as submitted. OA: data collection and manuscript writing; MJ: data collection; RN: arranging data collection logistics, maintained data folders, manuscript reviewed by all co-authors, drafting the manuscript; SST: cleaned and performed statistical analysis of the data and provided technical input in the data interpretation. All authors have contributed, designed and approved the study.
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Web Table I Association Between Equivocal Pediatric Appendicitis Score (PAS 4-6) and Histopathology or Ultrasound

	Histopathology	*Ultrasound*
Sensitivity	96.81 (90.96-99.34)	89.09 (77.75-95.89)
Specificity	80 (28.36-99.49)	25 (5.49-57.19)
Positive predictive value	98.91 (94.03-99.81)	84.48 (79.5-88.43)
Negative predictive value	57.14 (28.72-81.52)	33.3 (12.67-63.28)

Values are point estimate (95% CI).

RESEARCH PAPER

Clinical Profile and Outcome of Newborns Discharged Against Medical Advice From a Tertiary Care Centre

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Objective: To determine the clinical profile and outcome of neonates discharged against medical advice (DAMA) from the neonatal intensive care unit (NICU) of a tertiary care public hospital. **Methods**: We retrieved information from hospital records of infants who had been discharged against medical advice from the NICU between January, 2016 and December, 2020. This was followed by a telephonic interview to document the infant's outcome. **Results:** Out of the 187 (7.7%) neonates that had left DAMA, 165 case records were available, and 65 (39%) families could be contacted telephonically. Congenital malformations accounted for 96 (58%) of the cases; cardiac malformations accounting for 42 (43.7%). 52 (80%) out of the 65 infants had died after median (IQR) 11 (5-35) days of DAMA, and 13 (20%) were alive at a median (IQR) age of 31 (18.5-31.5) months. Post-DAMA medical care was continued at another health facility in 12 (18%). **Conclusions:** One out of every five infants was alive for a median age of 31 months after having left DAMA. Mechanisms to ensure continuation of care after DAMA need to be explored.

Key words: *Comorbidity*, *Management, Outcome, Survival*

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The Ministry of Health and Family Welfare (MoHFW), reports the rate of discharge against medical advice (DAMA) to be 4% among inborn and 7% among out born neonates [1]. Previous studies on neonates with DAMA have focused on patient profiles and causes [2,3]. However, no study from India has sought to find out the outcome of neonates who left after DAMA. Post-DAMA continuation of care is another aspect that remains unexplored. Suffering from life-limiting conditions, many of these infants deserve palliative care, a practice that is not widely followed in our country [4]. Assessing the burden of post-discharge mortality and morbidity in these neonates is necessary for ensuring continuity of medical care for these neonates, and might also serve as a stepping stone in scaling up neonatal palliative care services in our country.

METHODS

This cross-sectional study was conducted in the newborn follow up clinic of a public sector tertiary care hospital between July and December, 2020 after obtaining institutional ethics committee clearance. A list of all infants discharged against medical advice from our NICU between January, 2016 and December, 2020 was prepared. The case records of these infants were traced from the medical records department, and contact numbers of families retrieved. All these newborns were eligible for inclusion in the study. There were no exclusion criteria. Their clinical details were noted in the study form.

Major congenital malformations were defined as congenital anomalies that have medical, surgical, or cosmetic consequences [5]. As many of the infants had involvement of multiple systems, the authors decided by consensus to determine the predominant morbidity or the primary illness during the NICU stay.

Two research nurses called up these families. A family was labeled as 'not attended' if two phone calls made 24 hours apart went unanswered. If the family responded, verbal consent for participation was obtained, structured interview was carried out based on the study questionnaire. The questionnaire consisted of open-ended questions on the cause of DAMA, the infant's outcome, age of death in case the child had died, and if medical care was sought elsewhere after leaving the hospital. The calls were not recorded. A call log book was maintained and the replies were noted down in the study form.

Statistical analysis: Descriptive statistics were employed to present the results, after analysis using Microsoft Excel 2013. Gestational age and birth weight had a non-normal distribution, and were expressed as median with IQR. All categorical variables were expressed as percentages.

RESULTS

During the study period, 2407 newborns were admitted to the NICU, of which, 187 (7.7%) had been discharged against medical advice. During these 5 years, a falling trend in the number of DAMAs was noted from 10.9% in 2016, to 6.7% in 2020. Contact details and case records of only 165 neonates [median (IQR) birthweight, 2425 (1665-2910); *n*=160] could be retrieved. All of these 165 phone numbers were called of which 97 calls were unsuccessful (wrong number or not attended) and three families refused consent. Finally, 65 families (39.3%) participated in the telephonic interview.

More than 60% (102 out of 165) of DAMA infants were term, 100 (60%) were females, median gestational age at birth being 37 weeks (IQR 34-39 weeks). The median age at DAMA was 5 days. The commonest morbidities in these infants were major congenital malformations in 96 (58%), followed by perinatal asphyxia in 23 (14%) (**Table I**). Complications of prematurity like extreme prematurity, respiratory dis-tress syndrome, necrotizing enterocolitis, intraventricular hemorrhage and post-hemorrhagic hydrocephalus acco-unted for 18 (11%) of the cases and sepsis for another 10 (6%). Among congenital malformations, cardiac diseases followed by disorders of the central nervous system accounted for 42 (43.7%) and 27 (28%) of the cases, respectively. Among those in whom congenital heart disease was the major morbidity, 37 were isolated and 5 were associated with syndromes/anomalies. There were 11 cases of hypoplastic left heart syndrome (HLHS), 22 cases of other cyanotic heart diseases, and three infants with acyanotic conditions. In six neonates, a clinical diagnosis of complex congenital heart disease was made as the child had been taken DAMA even before echocardiographic confirmation could be done. Among neonates who were primarily syndromic or with multiple anomalies, five had heart disease- four acyanotic and one unconfirmed. In 5% the primary illness leading to DAMA was not evident from the case record. Eligibility for comfort care was found in 33 (20%) of the infants. In 14 of them, the decision for comfort care was taken soon after

Table I Clinical Characteristics and Outcome of Neonates Discharged Against Medical Advice (*N*=165)

Characteristics	*Value*
Gestational age, wk (*n*=163)[a]	37 (34,39)
Gestational age categories (n=163)	
Extremely preterm (<28 wk)	7 (4.3)
Very preterm (28-31 wk)	15 (9.2)
Moderate preterm (32-33 wk)	12 (7.3)
Late preterm (34-36 wk)	27 (16.5)
Term (≥37 wk)	102 (62.5)
Inborn neonate	142 (89)
Day of life at DAMA[a]	5 (2,10)
Ventilated during the hospital stay	53 (32)
Infants eligible for comfort care	33 (20)
Soon after birth	14
During course of treatment	19
DAMA after few days of decision for comfort care	23
DAMA immediately after decision for comfort care	10
Primary diagnosis associated with DAMA	
Congenital malformations[c]	96 (58)
Cardiac	42 (43.7)
Neurological	27 (28)
Syndromic /multiple anomalies[b]	15 (15.6)
Gastrointestinal	6 (6.2)
Hypoxic ischemic encephalopathy	23 (13.9)
Complications of prematurity	18 (10.9)
Neonatal sepsis	10 (6)
Miscellaneous[d]	7 (4.2)
Inborn errors of metabolism	3 (1.8)
Diagnosis unclear[e]	8 (4.8)

Data presented as no. (%) or [a]median (IQR). DAMA-discharged against medical advice. [b]includes 5 neonates who had heart disease as part of their syndrome/multiple anomalies; [c]two babies each had congenital renal anomalies, congenital diaphragmatic hernia, and miscellaneous condition; [d]included epidermolysis bullosa, Neonatal lupus, congenital nephrotic syndrome, term newborn with neonatal jaundice, term newborn with hypoglycemia, term newborn with meconium aspiration syndrome; [e]Neonatal illness leading to DAMA could not be determined from the case record.

Table II Characteristics of Infants Followed-up Telephonically After Discharge Against Medical Advice (*N*=65)

Characteristics	*Value*
Maternal age[a], y	27 (24,29)
Paternal age[a], y	31 (30,35)
Primary diagnosis	
Congenital malformations	40 (61.5)
Cardiac	21
Neurological	7
Others	12
Hypoxic ischemic encephalopathy	9 (13.8)
Complications of prematurity	4 (6)
Miscellaneous conditions	9 (13.8)
Diagnosis unclear[b]	3 (4.6)
Reason for DAMA	
Poor prognosis	48 (73.8)
Wanted better care	16 (24.6)
Social reasons	1 (1.5)
Sought medical care elsewhere after DAMA	12 (18.4)
Alive	13 (20)
Age at death[a]	11 (5, 35)
Age at follow-up[a], mo	31 (18.5, 35.5)

Data presented as no (%) or [a]median (IQR). [b]Neonatal illness leading to DAMA could not be determined from the case record. DAMA-discharged against medical advice.

birth. These included 11 cases of hypoplastic left heart syndrome (HLHS), 2 cases of anen-cephaly, and 1 case of suspected Edward's syndrome. In the remaining 19, the decision was taken during the course of treatment (**Table I**). In these 33 infants, the treating team was convinced about the cessation of aggressive medical care and redirection to comfort care as the best option. In all other cases required treatment was offered.

The details of neonates, whose parents participated in the telephonic follow-up, are provided in **Table II**. The telephonic interview with 65 families revealed poor long-term prognosis as the commonest reason cited for DAMA by parents in 48 (74%). Fifty-two infants (80%) had died after median (IQR) 11 (5-35) days of DAMA. Thirteen (20%) were alive at a median (IQR) age of 31 (18.5-31.5) months. Only 12 (18.4%) had sought medical care elsewhere after DAMA, of which, 5 survived (38.4% of all survivors) and 7 did not survive (13.4% of all non-survivors).

DISCUSSION

Between 2016 and 2020, the rate of DAMA in our unit was 7.7%. Congenital malformations, especially cardiac conditions, were the commonest morbidity associated with DAMA. After DAMA, 13 (20%) infants were alive at a median age of 31 months. Only 12 (18%) were given the benefit of continued medical care.

Although the MoHFW has reported the rate of DAMA to be 4% among inborn and 7% among outborn neonates [1], neonatal units from India have published DAMA rates ranging from 10% to 25% [2,3,6]. As inborns account for more than 90% of our NICU admissions, most of the infants discharged against medical advice were inborn (89%), Gender bias in medical care of children is a well-known phenomenon [7], reflected in our study by the higher proportion of female infants being taken DAMA. Term neonates had been taken DAMA more commonly than preterm ones because congenital malformations, the single largest contributing cause were more common among newborns with term gestation. Most studies report DAMA to be commonest within the first week of admission [2,8,9], similar to the median of 5 days in this study.

Sepsis, birth asphyxia and low birth weight (LBW) have been reported as the commonest morbidities associated with DAMA [2,3,8,9]. In our study congenital malformations followed by sepsis, perinatal asphyxia and prematurity related conditions were the main neonatal illnesses associated with DAMA. Being a tertiary level hospital we receive referrals of antenatally detected congenital anomalies. With outcomes of common neonatal morbidities being reasonably good, congenital malformations became the leading morbidity in DAMA. Majority of the malformations were cardiac in nature. Intervention for HLHS, of which we had 11 babies, is not offered in most centers in India, including ours. For duct dependent pulmonary circulation situations, our center performed Blalock-Taussig (BT) shunt until 2019, after which ductal stenting was also offered. All these conditions require definitive surgery at a later age. Despite advances in cardiac care, congenital heart diseases in our country remain largely untreated [10]. We found poor prognosis to be the commonest cause of DAMA. Apart from an obviously poor chance of survival, prolonged hospital stay, food and lodging expenses even if treatment is free, need for multiple surgeries and overall compromised quality of the child's life were factors that were most probably perceived as 'poor prognosis' by parents. Poor outcome has been universally identified as a cause of DAMA [2,3,9,11,12].

Post-DAMA continuation of medical care was sought in 18% of the children. Garten, et al. [13] reported 1.5% of newborns to have been subjected to comfort care in their NICU, of which 8.7% had been discharged home or into a hospice. Jiang, et al. [14] estimated a 7% absolute reduction of mortality among very preterm infants, assuming neo-nates who had been discharged against medical advice had not done so and had actually completed medical care. Continued provision of care after DAMA might be a way to reduce mortality in these neonates. Parents should be encouraged to bring the child for follow-up and physicians to be ready to readmit the child, if necessary, even after DAMA.

The study is limited by its retrospective single center nature, in addition to a large proportion of missing data. In cases of multi-system involvement, retrospectively determining the primary illness associated with DAMA is fallacious. A prospectively conducted study with preferably a qualitative arm and live rather than telephonic interviewing may more conclusively document the reasons for DAMA. The study; however, has brought to light a previously unaddressed area viz., of outcomes following DAMA. Studies involving follow-up of NICU DAMA infants would help understand the course and outcomes of these infants.

In our tertiary level NICU, congenital heart diseases were the single largest contributor to neonatal DAMA. Medical care was available to only a small number of these children. Continued provision of medical care after DAMA, whether with curative or palliative intent, is an area that deserves more attention from both policymakers and public health experts.

Ethics clearance: IEC, JIPMER; No. JIP/IEC/2019/355 dated Oct 18, 2019.

WHAT THIS STUDY ADDS?

- Congenital malformations, especially congenital heart diseases, were the commonest diagnosis in neonates discharged against medical advice.
- Only one-fifth of newborns discharged against medical advice from the neonatal intensive care unit were alive at a median age of 31 months.

Contributors: NM: conceived the study, collected data and drafted the manuscript; SS: designed the study protocol, performed the analysis and critically revised the manuscript. Both authors approved the final manuscript. NM should be approached for access to raw data.

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Diagnosis, Treatment and Prevention of Nutritional Anemia in Children: Recommendations of the Joint Committee of Pediatric Hematology-Oncology Chapter and Pediatric and Adolescent Nutrition Society of the Indian Academy of Pediatrics

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Justification: Anemia in children is a significant public health problem in our country. Comprehensive National Nutrition Survey 2016-18 provides evidence that more than 50% of childhood anemia is due to an underlying nutritional deficiency. The National Family Health Survey-5 has reported an increase in the prevalence of anemia in the under-five age group from 59% to 67.1% over the last 5 years. Clearly, the existing public health programs to decrease the prevalence of anemia have not shown the desired results. Hence, there is a need to develop nationally acceptable guidelines for the diagnosis, treatment and prevention of nutritional anemia.

Objective: To review the available literature and collate evidence-based observations to formulate guidelines for diagnosis, treatment and prevention of nutritional anemia in children.

Process: These guidelines have been developed by the experts from the Pediatric Hematology-Oncology Chapter and the Pediatric and Adolescent Nutrition (PAN) Society of the Indian Academy of Pediatrics (IAP). Key areas were identified as: epidemiology, nomenclature and definitions, etiology and diagnosis of iron deficiency anemia (IDA), treatment of IDA, etiology and diagnosis of vitamin B12 and/or folic acid deficiency, treatment of vitamin B12 and/or folic acid deficiency anemia and prevention of nutritional anemia. Each of these key areas were reviewed by at least 2 to 3 experts. Four virtual meetings were held in November, 2021 and all the key issues were deliberated upon. Based on review and inputs received during meetings, draft recommendations were prepared. After this, a writing group was constituted which prepared the draft guidelines. The draft was circulated and approved by all the expert group members.

Recommendations: We recommend use of World Health Organization (WHO) cut-off hemoglobin levels to define anemia in children and adolescents. Most cases suspected to have IDA can be started on treatment based on a compatible history, physical examination and hemogram report. Serum ferritin assay is recommended for the confirmation of the diagnosis of IDA. Most cases of IDA can be managed with oral iron therapy using 2-3 mg/kg elemental iron daily. The presence of macro-ovalocytes and hypersegmented neutrophils, along with an elevated mean corpuscular volume (MCV), should raise the suspicion of underlying vitamin B12 (cobalamin) or folic acid deficiency. Estimation of serum vitamin B12 and folate level are advisable in children with macrocytic anemia prior to starting treatment. When serum vitamin B12 and folate levels are unavailable, patients should be treated using both drugs. Vitamin B12 should preferably be started 10-14 days ahead of oral folic acid to avoid precipitating neurological symptoms. Children with macrocytic anemia in whom a quick response to treatment is required, such as those with pancytopenia, severe anemia, developmental delay and infantile tremor syndrome, should be managed using parenteral vitamin B12. Children with vitamin B12 deficiency having mild or moderate anemia may be managed using oral vitamin B12 preparations. After completing therapy for nutritional anemia, all infants and children should be advised to continue prophylactic iron-folic acid (IFA) supplementation as prescribed under Anemia Mukt Bharat guidelines. For prevention of anemia, in addition to age-appropriate IFA prophylaxis, routine screening of infants for anemia at 9 months during immunization visit is recommended.

Key words: *Cobalamin; Deficiency; Folic acid; Hemoglobin; Iron; Vitamin B12*.

Nutritional anemias develop when the hema topoietic nutrients required for hemoglobin synthesis and/or maintenance are insufficient to meet the demands of an individual. The vast majority of nutritional anemias are due to the deficiency of iron, vitamin B12 (cobalamin, Cbl) and/or folic acid [1]. In addition, the role of other nutrients like vitamin D, vitamin A, vitamin C, pyridoxine and proteins in erythropoiesis is being recognized [2].

The statistics from the National Family Health Survey (NFHS-5; 2019-21) have raised a red flag highlighting the rising prevalence of anemia across all ages [3]. The highest spike in anemia was reported among children (6-59 months) with a rise to 67.1% (NFHS-5) from 58.6% (NFHS-4, 2015-16) followed by girls aged 15-19 years [4]. The Comprehensive National Nutrition Survey (CNNS) conducted in 2016-2018, revealed that 41% of preschoolers (1-4 years), 24% school-age children (5-9 years) and 28% of adolescents (10-19 years) in India have anemia [5]. The etiology of anemia was nutritional in 68.9%, 50.9% and 65.1% in children aged 1-4 years, 5-9 years and 10-19 years, respectively [5]. Iron deficiency was common in under-five children, while folate and vitamin B12 deficiency was higher among school going and adolescent age groups. Folate or vitamin B12 deficiency anemia accounted for more than a third of anemia in these three age groups, and 10-18% of children and adolescents with anemia had combined iron and folate or vitamin B12 deficiency [4].

