Vitamin D Deficiency and Parathyroid Response in Critically-ill Children

We read with interest the recent article in Indian Pediatrics by Shah, *et al*. [1], and have the following comments to offer:

Though the authors have excluded patients with known parathyroid disease, rickets, renal tubular acidosis, chronic kidney disease or a diagnosis of acute kidney injury at admission, about 56% children were stated to have some underlying chronic illness. One would be really interested to know the nature of these chronic illnesses, as many diseases such as chronic liver disease [2] and nephrotic syndrome [3] are known to have low vitamin D levels. The authors have also not mentioned whether any of these children with chronic diseases were on long-term medications known to affect vitamin D-calcium-parathyroid axis such as Cortisteroids for nephrotic syndrome, Rifampicin for tuberculosis, and antiepileptics for epilepsy [4]. Authors stated that 15 patients were admitted with liver disease and 24 with neurological diseases; the disease condition and/or the medication used in these children can lead to a decrease in vitamin D and calcium levels.

In this study, 'parathyroid-responder' was defined as children with serum parathyroid hormone (PTH) >65 ng/mL with 25(OH)D <20 ng/mL, and/or calcium corrected for albumin <8.5 mg/dL. But it is not clear why the authors chose to analyze children with hyperparathyroidism secondary to 25(OH)D deficiency alone, and leave out non-vitamin D-deficient children with hypocalcemia-related hyperparathyroidism.

It would have been useful to evaluate the ionized calcium (iCa) levels of these critically-ill children in addition to the total calcium adjusted for albumin. Though iCa levels are nor reported, in view of very high incidence (59%) of hypocalcemia in the study population, one would be really inquisitive in knowing whether calcium supplemention was given to the hypocalcemic children, especially to those with septic shock.

The authors mention that data regarding type of milk-product consumption by the children was recorded but the same has not been presented in the results.

We would also like to point out to few errors: the unit for serum 25-hydroxy vitamin D level used in abstract is 'µg/mL' instead of 'ng/mL'; the abstract also mentions the non-vitamin D-deficient children to be 19.8%, whereas, it should be 16.9%.

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Authors' Reply

We thank the authors for the interest in our article. Some of the methodological details and results of the study were not included in the manuscript due to the word limit. We regret the errors in the abstract of this article, and thank the readers for pointing them out.

We agree with the comment regarding possibility of low vitamin D level in children with chronic disease/ drug intake for chronic conditions. Many of the children admitted to our intensive care unit had an underlying chronic illness. These conditions were: chronic liver disease (16), congenital heart disease (14) , metabolic disorder (9), congenital malformation (6), type-1 diabetes mellitus (6), asthma (4), tuberculosis (6), HIV (4), rheumatological diseases (6), cystic fibrosis (4), primary immunodeficiency (2) and others (9).

Many of the illnesses in childhood are associated with low Vitamin D levels. If we had excluded the children admitted with underlying/ chronic illnesses like liver disease and neurological disease, we would have been left with small subset of population in our sample. As children with central nervous system infections and liver disease

contribute significantly to intensive care hospitalizations in tropical countries, we did not exclude these conditions in order to get a true picture of vitamin D status in intensive care settings.

Most of the children who were vitamin D-deficient were also deficient in calcium. One of the objectives of the study was to characterize vitamin D deficiency status in relation to parathyroid response; therefore we presented data of, only those children who were vitamin D- deficient. We agree with your comment regarding importance of iCa levels in critical illness. It was not feasible to measure iCa in all the patients in our study. Blood samples for laboratory investigations (Calcium, PTH, Vitamin D, etc) were collected at the baseline at the time of admission. Therefore, calcium supplementation in hypocalcemic patients after PICU admission would not alter the laboratory values of calcium, PTH or vitamin D. Children with hypocalcemia were managed based on the unit protocol, supported by the clinical profile.

Regarding feeding status, most of the children consumed animal milk [local dairy company (28.6%); direct milk from animal sources (24.7%)]. Seven percent of the children were on commercially available formula feeds, 11.7% were on breast feed and 28% of children were on both formula and breast feeds. Those fed on both breast feed and formula were less likely to be vitamin D deficient compared to other types of milk supplementation.

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Primary Subphrenic Abscess in Infant

A 4½-month-old girl with insignificant past history presented to us with moderate grade fever for last four 4 days. Examination showed an afebrile, hemodynamically stable infant with hepatosplenomegaly and no obvious focus of infection. Blood investigations showed anemia, and negative dengue and malaria serology; the chest *X*-ray was normal. The fever persisted despite treatment with intravenous antibiotics (Ceftriaxone and Amikacin) for 48 hours. On the fifth day of hospitalization, a repeat blood panel showed leukocytosis, and a blood culture showed methicillin-resistant coagulase negative staphylococci. An ultrasound abdomen showed a right anterior subphrenic abscess. A diagnostic laparoscopy was performed to drain 20 mL of pus from the abscess between the diaphragm and liver. The post-procedure period was uneventful, and the infant recovered completely.

The right subphrenic space lies between the right lobe of the liver and diaphragm, and is one of the potential spaces for collection of pus under the diaphragm. A subphrenic abscess is usually secondary, with the primary disease process having a direct bearing on diagnosis, treatment and prognosis. It is seen most commonly with appendicitis, following hollow viscus perforation, as postoperative sequelae or in abdominal trauma [1]. The clinical manifestations are often obscured and varied, leading to delayed diagnosis, higher morbidity and mortality. Many of the symptoms and signs together make up a thoraco-abdominal clinical complex [1]. Swinging pyrexia, persistent hiccoughs, lung findings and tenderness on palpation in right hypochondrium are commonly noted. Radiography often reveals elevated hemidiaphragm, blunted costo-diaphragmatic angles and pulmonary infiltrates or atelectasis [2]. The bacteriological profile of these abscesses include aerobic and facultative bacteria like *Escherichia coli*, group D Enterococcus and *Staphylococcus aureus*; and less commonly, anerobic organisms like Bacteroides [3].

The subphrenic abscess occurs as a primary abscess without a causal lesion in only 4% of cases [1]. The focal lesion in these cases may be primary peritonitis or remote infection with hematogenous spread. Intra-abdominal abscess should be considered early on as a differential diagnosis for any child presenting with unexplained fever, leucocytosis, or poor antibiotic response.

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