

Is quarterly bolus vitamin D₃ supplementation adequate to prevent childhood pneumonia?

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Already in 1922, based on the observation of 64 malnourished Viennese infants, Chick and colleagues postulated a factor present in both cod-liver oil and sunlight that is able to cure rickets (1). This factor later turned out to be vitamin D. Today, it is evident that the actions of the active vitamin D metabolite, i.e. 1,25-dihydroxyvitamin D₃ (calcitriol), go far beyond bone health, including diverse actions on the immune system as recently reviewed (2). However, in children, evidence on its non-skeletal actions is lacking. In a recent community-based randomized controlled trial published in *The Lancet*, Manaseki-Holland and colleagues investigated whether treatment with vitamin D₃ (cholecalciferol) reduces the incidence and severity of pneumonia in infants in Kabul, Afghanistan, where vitamin D deficiency is highly prevalent and pneumonia is one of the leading causes of mortality in children (3). 3,046 infants aged 1 to 11 months were given either oral vitamin D₃ at a quarterly dose of 100.000 International Units or placebo over 18 months. The children were assessed every 2 weeks for clinical signs of pneumonia such as coughing, chest in-drawing, increased respiratory rate and body temperature and, if present, were admitted to the hospital for radiographic confirmation and treatment. In this study, the incidence of the first episode of pneumonia confirmed by chest radiograph did not differ between the two treatment groups (incidence rate ratio 1.06, 95% CI, 0.89-1.27). Unexpectedly, repeated episodes of pneumonia occurred significantly more often in children treated with vitamin D₃ (incidence rate ratio 1.68, 95% CI, 1.28-2.21).

One possible explanation for these findings might involve the treatment strategy used in this study, i.e.

quarterly boluses of 100.000 International Units of vitamin D₃. This led to a rapid increase in serum 25-hydroxyvitamin D₃ (calcidiol) levels immediately after the treatment. Subsequently, 25-hydroxyvitamin D₃ levels declined continuously and returned to baseline levels after approximately 3 to 4 months. It was suggested that strong variations in serum 25-hydroxyvitamin D₃ levels are harmful for adults and might explain the unusual U-shaped association of 25-hydroxyvitamin D₃ levels with increased risk for e.g., prostate cancer or all-cause mortality, as reported by Durup and colleagues (4,5). Moreover, the high dose might have triggered a short-term increase in expression of the renal 24-hydroxylase, the enzyme that catabolizes both 25-hydroxyvitamin D₃ and 1,25-dihydroxyvitamin D₃, leading to an early decrease of the vitamin D metabolites, thereby impeding the infection preventing effects. It is unknown also, whether these strong variations in 25-hydroxyvitamin D₃ levels influence the immune system in a way that is counterproductive for the clearance of infections, bearing in mind the pleiotropic immunomodulatory actions of the active vitamin D₃. On the one hand, the active vitamin D₃ boosts the innate immune system e.g., by up-regulating the expression of antimicrobial peptides such as cathelicidin, which is important for the clearance of pathogens as demonstrated for *Mycobacterium tuberculosis* (6). On the other hand, it exerts suppressive effects on the adaptive immune system. It shifts the T-cell response away from an inflammatory to a more regulatory T-helper cell phenotype. In a healthy population, monthly therapy with 140.000 International Units of vitamin D₃ over three months significantly increased the amount of

peripheral regulatory T-cells compared with placebo (7). However, whether this goes along with an impaired host defense, remains to be investigated. Guidelines of the American Academy of Pediatrics on vitamin D intake recommend 400 International Units of vitamin D₃ for all infants and children starting within days of birth (8). Administering lower doses of vitamin D₃ at shorter intervals raises and maintains 25-hydroxyvitamin D₃ levels in the optimal range (9), thereby possibly inducing different immunomodulatory effects. Even though not demonstrating a preventive effect of vitamin D₃ on childhood pneumonia, this study provides valuable information for the design of future clinical trials.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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