Deficiency of hematopoietic micronutrients not only results in anemia but also leads to impairment of cognitive function in children, which affects learning. Unfortunately, these changes may be irreversible in younger children emphasizing the need for timely prevention, diagnosis and treatment. Additionally, nutritional anemias have a deleterious impact on the physical strength of the individuals as well as decreased productivity and economic loss to the country [6,7].

In the majority of children with nutritional anemia, diagnosis is straightforward and can be established with minimum diagnostic workup. Occasionally, in children with co-existing chronic inflammatory states and chronic illnesses like chronic kidney disease, the diagnosis can be challenging [8]. Several tests have been added to our armamentarium that can assist in the accurate diagnosis, but these must be used judiciously. In addition, the role of newer oral and parenteral preparations of iron and vitamin B12 for treatment needs to be clearly defined. Taking cognizance of the above, a need was felt to develop guidelines for diagnosis, treatment and prevention of nutritional anemias in children.

OBJECTIVE

To review the available literature and amalgamate evidence-based observations to formulate guidelines for diagnosis, treatment and prevention of nutritional anemia in children.

PROCESS

These guidelines are a joint venture of the Pediatric Hematology-Oncology (PHO) Chapter and the Pediatric and Adolescent Nutrition (PAN) Society of the Indian Academy of Pediatrics. In September 2021, experts from both chapters interested in varying aspects of nutritional anemia were invited to join the group. Task groups were constituted to address the key issues, including *i*) Need for guidelines; *ii*) Epidemiology and definitions; *iii*) Nomenclature; *iv*) Etiology and diagnosis of iron deficiency anemia (IDA); *v*) Treatment of IDA; *vi*) IDA not responding to oral therapy; *vii*) Etiology and diagnosis of vitamin B12 and folate deficiency; *viii*) Treatment of folate deficiency and vitamin B12 deficiency anemia; and *ix*) Prevention of nutritional anemia. Two to three experts were assigned each key issue and were required to review the relevant literature, including the recent publications in the related field.

Online meetings were organized from 15 to 18 November 2021, wherein the experts assigned the individual tasks made a presentation. The group discussed each topic and the presenting faculty was then asked to make modifications based on the inputs received during deliberations. The revised versions were discussed amongst the group members for any further modifications. The group prepared the final document with recommendations for each assigned topic. The level of evidence (LoE) of each recommendation was graded as per the Oxford Centre for Evidence-Based Medicine (OCEBM) 2011 Guidelines [9]. The final draft guidelines were circulated to all the committee members for comments, modifications and final approval. The statements below are the consensus recommendations of the expert group.

Scope: While formulating these guidelines, the primary focus is the health benefits resulting from treatment and preventive nutrient supplementation. The age group under focus is from 6 months to 18 years. The recommendations are easy to understand and apply in day-to-day clinical practice. In smaller towns and rural areas, investigations may not be available. These guidelines aim to guide the management of children with suspected nutritional anemia in areas where facilities for laboratory diagnosis are scant. It is expected that these guidelines will enable the medical officers, pediatricians, and post-graduate trainees to manage children and adolescents with nutritional anemia scientifically. These guidelines are intended as an additional shot in the arm for tackling the increasing prevalence of nutritional anemia in children.

RECOMMENDATIONS

1. Definitions and Hemoglobin Cut-offs

The World Health Organization (WHO) suggests the use of hemoglobin cut-off levels below two standard deviations (SD) from the population mean (in a representative healthy population) to define anemia and its severity [10] as shown in **Table I**. However, whether these cut-offs are representative and applicable for children residing in low-income and middle-income countries (LMIC) is being questioned. It is argued that cut-off levels for defining anemia in children in LMIC, including in India, may be lower than the WHO cut-offs [11]. Using Comprehensive National Nutrition Survey (CNNS) 2019 data, Sachdeva, et al. [11] have recently published age and sex-specific hemoglobin percentiles. For these percentiles, the authors included only those children from CNNS for whom the serum levels of ferritin, folate, vitamin B12, and retinol were normal. They also excluded children with elevated C-reactive protein (CRP), variant hemoglobin and a history of smoking. The hemoglobin cut-offs thus derived are 1-2 g/dL lower than the WHO suggested cut-offs at all ages [12]. Although this data used by the authors is representative of the population, it has not yet been adopted by the national public health programs

Nutritional anemia is classified based on the morphological features of red blood cells (RBCs). Cases with iron deficiency have microcytic anemia and are characterized by RBCs with low mean corpuscular volume (MCV). The lower limit of MCV (fL) in children below 2 years is 70 fL (**Table II**). For children between 2-10 years, a lower limit of MCV is 70 plus age in years. In older children and adolescents (≥10 years), an MCV cut-off value <80 fL can be used to define microcytosis, as for adults. Anemia resulting from deficiency of vitamin B12 or FA is characterized by large RBCs (high MCV). The cut-off value for MCV to define the upper limit of MCV in children aged 2-10 years is 84 plus 0.6 X Age (years). Beyond 10 years, the upper limit of MCV to diagnose macrocytic anemia is 90 fL [13]. Not infrequently, children are described to have dimorphic anemia when deficiency of iron coexists with deficiency of vitamin B12 and/or folic acid resulting in two populations of RBCs seen on examination of peripheral smear [14]. RBC histogram on the electronic cell counter will show two peaks [15].

Table I Hemoglobin Thresholds (g/dL) to Define Severity of Anemia as per the World Health Organization

	Non-anemic	*Mild*	*Moderate*	*Severe*
Children 6-59 mo	>11	10-10.9	7-9.9	<7
Children 5-11 y	>11.5	11-11.4	8-10.9	<8
Children 12-14 y	>12	11-11.9	8-10.9	<8
Men aged ≥15 y	>13	11-12.9	8-10.9	<8
Women aged ≥15 y	>12	11-11.9	8-10.9	<8
Pregnant women	>11	10-10.9	7-9.9	<7

Recommendation

The group recommends using the existing hemoglobin cut-offs (age- and gender-specific) provided by the WHO until more reliable population-based age and gender-specific hemoglobin nomograms become available. **(LoE2)**

2. Iron Deficiency Anemia

2.1 Diagnosis of Iron Deficiency Anemia

In most clinical situations, a presumptive diagnosis of IDA can be made based on dietary history, clinical features and the peripheral blood picture suggestive of microcytic hypochromic anemia with anisopoikilocytosis. Unlike thalassemia trait, basophilic stippling is only rarely seen. The classical triad of low MCV, low mean corpuscular hemoglobin (MCH) and low mean corpuscular hemoglobin concentration (MCHC) for age is consistent with

Table II Cut-offs for Laboratory Estimates for the Diagnosis of Nutritional Anemia

Parameter	*Cut-off*
Microcytosis, MCV (fL)	
Upto 2 y	<70
2-10 y	<70 plus age (years)
>10 y	< 80
Macrocytosis, MCV (fL)	
2-10 y	>84 plus 0.6 X Age (years)
>10 y	>90
Serum ferritin (µg/L)	
<5 y	< 12 (IDA)
>5 y	< 15 (IDA)
With infection	< 30 (IDA)
Serum transferrin saturation	<16% (IDA)
Reticulocyte hemoglobin content (CHr) (pg)	<29 (IDA)
% hypochromic cells	>5% (IDA)
Free erythrocyte protoporphyrin level (FEP) (µg/dL)	
<5 y	>70 (IDA)
>5 y	>80 (IDA)
Serum folate (ng/mL)	<4 (Folate deficiency)
RBC folate (ng/mL)	<100 (Folate deficiency)
Vitamin B12 (pg/mL)	< 200 (Vitamin B12 deficiency)
Homocysteine (mol/L)	>15 (Folate deficiency)
Methyl Malonic Acid (nmol/L)	>750 (Vitamin B12 deficiency)

IDA–iron deficiency anemia, MCV-mean corpuscular volume.

the diagnosis of IDA. The diagnosis is often confirmed in a clinical setting by assessing response to empirical iron therapy [16,17]. Investigations to establish the diagnosis of IDA become necessary when an alternative diagnosis cannot be excluded clinically and in children who fail to respond to iron therapy. In such situations, the following investigations are useful:

Serum ferritin: Serum ferritin is a reliable indicator of body iron stores. It is the earliest marker of iron deficiency and has been widely recommended as the initial investigation. A systemic review of guidelines on diagnosis and treatment of iron deficiency observed that serum ferritin assay is recommended for diagnosis of IDA by all 22 guidelines included in this review [18]. However, the recommended cut-off of serum ferritin to diagnose ID is variable across these guidelines. WHO also strongly recommends using serum ferritin to diagnose IDA [19]. Serum ferritin <12 µg/L in children under-five years of age and serum ferritin <15 µg/L in individuals over 5 years of age in the absence of any active inflammation are suggestive of IDA. Similar cut-offs have also been recommended more recently by the British Society of Hematology [20]. In the presence of infection or inflammation, serum ferritin <30 µg/L is suggestive of IDA in children [19].

Serum iron, total iron binding capacity (TIBC) and tranferrin saturation (TS): Iron studies are recommended when serum ferritin results are equivocal. Serum iron levels are low in iron deficiency and IDA. However, there is a day-to-day variability in iron levels as they are influenced by recent intake. Hence, estimation of serum iron alone in the diagnostic workup of IDA is not recommended. It is estimated to calculate TS or TIBC [20]. Ten of the 22 guidelines in the systematic review recommended using TS as an alternative or complimentary to the estimation of serum ferritin [18]. The recommended threshold of TS to diagnose iron deficiency is <16% in young adults, although age-specific cut-offs can be used in children where the cut-offs used are slightly higher than adults [18,20,21].

Newer red cell indices: Since the lifespan of reticulocytes is very short, the measurement of reticulocyte hemoglobin helps determine the availability of iron to form hemoglobin. Additionally, unlike serum ferritin, reticulocyte hemoglobin is not affected significantly by inflammation. Reticulocyte hemoglobin is measured by two methods, viz, reticulocyte hemoglobin content (CHr), and reticulocyte hemoglobin equivalent (Ret-HE). An acceptable correlation has been demonstrated between Ret-HE and CHr in multiple clinical studies. Ret-HE has gained popularity for diagnosing iron deficiency and IDA and evaluating a patient's response to oral iron treatment [20,22,23]. Since CHr and Ret-HE reflect the hemoglobin content in reticulocytes, low values reliably indicate early iron-deficient erythropoiesis prior to the onset of anemia, serving as the earliest indicators of IDA. Although there are no standardized cut-offs of Ret-HE to determine IDA, commonly recommended cut-off in children vary between 25-30 pg [20]. A cut-off of <29 pg has been recommended by the British Society of Haematology for diagnosing IDA in children [20]. These indices can also be used to assess the response to the treatment being one of the earliest parameters to increase in response to treatment. It needs to be borne in mind that Ret-HE and CHr are also low in children with thalassemia trait [11,12].

Another novel parameter is the percentage of hypochromic red cells (Hypo%), which reflects iron status over the preceding 3 months. It may be useful for distinguishing thalassemia trait from ID. More than 5 % hypochromic red cell is the cut-off for defining iron deficiency [20]. Hypo% is also a valuable parameter to diagnose functional iron deficiency, i.e. inadequate incorporation of iron in the erythroid precursors despite having adequate iron stores as per the ferritin or bone marrow iron stores. This is frequently seen in chronic kidney disease [24].

Soluble transferrin receptor (sTfR): Soluble transferrin receptors (sTfR) are derived from actively developing red cells and reflect active erythropoiesis. A cut-off of sTfR >27.3 nmol/L has been proposed to detect IDA. A low ratio of sTfR/serum ferritin can help distinguish IDA from anemia of chronic disease [25]. However, due to poor sensitivity in early and intermediate iron deficiency, this test is routinely not recommended (20, 26).

Free erythrocyte protoporphyrin level (FEP): As iron deficiency limits the final step in heme synthesis, there is an accumulation of FEP in the red cell precursors. FEP is elevated in iron deficiency and rapidly falls as a response to treatment. The cut-off level of FEP is >80 µg/dL for children over 5 years of age and >70 µg/dL for children younger than 5 years of age [16]. Spuriously high levels of FEP are reported in the presence of hyperbilirubinemia [27]. Moreover, FEP is raised in thalassemia trait and hemoglobin E disease, two conditions common in our country [28]. Recent guidelines have not recommended its use for diagnosing iron deficiency [20].

Bone marrow studies: We do not recommend bone marrow aspiration and staining for iron using Perls Prussian blue stain, as the test is invasive and is rarely justifiable as a battery of non-invasive tests are available to assist the diagnosis [17,18].

Recommendations

- In most clinical situations, a presumptive diagnosis of

IDA can be made based on red cell indices and the blood picture suggestive of microcytic hypochromic anemia (**Table II**). The classical triad of low MCV, low mean corpuscular hemoglobin (MCH) and low mean corpuscular hemoglobin concentration (MCHC) for age is consistent with the diagnosis of IDA. Response to iron therapy should be documented for confirmation of diagnosis (**LoE 2**).

- Serum ferritin should be the first test to diagnose ID/ IDA where investigative workup is indicated (**LoE 1**).
- In situations where serum ferritin results are equivocal, transferrin saturation may be used (**LoE 2**).
- CHr and Ret-HE, and percentage of hypochromic cells, wherever available, can be used to diagnose IDA (**LoE 1**).

2.2 Treatment of Iron Deficiency Anemia

The treatment of IDA aims at providing iron therapy in the appropriate dose, formulation and duration to restore hemoglobin to normal range and replete body iron stores. The treatment of IDA should also be comprehensive and should include the identification of any secondary cause of ID and its management (this is beyond the scope of these guidelines). Treatment must also address dietary modifications, if required, and a periodic follow-up for assessment of therapeutic response. High quality evidence for the management of iron deficiency is limited in adults as well as in children.

2.2.1 Route of Iron Therapy

Oral iron therapy is the route of choice almost always. Oral iron may be initiated based on history, hemoglobin, MCV, and peripheral smear where possible, without the need for biochemical investigations. It is safe, effective, economical and leads to rapid improvement in hemoglobin if administered in the correct dose and followed up appropriately. It is convenient for parents and is well tolerated by almost all patients. Parenteral iron is rarely ever required in children.

Oral iron preparations: Oral iron preparations are available mainly in ferrous and ferric forms; the ferrous form is better absorbed [29]. The three most common ferrous iron preparations viz., ferrous sulphate (FS), ferrous fumarate and ferrous gluconate provide 20% (anhydrous 30%), 33% and 12% elemental iron, respectively. Elemental iron is the form of iron in the supplement that is available for absorption by the body. While prescribing oral iron, the amount of elemental iron in the preparation should be noted, and the dose should be calculated accordingly. All these three oral iron formulations have essentially equivalent bioavailability [30, 31]. Iron polymaltose complex (IPC) and ferrous ascorbate are other available iron preparations. The use of iron polymaltose complex (IPC) over ferrous iron preparations does not offer any therapeutic benefit. Patil, et al. [32] have demonstrated higher hemoglobin rise with comparable doses of ferrous ascorbate compared to IPC with a similar side effect profile. Ferrous sulphate has also shown an advantage over IPC in children with IDA in terms of therapeutic efficacy [33]. In another study, IPC was found to be inferior to iron bisglycinate for treating IDA [34]. Ferrous ascorbate has also shown better therapeutic efficacy compared to colloidal iron in children with IDA [35]. Given a similar adverse effect profile with lesser cost, FS may be preferred to IPC and ferrous ascorbate. Entericcoated and delayed-release iron supplements were developed to improve the compliance as their gastrointestinal side effect profile is better. However, they are not absorbed as well as the standard preparations because the release of iron occurs much below the site of absorption and these preparations are expensive [31]. The fractional iron absorbed from enteric-coated preparations is significantly less than from uncoated preparations [36]. **Box 1** summarizes the various iron compounds used to treat IDA in children.

2.2.2 Dose and schedule of oral iron therapy

The recommended therapeutic dose of iron for children is usually 3-6 mg/kg/day [37,38]. However, it has been noted that doses of 2-3 mg/kg/day of elemental iron are also efficacious and can improve patient compliance as they reduce the side effects such as abdominal pain and constipation. Powers, et al. [39] have recently shown a very good hematological response using a 3 mg/kg dose. The British Society of Gastroenterology (BSG) has recommended the beginning dose of oral iron for adults as one tablet of iron sulphate, fumarate, or gluconate, which usually has 66 mg elemental iron or less [31]. This, for an average weight adult, would mean about 1-1.5 mg/ kg.

