*Public Health Nutrition: 23(17), 3181–3186* doi:10.1017/S1368980020001895

# Prevalence and predictors of hypocalcaemia in severe acute malnutrition

Chabungbam Smilie[1,*], Dheeraj Shah[1], Prerna Batra[1], Rafat S Ahmed[2] and Piyush Gupta[1]

[1]Department of Paediatrics, University College of Medical Sciences, Guru Teg Bahadur Hospital, Delhi 110095, India: [2]Department of Biochemistry, University College of Medical Sciences, Guru Teg Bahadur Hospital, Delhi 110095, India

Submitted 10 February 2020: Final revision received 30 April 2020: Accepted 18 May 2020: First published online 24 July 2020

## Abstract

*Objective:* To determine the prevalence and predictors of hypocalcaemia in under-five children (1–59 months) hospitalised with severe acute malnutrition (SAM).

*Design:* A cross-sectional study was designed to determine the prevalence of hypocalcaemia among children hospitalised with SAM. Serum Ca and 25-hydroxy-cholecalciferol (25-(OH)D) were estimated. Hypocalcaemia was defined as serum Ca (albumin-adjusted) <2·12 mmol/l. To identify the clinical predictors of hypocalcaemia, a logistic regression model was constructed taking hypocalcaemia as a dependent variable, and sociodemographic and clinical variables as independent variables.

*Setting:* A tertiary care hospital in Delhi, between November 2017 and April 2019.

*Participants:* One-hundred and fifty children (1–59 months) hospitalised with SAM were enrolled.

*Results:* Hypocalcaemia was documented in thirty-nine (26 %) children hospitalised with SAM, the prevalence being comparable between children aged <6 months (11/41, 26·8 %) and those between 6 and 59 months (28/109, 25·7 %) ($P = 0·887$). Vitamin D deficiency (serum 25-(OH)D <30 nmol/l) and clinical rickets were observed in ninety-eight (65·3 %) and sixty-three (42 %) children, respectively. Hypocalcaemia occurred more frequently in severely malnourished children with clinical rickets (OR 6·6, 95 % CI 2·54, 17·15, $P < 0·001$), abdominal distension (OR 4·5, 95 % CI 1·39, 14·54, $P = 0·012$) and sepsis (OR 2·6, 95 % CI 1·00, 6·57, $P = 0·050$).

*Conclusion:* Rickets and hypocalcaemia are common in children with SAM. Routine supplementation of vitamin D should be considered for severely malnourished children. Ca may be empirically prescribed to severely malnourished children with clinical rickets, abdominal distension and/or sepsis.

**Keywords**
Hypocalcaemia
Predictors
Prevalence
Severe acute malnutrition

Severe acute malnutrition (SAM), currently affecting nearly 20 million pre-school-aged children globally, is a significant factor in approximately one-third of the nearly 8 million deaths of under-five children[1]. In India, almost 7·5 % under-five children are severely wasted (weight-for-height <–3 SD) and 21 % are wasted (weight-for-height <–2 SD) according to the National Family Health Survey-4 (NFHS-4) data[2].

SAM is a clinical syndrome due to an imbalance between the demand and supply of energy content, proteins and micronutrients, with a complex interplay of various pathological mechanisms. Severely malnourished children have increased total body water and sodium, while there is deficiency of K, Mg and phosphate stores[3–5]. However, there is paucity of data regarding serum Ca levels in severely malnourished children. Chisti *et al.*[6] found that hypocalcaemia was prevalent in 26 % of severely malnourished children aged <5 years admitted to an urban hospital in Bangladesh, and was associated with serious consequences such as seizures and death[6]. Abdominal distension, acute watery diarrhoea, vomiting, lethargy and severe sepsis were also more commonly seen in severely malnourished children with hypocalcaemia[6–9].

