

cultures. Up to 22% of patients intubated for >48 h had evidence of virus recoverable from tracheobronchial secretions in one study.<sup>12</sup> Whether viruses in VAP contribute to an actual pneumonic process remains unclear.

Very interestingly, IL-1 $\beta$  and IL-8 concentrations were similar in the patients with VAP with typical pathogenic microbes and those with microbes usually considered to be less pathogenic, for example coagulase-negative staphylococci or *Candida* species. It is not clear how many of these patients had simultaneous positive cultures for other microbes. If these are the sole isolates, the cytokine data suggest that these microbes do in fact induce an inflammatory response: by extrapolation, therefore, they may require treatment. Isolated *Candida* cultures, for example, are not routinely treated in clinical practice. This article raises the possibility that such "non-pathogenic" microbes are in fact true pathogens in the setting of VAP.

Finally, the use of a bronchoscopically derived biomarker for clinical practice presents certain practical considerations. BAL is labour intense, and cannot be performed safely in all ICU patients (and as in the methods described, the sicker patients with higher ventilatory support requirements were excluded). This study was carried out by one investigator across two clinical sites. Highly precise methods were used to perform BAL by the investigator, and it is unlikely that this methodological rigour could be easily reproduced by multiple clinicians in different ICUs in clinical practice. Although the authors have previously demonstrated that BAL-based microbiological techniques can improve the diagnosis of VAP<sup>8</sup> there remains widespread high variability

in the use of bronchoscopic sampling across ICUs throughout Europe.<sup>19</sup>

Nevertheless this study adds significantly to the diagnosis and understanding of VAP. The utility of these biomarkers for VAP in BAL now requires further evaluation in larger multicentre studies. It will be particularly interesting to see if the application of biomarker-based decisions could safely reduce antibiotic prescription, and whether biomarker measurements help our understanding of the role of atypical or "non-pathogenic" microbes in VAP.

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# Is vitamin D deficiency important in the natural history of COPD?

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Vitamin D consists of a group of fat-soluble prohormones, the most important of which are vitamin D2 and D3, with measurement of 25-hydroxyvitamin D (25-OHD) closely representing a person's vitamin D2 and D3 status. D2 (ergo-

calciferol) is plant and fungal derived, while vitamin D3 (cholecalciferol) is made from 7-dehydrocholesterol in the skin. This conversion of 7-dehydrocholesterol to previtamin D3 is governed by both the intensity and appropriate wavelength of the ultraviolet (UV) B irradiation reaching 7-dehydrocholesterol. Adequate amounts of vitamin D3 can be made in the skin after only 10–15 min of sun exposure at least twice a week without sunscreen. However, with longer exposure to UVB rays, equilibrium is achieved in the skin and the vitamin degrades as fast as it is generated. Serum concentrations of vitamin D have been found to vary with age, race, sex,

season and geographic location, and subclinical deficiency is common, particularly in temperate climates.<sup>1</sup>

Once in its physiologically active form vitamin D is released into the circulation, binds to a carrier protein in the plasma (vitamin D-binding protein (DBP)) and is transported to various target organs. The hormonally active form of vitamin D mediates its biological effects by binding to the vitamin D receptor (VDR), which is principally located in the nuclei of target cells. This VDR is constitutively expressed in monocytes, activated macrophages, dendritic cells, natural killer cells, and T and B cells. Activation has potent anti-proliferative, prodifferentiative and immunomodulatory functions; both immune enhancing and immunosuppressive.<sup>2</sup> It is these immunomodulatory properties of vitamin D that have particularly attracted interest in recent years with regards to chronic and autoimmune diseases and susceptibility to infection.