Whether iron should be administered as a single dose or in divided doses has conflicting evidence. Some authors [40] have demonstrated better absorption with a single morning dose and alternate-day dosing, while others [41] have demonstrated more intense reticulocytosis and better reticulocyte hemoglobin in patients receiving a twice-daily dose. Another study demonstrated equal efficacy of once or thrice daily iron dosing [42]. Overall, emerging evidence supports the treatment of IDA with a single daily dose of iron. The administration as a single dose ensures long-term compliance and administration of the drug in the evening atleast one and a half to two hours after dinner improves gastrointestinal tolerance [31]. Alternate day administration may be advised in cases with intolerance, although it may

Box I Various Oral Iron Formulations

Ferrous vs Ferric

1. All iron salts have to be reduced to ferrous form to enter mucosal cells. Bioavailability of ferric preparations is 3 to 4 times less than that of conventional ferrous preparations. Hence, ferrous salts are preferred.
2. Ferrous salts are among the cheapest preparations available

Ferrous sulphate

1. 20% elemental iron
2. Mainly as tablet forms; syrup form or elixirs (in sorbitol base) are not stable

Ferrous fumarate

1. 33% elemental iron
2. Similar efficacy and gastrointestinal tolerance to ferrous sulphate, more stable, tasteless
3. Less soluble in water / soluble in mild acid- gastric juice

Iron-Amino acid chelates

1. Ferric or ferrous ion with amino acid conjugates
   - Ferrous bisglycinate (20% elemental iron)
   - Ferric trisglycinate
   - Ferrous glycine sulphate (India)
2. No effect on colour or taste of food
3. Relatively high bioavailability in the presence of dietary inhibitors
4. Environmentally stable
5. Chance of toxicity on overdose less

Iron Polymaltose complex (IPC)

1. Non-ionic iron and polymaltose in stable complex
2. Equivalent bioavailability to FS
3. Absorption better when taken with meals
4. No teeth staining
5. Poisoning risk less as intestinal transport gets saturated at higher dose
6. Slower improvement in hemoglobin

result in a slower response. Absorption of the drug is better if given on an empty stomach, but oral iron is better tolerated after a meal [43]. Iron should not be administered with milk, curd, calcium syrup/ tablets and is best given with water if needed. Tea, coffee, and drugs interfering with absorption, such as proton pump inhibitors and antacids should be avoided with iron.

2.2.3 Duration of iron therapy

Recent BSH guidelines highlighted that duration required to replenish the body iron store is unclear. They have persisted with 'traditional' 2-3 months after hemoglobin normalizes [31]. Continued iron therapy in a therapeutic dose for this period allows replenishment of stores so that iron-restricted erythropoiesis is resolved [38].

We recommend that iron therapy be continued for 2-3 months after hemoglobin normalizes. The group recommends that the family/ caregiver be educated about the need for continuing iron supplementation after correcting anemia. Before stopping the therapeutic dose, one should ensure that the family feeding practices have been rectified and the cause for secondary iron deficiency, if any, has been ameliorated. Since iron prophylaxis is recommended till adolescence the prophylactic dose should be adminis-tered as recommended by the national program [1].

2.2.4 Assessing response in iron deficiency anemia

After initiating therapy, the first response expected is a decrease in irritability, lethargy and a sense of well-being. Appetite generally improves within 24 hours [37]. Compared to mild and moderate anemia, the rise in reticulocytes is much higher in severe anemia, as is also seen with the rise in hemoglobin. Peak reticulocyte count is seen on days 5-10 following initiation of iron therapy, and wherever available, reticulocyte response should be assessed in addition to the rise in hemoglobin. Hemoglobin rises on an average by 0.25-0.4 g/dL/day, or hematocrit rises 1%/day during the first 7-10 days. Thereafter, a slower rise of 0.1-0.15 g/dL/day is seen in hemoglobin.

The timing for scheduled follow-up visits also varies depending upon the severity of anemia. Children with severe anemia who do not receive a blood transfusion and are initiated on oral iron therapy need to be called on day 7 and day 14 for clinical evaluation and complete blood count (CBC) or earlier if the child develops any danger signs like edema, fast breathing, lethargy or irritability and any adverse effects such as vomiting or diarrhea. Children with moderate or mild anemia need to be called for a repeat hemoglobin or CBC on day 14 of therapy.

In the case of moderate/severe anemia, once improvement in hemoglobin has been documented, further followup should be done at 2-4 weekly intervals till hemoglobin is >7g/dL, and then monthly. The usual rate of increase in hemoglobin is ≥1 g/dL in 14 days. By 8-12 weeks, hemoglobin rises by 3-5 g/dL and in most cases, anemia is corrected [32,35,44].

Follow-up visits should also be utilized to reinforce the need for food diversity and increased consumption of iron and vitamin C rich food items, including poultry items (like eggs, meat, organ meats like liver), fish, citrus fruits, potatoes and tomatoes. Consumption of tea, phytates (whole grains, cereals, soy, nuts and legumes) and phosphates should be curtailed.

2.2.5 Role of co-administration of cobalamin, folic acid, or vitamin C along with iron

Folic acid is usually a part of all oral iron-containing preparations and hence routinely given to all children with IDA. Oral vitamin B12 may be added where there is a poor response to oral iron alone or in children with combined

vitamin B12 and iron deficiency anemia (dimorphic anemia). Combined deficiency is expected in up to 30% of children with nutritional anemia. The presence of near-normal MCV, dimorphic red cells in the peripheral smear, features of megaloblastic anemia such as hyper-segmented neutrophils, thrombocytopenia, macro-ovalocytes, etc. warrants investigations for associated folate and/or vitamin B12 deficiency. If documented, the addition of folic acid and vitamin B12 in the therapeutic dose is required. Contrary to earlier observations, a randomized clinical trial in adults has shown no benefit of adding vitamin C to iron therapy [45]. Hence, vitamin C is not recommended in pharmaceutical forms. However, the addition of citrus fruits to the diet immediately prior to medication aids in iron absorption.

Recommendations

- We recommend ferrous salts (ferrous sulphate or ferrous fumarate, or ferrous gluconate) for treating IDA in children (**LoE 2**).
- We do not recommend the use of prolonged-release or enteric-coated iron tablets or liposomal iron formulations for the treatment of IDA (**LoE 1**).
- We recommend an oral dose of 2-3 mg/kg/day of elemental iron along with folic acid for treating IDA given for upto 2-3 months after hemoglobin normalizes (**LoE 1**).
- We recommend single daily dosing of oral iron. Divided doses can be given in cases of gastrointestinal adverse effects (**LoE 1**).
- While on treatment, patients with severe anemia should be called for first follow-up on day 7 while patients with moderate and mild anemia should be called for follow-up on day 14 (**LoE 2**).

3. Iron Deficiency Anemia Not Responding to Oral Iron Therapy

Standard texts and review articles have listed causes of failure of an adequate response, but which cases qualify to be labeled as poor responders /non-responders is not well defined [37,38,46]. The absence of hemoglobin rise of less than 1 g/dL after 2 weeks of daily oral iron therapy in adults has been described as predictive of lack of response [31]. Okam, et al. [47], in a pooled analysis of five studies in women, have also defined non-responder as having less than 1 g/dL rise in hemoglobin by day 14 of therapy. Bhatia, et al. [48,49], while evaluating Indian children for iron refractory iron deficiency anemia (IRIDA), have used criteria of less than 1 g/dL rise in hemoglobin after 4 weeks of daily iron therapy to define non-response, as has been used by others as well. While most cases with moderate and severe anemia will have hemoglobin rise of 1 g/dL or more by day 14, it may not be so for cases with mild anemia.

3.1 Evaluation of Non-responders

Ensuring compliance to therapy with adequate dosages should be an integral part of follow-up evaluation and a pre-requisite before labeling non-response to oral iron therapy. A detailed review of dietary history and any intercurrent illnesses that might interfere with iron absorption should be done. The following points should be revisited:

i) Conditions interfering with iron absorption like celiac disease, *Helicobacter pylori* infection, autoimmune gastritis, or anemia of chronic disease should be ruled out by appropriate testing as indicated in a given child [50, 51].

ii) Patients should be evaluated for gastrointestinal blood loss: Three consecutive stool samples should be evaluated for occult blood. Cow milk protein intolerance, Meckel diverticulum and inflammatory bowel disease should be considered in case of a positive stool occult blood [52-54].

iii) Evaluation of other causes of microcytic hypochromic anemia: Celiac disease is a common cause of refractory IDA in children in certain states. All cases of refractory IDA should be screened for celiac disease using tissue transglutaminase antibodies (tTG) along with serum IgA, whenever suspected [55]. Children with betathalassemia trait (BTT) have a blood picture of microcytic hypochromic anemia and can mimic IDA. BTT and IDA can be differentiated by following investigations [56,57]:

- RBC count >5 million/mm^3 suggests BTT, RBC count< 5 million/mm^3 suggests IDA
- Red cell distribution width co-efficient of variation (RDW CV) <14% BTT, RDW CV >14% in IDA
- Mentzer index (MCV divided by RBC count) is <13 in BTT and >13 in IDA
- High performance liquid chromatograhy will confirm the diagnosis of BTT by showing elevated hemoglobin A2 (>3.5 %).

iv) Anemia of chronic disease (ACD) is usually normocytic normochromic. However, in some cases, it may be microcytic hypochromic. In a patient where a chronic infection is suspected, the diagnostic evaluation needs to be directed towards the diagnosis of the underlying disease [58]. Additionally, in children with suspected ACD evaluate for underlying chronic renal disease or connective tissue disease.

v) Iron refractory iron deficiency anemia (IRIDA) is a rare inherited disorder in which absorption of oral iron is markedly impaired. IRIDA is caused by loss of function of the *TMPRSS6/matriptase 2* gene, which causes iron deficiency due to inappropriately high hepcidin levels with markedly reduced iron absorption and increased sequestration of iron in macrophages. Patients present with a mild hypochromic, microcytic anemia with very low serum iron levels and low transferrin saturation. Serum ferritin levels are mostly within the normal range or even slightly elevated following treatment with intravenous iron. The diagnosis of IRIDA is confirmed by demonstrating biallelic mutation in the *TMPRSS6* gene. These patients can be treated with a trial of intravenous iron therapy [49,59].

3.2 Parenteral Iron Therapy

Most cases with IDA can be successfully managed by oral iron supplementation. However, in some situations, parenteral iron therapy is required (see below). As the new intravenous (IV) iron formulations are devoid of major adverse effects, these are the preferred preparations for parenteral iron therapy [47]. The intramuscular route is not recommended as it is painful and can lead to staining of the overlying skin.

3.2.1 Indications for parenteral iron therapy

The conditions where the use of intravenous iron may be required [7,38,47] are noted in **Box II**. In a retrospective review, amongst children aged 3 months to 18 years requiring intravenous iron in a US hospital, most cases (73.8%) were related to kidney diseases. Of the remaining 38 cases, 13 were unresponsive to oral iron due to poor compliance or side effects, 13 due to malabsorptive states, seven due to ongoing blood losses, and two had IRIDA [60].

Box II Conditions Where the Use of Intravenous Iron May be Required [37,38,47]

- Poor adherence or intolerability due to gastro-intestinal side effects of oral iron
- Need for rapid replenishment of hemoglobin and iron stores rather than over the course of several months, e.g., in preoperative situations
- Ongoing blood loss that exceeds the capacity of oral iron to meet needs (heavy uterine bleeding, mucosal telangiectasias).
- Iron malabsorption due to pre-existing anatomic or physiologic condition, e.g., short bowel syndrome
- Coexisting inflammatory state that interferes with iron homeostasis
- Chronic kidney disease
- Genetic forms refractory to oral iron (IRIDA etc.)

3.2.2 Preparations of intravenous iron

The following preparations of iron are available for parenteral use:

- *Iron sucrose*: It is the most common form of IV iron used in children [60]. Adverse events, including anaphylaxis, are rarely reported, so a test dose or routine pre-medications are not indicated. The recommended dose ranges from 1-4 mg/kg elemental iron IV infusion over 1 hour every week with a maximum dosing of 200 mg elemental iron per infusion for adolescents and 100 mg of elemental iron per infusion for children. Most patients require multiple infusions to complete the replacement of their calculated iron deficit.
- *Ferric gluconate*: It is approved for children with chronic kidney disease on dialysis and erythropoietin-stimulating agents aged ≥6y. No test dose or routine premedications are indicated. The maximum dose is 125 mg elemental iron per infusion. Adverse events are rarely reported.
- *Iron dextran*: Low-molecular weight (LMW) iron dextran is commonly given as a single replacement dose (e.g., up to 1000 mg elemental iron in adults).
- *Ferric carboxymaltose* (FCM): It is increasingly used for adults who are intolerant to oral iron therapy and also permits administration of the full replacement dose in a single infusion in the majority of patients. Data in the pediatric population is limited but promising [61]. Hypophosphatemia is a common complication with its use. It is used in a dose of 15mg/kg single rapid (over 15 minutes) intravenous infusion without any test dose.

United States Food and Drugs Administration (FDA) has approved low molecular weight iron dextran, ferric gluconate, iron sucrose and FCM for use in children [62]. The use of iron dextran for intravenous iron therapy is no longer recommended and it has been discontinued. Iron sucrose, FCM and ferric derisomaltose (isomaltoside), are approved for treatment of iron deficiency in India.

3.2.3 Dose calculation for parenteral iron therapy

Hemoglobin iron deficit (mg) = Body weight (kg) X (Ideal hemoglobin – desired hemoglobin) X (2.145) + iron to replenish stores, if desired (mg).

Volume of product required (mL) = Bodyweight X (14 - hemoglobin) x (2.145) ÷ Concentration of elemental iron in the product used (mg/mL) [62-64].

For example, a 6-year-old child weighing 20 kg with hemoglobin of 6 g/dL would need 343.2 mg of elemental iron, equivalent to 1.7 mL of iron sucrose injection

containing 200 mg/mL of elemental iron (20 X 8 X 2.145 ÷ 200). This child will be given 343.2 mg of elemental iron in four divided weekly doses; 0.43 mL iron sucrose dissolved in 100-200 mL of normal saline and infused over 1-3 hours every week X 4 weeks.

An intravenous dose of iron for undernourished children should be calculated with present weight, while for obese patients, ideal/lean body weight should be used for calculation. Lean body weight can be calculated by the formula: Lean body weight = BMI_{50} X Ht^2 [65].

3.2.4 Precautions

Routinely no premedication is indicated. Patients with comorbidity of bronchial asthma, drug allergy and inflammatory arthritis require premedication with 1-2 mg/kg of parenteral methylprednisolone before intravenous iron administration.

3.2.5 Response to parenteral therapy

Subjective improvement in uncomplicated cases occurs within a few days of intravenous therapy. Reticulocytosis peaks at about 10 days. Symptomatic improvement occurs in 1-2 weeks parallel to a rise in hematocrit. However, the complete response may take approximately four to six weeks after the dose is given. The follow-up evaluation should be done between six to eight weeks after administration because intravenous iron interferes with most iron studies [66].

Recommendations

- We recommend that children with moderate to severe iron deficiency anemia who do not show an increase in hemoglobin of 1 g/dL from baseline at the end of two weeks and those with mild anemia not showing Hemoglobin rise by 1 g/dL at 4 weeks of supplementation should be evaluated for non-response to oral iron (**LoE 2**).
- In situations when parenteral therapy is indicated, we recommend intravenous iron therapy. Intramuscular and transdermal administration is not recommended (**LoE 2**).
- We recommend iron sucrose, FCM and ferric derisomaltose (isomaltoside) preparations for parenteral use (**LoE 1**).
- We recommend that follow-up evaluation be done between six to eight weeks after intravenous iron administration (**LoE 2**).

4. Macrocytic Anemia of Nutritional Etiology

Macrocytic anemia can be attributed to both vitamin B12 (cobalamin, Cbl) and folic acid deficiency in children. Vitamin B12 deficiency is more common than folic acid deficiency. Vitamin B12 deficiency is more common in infants born to vitamin B12 deficient mothers and in adolescents [67-69]; the problem is widespread in the Indian population as the majority are vegetarians.

Infants deficient in vitamin B12 may present with developmental delay, tremors, or infantile tremor syndrome. Neurologic symptoms include paresthesias, hypotonia, seizures, sensory deficits, developmental delay or regression, irritability, or cognitive delay [70,71]. Severe deficiency may cause bleeding manifestations due to thrombocytopenia. Mild enlargement of liver and/or spleen may be found. Thus, these patients may mimic cases with acute leukemia and aplastic anemia [72]. Dermatological manifestations like hyperpigmentation of knuckles, icterus and angular stomatitis are commonly seen in children with underlying vitamin B12 deficiency. These may occur even before the development of hematological and neurological complications and hence these findings may aid early diagnosis.

4.1 Diagnosis of Macrocytic Anemia

a. Mean corpuscular volume (MCV) cut-off

Macrocytosis is a common finding in vitamin B12 deficiency. MCV is only a screening test (see **Table II**).

b. Peripheral smear findings

Peripheral smear shows the presence of macrocytes/macro-ovalocytes. The presence of hypersegmented neutrophils (≥5 lobed nuclei) in more than 5% of neutrophils and leucopenia are commonly seen [73,74]. In case of severe deficiency, thrombocytopenia may be observed. A low reticulocyte is usually seen. With severe anemia, circulating nucleated erythroid precursors, Cabot rings, and Howell Jolly bodies can appear. Circulating megaloblasts may also be seen [73].

c. Serum folate assay

Serum folate is estimated by an automated chemiluminescent assay. The normal serum folate level is 6-20 ng/mL. The group suggests a level of 4 ng/mL (10 nMol/L) to define folate deficiency as recommended by WHO [75].

d. Red Blood Cell Folate Assay

Red blood cell (RBC) folate content is unaltered after the reticulocyte stage in the maturation of RBC. Hence, it is less susceptible to transient fluctuations in folate levels. It reflects the folate status over the 120 days lifespan of the RBC. RBC folate level below 100 ng/mL suggests folate deficiency [73, 75]. RBC folate may be falsely low in

pernicious anemia while it may be falsely high in hemolytic anemia, IDA and after blood transfusion.

e. Serum Vitamin B12 (cobalamin) Assay

The endogenous forms of vitamin B12 include Cbl and holotranscobalamin (HoloTC), which represents the active fraction of plasma Cbl. Cbl assay quantitates both the 'inactive' forms (transcobalamin I- and transcobalamin III-bound or holohaptocorrin) and the 'active' form (transcobalamin II-bound or holotranscobalamin) of vitamin B12 in serum. Levels between 200 to 300 pg/mL (148 to 221 pmol/L) are considered borderline. Levels >300 pg/mL (>221 pmol/L) are considered normal and exclude significant vitamin B12 deficiency. Levels <200 pg/mL (< 148 pmol/L) are suggested to be used to define vitamin B12 deficiency [73,75]. In the presence of inflammation and malignancies, serum Cbl may be falsely high [73,76]. Cbl levels may be spuriously low in certain conditions like pregnancy, intake of drugs like phenytoin, technical issues, or coexistent folate deficiency [73,77].