According to the WHO and Indian Academy of Pediatrics (IAP) guidelines on hospital-based management

*Corresponding author: Email smiliecha55@gmail.com

of severely malnourished children, all severely malnourished children should be given supplemental K, Mg, vitamin A, folic acid, Zn, Cu, Fe and multivitamins routinely[10,11]. The multivitamin supplement should preferably contain vitamins A, C, D, E and $B_{12}$ besides thiamine, riboflavin and nicotinic acid. There is no recommendation on routine supplementation of Ca or vitamin D, although the F-75 and F-100 diets in the stabilisation and nutritional rehabilitation phases, respectively, contain approximately 320 mg Ca/l, and ready-to-use therapeutic food (RUTF) contains some vitamin D (15 μg per sachet, with each child receiving 1·5–5·0 sachets per day according to body weight)[12]. Intake from these sources may not be sufficient to consistently elevate the circulating concentrations of serum 25-hydroxycholecalciferol (25-(OH)D) in children with SAM, considering a high prevalence of vitamin D deficiency in this group[13–15]. Systemic inflammatory response may also dysregulate vitamin D metabolism and increase requirement of the same[16].

A better understanding of the prevalence and clinical predictors of hypocalcaemia in children with SAM shall contribute to more focused strategies, reducing hypocalcaemia-related morbidity, especially in resource-poor settings. We conducted the current study to estimate the prevalence of hypocalcaemia and determine its predictors in under-five children with SAM. Secondary outcome measures included serum vitamin D status and clinical rickets.

## Methods

This was a cross-sectional study conducted in children aged between 1 and 59 months hospitalised with SAM in the paediatrics ward of a tertiary care hospital in Delhi, between November 2017 and April 2019. SAM was defined as weight-for-length/height <–3 *z*-score of the WHO growth standards, or bilateral pedal oedema of nutritional origin, or mid-upper arm circumference (MUAC) <11·5 cm (for children aged 6–59 months)[17]. Children taking Ca or vitamin D supplements at the time of admission or within the last 2 weeks prior to admission and those with chronic illnesses such as heart defects, renal diseases, cancer and congenital anomalies were excluded.

### *Sample size*

Using an estimated prevalence (*P*) of hypocalcaemia in SAM at 26 % as per data from Chisti *et al.*[6] and an acceptable absolute precision (*d*) of ±7 % (acceptable relative precision of 25 %) with 95 % CI, the sample size was estimated to be 150.

### *Patient details and laboratory measurements*

Patient's information, case history and relevant examination, laboratory investigations, treatment received, duration of admission and final diagnosis at the time of discharge/death were recorded in a predesigned case record form. Biochemical parameters analysed included serum Ca, serum phosphate, serum alkaline phosphatase (ALP), serum 25-(OH)D, serum Mg, serum albumin, serum Na and serum potassium. Venous blood (3 ml) was collected, and the sample centrifuged within 15 min from the time of collection, and the separated serum was stored at −20°C.

Serum Ca was estimated using a UniCel DxC 600 automatic analyser (Beckman Coulter India Pvt. Ltd) by ion-selective electrode (ISE) method, measured in mg/dl, corrected for serum albumin levels and then converted into mmol/l for classification of hypocalcaemia. Formulae for calculated parameters are as follows[18]:

1. Corrected total Ca (mg/dl) = Total Ca (mg/dl) + 0·8 × (4 – serum albumin in g/dl)
2. Corrected total Ca (mmol/l) = Corrected total Ca (mg/dl) × 0·25

Hypocalcaemia was defined as serum Ca (albumin-adjusted) <2·12 mmol/l[19]. Serum 25-(OH)D levels were estimated with an immunoassay analyser by chemiluminescence method and commercially available kits (Beckman Coulter Inc.). Serum 25-(OH)D between 30 and 50 nmol/l was considered as vitamin D insufficiency and <30 nmol/l as vitamin D deficiency[20].

