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Vitamin D, Covid-19 and Children

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The multi-organ and systemic importance of Vitamin D is increasingly recognised[1]. Low vitamin D is associated with morbidity in children and adults[2]. In addition, Vitamin D3 appears to decrease mortality in elderly people living independently or in institutional care[3]. Increasing use of sunblock and prevention of melanoma have resulted in lower levels of vitamin D especially on countries of higher latitude in the winter months[4,5]. This has resulted in public health programmes for vitamin D supplementation in newborns and children[6].

There has been a well-established link between respiratory illness and vitamin D deficiency from TB to respiratory syncytial virus[7]. Children in interventional studies of vitamin D supplementation had reduced incidence of influenza a infections and other acute respiratory infections[8,9]. However Agilpay et al. found no difference in viral respiratory illness in 703 healthy children randomised to either conventional (400 IU/d) or high-dose (2000 IU/d) of vitamin D oral supplementation[10]. In contrast, a systematic review of children with a history of asthma demonstrated that vitamin D supplementation may prevent childhood acute respiratory infections[11]. There is a high prevalence of low Vitamin D levels [25OHD (<30 nmol/L)] in preterm infants and an association between vitamin D status and acute respiratory morbidity in preterm infants after birth[12]. In preterm infants vitamin D deficiency was also associated with increased resuscitation requirement at delivery, increased oxygen requirement, increased duration of intermittent positive-pressure ventilation during resuscitation at delivery and greater need for assisted ventilation. Vitamin D insufficiency is common in children and adolescence with key determinants being season, ethnicity, time outdoors and supplementation[4].

In acute illness vitamin D is frequently low and may be an epiphenomenon secondary to acute inflammation. There is debate about the value of giving mega doses of vitamin D during acute sepsis or critical illness. The VITdAL-ICU trial is the largest published trial to date in adults in ICU regarding vitamin D supplementation and showed no benefits on mortality on primary analysis but improvement suggested in those who were severely deficient (<12 ng/mL)(13)and further information is expected in 2023 from the VITDALIZE Study (NCT03188796)[14,15]. Children in Paediatric intensive care had lower vitamin D levels in suspected sepsis compared to controls[16] and inadequate vitamin D levels were associated with confirmed sepsis and poor outcomes[16]. However vitamin D status may not be accurately assessed by a single sample during critical illness due to several confounders such as albumin levels, binding proteins and haemodilution during resuscitation and free vitamin D metabolites[17].

High doses of vitamin D are not uniformly immunosuppressive *in vitro*. In preterm infants, pre but not post treatment with vitamin D before an *in vitro* endotoxin challenge reversed immune dysfunction[18]. Vitamin D (1,25OHD) may enhance neonatal neutrophil function in the presence of infection thus overcoming endotoxin tolerance which may be beneficial in sepsis. The potential role of vitamin D status in reducing secondary bacterial infections and loss of life

in pandemic influenza requires further evaluation especially in view of the lack of pharmaceutical interventions[19]. There are several proposed mechanisms for the anti-inflammatory and immunomodulatory properties of Vitamin D[20]. Cathelicidin (LL-37 or hCAP-18) is upregulated by Vitamin D which has both and antiendotoxin and antimicrobial properties. Cathelicidin levels correlated well with clinical outcomes in children with RSV bronchiolitis (n=82) and may be a relevant biomarker even if vitamin D levels are normal[21]. Vitamin D also reduces the production of proinflammatory cytokines, which could also explain some of the benefit of vitamin D since Covid-19 infection gives rise to a cytokine storm.

Therefore in agreement with the paper by McCartney[22] in this journal we suggest that ensuring baseline vitamin D sufficiency is appropriate but acute large doses of vitamin D have not been proven to be beneficial in critical illness.

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