The levels described above for defining vitamin B12 or folate deficiency should be cautiously interpreted. The low levels only substantiate the diagnosis, but normal levels do not exclude the diagnosis in children with a consistent clinical picture [72,73].

f. Holotranscobalamin (Holo TC) Assay

The HoloTC assay has better sensitivity and specificity in identifying B12 deficiency than serum Cbl assays. The expected values for HoloTC in healthy individuals are 35-171 pmol/L. A cut-off of less than 35 pmol/L is suggested for defining deficiency [73,74]. Though it has been used in studies, it is not available widely in India.

g. Assessing Functional Deficiency of Vitamin B12 and/ or Folate

Testing for metabolites in vitamin B12 and folate pathways, including homocysteine (Hcy) and serum methyl malonic acid (MMA), are useful to evaluate vitamin B12 /folate deficiency in the following situations:

- Levels of vitamin B12 and/ or folate are normal or borderline low in cases with a consistent clinical profile.
- Discordant laboratory findings and clinical picture (unexplained macrocytic anemia or unexplained neurologic/neuropsychiatric symptoms with low normal laboratory values of B12 and /or folate)

Vitamin B12 is a cofactor in the conversion of methylmalonyl-CoA to succinyl-CoA and a deficiency of vitamin B12 leads to elevated levels of MMA. Both vitamin B12 and folate are required for the metabolism of homocysteine to methionine, and hence deficiency of either can lead to accumulation and elevated levels of homocysteine. In case both MMA and homocysteine are elevated, vitamin B12 deficiency is likely. If MMA is normal and homocysteine is raised, folate deficiency would be more likely [73,74].

The accuracy of Cbl and/or folate levels alone has limitations. Hence, it is recommended to evaluate for functional folate/ vitamin B12 deficiency by estimating serum MMA or Hcy level to confirm a diagnosis of vitamin B12 and/or folate deficiency where the diagnosis is doubtful [73,74]. The normal range of plasma MMA is 70 to 270 nmol/L and of homocysteine is 5 to 15 µmol/L. Plasma total homocysteine is more sensitive, but plasma MMA is more specific. The British Society of Hematology suggests MMA >750 nmol/L is indicative of vitamin B12 deficiency, and Hcys above 15 mol/L could be indicative of folate deficiency [73]. MMA may be spuriously high in children with renal disease, small bowel overgrowth and hemoconcentration. Hcy may also be elevated in hypothyroidism, renal failure and certain genetic polymorphisms. If Hcy and MMA are found to be normal with borderline Cbl levels, no further tests are needed [73,74].

h. Bone Marrow Examination

Bone marrow aspiration (BMA) to prove megaloblastic anemia is not required when the clinical picture, complete blood count (CBC) and peripheral blood findings are diagnostic [73,74]. In the presence of atypical clinical features or a CBC which does not corroborate the diagnosis, it is preferable to perform a bone marrow aspiration prior to initiating therapy to exclude other causes, like aplastic anemia, acute leukemia, or myelodysplastic syndrome, which could mimic megaloblastic anemia [72]. BMA findings do not help distinguish between vitamin B12 and folate deficiency.

i. Investigations for Suspected Pernicious Anemia

Pernicious anemia has hardly ever been reported in children in India. Anti-intrinsic factor antibody (anti-IF Ab) test is used to evaluate pernicious anemia in adults. It has a high positive predictive value (95%) and a high specificity (98-99%). However, sensitivity is only 40-60%, as seen in studies amongst adults. The sensitivity of gastric parietal cell antibody is 80% for the diagnosis of pernicious anemia. However, it is positive in 10% of normal individuals as well. Hence, a positive antibody is not definitive for pernicious anemia [73]. Even in developed countries where nutritional deficiency is rare, pernicious anemia and the presence of anti-IF Ab is rarely reported in children.

j. Tests for Genetic Disorders or Inborn Errors of Metabolism causing Megaloblastic Anemia

Disorders affecting uptake and metabolism of folate or vitamin B12, as well as thiamine-responsive megaloblastic anemia, orotic aciduria, and 3-phosphoglyceride dehydrogenase deficiency, may also cause megaloblastic anemia. These conditions warrant evaluation for specific mutations and biochemical assays which are beyond the scope of these recommendations.

Recommendations

- A peripheral smear with the presence of macrocytes and hypersegmented neutrophils along with an elevated MCV should arouse suspicion of underlying vitamin B12 or folate deficiency (**LoE 2**)
- Cbl and folate assays should be done simultaneously due to the close relationship in metabolism (**LoE 1**)
- We recommend that serum folate levels should be estimated before the RBC folate level (**LoE 1**).
- RBC folate levels need to be estimated if there is a strong suspicion of underlying folate deficiency despite normal folate levels or as corroborative evidence for folate deficiency, wherever available (**LoE 2**).
- Plasma total Hcy and/or plasma MMA should be considered as supplementary tests to diagnose biochemical vitamin B12 deficiency in a suspected clinical situation with borderline serum Cbl or folate level (**LoE 2**).
- We do not recommend routine testing of anti-gastric parietal cell or anti-intrinsic factor antibody (**LoE 1**).

4.2 Treatment of Vitamin B12 and Folic Acid Deficiency Anemia

4.2.1 Starting replacement therapy

Once the clinical features, dietary history and laboratory findings (anemia with raised MCV) corroborate to suggest nutritional macrocytic anemia, replacement therapy should be initiated with vitamin B12 and folic acid. An assay of serum vitamin B12 and folate is advisable prior to therapy. When it is not possible to estimate serum levels, treatment with both vitamin B12 and folic acid should be provided. Vitamin B12 alone should be started in the initial 10-14 days, followed by the addition of folic acid. Folic acid should not be instituted alone if vitamin B12 deficiency has not been excluded, as the neurological symptoms due to vitamin B12 deficiency may precipitate or worsen [78,79]. Treatment of children with dimorphic anemia should include iron, folic acid and vitamin B12.

Treatment regimens in children have not been well studied, and the preferences of the route of administration and dose of vitamin B12 are varied [73,74,80-82]. Currently available guidelines are restricted to the adult population [73].

4.2.2 Route of vitamin B12 administration

Parenteral [(intramuscular (IM) deep subcutaneous (SC) intravenous (IV) infusion) administration of vitamin B12 rapidly and reliably restores the vitamin B12 stores [83]. Parenteral vitamin B12 is preferably administered by IM or deep SC injection as vitamin B12 is rapidly excreted after IV administration. Lately, sublingual [84,85] and intranasal [86] routes of vitamin B12 administration have also been tried in children with vitamin B12 deficiency. Due to the paucity of robust scientific evidence, we do not recommend intranasal and transdermal routes of vitamin B12 therapy in children. Oral vitamin B12 supplements are convenient and cheaper compared to parenteral vitamin B12 and can ensure better compliance in the long term. Evidence in adults suggests that oral vitamin B12 may be given as an alternative to parenteral vitamin B12 with comparable efficacy and safety [87-90].

Comparative studies of oral vs. parenteral vitamin B12 in children are scant, although there are a few prospective studies and case series assessing the response to oral vitamin B12 [91-97]. A comparative group study in children with symptomatic vitamin B12 deficiency showed comparable efficacy of parenteral and oral cyanocobalamin (CN-Cbl) in terms of hematological response measured by a rise in hemoglobin, MCV and hematocrit [98].

As most cases of vitamin B12 deficiency in India are of dietary origin, injectable vitamin B12 should be used only in cases where a fast response is required or compliance with oral medication is not ensured. Faster and assured response will be particularly required in children with neurological manifestations and pancytopenia. Children with severe thrombocytopenia should be treated with IV vitamin B12 as IM administration may lead to hematoma formation. In patients being started on injectable treatment, after the initial response, maintenance therapy with oral vitamin B12 should be considered [83,92,93, 98].

Varied protocols of vitamin B12 supplementation have been tried in children with neurological manifestations of vitamin B12 deficiency using parenteral [99,100] or oral vitamin B12 [93,101], with different doses and duration of therapy. However, due to the need for quick and assured response in children with neurological manifestations, we recommend initial treatment with parenteral vitamin B12 [73,74].

In patients with malabsorption due to irreversible

causes of vitamin B12 malabsorption, including surgical cases, underlying autoimmune conditions, or genetic defects in vitamin B12 absorption and transport, therapy with parenteral vitamin B12 may be preferred [83]. Alternately, as shown by some studies, life-long daily oral or sublingual vitamin B12 may be given to children with irreversible causes of malabsorption [87]. In two separate randomized controlled trials, which included adults with vitamin B12 deficiency due to chronic atrophic gastritis or perniciones anemia, oral vitamin B12 was as effective as parenteral vitamin B12 [88,89].

4.2.3 Dose of vitamin B12

As the route of therapy is varied, so is the dose and duration of vitamin B12 therapy in children depending upon the age (infant, child, adolescent). Daily oral vitamin B12 in varying doses of 100 µg - 1000 µg [73,92,93,95,98] and parenteral vitamin B12 in doses of 25-1000 µg [73,74,80-82] have been used in children for treating vitamin B12 deficiency anemia. Oral vitamin B12 needs to be given in a fasting state as food interferes with the absorption of vitamin B12 [102]. Based on the various studies, our recommendation is:

Oral: Oral vitamin B12 therapy (500 µg in infants, 1000 µg in older children) to be used to treat macrocytic anemia due to dietary vitamin B12 deficiency. This dose may be given every day for a week, every other day for the next week, 2 times a week, once a week, once every 15 days for a month and then once a month to complete at least 3 months duration of therapy [92].

Alternatively, daily oral vitamin B12 therapy (500 µg in infants, 1000 µg in older children) can be given for 3 months [92].

Parenteral: We recommend starting treatment with 25 µg of vitamin B12 given daily by IM (or deep SC or IV) route for the initial 2-3 days. This is followed by 100 µg (50 µg in infants) of parenteral vitamin B12 given daily for the next 7 days (till 3 weeks in children with neurological features), followed by 100 µg vitamin B12 IM/deep SC/IV on alternate days for next 7 days, and followed by 1000 µg vitamin B12 given IM/deep SC/IV every week over the next 1 month.

The starting dose of vitamin B12 in younger children, especially those who are malnourished or have severe anemia, must be lower (25-50 µg) as there is a risk of life-threatening hypokalemia [103] as well as a risk of neurological deterioration in the form of worsening or appearance of tremors and other involuntary movements [104].

Further maintenance therapy (1000 µg monthly) can be given by oral or parenteral route as necessary [87].

The intravenous route to be used where the patient has thrombocytopenia as giving IM or SC injections may lead to hematoma formation.

4.2.4 Duration of vitamin B12 therapy

Children with hematological manifestations due to vitamin B12 deficiency need treatment for at least 3 months [74,83,92]. Children with neurological manifestations should be treated for at least 6 months [83,92,105]. Children with an irreversible underlying cause of vitamin B12 deficiency (e.g., pernicious anemia, inherited disorders of vitamin B12 metabolism), underlying malabsorption disorders and those with strong cultural practices (e.g., strict veganism) leading to vitamin B12 deficiency require lifelong vitamin B12 therapy [73,74,83].

4.2.5 Choice of pharmacological compound

Cyanocobalamin (CN-Cbl) is the synthetic form of vitamin B12, which requires conversion to metabolically active coenzymes viz., methlycobalamin (Me-Cbl) and 5'-deoxyadenosylcobalamin (Ado-Cbl) (106). Hydroxo-cobalamin (HO-Cbl) is the long-acting form of Vitamin B12, needs less frequent injections and is hence preferred in children with persicious anema or inherited disorders of metabolic Vitamin B12 processing [107,108]. Currently, there is insufficient evidence to suggest the benefits of using Me-Cbl or Ado-Cbl over CN-Cbl or HO-Cbl in terms of bioavailability, biochemical effects, or clinical efficacy. Me-Cbl is the formulation most readily available in the market and can be prescribed for treating anemia due to Vitamin B12 deficiency.

4.2.6 Side effects of vitamin B12 administration

Unlike oral formulations, injections are more allergenic; HO-Cbl is more allergenic than CN-Cbl, but allergic reactions occur with all cobalamin forms and routes [107,108]. Side effects like nausea, itching, chills, fever, hot flushes, nausea, dizziness, or rarely anaphylaxis can occur. A sensitivity history should be obtained from the patient prior to administration of parenteral vitamin B12. In case of allergic reactions, hydrocortisone can be used for premedication or desensitization can be tried [108]. IV vitamin B12 should be administered as an infusion over 45-60 minutes. Some children may even experience transient worsening of neurological symptoms [109,110]. CN-Cbl should be avoided in children with optic nerve atrophy or Leber's disease, as CN-Cbl may cause optic nerve damage [107].

There is a need to monitor serum potassium levels in the initial few days of therapy as there is a risk of transient hypokalemia after starting vitamin B12 therapy, especially in those with severe anemia [73,103,111].

4.2.7 Treatment of Infants with vitamin B12 deficiency

Infants born to vegetarian mothers deficient in vitamin B12 who receive exclusive breastfeeding for a prolonged period are particularly prone to develop vitamin B12 deficiency [104,109-111]. We recommend checking mothers' anemia and vitamin B12 status while treating symptomatic infants with vitamin B12 deficiency. These infants must be closely followed up for neurological development. Additionally, if the mother is found to be vitamin B12 replete, such infants should be assessed to exclude any genetic causes of vitamin B12 metabolism, which may need specific treatment depending upon the underlying condition.

Treatment of infantile tremor syndrome (ITS) involves therapeutic supplementation of vitamin B12 along with other micronutrients. Severe tremors may require treatment with one (or more) of the following drugs - oral propranolol, phenobarbitone, phenytoin, or uncommonly with carbamazepine or steroids [112].

4.2.8 Treatment of folic acid deficiency

Anemia due to dietary folic acid deficiency in children above one year of age and adults should be treated using oral folic acid 1-5 mg daily [74]; in infants, oral doses up to 50 µg/day may suffice. A meta-analysis showed that daily doses of ≥0.8 mg of folic acid are typically required to achieve the maximal reduction in plasma homocysteine concentrations produced by folic acid supplementation [113]. Doses of 0.2 and 0.4 mg are associated with 60% and 90%, respectively, of this maximal effect [113]. However, more recently, a dose of 0.2 mg/d over at least 6 months was shown to have optimal effects [114]. The British Society for Hematology Guidelines [73] recommend 5 mg of FA to be given for 4 months to treat megaloblastic anemia due to dietary folic acid deficiency in adults. In children with underlying malabsorption, higher daily doses of 5 mg are preferred. The duration of folic acid therapy is for 3-4 months in order to replenish the depleted stores. Vitamin B12, even if found to be normal, should be continued alongside in doses of at least 1-2 µg/day to prevent neurological deterioration.

If the anemia or macrocytosis does not resolve with folic acid therapy and/or the child develops new neurologic symptoms, serum vitamin B12 must be tested again. Such children should be treated with parenteral vitamin B12 [115]. Reduced folate form, viz, folinic acid, is used to treat certain specific folate metabolism disorders or toxic effects of chemotherapy [116].

4.2.9 Assessing response to treatment

Clinical improvement with a sense of well-being starts within 24 hours of treatment. Glossitis starts improving by day 2 and resolves by the end of the second week of treatment. The clinical evaluation can be scheduled within the first week for those with severe anemia and in the second week for children with moderate or mild anemia. However, if there is no improvement, worsening of symptoms, or appearance of neurological signs, he/she needs to be assessed earlier.

In addition to symptomatic improvement, we recommend laboratory evaluation with complete blood counts (CBC) and MCV. The timing of the first follow-up visit for laboratory investigations (hemoglobin, CBC) can be day 7 for those with severe anemia, day 14 for moderate anemia and day 28 for mild anemia. Where there are concerns regarding absorption of oral vitamin B12, we can assay serum vitamin B12 levels.

The most useful objective parameter is the rise in reticulocyte count which starts within 48-72h and peaks at the end of the first week after starting treatment; the reticulocytosis is usually proportional to the severity of the anemia. MCV begins to fall by day 14 and usually normalizes by week 6-8. Hypersegmented neutrophils disappear by 10-14 days of treatment. The CBC, including mean corpuscular volume (MCV), should be completely normal by 6-8 weeks. In the case of suboptimal response, it is important to look for coexisting iron deficiency as well as alternate diagnoses.

Neurologic improvement also begins within the first week and is typically complete in 6-12 weeks [74]. An alternate diagnosis should be looked for in case of worsening neurological symptoms despite treatment. Permanent neurological sequelae with vitamin B12 deficiency are common, especially in infants and younger children [104,109,111].

As per existing evidence, we do not recommend estimating serum vitamin B12 and holotranscobalamin II to assess response to treatment as their levels may rise rapidly after administration.

4.2.10 Evaluation of a child with sub-optimal response

In case of inadequate response, the compliance and dose of medication should be rechecked. If initially started on oral therapy, it may be preferable to switch to parenteral vitamin B12 therapy and re-evaluate the response. It is recommended to evaluate for other causes of macrocytic anemia like hypothyroidism, thiamine-responsive macrocytic anemia, chronic hemolytic anemia, hypoplastic anemia, myelodysplastic syndrome, genetic disorders of vitamin B12 and (or) folate metabolism and underlying liver disease. We also recommend evaluating coexisting iron deficiency and testing for other causes of anemia [74].