Severely malnourished children with hypocalcaemia were compared with those without hypocalcaemia with regard to gender, age, socioeconomic status, duration of exclusive breastfeeding, diarrhoea, vomiting, lethargy, shock, convulsion, respiratory rate per minute, diastolic blood pressure, sepsis, abdominal distension, hypoxaemia ($spO_2$ <90 %), anthropometric parameters, serum Na, serum potassium, serum phosphate, serum 25-(OH)D and serum Mg. Sepsis was defined as the presence of inflammation (abnormal leucocytes count (>12 000 or <4000/$mm^3$) or band and neutrophil ratio (≥0·1)) plus the presence or presumed presence of infection with thermo-instability (hypothermia (≤35°C) or hyperthermia (≥38·5°C)) and tachycardia[21,22]. Rickets was defined based on clinical examination (presence of rachitic rosary, frontal bossing, wrist widening, wide-open fontanel, pot-belly abdomen, Harrison's sulcus, genu valgum and/or double malleoli) aided by biochemical tests and confirmed by radiographs.

### *Patient management*

All enrolled children were managed as per WHO and IAP guidelines[10–12], including supportive care, intravenous fluids, oral rehydration salts solution, antibiotics depending on the local resistance pattern and availability, oxygen therapy, blood transfusions if required, frequent monitoring and assessment and nutritional supplements. We used local preparations of F-75 and F-100 diets in the stabilisation and rehabilitation phases. In the emergency treatment of children presenting with hypocalcaemic seizures,

https://doi.org/10.1017/S1368980020001895 Published online by Cambridge University Press

**Table 1** Univariate analysis of predictors of hypocalcaemia in children with severe acute malnutrition (*n* 150)

| | Hypocalcaemia (corrected serum Ca <2·12 mmol/l) (*n* 39) | | | | Normocalcaemia (corrected serum Ca ≥2·12 mmol/l) (*n* 111) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Characteristics | *n* | % | Mean | SD | *n* | % | Mean | SD | *P* |
| Baseline characteristics | | | | | | | | | |
| Age < 6 months | 11 | 28·2 | | | 30 | 27 | | | 0·887 |
| Age (months) | | | 14 | 13 | | | 13 | 11 | 0·883 |
| Male gender | 18 | 46·2 | | | 58 | 52·2 | | | 0·512 |
| Low socioeconomic status* | 34 | 87·2 | | | 100 | 90 | | | 0·563 |
| Exclusive breastfeeding in the first 6 months of age† | 14 | 35·9 | | | 30 | 27 | | | 0·295 |
| Presenting complaints | | | | | | | | | |
| Vomiting | 19 | 48·7 | | | 75 | 67·6 | | | 0·036 |
| Diarrhoea | 23 | 59 | | | 82 | 73·9 | | | 0·081 |
| Abdominal distension | 10 | 25·6 | | | 10 | 9 | | | 0·009 |
| Seizures | 7 | 17·9 | | | 11 | 9·9 | | | 0·250 |
| Fast breathing | 10 | 25·6 | | | 23 | 20·7 | | | 0·523 |
| Duration of illness (days) | | | 18 | 41·9 | | | 14 | 27·2 | 0·534 |
| Examination findings | | | | | | | | | |
| Hypoxia | 8 | 20·5 | | | 9 | 8·1 | | | 0·044 |
| Shock | 6 | 15·4 | | | 7 | 6·3 | | | 0·083 |
| Sepsis | 2 | 53·8 | | | 39 | 35 | | | 0·050 |
| Rachitic features | 26 | 66·7 | | | 37 | 33·3 | | | <0·001 |
| Anthropometric parameters (*z*-score) | | | | | | | | | |
| Weight-for-age | | | –4·6 | 1·2 | | | –4·4 | 1·2 | 0·371 |
| Length/height-for-age | | | –2·9 | 1·7 | | | –2·6 | 1·8 | 0·252 |
| Weight-for-length/height | | | –4·2 | 1·0 | | | –4·2 | 0·9 | 0·934 |
| Mid-upper arm circumference‡ | | | –4·1 | 1·2 | | | –4·0 | 1·2 | 0·729 |
| Laboratory findings | | | | | | | | | |
| Serum Na (mEq/l) | | | 137·5 | 6·9 | | | 136·6 | 8·1 | 0·536 |
| Serum potassium (mEq/l) | | | 3·9 | 0·9 | | | 4·2 | 0·9 | 0·079 |
| Serum phosphate (mmol/l) | | | 2·3 | 0·9 | | | 2·0 | 0·9 | 0·097 |
| Serum alkaline phosphatase (U/l) | | | 284 | 206 | | | 180 | 109 | 0·004 |
| Serum 25-(OH)D (nmol/l) | | | 22·7 | 23·5 | | | 28·7 | 20·7 | 0·127 |
| Serum Mg (mmol/l) | | | 0·7 | 0·3 | | | 0·7 | 0·3 | 0·944 |
| Died | 3 | 8 | | | 7 | 6·3 | | | 0·765 |

