Two studies published this month in Pediatrics provide new and unique information regarding the relationship between vitamin D status and critical illnesses in children admitted to PICUs in the United States and Canada.1,2 These 2 studies, from Boston Children's Hospital and 6 PICUs in Canada, demonstrated that low vitamin D status, as reflected by a low serum 25-hydroxyvitamin D (25(OH)D) level on admission, was highly prevalent and associated with increased illness severity and generally reflected longer hospital stays and some limited biochemical evidence of lower calcium status.

Neither study clearly identifies a level of 25(OH)D associated with worse PICU outcomes, although the level of 50 nmol/L (20 ng/mL) is generally used as a cutoff level to identify vitamin D deficiency.1,2 This value is consistent with the view of the Institute of Medicine that serum 25(OH)D values >50 nmol/L are associated with an adequate vitamin D status.3,4 Furthermore, relatively few children seemed to have 25(OH)D levels <30 nmol/L, a level more commonly associated with clinical signs of rickets or severe vitamin D deficiency.

The strengths of these studies1,2 are their large sample size and the identification of clear and important clinical outcomes, including severity of illness score, length of hospital stay, and presence of septic shock associated with lower serum levels of 25(OH)D. Outcome scores, including the Pediatric Risk of Mortality III score and the Sequential Organ Failure Assessment Score, are well-validated outcome measures of illness severity and organ dysfunction. Use of such scores therefore adds reliability to the relation with low vitamin D levels.5 The availability of repeated measures of vitamin D in some subjects is also valuable in considering the time-dependent and illness-dependent changes in health and their relationship with vitamin D status.

Both studies included similar numbers of patients receiving ventilatory support, but there are some differences, particularly the percentage of medical versus surgical patients; 38.4% of patients in the study by Madden et al2 had a surgical diagnosis, whereas 70% of patients in the study by McNally et al1 had a surgical diagnosis. Neither study found an association between vitamin D status and medical or surgical diagnosis; only the study by Madden et al found a significant association between low vitamin D levels and the presence of septic shock as assessed by using the Sequential Organ Failure Assessment Score. These data are limited in that uncontrollable variables, such as fluid resuscitation before and after hospitalization, cannot and were not fully controlled for in the analysis. The large diversity in illness types and care practices makes interpretation of some outcomes, including length of hospital stay, more uncertain but do point to a possibility of a biological relationship.
Only the study by McNally et al 1 assessed the degree of malnutrition on admission by using the weight-for-age ratio. They found that malnutrition was not associated with vitamin D deficiency. However, additional data should evaluate malnutrition by assessing height z scores and weight-for-height data by using the new World Health Organization curves.5,7 It is likely that a severely or chronically malnourished child will have lower levels of vitamins and minerals.8 A recent study in 35 children’s hospitals in the United States found that from a total of 44,693 admissions to the PICU, 52.1% had a chronic diagnosis, underscoring the importance of the presence of a chronic condition in relation to outcomes. Neither study showed a significant association between the presence of medical history or preexisting illness and a deficient vitamin D state. Prospective interventional studies should include stratifications according to degree of malnutrition and presence of a chronic diagnosis.

For pediatric caregivers, the real questions posed by these studies are: (1) What do they mean for the care of critically ill children; and (2) How do we move forward with further research to understand the mechanisms and interventions that might improve our care of critically ill children?

In terms of interpreting these data in clinical practice, they can be understood as supporting programs and interventions designed to prevent vitamin D deficiency. What exactly this might entail is controversial, but at a minimum, comprehensive efforts to ensure that children receive at least the recommended intake of vitamin D (400 IU/day for infants, 600 IU/day for children aged >1 year) should be developed and emphasized.3,4,9 Current intakes of vitamin D are far below the recommended amounts.3 Whether these studies mean that all children admitted to a PICU should have serum 25(OH)D levels measured remains unanswered by the data provided in these studies. Targeted assessments for those at highest risk might be considered but would likely be difficult to implement in a PICU setting.

With regard to research, the authors of both articles recognize the need for controlled intervention trials.1,2 However, in the case of critically ill children, especially those who have sepsis and other illnesses such that enteral nutrition is difficult or impossible, designed research protocols to evaluate interventions will be difficult and expensive and certainly require collaboration among multiple PICUs. As such, it may be best to consider carefully the role of animal models of pediatric critical illnesses and smaller studies of well-identified disease processes rather than attempting to conduct trials of all patients admitted to a PICU.

Regardless, these studies1,2 move forward and to the front concerns regarding vitamin D status in critically ill children. They do not yet tell us the best way of assessing or treating low serum 25(OH)D levels in a PICU setting but point us to a program of public health and research on this topic, with clear identification of final outcomes and their clinical significance, focusing on both efficacy and safety of any proposed interventions.
Vitamin D Deficiency in Critically Ill Children: A Roadmap to Interventional Research

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