Recommendations

- In the presence of discordance between the laboratory results and strong clinical features of vitamin B12 deficiency, treatment should not be delayed to avoid neurological impairment (**LoE4**)
- Mild to moderate macrocytic anemia due to dietary vitamin B12 deficiency can be treated with oral vitamin B12 **(LoE3)**.
- The group recommends initial parenteral Vitamin B12 therapy in children with neurological manifestations, underlying malabsorption of vitamin B12**,** severe anemia / pancytopenia or disorders of vitamin B12 metabolism **(LoE3)**.
- In patients being started on parenteral treatment, after the initial response, maintenance therapy with oral Vitamin B12 can be considered **(LoE1).**
- Children without neurological manifestations due to vitamin B12 deficiency need treatment for at least 3 months, and those with neurological signs and symptoms need at least 6 months of therapy (**LoE3**).
- Treatment of folic acid deficiency should be initiated only after excluding co-existing vitamin B12 deficiency (**LoE2)**.
- Folic acid deficiency is treated with oral folic acid 1-5 mg per day for 3-4 months (**LoE1**).

5. Indication for Blood Transfusion in Nutritional Anemia

Blood transfusion (packed red cells/whole blood) is rarely required to treat nutritional anemias in children. Iron/ vitamin B12/folic acid deficiency results in chronic compensated anemia where intravascular volume is maintained despite severely low hemoglobin. Blood transfusion is often dangerous as it increases the risk of transfusion-associated circulatory overload and may delay bone marrow recovery. The only indication of packed red cell transfusion in children with nutritional anemia is the presence of cardiac decompensation in severe anemia, where rapid restoration of oxygen-carrying capacity is vital for survival [117,118]. Severe anemia with no cardiac decompensation may be managed successfully with supplementation therapy, provided compliance is ensured. As recommended by WHO, the indications for blood transfusion for children are with hemoglobin ≤4 g/dL or hemoglobin between 4-6 g/dL associated with cardiac decompensation [119]. In case of an absolute indication, packed red cells may be transfused at a volume of 5-10 mL/ kg over 4 hours under close cardiac monitoring with the administration of furosemide, if required.

6. Dietary Counselling in Nutritional Anemia

All children being treated for nutritional anemia should be provided an appropriate diet in addition to micronutrient supplementation. During the second year of life, a daily milk intake of 400-600 mL is appropriate to meet calcium needs and intakes above 800 mL per day can predispose to iron deficiency [120]. If the infant/ child is being given excess milk, it should be replaced by complementary feeds (see below). The family needs to be counseled to improve the diet of the patient. This will not only help faster recovery from anemia, it will also prevent further recurrence. Nutrition education and counseling to improve dietary diversity and quality is a key intervention for the prevention of anemia in children [121-123]

After 6 months of life, infants should be started on appropriate complementary feeding. Green leafy vegetables such as palak (spinach), cholai (amaranth leaves), cabbage, sarson (mustard leaves), drum stick leaves, turnip, radish, beetroot, lotus stems, sweet potato, tomatoes, etc. are good sources of iron. Oranges, lemon, watermelon, pomegranate, apple, grapes, guava, musk melon, and goose berries are rich in iron. Dry fruits such as dates, raisins, walnuts, almonds as well as ragi seeds also are good sources of iron. Use of jaggery or palm sugar instead of refined sugar should be encouraged. Non-vegetarian food such as red meat is a good source of heme iron which has better bioavailability than non-heme iron. Nutritional counselling should consider regional and local variations in the diet, varied cultural practices, methods of food processing and meal preparation and affordability [1,124].

Intake of foods rich in vitamin B12 and folic acid should be adequate. Food rich in vitamin B12 includes meat, poultry, shellfish, eggs, dairy products, mushrooms and fermented foods like curd and yogurt. Foods like leafy green vegetables (spinach, lettuce), broccoli, sprouts, lemons, bananas, melons, liver, oranges, beetroot, mango, okra, and flaxseed contain useful amounts of folate. To prevent loss of folate, foods should not be overcooked and should not be repeatedly washed in large amounts of water [125].

Recommendations

- We recommend that caregivers of all infants and children being treated for nutritional anemia should be counselled to improve the diet. All infants must be exclusively breastfed till 6 months of age. Age-appropriate, adequate and diverse complementary foods after 6 months are recommended to optimize the micronutrient intake in children. For children older than 12 months of age, intake of milk should be less than 600

mL per day and bottle feeding should be discontinued to limit milk intake (**LoE 1**).

7. Prevention of Nutritional Anemia

For prevention of anemia in children following strategies are required:

- All infants should be exclusively breastfed till 6 months of age as mother's milk is a good source of iron compared to cow's milk [126]. After 6 months of age, infants should be started on complementary feeding.
- Iron supplementation: Under public health programs, iron supplementation across age groups is recommended [1]. Iron supplementation is particularly needed for high-risk age groups, i.e., infants born preterm or low birth weight, pre-schoolers and adolescents, to replenish the iron sores. Preterm infants do not have adequate hepatic iron stores and require larger amounts of iron for catch-up growth. Targeted laboratory screening for iron deficiency anemia (IDA) should be performed in infants and children with risk factors like malnutrition, prematurity, low birth weight, poor diet or symptoms of IDA. The published literature supports the role of early iron supplementation in preterm or low birth weight (LBW) infants in improving hemoglobin level and iron stores, with a lower risk for IDA in infancy [126-128]. American Academy of Pediatrics (AAP) recommends iron supplementation (dose of 2 mg/kg/day of elemental iron, maximum 15 mg) in breastfed preterm or low birth weight infants as early as two weeks of age and continued in infancy until adequate iron intake from complementary food is assured [128]. Oral iron supplementation in a dose of 2-4 mg/kg/day (elemental iron) in LBW infants from 2-4 weeks of life to 12 months of age is recommended by National Neonatology Forum, India [129].
- Older infants (>6 months) and toddlers are at high risk of nutritional anemia due to inadequate and poor-quality complementary diet. Therefore, screening for anemia using hemoglobin estimation should be done at 9-12 months when these infants visit for measles vaccination. This contact point should be utilized to assess the adequacy of complementary food intake and provide appropriate counselling if required. Further, daily iron supplementation in a dose of 1-2 mg/kg/day can be considered in them individually, especially where dietary intake is inadequate. In young children and adolescents, additional screening may be done at any time if there is clinical suspicion or risk factor for anemia secondary to nutritional or a non-nutritional cause. Additionally, siblings of any child diagnosed with IDA must also be assessed for ID and managed accordingly. Daily iron supplementation is also suggested for adolescent children, especially girls (60-100 mg elemental iron), to replenish the iron stores for pubertal growth and development [130].
- Iron prophylaxis for prevention of anemia in children and adolescents at the community level: In the last 5 decades, the national programs for the prevention and control of anemia have evolved from National Nutritional Anemia Prophylaxis Program (NNAPP) in 1971, National Nutritional Anemia Control Programme (NNACP) in 1993, National Iron Plus Initiative (NIPI) program in 2013 to the current Anemia Mukt Bharat (AMB) program in 2018 [12]. The focus of all government programs has been primarily on combating iron and folate deficiency by strengthening the distribution of iron and folic acid (IFA) supplements to the beneficiaries. Under AMB program, screening for anemia is recommended for all children 6-59 months, in-school and out-of-school children (5-9 years), school-going adolescents 10-19 years in government/ government-aided schools and all children with clinical signs and symptoms of anemia (12). Iron folic acid supplementation in an age-appropriate dose is provided to infants and preschool children and school-going children and adolescents biweekly and weekly, respectively. WHO (2016) guidelines recommend the use of daily iron-folic acid supplementation for all beneficiaries in areas where the prevalence of anemia is >40% [130]. Daily therapy results in poor adherence due to the long duration of treatment and increased side effects. Recently, Cochrane systematic review has reported that intermittent iron supplementation is better for improving hemoglobin concentration and decreasing the risk of anemia in children <12 years compared to placebo or no intervention [131].
- WASH strategies and deworming: There is enough evidence to suggest that children exposed to poor sanitation and hygiene conditions and open defecation have lower hemoglobin levels due to an increased risk of intestinal infection and chronic gut inflammation [132, 133]. It has been observed through clinical trials that the implementation of adequate water, sanitation, and hygiene (WASH) strategies have been successful in reducing the prevalence of anemia in children [134,135]. There is evidence to support the use of mass administration of anti-helminths in decreasing the prevalence of anemia [136,137]. To intensify efforts toward soil-transmitted helminths (STH) control in India, the National Deworming Day program is implemented. Biannual mass deworming (albendazole tablet) is carried out for children and adolescents (1-19 years) every year under the AMB program [12]. Under

this strategy, under-five children, out-of-school children and adolescents are provided deworming tablets at Anganwadi centers by AWWs, while school-going children and adolescents are provided the same through school teachers.

- Delayed umbilical cord clamping: To build and regain the iron stores in infants after birth, delayed umbilical cord clamping (by at least 3 minutes, not earlier than 1 min, or until cord pulsations cease) is recommended by WHO and AMB guidelines [12,138], especially for infants born to anemic mothers [139]. Efforts are required to operationalize this practice at all healthcare levels.

Recommendations

- Iron supplementation is recommended for preterm and low birth weight infants to replenish the iron stores and prevent iron deficiency anemia and continued in infancy until adequate iron from complementary food is assured. (**LoE 1**)
- All children, especially those with risk factors for the development of anemia, should be screened for anemia at 9-12 months, 5 years and adolescence.
- In view of operational feasibility and better compliance, intermittent iron-folic acid supplementation (under the Anemia Mukt Bharat program) is recommended for all infants (>6 months), pre-schoolers, school-age children and adolescents for the prevention of nutritional anemia. (**LoE 1**).
- Delayed cord clamping is recommended for deliveries in all health care facilities. (**LoE 1**)

CONCLUSIONS

Considering the increased prevalence of nutritional anemias in children despite the introduction of preventive programs by the Government of India, the expert group felt a need to provide evidence-based guidelines for managing nutritional anemias in children. Most of the available guidelines for managing nutritional anemias are for adult populations. The committee noted the lack of robust scientific evidence for certain recommendations and felt these key areas need to be studied scientifically in Indian settings (**Box III**).

We endorse the hemoglobin cut-offs recommended by the World Health Organization to define anemia in children. Keeping the feasibility and reliability of available laboratory tests, we suggest that IDA be diagnosed based on examination of CBC, including RBC indices and peripheral smear; diagnosis can be confirmed by the therapeutic response to oral iron. Most cases of IDA can be treated with oral iron. Our guidelines also provide answers to seemingly minor but clinically relevant issues such as duration of treatment in IDA, evaluation of response to treatment and management of non-responders. There is sparse evidence for managing vitamin B12 and folic acid deficiency anemia, and we could only retrieve one guideline for the adult population. We have attempted to provide treatment guidelines for macrocytic anemia due to deficiency of vitamin B12 and FA in children as evidence-based as possible. We recommend treatment with vitamin B12 without further delay where there are clinical features of vitamin B12 deficiency even if laboratory tests are equivocal to prevent neurological impairment. Mild to moderate macrocytic anemia due to dietary vitamin B12 deficiency can be treated with oral vitamin B12. However, patients with neurological manifestations, those with pancytopenia, severe anemia, or malabsorption warrant parenteral vitamin B12 therapy. In patients being started on parenteral treatment, after the initial response, maintenance therapy with oral vitamin B12 can be considered. Treatment of FA deficiency should be initiated only after excluding co-existing vitamin B12 deficiency. We recommend screening children for anemia at 9-12 months of age, 5 years and during adolescence, in addition to intermittent iron FA supplementation as advocated under the Anemia Mukt Bharat Program.

Box III Areas for Future Research in Nutritional Anemias

- Single dose versus divided doses of oral iron for treatment of iron deficiency anemia in children
- Therapeutic response to different doses and preparations of oral iron
- Management of non-responders to oral iron
- Use of intravenous iron in children
- Diagnostic role of methyl malonic acid and holotranscobalamin in children with borderline vitamin B12 levels.
- Therapeutic response to oral vitamin B12 therapy in children.
- Optimum therapeutic dose and schedule of vitamin B12 in children

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Prediction Models for Pneumonia Among Children in the Emergency Department

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SUMMARY

We evaluated five previously published prediction models for radiographic pneumonia (Neuman, Oostenbrink, Lynch, Mahabee-Gittens, and Lipsett) using data from a single-center prospective study of patients 3 months to 18 years with signs of lower respiratory tract infection. Our outcome was radiographic pneumonia. We compared each model's area under the receiver operating characteristic curve (AUROC) and evaluated their diagnostic accuracy at statistically-derived cutpoints.

Radiographic pneumonia was identified in 253 (22.2%) of 1142 patients. When using model coefficients derived from the study dataset, AUROC ranged from 0.58 (95% confidence interval, 0.52-0.64) to 0.79 (95% confidence interval, 0.75-0.82). When using coefficients derived from original study models, two studies demonstrated an AUROC >0.70 (Neuman and Lipsett); this increased to three after deriving regression coefficients from the study cohort (Neuman, Lipsett, and Oostenbrink). Two models required historical and clinical data (Neuman and Lipsett), and the third additionally required C-reactive protein (Oostenbrink). At a statistically derived cutpoint of predicted risk from each model, sensitivity ranged from 51.2% to 70.4%, specificity 49.9% to 87.5%, positive predictive value 16.1% to 54.4%, and negative predictive value 83.9% to 90.7%.

Prediction models for radiographic pneumonia had varying performance. The three models with higher performance may facilitate clinical management by predicting the risk of radiographic pneumonia among children with lower respiratory tract infection.

COMMENTARIES

Evidence-based Medicine Viewpoint

Ramgopal, et al. [1] evaluated various models designed to predict the presence of radiographic pneumonia among children with clinical features of lower respiratory tract infection (LRTI) [1]. The justification was that this could reduce the tendency to perform chest *X*-rays, especially as radiography is not recommended in routine cases. Further, as clinicians tend to prescribe antibiotics to those with radiographic pneumonia, reducing the need for chest *X*-rays may indirectly reduce the indiscriminate use of antimicrobials also. The investigators evaluated the models, by conducting secondary data analysis of a study conducted by them, wherein children aged 3mo-18y with clinical criteria of LRTI undergoing chest *X*-rays for suspected pneumonia, were prospectively enrolled [2]. In the original study [2], they also developed a prediction model for radiographic pneumonia, and compared their own model to the external models.

Five prediction models published between 2004 and 2021 were evaluated [3-7]. Briefly, *X*-rays of the children in the prospective cohort [2] meeting the criteria in each of the prediction models, were independently examined by two qualified radiologists, who were blinded to the clinical information [1]. Their reporting determined the presence or absence of radiographic pneumonia, based on which the predictive capability of each of the models was determined. The investigators used two methods to analyze the data, first using the values (of regression coefficients) as published in the original studies, and second using their own dataset to estimate new regression coefficients for the variables in the models.

The main results are summarized in **Table 1**, along with calculations of the accuracy of each model at hypothetical prevalence of 10%, 20% and 40% radio-graphic pneumonia. Firstly, none of the five prediction models reliably predicts the presence or absence of radiographic pneumonia. Second, there are wide variations in the performance of the models. Third, the specificity of the five models improved when the regression coefficients of the investigators' dataset [1] were used. An older systematic review [8] evaluating the prediction of radio-graphic pneumonia from clinical symptoms and signs, also identified only moderate sensitivity and specificity.

Critical Appraisal

The study methods broadly met the standards expected for

Table 1: Summary of the Study Results With Estimates of Accuracy Using Hypothetical Prevalences of Radiographic Pneumonia

	Data analysis using regression coefficients as published in the original studies				*Accuracy at an estimated prevalence of:*			*Data analysis using regression coefficients derived for the prospective study*				*Accuracy at an estimated prevalence of:*		
	Sn	Sp	LR+	LR-	10%	20%	40%	Sn	Sp	LR+	LR-	10%	20%	40%
Lynch (2004)	83.0	30.0	1.19	0.57	35.3	40.6	45.9	70.4	49.9	1.41	0.59	52.0	54.0	56.1
Mahabee-Gittens (2005)	95.3	8.0	1.04	0.58	16.7	25.5	34.2	51.2	64.0	1.42	0.76	62.7	61.4	60.2
Neuman (2011)	70.0	65.4	2.02	0.46	65.9	66.3	66.8	69.6	77.1	3.03	0.39	76.4	75.6	74.9
Oostenbrink (2013)	63.4	49.8	1.26	0.73	51.2	52.5	53.9	52.8	87.5	4.23	0.54	84.0	80.6	77.1
Lipsett (2021)	81.7	52.6	1.72	0.35	55.5	58.4	61.3	60.1	79.9	2.98	0.50	77.9	75.9	74.0

LR+ = Likelihood ratio (positive test result), LR- = Likelihood ratio (negative test result), Sn = Sensitivity, Sp = Specificity.

undertaking external validation of diagnostic tools. In addition, there were several methodological refinements. The investigators used a fairly robust system of imputing missing pieces of data in their cohort, rather than using the averages of available data. Since CRP measurement was not done in all the children enrolled in the pros-pective cohort, the analysis was carried out with actual (rather than imputed) CRP values. The investigators also undertook a separate analysis of the performance of the prediction models for children younger than five years old. Limitations of the study methods and data inter-pretation are elaborated below.

The goal was to predict radiographic pneumonia among children with 'suspected community acquired pneumonia (CAP).' However, instead of employing the commonly used criteria for suspected CAP (such as the revised 2014 WHO criteria [9], or the 2012 PERCH criteria [10] among children <5y) or even the broader severe acute respiratory illness (SARI) criteria for suspected influenza [11], the investigators suspected CAP based on symptoms and signs of LRTI (which they defined as new or different cough or sputum production, chest pain, dyspnea, tachypnea, or abnormal auscultatory findings). First, it is unclear whether any one, or some, or all these criteria were required to label a child as having LRTI. Second, the relationship between these criteria (for LRTI) and the diagnosis of pneumonia is also unclear. Third, some of the components in the definition (for example sputum, chest pain, dyspnea) are oriented towards older children and adolescents; and difficult to determine in younger children and infants.