25-(OH)D, 25-hydroxycholecalciferol.
*Children belonging to the lower and upper-lower socioeconomic class as per modified Kuppuswamy scale.
†Till the date of enrolment in infants <6 months.
‡*n* 21 and 81, respectively, in hypocalcaemic and normocalcaemic groups.

intravenous 10 % calcium gluconate was administered slowly at a dose of 2 ml/kg (maximum 10 ml) followed by an infusion of calcium gluconate (1–5 ml/kg per day) titrated to maintain eucalcaemia. Those children with asymptomatic hypocalcaemia were supplemented with oral Ca (500–800 mg/d)[23]. For the treatment of nutritional rickets and vitamin D deficiency, daily doses of 50 µg of vitamin D were given to children between 1 and 3 months; a single dose of 1·25 mg or daily doses of 50 µg for children between 3 and 12 months; and a single dose of 3.75 mg or daily doses of 75–150 µg for children between 12 and 59 months[23,24]. Oral vitamin D doses were given along with oral Ca 500–800 mg/d, regardless of age or weight, for a minimum duration of 3 months[23,24].

### *Statistical analysis*

Data and findings of the current study were entered into a personal computer using SPSS for Windows (version 20.0). The prevalence of hypocalcaemia in under-five children hospitalised with SAM was calculated. Differences in proportions (for categorical data) and in means (for continuous data) were calculated using $\chi^2$ test and Student's *t* test, respectively. Clinical predictors of hypocalcaemia in severely malnourished children were identified as per the following process: sociodemographic and clinical characteristics were analysed initially in a univariate model, and further a logistic regression model was constructed taking hypocalcaemia as a dependent variable and co-variates with $P < 0{\cdot}1$ (on univariate analysis) as independent variables. $P < 0{\cdot}05$ was considered significant.

## Results

We enrolled 150 children, out of which seventy-six (50·7 %) were boys; 129 (86 %) hailed from urban areas, nineteen (12·7 %) from rural areas and two (1·3 %) from urban slums. A majority (*n* 126, 84 %) of children were aged <24 months.

Hypocalcaemia with corrected serum Ca <2·12 mmol/l was documented in thirty-nine (26 %) out of 150 children with SAM. Of these, eleven were <6 months of age. The prevalence of hypocalcaemia was comparable between

https://doi.org/10.1017/S1368980020001895 Published online by Cambridge University Press

**Table 2** Results of logistic regression to explore the independent clinical predictors of hypocalcaemia in under-five children with severe acute malnutrition (*n* 150)

| Predictors | OR | 95 % CI | *P* |
|---|---|---|---|
| Clinical rickets | 6·6 | 2·54, 17·15 | <0·001 |
| Abdominal distension | 4·5 | 1·39, 14·54 | 0·012 |
| Sepsis | 2·6 | 1·00, 6·57 | 0·050 |
| Diarrhoea | 0·6 | 0·21, 1·56 | 0·277 |
| Vomiting | 0·7 | 0·27, 1·85 | 0·482 |
| Hypoxia | 1·7 | 0·47, 6·24 | 0·410 |
| Shock | 1·8 | 0·43, 7·75 | 0·413 |

children <6 months (11/41, 26·8 %) and those between 6 and 59 months (28/109, 25·7 %) ($P = 0·887$). The mean and median values of corrected serum Ca in severely malnourished children were 2·23 (SD 0·26) and 2·27 (IQR 2·09, 2·38) mmol/l, respectively.