Two radiologists blinded to the clinical details, were expected to provide one among the following four reports viz., normal *X*-ray, probable or definite atelectasis, atelectasis versus pneumonia, or definite pneumonia [1]. The last two categories were used to define 'radiographic pneumonia'. Here, it is important to note that 'pneu-monia' is not a radiological finding. Therefore, it would be relevant to know what radiologic criteria were used to report an *X*-ray as having pneumonia. The paper does not clarify this point [1]. Almost two decades back, the World Health Organization (WHO) proposed radiographic pneumonia as the "presence of consolidation (further clarified as dense or fluffy opacity with or without air bronchograms), other infiltrate (evidenced by linear and patchy alveolar or interstitial densities), or pleural effusion" [12]. In fact, these criteria have been used in large studies on childhood pneumonia [13,14]. There-fore, it is intriguing why the investigators failed to define the radiologic criteria for pneumonia [1,2].

Second, the original study [2] had different reporting criteria. The fourth category therein was "probable or definite pneumonia", compared to "definite pneumonia" in the more recent publication [1]. Despite this difference, the authors reported the same number of children with radiographic pneumonia in both publications - there were 203 children with "definite pneumonia" in the recent study [1], and 203 with "probable or definite pneumonia" in the previous publication [2]. This is only possible if there were zero reports of "probable pneumonia" in the cohort of 1142 patients (which seems implausible). Third, although the recent publication [1] stated that the radiologists were blinded to the clinical details, the previous publication [2] stated that "persistent discordant interpretations" were resolved after considering the clinical interpretation, suggesting that blinding was absent at least in some cases.

Detailed examination of the five prediction tools evaluated [3-7] revealed considerable heterogeneity in the included population, enrolment criteria, basis for suspecting pneumonia clinically, definition of pneu-monia, variables studied, and the criteria used to define "radiographic pneumonia." These are summarized in **Table 2**. Given the lack of clear definitions in most of the studies [3-7], it is not

Table 2 Summary of the Characteristics of Studies From Which Prediction Models Were Derived

Study(year) reference	*Inclusion criteria*	*Criteria used to suspect pneumonia*	*Variables in the prediction model*	*Definition of radiographic pneumonia*	*No. (%) with radiographic pneumonia*
Lynch (2004) [3]	1-16y old with "clinical suspicion of pneumonia" who underwent chest x-ray (n=570). The mean/ median age was not reported.	Not defined	Fever, decreased breath sounds, crackles, tachypnea	Consensus among two of three pediatric radiologists on the presence of "pulmonary opacities". At another place, the term "focal pulmonary infiltrates" is also used.	204 (35.8)
Mahabee-Gittens (2005) [4]	2-59 mo old presenting with symptoms of LRTI who underwent chest x-ray. (*n*=510). The mean/median age was not reported, but 54.9% were <12mo.	LRTI was based on the presence of cough and >1 of: labored, rapid,or noisy breathing; chest or abdominal pain; or fever.	Age >12mo, Respiratory rate >50 /min, Oxygen saturation <96%, Nasal flaring in infants <12 mo.	Consensus among two radiologists who provided "overall clinical impressions" of pneumonia, considering the following features suggestive: "confluent opacification without volume loss, peripheral rather than central opacification, and pleural effusion". Features like hyperinflation, increased peribronchial markings, or subsegmental atelectasis, were not considered pneumonia.	44 (8.6)
Neuman (2011) [5]	<21y old with "possible pneumonia" who underwent chest x-ray in an emergency department (*n* 2574).The median (IQR) age was 2.3 (0.9–5.2) y; 73.9% were <5y.	Not described.	History of fever, history of chest pain, focal diminished breath sounds, focal rales, temperature at triage, oxygen saturation at triage, wheezing.	The final report of the attending pediatric radiologist was used to label radiographic pneumonia, which included "definite pneumonia" and also "equivocal findings of pneumonia". The former term included reports with terms such as consolidation, infiltrate, or pneumonia. The latter included terms such as "atelectasis versus infiltrate," "atelectasis versus pneumonia,"or "likely atelectasis but cannot exclude (or rule out) pneumonia." *X*-ray reports with terms like "normal chest," "normal radiograph," "clear lungs," "no acute pulmonary findings," "atelectasis," or "peribronchial cuffing," were considered as "not radiographic pneumonia".	422 (16.4)
Oostenbrink (2013) [6]	1mo-16y old presenting to the emergency department of 4 hospitals. In one hospital (Population 1), those	Not described	Ill appearance, tachypnea, oxygen saturation <94%,	*X*-rays were reported by two blinded radiologists in Population 1, a single unblinded radiologist in Population 2nd a single a blinded	Population 1:78 (15.5), Population 2:58 (13.8), Population 3:27 (7.4)

Contd....2/-

Table contd....

	with fever (rectal temp >38.0) and cough were included (*n*=504); in two fever (axillary temp >38.0) and "lower respiratory signs" (cough, difficulty breathing, or wheeze were included (*n*=420); and in the fourth hospital (Population 3), those with temp >38.5) and "acute breathing were included (n=366) The respective median (IQR) ages were: 1.6 (0.8-2.9)y, 2.3 (1.2-5.5)y, and 2.3 (1.1-5.3)y.		elevated CRP.	radiologist (who could consult a colleague) in Population 3. The presence of micronodular or macronodular infiltrationsor consolidation was used to label pneumonia. If *X*-ray had not been done, "1-week noneventful follow-up" (determined either by a telephonic or personal visits, need for re-attendance, or independent review of medical records) for alternate diagnosis ruled out pneumonia.	
Lipsett (2021) [7]	3mo-18y presenting to ED with suspected pneumonia who underwent chest x-ray (n=1181). The median (IQR) age was 3.0 (1.4, 5.8)y.	Not described	Oxygen saturation at triage,presence of fever, wheeze, rales.	*X*-rays were read by a board-certified radiologist whose reports were categorized independently by three investigators as one definite of the following: pneumonia, probable pneumonia, equivocal, unlikely pneumonia, or no pneumonia. Disagreements were resolved by discussion. The first two categories were labeled as radiographic pneumonia.	206 (17.4)

CRP = serum C-reactive protein, ED = Emergency Department.

surprising that the yield of "radio-graphic pneumonia" (in a cohort of children suspected to have pneumonia), varied from, as low as 7.4% to a maxi-mum of 35.8%. This aligns with the data from a syste-matic review reporting that only 19% children with suspected pneumonia, had radiographic pneumonia in developed countries [15]. In developing countries also, the previous WHO pneumonia criteria of cough or breathing difficulty, with age specific tachypnea identified radiographic pneumonia in only a minority [16,17].

Clinical experience and the recent multi-country PERCH studies also suggest that chest radiography does not correlate with microbial etiology. In fact, in Thailand, Zambia, Bangladesh, and Mali, the most common organism identified among children with radiologically confirmed pneumonia was RSV followed by *M. tuberculosis* [18-21]. In the Gambia also, RSV dominated, although *S. pneumoniae* was a distant second [22]. In Kenya, viruses accounted for over three quarters of radiologically confirmed pneumonia, whereas bacterial etiology was seen in only 16% [23]. Even 'primary end-point pneumonia'; oft-quoted to correlate with Pneumococcal etiology, could not be accurately predicted by clinical characteristics alone [24]. A systematic review on the efficacy of Pneumococcal conjugate vaccine [25] showed that while the vaccine had 80% efficacy against vaccine-serotype invasive disease, it had only 27% efficacy against radiographic pneumonia, suggesting that the majority of radiographic pneumonia were non-bacterial.

Neither the current study [1,2] nor the previous studies [3-7] attempted to determine the microbial etiology in suspected or radiographically confirmed pneumonia. It is therefore hard to conceptualize that prediction of "radiographic pneumonia" could somehow lead to reduction in antibiotic usage, as the investigators claimed [1].

How to interpret the yield of 22.2% radiographic pneumonia among those with clinical LRTI, in this study [1]? On the one hand, this suggests that only a minority of children with (clinically suspected) pneumonia have chest *X*-ray findings, as has been shown in previous studies also. On the other hand, most children with LRTI (as per the definition used in the study) probably did not have pneumonia. In this context, the previous publication [2] provides some additional valuable insights. The median (IQR) age of children with radiographic pneu-monia was completely different from those without radiographic pneumonia (8.1 vs 2.8y), suggesting almost two different cohorts. Therefore, it is not surprising that some clinical characteristics were also quite different. For example, rhinorrhea was more frequent in those without radiographic pneumonia, whereas chest pain was more common in those with radiographic pneumonia. Interes-tingly, chest retractions were observed more often in those without radiographic pneumonia. Rhonchi and wheeze were auscultable more often in those without radiographic pneumonia, although the distinction between the two was not specified. It is also possible to argue that 22.2% may be an over-estimate as the cohort included only those children with LRTI, who underwent chest *X*-ray. In other words, there may have been children where the clinicians decided against an *X*-ray despite the clinical criteria for LRTI. The radiographic yield would be lower if such children also underwent *X*-ray.

Conclusion

There is no single mathematical model to reliably predict the presence or absence of radiographic pneumonia in children with pneumonia suspected on clinical grounds. Given the poor correlation of radiographic pneumonia with bacterial etiology (which could have reduced empiric antibiotic usage), there is no pressing reason to strive for this either.

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Pediatric Emergency Physician's Viewpoint

Ramgopal and colleagues [1] describe a sophisticated study to validate the prediction models for radiographic pneumonia in a child in the emergency department (ED). Centers for Disease Control (CDC) defines pneumonia as "an infection of the lungs that can cause mild to severe illness in people of all ages" [1]. The World Health Organization (WHO) defines pneumonia as, "In children under five years of age, who have cough and/or difficult breathing, with or without fever, pneumonia is diagnosed by the presence of either fast breathing or lower chest wall indrawing where their chest moves in or retracts during inhalation" [2]. Although, the diagnosis of pneumonia is clinical and the Infectious Disease Society of America (IDSA) does not recommend the routine use of a chest radiograph, a chest radiograph is frequently obtained in primary care and ED settings [4]. This study attempts to answer an important clinical question, can a prediction rule assist in predicting the presence of radiographic pneumonia?

An ideal clinical prediction rule requires internally and externally validated for its use across different populations after initial computation. This study is one of the first studies attempting external validation of previously published models for radiographic pneumonia. The following studies, Mahabee-Gittens, Neuman, andf Lipsett, were conducted in the United States, and thus the model attempts to validate samples from different hospitals within the same country [5-7]. At the same time, the cohort from Lynch, et al. (Canadian ED) [8] and Oostenbrink, et al. [9] (European ED) represents a sample from different countries. The inclusion, exclusion criteria, and outcome measures are well defined and can be extended to any clinical setting.

The study results are reported as the area under the receiver operating curve (AUROC) in how the various models perform [1]. The ROC curve is a plot of test sensitivity along the *y*-axis versus false positive results along the *x*-axis [10]. AUC, interpreted as the average sensitivity value for all possible specificity values, is a measure of the overall performance of a diagnostic test. Based on the results, the model of Neuman [6] exhibited the highest AUROC (0.79, 95% CI 0.75-0.82), followed by Lipsett [7] (0.76, 95% CI 0.73-0.80). In the Oostenbrink model [9], among the 432 CARPE DIEM patients with CRP data available, the AUROC of originally published coefficients was 0.55 (95% CI 0.49-0.60), which improved to 0.75 (95% CI 0.70-0.80) when using coefficients derived from the CARPE DIEM dataset.

Extension of the study results in the clinical setting is challenging for the following reasons: *a*) There is significant variability amongst the models regarding the parameters used for derivation of the pneumonia prediction rule; *b*) ROC works best when the data has a binary distribution [10]; *c*) The pneumonia prediction models fail to answer the clinical question of the probability of radiographic pneumonia in the inter-mediate-risk population; and *d*) The prediction rules have been

computed in developed countries, limiting its application in developing and resource-limited settings, where the etiology of pneumonia would also differ.

In summary, this study makes a significant effort toward validating the radiographic pneumonia prediction rule. Although the Neuman model [6] performed well, its practical application is limited due to the multiple data points that are required. The application of the Lipsett model [7] is more realistic in the clinical setting. Oostenbrink model [9] also performed well; however, the requirement of a laboratory parameter, C-reactive protein, limits its application in the clinical setting. The study reinforces that routine chest radiograph is not indicated in well-appearing patients without fever, hypoxia, and focal auscultatory findings. This can undoubtedly limit unnecessary radiation exposure and antibiotic use.

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Pediatrician's Viewpoint

Over the world, a child dies of pneumonia every 43 seconds [1]. Most of these deaths are preventable with timely diagnosis and appropriate management. Clinicians mostly rely on fever, fast breathing, lower chest indrawing and danger signs to classify and treat pneumonia with antibiotics [2]. Similar clinical picture may be seen in children with acute bronchiolitis and viral pneumonias; antibiotics are given, but do not work in these scenarios. Upper respiratory infections are mostly viral in origin, but they also often land up with prescriptions for chest *X*-rays and antibiotics. On the contrary, some cases of pneumonia may be missed due to atypical presentations. Diagnosis of pneumonia and its etiology is challenging to the clinician. The outcome considered in this study is radiological pneumonia; clinicians see pneumonias without much radiological features as well.

The clinician will surely benefit from prediction models that diagnose pneumonias accurately. Once a prediction model is developed from a data set, it is strongly recommended to evaluate the performance of the same on another data set; this process called external validation is crucial for its further use among clinicians [3]. The study has externally validated and compared five prediction models for the clinician to decide upon further use. Prediction model equations are difficult for bedside clinical use. Clinicians are more comfortable with prediction scores that include simple clinical and laboratory variables.

As the authors have rightly pointed out, these prediction models may reduce prescriptions of chest *X*-rays and antibiotics. This external validation study has opened up scope for updating these prediction models.

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RESEARCH LETTER

Anti-SARS-CoV-2 Seropositivity Among Children With Newly Diagnosed Type 1 Diabetes Mellitus: A Case-Control Study

A sudden increase in the number of children with newly diagnosed type 1 diabetes mellitus (T1DM) was experienced during the third wave of COVID-19 epidemic in Hungary. The newly diagnosed T1DM patients had a significantly higher rate of anti-SARS-CoV-2 positivity as compared to prevalent T1DM children [OR (95% CI) 3.74 (1,08,13.55); *P*=0.04]. The relationship between SARS-CoV-2 infection and diabetes needs to be investigated further.

Keywords: *COVID-19, Pancreas, Outcome, Sequelae*.

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Recent reports suggest that increased incidence of type 1 diabetes mellitus (T1DM) may be a consequence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. Coronavirus disease 2019 (COVID-19) is primarily characterized by respiratory symptoms, but other organs expressing the angiotensin-converting enzyme 2 (ACE-2) receptor of the viral spike protein may also be affected [3]. Ex vivo and postmortem studies indicate that SARS-CoV-2 can cause pancreatic dysfunction [4]. Centers for Disease Control and Prevention reported a much higher incidence of diabetes (type 1 and type 2) among children with history of COVID-19, than those who did not contract the disease [2]. Our clinical experience showed that the number of newly diagnosed T1DM patients increased remarkably during the spring of 2021. In the previous decades, the incidence of childhood T1DM rose significantly in Hungary; however, in recent years, the annual incidence remained stable, around 22/100,000 children/year [5]. Based on emerging evidence regarding this aspect, we hypothesized that COVID-19 might have been responsible for the rise in new T1DM during this period. So we began systematic testing of new cases of T1DM for the presence of anti-SARS-CoV-2 spike antibody to look for any association.

All children (aged 0-18 years) hospitalized between 1 March, and 15 June, 2021, with new onset T1DM were evaluated for antibody against SARS-CoV-2 spike protein at the time of admission or within three months after discharge. Electrochemiluminescence immunoassay was used for anti-SARS-CoV-2 serology test (Elecsys, Roche) and was considered to be positive above 0.8 µ/mL. Non-vaccinated, otherwise healthy, known T1DM children of the same Diabetes unit coming for regular checkup during June-July, 2021, were taken as controls. We excluded vaccinated children from both groups to avoid misinterpretation of serology results. The study was performed in accordance with the ethical standards of the Institutional Review Board and with the Declaration of Helsinki.

Statistical analysis was conducted using GraphPad Prism, Version 8.0.1. We compared anti-SARS-CoV-2 positivity between newly diagnosed T1DM patients and prevalent T1DM children by calculating odds ratios. The level of significance was taken at a *P* value of 0.05.

A total of 26 new T1DM patients (16 males) with mean (SD) age of 8.53 (5.02) years and 22 controls were enrolled during the study period. In the same period of the last pre-pandemic year (2019), there were 12 new patients, and an average of 17 new patients per year, during the previous five years (2015-2019). All newly diagnosed T1DM children had at least one diabetes autoantibody.

Anti-SARS-CoV-2 test was estimated in 21 new patients, and 11 (52.4%) showed positive results. Among the control group, 22.7% (*n*=5) had serological evidence of previous COVID-19. Thus, the newly diagnosed T1DM patients had a significantly higher rate of anti-SARS-CoV-2 positivity as compared to prevalent T1DM children [OR (95% CI) 3.74 (1.08, 13.55); *P*=0.04]. None of the new T1DM patients with a positive serology had known anamnesis for COVID-19 as per their parents. Of the 26 newly diagnosed T1DM patients, tested for rapid antigen and/or polymerase chain reaction (PCR) at admission, two children had a positive PCR test, one having negative IgG serology for COVID-19, the other did not have a serological test. Various characteristics of the two groups are shown in **Table I.**

Our results indicate that the incidence of childhood autoimmune T1DM increased during the third wave of the COVID-19 epidemic with more than half (52%) of the tested children having a previous coronavirus infection as proven by a positive anti-SARS-CoV-2 serological test. Our findings are in contrast with the results of two studies demonstrating no increase of SARS-CoV-2 seropositivity among newly diagnosed diabetic children [6,7]. However, these studies were conducted during the first year of the pandemic, while we examined our children during the third wave in Hungary.

The proposed theories for association of SARS-CoV-2 and TIDM include the novel coronavirus can induce or accelerate an autoimmune process, the infection could be the last step in an already ongoing progression, which leads to the clinical presentation of T1DM, and SARS-CoV-2 is capable of directly inducing T1DM by the destruction of beta cells. All of our patients had at least one positive autoantibody, indicating no direct beta cell cytopathy. Therefore, based on our results, we hypothesize that SARS-CoV-2 either can accelerate the autoimmune process or it may be the last step which converts latent to manifest T1DM.

A small sample size and a relatively short study period are limitations of our study. The long term epidemiology of T1DM may be affected by different phases of the COVID-19 pandemic.

In summary, our results suggest that during the third wave of COVID-19, a higher proportion of newly diagnosed T1DM children showed serologically confirmed evidence of previous SARS-CoV-2 infections, compared to prevalent cases of T1DM. Further studies and global registries [8] with long follow-ups are

Table I Clinical Characteristics of Children With Newly Diagnosed and Previously Known Type 1 Diabetes Mellitus

Characteristics	*Newly diagnosed children (n=21)*	*Children with pre-existing disease (n=22)*	*P value*
SARS-CoV-2 seropositivity	11 (52.4)	5 (22.7)	0.04
Age (y) [a]	8.84 (4.63)	10.39 (3.46)	0.22
SARS-CoV-2 +ve	9.40 (3.74)	9.92 (1.70)	
SARS-CoV-2 –ve	8.07 (5.51)	10.53 (3.86)	
Male: Female	11 (52.4) : 10 (47.6)	12 (54.55) : 10 (45.45)	0.89
SARS-CoV-2 +ve	3:8[c]	3:9	
SARS-CoV-2 –ve	8:2[c]	2:8	
Insulin requirement (unit/kg) [a,b]			
SARS-CoV-2 +ve	0.56 (0.20)	–	–
SARS-CoV-2 –ve	0.43 (0.18)	–	–

Data presented as frequency (%) or [a]mean (SD). [b]3 months after T1DM diagnosis. [c]P=0.03. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; +ve seropositive, –ve seronegative.

needed to clarify the controversies regarding the correlation of COVID-19 and T1DM.

Ethics clearance: This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the Institutional Review Board (IRB) of the 1st Department of Pediatrics, Semmelweis University who determined that our study did not need ethical approval. Our study has been performed in accordance with the ethical standards laid down in an appropriate version of the Declaration of Helsinki.

Contributors: VH: conceptualized and designed the study, analysed and interpreted the results, wrote the manuscript and reviewed and revised the final manuscript; AL,NT,GC: conceptualize and design the study, collected data, interpreted the results, helped draft the initial manuscript; PTH: conceptualized and designed the study, supervised the investigation, analyzed and interpreted the results, wrote the manuscript, reviewed and revised the final manuscript and critically reviewed the manuscript for important intellectual content. He should be approached for raw data. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Congenital Glucose-Galactose Malabsorption in a Child

Congenital glucose-galactose malabsorption (cGGM) is a rare autosomal recessive disorder [1] resulting from defective transport of glucose and galactose across intestinal epithelium due to mutations of *SLC5A1* gene encoding the intestinal sodium-dependent glucose transporter (SGLT1). It presents in newborns with severe osmotic diarrhea, hypernatremic dehydration, medullary nephrocalcinosis and distal renal tubular acidosis. If treated early with elimination of oral glucose and galactose containing diet, patients recover and develop normally [2, 3]. We report a novel mutation of *SLC5A1* gene in a child with cGGM for the first time from India.

A 6-month-old boy, product of 3rd degree consanguineous marriage with birth weight of 2.8kg presented with history of recurrent episodes of explosive watery diarrhea with perianal excoriation from 1st week of life. Repeated episodes of diarrhea with severe dehydration would warrant frequent hospitalizations. There was no history of blood or mucous with stools, vomiting, abdominal distension, rash or fever. Baby was exclusively breastfed for first 6 weeks. Thereafter, in view of persistent diarrhea breastfeeding was stopped and child was given soy milk formula.

On examination, child was severely dehydrated and malnourished [weight 3.1 kg (<-3SD), length 55cm (<-3SD) and weight for length < -3SD as per WHO charts], with glossitis and cheilitis. Polyuria was present (6.5 mL/kg/h) despite dehydration. Blood investigations showed severe metabolic acidosis (pH 7.04, HCO3 7.8 mEq/L, anion gap 10), severe hypokalemia (1.4 mEq/L), hypernatremia (155 mEq/L), with anemia (hemoglobin 6.8 g/dL). Total leucocyte count (10.8×10^3/µL), platelet count: (280×10^3/µL) and serum creatinine (0.2 mg/d) were normal. There was no clinical evidence of fat malabsorption. There was laboratory evidence of protein gut losses evidenced by hypoproteinemia (4.7 g/dL) and hypoalbuminemia (2.6 g/dL). Child was stabilized with intravenous fluids and potassium supplementation. Stool pH was 5 and was positive for reducing substances depicting osmotic diarrhea. During hospitalization, diarrhea would improve with fasting and worsen with introduction of WHO ORS. Therefore soy feeds were stopped and child started on amino acid formulation (*Neocate; Nutricia*) but had no improvement. Baseline workup for immunodeficiency disorders were unremarkable. Computerized tomography (CT) enterography showed normal bowel and pancreas. However, CT showed bilateral medullary nephrocalcinosis. Esophagogastroduodenoscopy was done with neonatal endoscope for obtaining biopsies from second part of duodenum as a work up for intractable diarrhea, which were both normal. In view of repeated episodes of severe dehydration requiring repeated hospitalizations high-lighted the possibility of osmotic with a component of secretary diarrhea. Normal anion gap metabolic acidosis, hypokalemia and bilateral nephrocalcinosis suggested possibility of distal renal tubular acidosis (RTA).

In view of early neonatal onset diarrhea that would worsen with ORS, acidic stool with stool positive for reducing substance (glucose), evidence of medullary nephrocalcinosis and distal RTA a diagnosis of cGGM was considered. Empirically glucose and galactose free diet was started. Since, there is no commercial formula specific to this disorder available in India, a carbohydrate-free formula designed for carbohydrate metabolic disorder (Metanutrition CMD by *Pristine organics, India*) was supplemented with fructose powder. Three grams of carbohydrate-free formula and 6g of fructose were mixed in 50 mL of water and the mixture was fed orally every 3 hours. The volume of the formula was tailored according to the weight. Child showed dramatic response with cessation of loose stools. Clinical exome sequencing of the child showed novel homozygous missense variation in exon 13 of the *SLC5A1* gene (c.1601T>C; p. Phe534Ser; ENST00000266088.4) classified as variant of uncertain significance as per ACMG guidelines [4]. Mutation was further confirmed by Sanger sequencing, confirming the diagnosis of cGGM. The human genome reference assembly used in this analysis was GRCh37/hg19. This variant has not been previously reported in the genome databases 1000 genomes, gnom-AD, Genome Asia 100k and dbSNP and described to be damaging by in-silico analysis. Parents were found to be heterozygous carriers of the same mutation and have been advised prenatal testing for future pregnancies.

After 3 months of exclusive formula feeding, child was supplemented with fruits (apple, mango, and banana), vegetables (beans, carrot) and pulses (green gram) in a graded manner. On follow-up, the child is asymptomatic and continues to have good weight gain (12 kg, 50th percentile) at 21 months of age.

Intractable diarrhea of early neonatal onset can be due to congenital enteropathies and structural gut abnormalities (malrotation, congenital short -gut) [5]. Structural abnormalities were ruled out with CT enterography, while normal villous/crypt architecture on histology excluded microvillus inclusion disease and other disorders of epithelial trafficking and polarity. As the diarrhea persisted even after lactose exclusion, congenital lactase deficiency was ruled out. In the absence of clinical steatorrhea, congenital bile acid synthesis defect and pancreatic insufficiency were unlikely.

Treating these rare diseases is challenging in resource poor settings. However, trial of combination of two different preparations was found to be affordable and effective. A previous literature review on cGGM reported 61 out of 107 cases from Middle East countries [1], and this is the first case reported from India.

We conclude that diagnosis of such a rare disease of cGGM is possible with appropriate clinical and investigative approach. Dietary modifications results in good outcome.

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Delayed Rise of Serum Thyroid Stimulating Hormone in a Micro-preemie With Congenital Hypothyroidism

Preterm neonates are at higher risk for deranged thyroid function test (TFT). Repeated thyroid screening tests by measuring thyroid stimulating hormone (TSH) and free thyroxine (FT4) levels are recommended in preterm and very low birth weight (VLBW) neonates [1]. Delayed TSH elevation, either alone or in association with low thyroxine level are more common in preterms as compared to term babies. We managed a preterm micro-preemie with congenital hypothyroidism (CH) diagnosed at 10 weeks of age.

A third order preterm (28+4 weeks) girl with birth weight of 630 g (IUGR), was delivered by caesarean section for abnormal doppler with fetal distress. Product of non-consanguineous marriage, was a spontaneous conception with antenatal history of two previous first trimester abortions and no drug or radiation exposure. Mother was diagnosed with hypothyroidism during second trimester, remained euthyroid on oral thyroxine 25 µg/day. Anticipating preterm delivery, antenatal steroids were given. Baby was limp at birth requiring intubation in delivery room with APGAR 4/10 and 5/10 at 1 min. and 5 min, respectively. Baby had respiratory distress syndrome (RDS), sepsis with shock (received dopamine infusion for initial 3 postnatal days), hemo-dynamically significant PDA, neonatal jaundice and was managed conservatively as per NICU protocol. Screening cranial ultra-sound revealed Grade I intraventricular hemorrhage. Baby was weaned off to nasal CPAP on day 13 and to room air on day 37 of life. Trophic feeding was started on day 2 along with total parenteral nutrition (TPN), on increasing feeds baby developed feed intolerance with NEC like features on day 6 and therefore, was continued on TPN only. Feeding was restarted on day 13, gradually increased to reach full feeds (120 mL/kg/day) by day 20. Baby received four units of packed red blood cell (PRBC) transfusions during hospital stay. Pale stool with high coloured urine and yellowish discoloration of body was noticed in third week of life and liver function test suggested neonatal cholestasis. Sepsis evaluation including urine culture, metabolic screening, TFT, TORCH profile, urine CMV PCR and eye examination were done for cholestasis evaluation. She was managed conservatively for TPN induced cholestasis and it improved gradually over next ten weeks. She had fully vascularized retina and normal cranial ultrasound at 40 weeks corrected gestational age (CGA). Initial thyroid profile on day 5 of life showed FT4 - 1.1 ng/dL, TSH - 4.6 µIU/mL; on day 27 FT4 - 1.6ng/dL, TSH 9.58 µIU/mL and on day 48 FT4 - 1.2 ng/dL, TSH - 14.8 µIU/mL. Considering rising trend of TSH and multiple prematurity related illness, repeat TFT was done at 10 weeks showing FT4 - 0.2 ng/dL and TSH >100 µIU/mL. Neck ultrasound showed normal sized thyroid gland with isthmus and *X* ray bilateral knee had presence of femoral and tibial epiphyses. A diagnosis of atypical CH was made at 2 months CGA and baby was started with oral levothyroxine at 15 µg/kg and dose adjusted as per serial TFT [2]. Currently baby weighs 7.75 kg at corrected age of 9 months, in euthyroid state on levothyroxine at a dose of 16 µg/day and planned to be followed up every three monthly till three years of age.

The thyroid profile on day 5 of our baby was not absolutely normal (low FT4 and normal TSH), which could be attributed to sick euthyroid syndrome, prematurity or dopamine infusion. Subsequent rising TSH with normal FT4 at 4 and 7 weeks is suggestive of either improvement from sick euthyroid syndrome or progressive maturity of hypothalamic pituitary adrenal (HPA) axis. In sick euthyroid syndrome, neonates may have lower T3/FT3, normal or low T4/FT4 with normal TSH during stress (RDS, IUGR) and usually manifest with rising trends of TSH during recovery [3]. Few ELBW neonates develop hypothy-roxinemia with delayed TSH rise during recovery from sick euthyroid syndrome labelled as atypical CH [4]. This should be distinguished from delayed rise of TSH, which warrants starting lower dose of levothyroxine (8µg/kg/day). The dose of levothy-roxine supplementation for maintenance of normal TFT with advancing age may help to differentiate transient CH from permanent CH. In this neonate as need of levothyroxine dose is declining with age it might be a case of transient CH. So brief trial of stoppage of medication may be considered after 3 years of age.

The incidence of delayed TSH elevation is inversely related to gestational age and birth weight; neonates born at gestational age 23-24 weeks or birth weight <800 gm are at higher risk [5]. In a cohort of preterm neonates caesarean section, mechanical ventilation, PDA, pneumothorax, PRBC transfusion and some specific medications (antibiotics, dopamine, postnatal steroids) found to be risk factors of delayed TSH elevation [6]. Therefore, this case

report recommends serial repetition of TFT in ELBW neonates, particularly those having initial stormy course during hospitalisation.

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Adenomyomatosis of Gallbladder in a Neonate

Adenomyomatosis of gallbladder is defined as hypertrophy of gallbladder mucosal epithelium that invaginate into thickened muscularis propria, leading to formation of intramural diverti-cula. It is mainly seen in adults and the incidences increases with increasing age, as most of the documented cases are above 50 years of age, and many were detected in cholecystectomy specimens. Adenomyomatosis of gallbladder is very rare in the paediatric population. We herein report a case of adenomyo-matosis of gallbladder in a newborn infant.

A term infant was delivered to a primigravida mother at 37 weeks of gestation at our hospital. Post-natal transition of the baby was smooth. We noted that one of the antenatal ultrasonographic scan of the mother was suggestive of umbilical varices in the fetus. To detect any associated abnormality in the neonate due to the umbilical arices, a postnatal ultrasound was done. The scan showed a partially distended gallbladder with diffuse wall thickening and multiple tiny echogenic foci in anterior and posterior walls involving entire gallbladder showing comet tail artefacts (**Fig.1**). The imaging findings were consistent with the adenomyomatosis of gallbladder. The baby continued to do well clinically and discharged with the advice to repeat the abdominal USG later.

The exact pathophysiology of adenomyomatosis of gallbladder is not clearly known. One theory suggests that change in intra-cystic pressure because of disruption of gallbladder function may lead to proliferation of cells in the gallbladder mucosa and hyperplasia of the muscle layer. The epithelial layer can then invaginate into the muscular layer, leading to the formation of Rokitensky Ashoff Sinuses (RAS) [1]. This is also seen on histopathology, which generally shows hyperplasia of the epithelium and mucosal out pouching through the muscular layer [2].

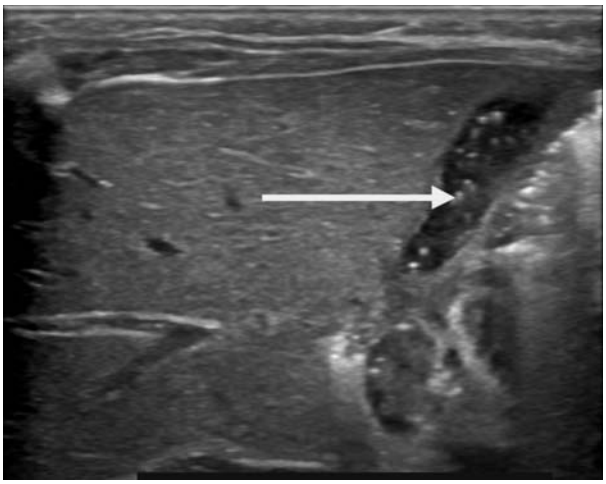

Fig. 1 Ultrasonography of abdomen showing adenomyomatosis of gall bladder.

Most of the cases in adults were diagnosed when they developed cholelithiasis or any other gall bladder condition. Although, there are some reports suggesting an association between adenomyomatosis and gallbladder cancer, there is no concrete evidence to prove this association [3].

A review of the literature showed only nine reported cases of paediatric gallbladder adenomyomatosis, with ages ranging from 1 day to 14 years. The most common symptom was abdominal pain, which was seen in 7 of the patients. Cholecystectomy was performed in seven paediatric cases [4]. One patient was a 1-day old newborn baby with suspected heterotaxy syndrome and complete atrioventricular canal. Patients generally did not have other significant comorbid conditions [5].

In children, adenomyomatosis of gall bladder remains an incidental finding on USG scan for some other reason as there are no specific clinical symptoms. Computed tomography and magnetic resonance imaging have also been used in the diagnosis of this

condition [1]. Usually, no treatment is recommended. cholecystectomy is required in patient who are symptomatic with right upper quadrant pain.

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Thiamine-Responsive Acute Pulmonary Hypertension in an Exclusively Breastfed Infant

Thiamine deficiency presenting as acute severe pulmonary hypertension (PAH) in exclusively breastfed babies has been reported from various parts of India recently [1-3]. Here we report a male infant who presented with acute pulmonary hypertension and responded to thiamine.

A 4-month-old male infant, first born to non-consanguineous parents, belonging to the Chetty community from Mysuru district of Karnataka was referred to our hospital in view of acute onset of cough and respiratory distress. There was a history of approximately ten recent deaths in their community in babies of the same age group, one of them being this baby's first cousin. Most of them presented with bronchiolitis like symptoms, rapidly progressing to acute respiratory distress syndrome (ARDS). This baby was referred to our hospital with the possibility of inborn errors of metabolism.