A large proportion of the enrolled children (*n* 126, 84 %) were either deficient (*n* 98, 65·3 %) or insufficient (*n* 28, 18·7 %) in serum 25-(OH)D. Of thirty-nine children with hypocalcaemia, thirty (76·9 %) were deficient in serum 25-(OH)D, four (10·2 %) were insufficient and five (12·8 %) had normal serum 25-(OH)D; corresponding values for children with normocalcaemia (*n* 111) were sixty-eight (61·3 %), twenty-four (21·6 %) and nineteen (17·1 %), respectively. Clinical rickets were observed in sixty-three (42 %) of 150 children.

Results of a univariate analysis comparing hypocalcaemic with normocalcaemic children for various sociodemographic and clinical characteristics are shown in Table 1. Results of a logistic regression analysis are depicted in Table 2. The presence of clinical rickets had 6·6 times higher odds of having hypocalcaemia compared with those without rickets (95 % CI 2·54, 17·15). The odds of hypocalcaemia were 4·5 and 2·6 times higher in children with abdominal distension and sepsis, respectively.

## Discussion

Hypocalcaemia was present in about one-fourth of severely malnourished children, the prevalence being comparable between children under and over 6 months of age. The presence of clinical rickets, abdominal distension and sepsis was recognised as an independent predictor of hypocalcaemia in severely malnourished children.

Our results are consistent with those reported by Chisti *et al.*[6] A cross-sectional, descriptive study conducted in Kathmandu, Nepal, by Mishra *et al.*[25] has found that hypocalcaemia was prevalent in 46·7 % of malnourished children, which is higher than that reported by the current study. This difference in findings despite similar age groups of participants might be because of the difference in the selection of participants, in which Mishra *et al.*[25] included sixty children (aged 6–59 months) with protein energy malnutrition (PEM) (weight-for-height below the 80 % of 50th percentile of weight-for-height based on the growth chart of the National Centre of Health Statistics), while our study included children aged 1–59 months hospitalised with SAM (defined as per WHO 2013)[25]. In another study from Uganda on children aged 6–24 months[26], the prevalence of hypocalcaemia was 43·5 %. However, the participants included children with both SAM and moderate acute malnutrition (MAM). The prevalence of rickets and the cut-off used for defining hypocalcaemia (2·2 mmol/l) were higher in these children. Rickets in African settings is more likely to be due to dietary insufficiency of Ca[27–30].

We observed vitamin D deficiency in 65·3 % of severely acute malnourished children. This is much higher than the findings of a cross-sectional study by Nabeta *et al.*[26] (14·6 %). It is possible that our children might have had combinations of dietary deficiencies of Ca and vitamin D and limited sun exposure, considering that a major proportion (86 %) hailed from urban areas and 84 % were between 1 and 24 months of age (with infants and younger children less likely to be out in sunshine). These inconsistent findings between the two studies can be explained by the differences in age groups, criteria of malnutrition used for recruitment of cases, and the cut-offs used for defining vitamin D deficiency. Nabeta *et al.*[26] recruited 117 children in Uganda between the ages of 6 and 24 months with malnutrition defined as SAM (weight-for-length/height <–3 SD) or MAM (weight-for-length/height <–2 and up to –3 SD), and cut-off used was ≤20 ng/ml. Moreover, vitamin D status can be influenced by geography, climate, food production and availability, or religious and cultural practices, skin pigmentation and burden of infectious and chronic diseases in different regions[31].

The presence of clinical rickets was identified as the most significant independent predictor of hypocalcaemia in children with SAM. Rickets is supposed to be uncommon in children with malnutrition[32–34], but recent studies have reported a strong association between the two[35–37]. Severely malnourished children with clinical signs of rickets indicate a fluctuating nutritional course, with periods of infection and nutritional deprivation alternating with periods of recovery, while those without clinical signs of rickets have a chronic steady nutritional deprivation[35]. Further, it is now well known that the aetiology of nutritional rickets ranges from isolated vitamin D deficiency to isolated Ca deficiency[30,38].