Baby was delivered at term, was on exclusive breast feeds, thriving well (birth weight 3 kg, present weight 6.5 kg) and had normal development. At presentation, the baby had tachypnea, tachycardia, hypoxia (SpO2 92% in room air) and respiratory distress. Liver was palpable 3 cm below costal margin. Second heart sound was loud and wide split. There was hypotonia and deep tendon reflexes were absent. The arterial blood gas showed mixed disorder with metabolic acidosis and respiratory alkalosis. Tandem mass spectroscopy was normal. Electrocardiogram showed evidence of right atrial (RA) dilatation and right ventricular (RV) hypertrophy (RVH). Echocardiography showed features of severe PAH (RA, RV dilated, moderate tricuspid regurgitation, inter-atrial septum bulging into left atrium) without any evidence of structural heart disease. Contrast enhanced computed tomography (CECT) of lung showed pulmonary plethora with features of PAH without any intrinsic pulmonary pathology.

A detailed dietary history revealed that mother's diet mainly consisted of polished white rice and *Rasam* (a sour soup made with tomato and lentil). There was traditional avoidance of other foods like pulses, vegetables, and non-vegetarian foods during postpartum period. Considering the probability of thiamine deficiency, thiamine was started in a dose of 10 mg/kg, orally. The baby showed clinical improvement, could be weaned off oxygen by 12 hours, and respiratory distress subsided by 48 hours. A repeat echocardiography at 48 hours showed marked improvement with only mild PAH, and subsequently showed complete resolution of PAH at 96 hours. No pulmonary vasodilators other than oxygen were given.

The whole blood thiamine level estimated by HPLC of both baby and mother were low (25 µgm/L and 27.25 µgm/L, respectively, normal range being 28 to 85 µgm/L). There was no history of aphonia, encephalopathy, seizures, or oedema. Serum 25-hydroxy vitamin D3 level was normal. The history, geographic background, clinical features, investigations, and dramatic response to thiamine confirmed the diagnosis of Thiamine responsive acute pulmonary hypertension of early infancy (TRAPHEI). Family was counselled about the dietary modification and both mother and baby were put on thiamine supplementation at 2 mg/kg/day. A repeat echocardiography at one month follow-up visit showed complete recovery. ECG normalized by two months. Muscle tone and deep tendon reflexes normalised after two months of thiamine therapy, suggestive of coexistent neuropathic form of thiamine deficiency. Neuroimaging was not done, as the baby had improved.

Thiamine has an important role in the metabolism of carbohydrates and synthesis of nucleic acid, myelin, and neurotransmitters. A regular dietary supply is must for preventing deficiency because of high turnover rate and low body stores of thiamine. Thiamine causes preferential injury to tissues with heavy metabolic turnover like neurons and cardiac myocytes. The clinical spectrum of thiamine deficiency in children can be acute cardiac form, aphonic form, pseudo meningitic form or neuropathic form [4]. Thiamine deficiency has been documented in those consuming polished cereals and with other dietary restrictions. Infants are at highest risk due to rapid growth rate and high energy needs. In exclusively breastfed babies of thiamine deficient mothers, thiamine levels rapidly decline in the third month of life. As in our case, culturally determined food restrictions during the postpartum period are prevalent in various parts of India [5].

Thiamine deficiency has been identified as a cause of reversible acute PAH attributed to block in glycolysis resulting in ventricular dysfunction and lactic acidosis [1-3,6]. In a relevant geographical and cultural setting, it should be considered in all previously normal babies presenting with acute respiratory distress, tachycardia, and hepatomegaly. Whole blood thiamine estimation is not easily available and may not represent the body thiamine status [4]. So, empirical administration of thiamine is recommended in these infants. Resolution of PAH on thiamine administration is considered as diagnostic. The clinical presentation of this condition is acute, and in untreated cases, fatality is high. Moreover, untreated long-term deficiency can cause intellectual and motor disabilities [4]. For timely diagnosis and treatment, a high index of suspicion among pediatricians is essential. Primary prevention through health education and social reforms is also needs to be addressed.

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Modified BG Prasad Socioeconomic Status Scale: Updated for the Year 2022

Socioeconomic status (SES) can be defined as "a position attained by an individual within a system of hierarchical social structure [1]. The concept of socioeconomic status is being widely used in medical sociology. It is one of the key factors that have an influence on the health of an individual and family, social security system, as well as family health statistics [2]. Individual usually inherit the social status from his family, but in modern society it is determined on the basis of occupation, income, type of housing and neighbourhood, membership of the certain associations and organizations, material posses-sions, etc. [3].

To measure the socioeconomic status, different scales are used, of which, BG Prasad scale and Kuppuswamy scale are used widely. Whereas Kuppuswamy scale is applicable only for urban areas, BG Prasad scale is applicable for both rural as well as urban population [4, 5].

BG Prasad scale was first formulated in 1961, which was modified later in 1968 and 1970 by the developer of the scale himself [5,6]. The scale is based on the per capita monthly income (per capita monthly income = total monthly family income/total family members) and therefore it is applicable to individuals. The benefit of using the scale is that, as it depends only on the income variable, therefore simple and easy to calculate. However, as the value of rupee changes due to inflation, income is required to be updated from time to time to keep the scale relevant with time. Therefore, it is very important to continuously update the income categories of the scale.

The income categories of the scale can be updated considering the Consumer Price Index (CPI), the widely used indicator of inflation. The most appropriate CPI for revision of socioeconomic classifications is CPI (industrial workers), which is likely to reflect the expenditure of a workingclass family.

The BG Prasad scale developed initially, considered the base of CPI for 1960 as 100 [5]. There was an amendment in the base year by the Ministry of Labour in October, 2020 and the base year has been changed from 2001 to 2016 by introducing a linking factor of 2.88 [7]. Considering the new base year as 2016, there have been some updates of the scale in the recent past [8, 9], and an online tool was also developed previously to update the scale in real time [10]. However, as this calculator considers the base year as 2001(the older base year), the values given by the calculator are no longer valid.

Table I Revised BG Prasad Socioeconomic Status Classification, January, 2022

Socioeconomic classes	*Original classification (1961) of the per capita income*	*Revision for January, 2022*[a]
I (Upper)	100 and above	8220 and above
II (Upper middle)	50 99	4110-8219
III (Middle)	30 49	2465-4109
IV (Lower middle)	15 29	1230-2464
V (Lower)	<15	<1230

Values in INR/month. [a]Rounded off to nearest 10/-.

To update the scale for 2022, we took the latest CPI (IW) available from the website of Labour Bureau which is 125.1 for January, 2022.

Multiplication factor = current CPI (125.1)/Base index value in 2016 (100) =1.251.

The new income ranges can now be calculated using the following equation:

New income value = Multiplication factor × Old income value × 4.63 × 4.93 × 2.88. Where 4.63, 4.93, and 2.88 are the linking factors given by the Labour Bureau. Using the above equation, the updated ranges for the scale for January, 2022 were calculated, as shown in **Table I**.

To conclude, there is a need to periodically update the income-based socioeconomic scales due to continuous changes in the price of the goods and services as a consequence of inflation.

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NEWS IN BRIEF

Recent Guidelines to Manage Neonatal Hyperbilirubinemia

The American Academy of Pediatrics recently updated the guidelines to manage hyperbilirubinemia in newborns more than 35 weeks of gestation. The last recommendation in 2004 was followed by some modifications in 2009. One key guideline had been to suggest universal pre-discharge screening of all babies by total serum bilirubin (TSB) or transcutaneous bilirubin (TcB). Newer evidence discovered since the last guideline has been reviewed to develop the new guidelines in 2022.

Breast feeding jaundice which has been seen in babies on inadequate feeds and excessive weight loss, between 3-5 days has been renamed "suboptimal intake hyperbilirubinemia". Pediatricians are advised to encourage breast feeding within the first hour after birth and at least 8 times in 24 hours. Hemolysis must be suspected if TSB or TcB rises >0.3 mg/dL/hour in the first 24 hours and >0.2 mg/dL/hor in next 24 hours. A DAT (direct antibody test) is recommended if hemolysis is suspected. End tidal CO measurement may also be useful to identify hemolysis. Risk for neurotoxicity is increased if gestational age is <38 weeks, serum albumin <3 gm/dL and in presence of hemolysis, sepsis or clinical instability. All infants should be visually assessed for jaundice every 12 hours till discharge. Any newborn who is clinically jaundiced in the first 24 hours must undergo TSB or TcB. All newborns must have a TcB or TSB between 24-48 hours after birth or pre discharge if that is earlier. Breast fed babies who are still jaundiced at 3-4 weeks or formula fed babies who are jaundice beyond 2 weeks must undergo testing for direct hyperbilirubinemia.

The phototherapy thresholds based on gestational age and hour of life have been slightly increased. Whenever possible phototherapy must be provided in the mothers room. If TSB reaches 2 mg/dl below exchange transfusion levels, escalation of care protocols must be instated. This includes intravenous fluids, intensive phototherapy and 2 hourly TSB measurements. IVIG 0.5-1 gm/kg may be given over 2 hours and repeated after 12 hours if DAT is positive. Bilirubin to albumin ratio cut off's for gestation may be used to decide need for exchange transmission. (*Pediatrics. 2022;150: e2022058859*).

Adopt a Child With Tuberculosis Campaign

An innovative idea in India's drive to eliminate tuberculosis is the *Nikshay Mitra* concept. As part of the TB Mukt Bharat Abhiyan started in September, 2022, individuals as well as organizations can adopt one or more patients with tuberculosis and support them in various ways. This includes nutritional support, additional investigations or vocational support. A minimal commitment of one year is required, e.g., one may provide a child with a food basket every month. In order to become a *Nikshay Mitra*, a person has to visit the official website of the scheme (*https://communitysupport.nikshay.in/*). They then have to search for the state, district, block and peripheral health institution to make a donation or adopt a TB patient. The aim is to reduce the financial burden of patients with tuberculosis, increase community support and reduce the stigma of tuberculosis. Consent will be taken from patients prior to enrolling them in the campaign. The aim is to make India tuberculosis free by 2025, about 5 years before the global target.

India witnessed a 19% spike in patients with tuberculosis in 2021 compared to 2020, and presently has the maximum number of new cases in the world. It is hoped that public participation will help in winning India's long standing battle against tuberculosis. (*Indian Express 19 September, 2022*)

CAR-T Cell Therapy for SLE

Five patients with treatment resistant systemic lupus erythematosus (SLE) were treated with CAR-T cell therapy with favorable results. The core problem in SLE are auto-antibodies against double stranded DNA and other nuclear antigens, which trigger an immune complex mediated injury in various organs including kidneys, heart, lungs and skin. Hence, B cell depletion is an attractive approach to treatment of SLE. While rituximab is one of the commonest B cell depleting agents in use, it fails to completely eliminate all autoreactive B cells, especially those in lymphatic organs and inflamed tissues. In CAR-T cell therapy, T-cells of the patients are genetically modified to encode a receptor which binds to the target to be eliminated. In this trial, autologous T cells from patients with SLE were transduced with a lentiviral anti-CD19 CAR vector, expanded and re-infused. This resulted in a deep B cell depletion and complete remission of all five patients. Even after reappearance of B cells after a mean of 110 days, there was no recurrence of symptoms, suggesting that there had been a complete reset of the immune system. CAR-T cell therapy is promising to revolutionize medicine, especially in the field of oncology and immunology. (*Nature Medicine 15 September 2022*)

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CLIPPINGS

Aerosolization of *Mycobacterium tuberculosis* by tidal breathing (Am J Respir Crit Care Med. 2022;206:206-16)

Coughing is believed to be an important source of transmission of *Mycobacterium tuberculosis* (Mtb) among susceptible individuals and house hold contacts. However, coughing alone might not explain the disease transmission in asymptomatic patients with pulmonary tuberculosis confirmed bacteriologically. Dinkele and colleagues tried to look at the aerosolization of Mtb in 38 patients with Gene-Xpert positive tuberculosis (TB) during three different maneuvers- tidal breathing, forced vital capacity maneuver and coughing. The proportion of respiratory particles of different sizes retrieved were similar in all three maneuvers; however, the number of particles were higher during cough maneuver compared to other maneuvers. In addition, the study also found that the return of positive results for Mtb was similar in all three maneuver. On modelling based on 24-hours breath and cough frequencies, it was found that tidal breathing per se could contribute to more than 90% of Mtb aerosols among symptomatic patients with tuberculosis, and could possibly act as an important contributor to TB transmission among active cases. The results of this study have implications for case detection among children in the household of asymptomatic TB patients.

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension (Eur Respir J. 2022:2200879)

The following an excerpt from the recommendations for management of paediatric pulmonary hypertension (PH) proposed by ESC/ERS extrapolated from adult data. A full diagnostic workup including right heart catheterization (RHC) and workup for specific age-appropriate etiology and acute vasodilator testing are recommended to treat children with PH at centres with capability of managing pediatric PH (Class I, Level C evidence). For confirming a diagnosis of PH, RHC is recommended before starting PAH therapy (Class I, Level C evidence). In children with idiopathic or hereditary pulmonary arterial hypertension (PAH), acute vasoreactivity testing is recommended to document magnitude of benefit that might occur on starting calcium channel blockers (Class I, Level C evidence). A positive response to vasoreactivity testing is defined (for both children and adults) as reduction in mean pulmonary arterial pressure (mPAP) ≥10 mm Hg to reach an absolute value of mPAP ≤40 mm Hg with either a rise in cardiac output or unchanged cardiac output (Class I, Level C evidence). Screening for PH is recommended for infants with bronchopulmonary dysplasia (Class I, Level B evidence). In infants with bronchopulmonary dysplasia, treatment of lung disease and optimization of respiratory support is recommended before initiating PAH therapy (Class I, Level B evidence).

Height and bone mineral content after inhaled corticosteroid use in the first 6 years of life (Thorax 2022; 77:745-51)

Long-term steroid therapy is known to affect height velocity and bone mineral content (BMC). It is not known whether inhaled corticosteroids (ICS) also do the same, especially in children in the first six years of life. In this study, the authors had chosen two Danish "asthma in childhood" cohorts with children up to 6 years of age who had been on inhaled corticosteroid therapy and who have had a height and BMC determined at 6 years of age. About a third of the children in that cohort had received a cumulative dose of ICS equivalent to or more than 10 weeks of standard therapy. The study found an inverse relationship between ICS use and height per each year of standard treatment (-0.26; 95% CI -0.45 to -0.07) in children 0-6 years (P=0.006). This effect was mainly seen to be contributed by a group of children with ongoing treatment at 5-6 years of age. No significant association was found in those children who had discontinued treatment for at least one year before the age of six. Similarly, no association was seen between ICS use and BMC at age six. In conclusion it appears that ICS use in early childhood and continued usage at age 5-6 years is associated with decreased height at 6 years of age.

Effect of high-flow nasal cannula therapy vs continuous positive airway pressure therapy on liberation from respiratory support in acutely ill children admitted to pediatric critical care units (JAMA. 2022;328:162-72)

This RCT was conducted to answer a research question whether in acutely ill children assessed to require non-invasive respiratory support, is the use of high flow nasal cannula (HFNC) therapy as the initial therapy noninferior to the use of continuous positive airway pressure (CPAP) therapy in time to become free of all forms of respiratory support. The investigators randomized 600 acutely ill children from 24 pediatric intensive care units across the United Kingdom, who were assessed to require non-invasive respiratory support, to either receive HFNC or CPAP. The median time for liberation from all forms of respiratory support, which was the primary outcome of the study, was found to be 52.9 h in the HFNC group and 47.9 h in the CPAP group with a one sided 97.5% confidence limit for hazard ratio of 0.86 which fell within the non-inferiority margin of 0.75, meaning that initial use of HFNC in a critically ill child assessed to require non-invasive respiratory support is non inferior to initial use of CPAP. The study also assessed about seven secondary outcomes including mortality at discharge from the intensive care unit, intubation within 48 hours, need for sedation, mean duration of critical care stay, mean duration of acute hospital stay. It was found that need for sedation, mean duration of critical care unit stay, and mean duration of acute hospital stay were significantly lower in the HFNC group compared to the CPAP group.

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IMAGE

Parameatal Urethral Cyst

A 10-year-old child presented with a soft globular swelling near opening of glans penis, present since two years. It was associated with mild dysuria, but without obstruction of stream of urine. Examination showed solitary, well-defined, non-tender, spherical cyst measuring 1×1cm, adjacent to meatal opening (**Fig. 1**).

Parameatal urethral cyst is rare clinical entity, first reported by Thomson and Lantin in 1956. Usual diameter of these cysts is 1 cm and it occurs on lateral or ventral margin of urethral meatus. These cysts may present at birth or spontaneously in early childhood. Exact etiology for the development of cysts is not known; however, infections may be a possible trigger. They are usually asymptomatic but few children may present with dysuria, poor stream of urine or urinary retention.

Possible treatment options available are watchful waiting, needle aspiration, marsupialization and complete surgical excision. For good cosmetic results and less recurrence, complete surgical excision of the cyst is best option. Differential diagnosis includes fibro-epithelial cyst, pilo-sebaceous cyst and epidermoid cyst.

Fig. 1 Translucent cyst measuring 1X 1cm on ventral aspect of uretheral meatus.

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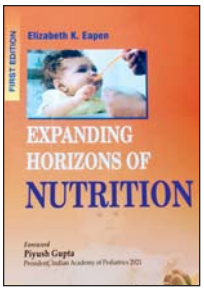
BOOK REVIEW



Expanding Horizons of Nutrition
Elizabeth K Eepen
Published by:
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Total Pages: 217; Price: 600/-.

Nutrition Science knowledge is an important component of practicing pediatrician. This informative book 'Expanding Horizons of Nutrition' contains ten sections. It provides concise updated information on interactions between Nutrition and Immunity, Nutrition Transition and Triple burden of Nutrition disorders, nutrition needs in infancy and adolescence, and Nutrition needs of children actively participating in sports. The authors have provided a commendable summary of nutrition issues pertinent in today's context, especially about nutrition transition and triple pandemic burden in the country. Adequate Nutrition is essential for immunity and prevention of diseases. A unique section is on eating disorders from infancy to adolescents. This section provides excellent information on recent advances.

This book is strongly recommended for practicing pediatricians and also for under-graduate medical students.

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