Apart from nutritional rickets, the presence of abdominal distension and sepsis also contributed significantly to the predictors of hypocalcaemia in children with SAM. Abdominal distension in hypocalcaemia might indicate pot-belly abdomen, which is one of the classical findings of rickets in children[30]. In addition, a frequent observation of abdominal distension and hypocalcaemia in children with SAM indicates ileus in such children[8,9]. The current study also indicated that severely malnourished children with hypocalcaemia had significantly higher proportion of sepsis compared with normocalcaemic ones. This

https://doi.org/10.1017/S1368980020001895 Published online by Cambridge University Press

corroborates with a finding of earlier studies that there is a strong association between hypocalcaemia and sepsis[8,9]. Various other studies also postulated that severe pneumonia, gastrointestinal and ear infections are associated with vitamin D deficiency[39,40], and so with hypocalcaemia. Apart from its role in bone mineralisation, vitamin D has a vital role in regulating immune responses to infection[41].

Limitations of the current study include it being a cross-sectional hospital-based study with limited sample size and no control group. It is possible that vitamin D deficiency (and resultant hypocalcaemia) in enrolled children was just a reflection of deficiency in community rather than an accompaniment of malnutrition; however, a recent Comprehensive National Nutrition Survey[42] documented only 14 % of pre-schoolers (1–4 years) in India, and 32·5 % in Delhi to be deficient in 25-(OH)D, whereas in the current study, 65·3 % were deficient, reflecting a likely association of hypocalcaemia and vitamin D deficiency with SAM. Another limitation is a lack of measurement of ionised Ca, which may be a more accurate reflection of the physiologic Ca state. However, we had adjusted total serum Ca values for serum albumin levels; this reduces the chances of false low serum Ca levels in malnourished children due to hypoproteinaemia[18,43]. We feel that despite the limitations, the results still have clinical relevance in resource-poor settings where there is lack of facility to measure ionised Ca.

Our findings may help in decision-making regarding Ca supplements, particularly in resource-poor settings where routine estimation of serum Ca and serum 25-(OH)D is not immediately possible. We recommend routine supplementation of vitamin D in conjunction with oral Ca for a sufficient duration in severely malnourished children in view of the high prevalence of vitamin D deficiency/insufficiency in this group. The therapeutic approach recommended in the management of SAM contains vitamin D and Ca but not in sufficient quantities to take care of hypocalcaemia and vitamin D deficiency of the magnitude observed in the current study. Moreover, local preparations of therapeutic diets are often used, which usually lack these nutrients in adequate amounts. Also, the duration of administration of these diets is variable for different patients (ranging from a few days to 2–6 weeks) depending on the clinical condition and response of each child, after which we shift to home-based diets. We therefore feel that an intake of these sources for a short duration may not be sufficient enough to consistently elevate the concentrations of Ca and vitamin D. Further studies are required to establish appropriate dosages of Ca and vitamin D supplements in severely malnourished children and monitor for efficacy and safety.

## Acknowledgements

*Acknowledgement:* None. *Financial support:* The current work was supported by the Indian Council of Medical Research (ICMR), New Delhi, under MD/MS/DM/MCH thesis financial assistance programme of ICMR, Human Resource Development grant no. 3/2/June-2017/PG-Thesis-HRD(36). *Conflict of interest:* There are no conflicts of interest. *Authorship*: Conception and design: P.G.; collection and assembly of data: C.S.; review of literature, intellectual inputs: C.S., P.B., R.S.A.; data analysis and interpretation: C.S., P.G., D.S.; manuscript writing: C.S., P.G., D.S., P.B., R.S.A.; final approval of manuscript: all authors are accountable for all aspects of the work. *Ethics of human subject participation:* The current study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving research study participants were approved by the Institutional Ethics Committee–Human Research (IEC-HR) of the University College of Medical Sciences, Delhi. Written informed consent was obtained from all guardians/caregivers of children.

## References

1. World Health Organization (2013) WHO Guidelines: Updates on the Management of Severe Acute Malnutrition in Infants and Children. http://www.ncbi.nlm.nih.gov/books/NBK190328/ (accessed November 2018).
2. International Institute for Population Sciences (IIPS) (2015–2016) National Family Health Survey-4 (NFHS-4). http://rchiips.org/nfhs/pdf/NFHS4/India.pdf (accessed November 2018).
3. Halliday D (1967) Chemical composition of the whole body and individual tissues of two Jamaican children whose death resulted primarily from malnutrition. *Clin Sci* **33**, 365–370.
4. Khalil M, Kabiel A, El-Khateeb S *et al.* (1974) Plasma and red cell water and elements in protein-calorie malnutrition. *Am J Clin Nutr* **27**, 260–267.
5. Hother A-L, Girma T, Rytter MJH *et al.* (2016) Serum phosphate and magnesium in children recovering from severe acute undernutrition in Ethiopia: an observational study. *BMC Pediatr* **16**, 178.
6. Chisti MJ, Salam MA, Ashraf H *et al.* (2014) Prevalence, clinical predictors, and outcome of hypocalcaemia in severely-malnourished under-five children admitted to an urban hospital in Bangladesh: a case–control study. *J Health Popul Nutr* **32**, 270–275.
7. Juan D (1979) Hypocalcemia: differential diagnosis and mechanisms. *Arch Intern Med* **139**, 1166–1171.
8. Chisti MJ, Ahmed T, Faruque ASG *et al.* (2009) Factors associated with sclerema in infants with diarrhoeal disease: a matched case–control study. *Acta Paediatr* **98**, 873–878.
9. Rudick JH & Sheehan JP (1987) Hypomagnesemia, hypocalcemia, and toxic-shock syndrome: a case report. *Magnesium* **6**, 325–329.
10. Dalwai S, Choudhury P, Bavdekar SB *et al.* (2013) Consensus Statement of the Indian Academy of Pediatrics on integrated management of severe acute malnutrition. *Indian Pediatr* **50**, 399–404.
11. Bhatnagar S, Lodha R, Choudhury P *et al.* (2007) IAP Guidelines 2006 on hospital based management of severely malnourished children (adapted from the WHO Guidelines). *Indian Pediatr* **44**, 443–461.
12. World Health Organization (editor) (2013) *Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses*, 2nd ed., pp. 197–222. Geneva: World Health Organization.

https://doi.org/10.1017/S1368980020001895 Published online by Cambridge University Press

13. Ejaz MS & Latif N (2010) Stunting and micronutrient deficiencies in malnourished children. *J Pak Med Assoc* **60**, 543–547.
14. Raghuramulu N & Reddy V (1980) Serum 25-hydroxy-vitamin D levels in malnourished children with rickets. *Arch Dis Child* **55**, 285–287.
15. Berkley JA, Ngari M, Thitiri J *et al.* (2016) Daily co-trimoxazole prophylaxis to prevent mortality in children with complicated severe acute malnutrition: a multicentre, double-blind, randomised placebo-controlled trial. *Lancet Glob Health* **4**, e464–e473.
16. Jones KDJ, Hachmeister CU, Khasira M *et al.* (2018) Vitamin D deficiency causes rickets in an urban informal settlement in Kenya and is associated with malnutrition. *Matern Child Nutr* **14**, e12452.
17. World Health Organization (2009) Child Growth Standards and Identification of SAM. http://apps.who.int/iris/bitstream/handle/10665/44129/9789241598163_eng.pdf?sequence=1 (accessed November 2018).
18. Sava L, Pillai S, More U *et al.* (2005) Serum calcium measurement: total versus free (ionized) calcium. *Indian J Clin Biochem* **20**, 158–161.
19. Fong J & Khan A (2012) Hypocalcemia: updates in diagnosis and management for primary care. *Can Fam Physician* **58**, 158–162.
20. Sahota O (2014) Understanding vitamin D deficiency. *Age Ageing* **43**, 589–591.
21. Chisti MJ, Duke T, Robertson CF *et al.* (2012) Clinical predictors and outcome of hypoxaemia among under-five diarrhoeal children with or without pneumonia in an urban hospital, Dhaka, Bangladesh. *Trop Med Int Health* **17**, 106–111.
22. Dellinger RP, Levy MM, Rhodes A *et al.* (2013) Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med* **39**, 165–228.
23. Khadilkar A, Khadilkar V, Chinnappa J *et al.* (2017) Prevention and treatment of vitamin D and calcium deficiency in children and adolescents: Indian Academy of Pediatrics (IAP) Guidelines. *Indian Pediatr* **54**, 567–573.
24. Munns CF, Shaw N, Kiely M *et al.* (2016) Global consensus recommendations on prevention and management of nutritional rickets. *J Clin Endocrinol Metab* **101**, 394–415.
25. Mishra SK, Bastola SP & Jha B (2009) Biochemical nutritional indicators in children with protein energy malnutrition attending Kanti Children Hospital, Kathmandu, Nepal. *Kathmandu Univ Med J* **7**, 129–134.
26. Nabeta HW, Kasolo J, Kiggundu RK *et al.* (2015) Serum vitamin D status in children with protein-energy malnutrition admitted to a national referral hospital in Uganda. *BMC Res Notes* **8**, 418.
27. Edwards JK, Thiongó A, Van den Bergh R *et al.* (2014) Preventable but neglected: rickets in an informal settlement, Nairobi, Kenya. *Public Health Action* **4**, 122–127.
28. Thandrayen K & Pettifor JM (2012) Maternal vitamin D status: implications for the development of infantile nutritional rickets. *Rheum Dis Clin North Am* **38**, 61–79.
29. Hatun S, Ozkan B, Orbak Z *et al.* (2005) Vitamin D deficiency in early infancy. *J Nutr* **135**, 279–282.
30. Özkan B (2010) Nutritional rickets. *J Clin Res Pediatr Endocrinol* **2**, 137–143.
31. Prentice A, Schoenmakers I, Jones KS *et al.* (2009) Vitamin D deficiency and its health consequences in Africa. *Clin Rev Bone Miner Metab* **7**, 94–106.
32. Salimpour R (1975) Rickets in Tehran: study of 200 cases. *Arch Dis Child* **50**, 63–66.
33. Höjer B, Gebre-Medhin M, Sterky G *et al.* (1977) Combined vitamin-D deficiency rickets and protein-energy malnutrition in Ethiopian infants. *J Trop Pediatr Environ Child Health* **23**, 73–79.
34. Thirupuram S, Srivastava G & Gupta S (1973) Bone growth in protein calorie malnutrition. *Indian Pediatr* **10**, 661–666.
35. Soliman AT, Madina EH & Morsi MR (1996) Radiological, biochemical, and hormonal changes in malnourished children with rachitic manifestations. *J Trop Pediatr* **42**, 34–37.
36. Walter EA, Scariano JK, Easington CR *et al.* (1997) Rickets and protein malnutrition in northern Nigeria. *J Trop Pediatr* **43**, 98–102.
37. Lulseged S & Fitwi G (1999) Vitamin D deficiency rickets: socio-demographic and clinical risk factors in children seen at a referral hospital in Addis Ababa. *East Afr Med J* **76**, 457–461.
38. Thacher TD, Fischer PR, Tebben PJ *et al.* (2013) Increasing incidence of nutritional rickets: a population-based study in Olmsted County, Minnesota. *Mayo Clin Proc* **88**, 176–183.
39. Thornton KA, Marín C, Mora-Plazas M *et al.* (2013) Vitamin D deficiency associated with increased incidence of gastrointestinal and ear infections in school-age children. *Pediatr Infect Dis J* **32**, 585–593.
40. Haider N, Nagi AG & Khan KMA (2010) Frequency of nutritional rickets in children admitted with severe pneumonia. *J Pak Med Assoc* **60**, 729–732.
41. Lang PO & Aspinall R (2017) Vitamin D status and the host resistance to infections: what it is currently (not) understood. *Clin Ther* **39**, 930–945.
42. Ministry of Health and Family Welfare (MoHFW), Government of India, United Nations International Children's Emergency Fund and Population Council (2019) Comprehensive National Nutrition Survey (CNNS) National Report. New Delhi.
43. Kragh-Hansen U & Vorum H (1993) Quantitative analyses of the interaction between calcium ions and human serum albumin. *Clin Chem* **39**, 202–208.


https://doi.org/10.1017/S1368980020001895 Published online by Cambridge University Press