Deficiency in vitamin D results from a number of causes, including insufficient intake coupled with inadequate sunlight exposure, from disorders that limit its absorption, hereditary disorders and conditions that impair conversion into active metabolites. For a long time it has been known that deficiency leads to rickets, osteomalacia and osteoporosis, but more recently it has been linked with colon cancer, breast cancer, higher risk of heart attack in men, and an increased risk of infections, for example influenza, tuberculosis (TB) and pneumonia.<sup>3</sup> It has even been proposed that in autoimmune disorders vitamin D deficiency arises from chronic infection with intracellular bacteria that dysregulate vitamin D metabolism by causing VDR dysfunction. This VDR dysfunction is thought to cause a decline in innate immune function that increases susceptibility to additional infections contributing to disease progression.<sup>4</sup>

However, what actually constitutes the degree of vitamin D deficiency, particularly in the context of its immunomodulatory properties, is highly debated. In terms of calcaemic effects, levels <50 nmol/l are probably deficient,<sup>3–5</sup> whereas levels may need to be even lower for parathyroid insufficiency. With regards to the immunomodulatory mechanisms of vitamin D it has even been suggested that levels >100 nmol/l are needed for optimal immune functioning.

So does vitamin D deficiency have a role in chronic obstructive pulmonary disease (COPD)? In this issue of *Thorax* (see page

215), Janssens and colleagues report that vitamin D deficiency is more common in patients with COPD, that this deficiency correlates with forced expiratory volume in 1 s (FEV<sub>1</sub>) and that vitamin D levels decrease with increasing disease severity.<sup>6</sup> They have defined deficiency in COPD as levels <20 ng/ml (conversion factor 2.5 for nmol/l). A strong relationship has been shown previously between pulmonary function and serum vitamin D levels independently of a diagnosis of COPD,<sup>7</sup> with deficiency associated with lower FEV<sub>1</sub>. It is difficult to establish the cause and effect in this situation, particularly within the COPD population.

Maternal vitamin D in pregnancy has been associated with asthma symptoms in childhood,<sup>8–9</sup> and prenatal vitamin D deficiency is thought to affect fetal lung and immune system development. Thus it is possible that vitamin D deficiency early on in life predisposes individuals to a lower FEV<sub>1</sub>. Studies in asthma linking low vitamin D levels with disease severity have postulated that the relationship may be secondary to diet and time spent indoors, which in themselves are influenced by a diagnosis of asthma.<sup>10</sup> This is also likely to be important in COPD; we know that patients with more severe COPD spend less time outdoors<sup>11</sup> and these patients are therefore less likely to be exposed to sunlight and subsequently have lower vitamin D levels. So is vitamin D deficiency just a marker of disease severity rather than a contributing factor? Surely if this is all there is to it, patients with COPD living in the tropics should have milder disease and fewer exacerbations.

The authors also report that genetic variants in the vitamin D-binding gene correlate significantly with vitamin D levels, and suggest that individuals with COPD carrying two T alleles of the rs7041 variant are at particularly high risk for vitamin D deficiency. Other genetic variants in the vitamin D pathway have also been associated with COPD. A single nucleotide polymorphism (SNP) in the DBP has been shown to be protective for COPD,<sup>12</sup> and some of the SNPs in the DBP influence circulating vitamin D levels.<sup>13</sup> Many polymorphisms also exist in the VDR gene, and the influence of these polymorphisms on VDR protein function may influence immunomodulatory responses.<sup>14</sup> To date no study has found a link with VDR polymorphisms and airway infection in COPD, although these polymorphisms have been linked with TB. *FokI* common variants and *BsmI* poly-

morphisms have been associated with muscle strength in COPD.<sup>15</sup>

Perhaps vitamin D deficiency in COPD is more important with relation to exacerbation risk, and this is how it influences disease severity. We know that exacerbations increase the rate of FEV<sub>1</sub> decline,<sup>16</sup> so it is possible that those with lower vitamin D levels have more exacerbations and subsequently worse disease. Certainly data are available suggesting that the seasonality of influenza (and possibly other viruses) is related to sunlight exposure and consequently vitamin D levels.<sup>17</sup> Viral host defence is complex, involving both innate and acquired immunity; however, we may be closer to establishing markers of viral COPD exacerbations.<sup>18</sup> Vitamin D modulates macrophage response by preventing the release of too many cytokines and chemokines,<sup>19–20</sup> and it also prevents macrophage maturation.<sup>21–22</sup> Multiple studies have linked vitamin D deficiency with TB,<sup>23–25</sup> though supplementation studies have shown mixed results.<sup>26–27</sup> Several studies have also linked VDR polymorphisms and infection. A study in young Canadian children found the *FokI* polymorphism to be strongly associated with respiratory syncytial virus (RSV) bronchiolitis.<sup>28</sup> Although the f allele encodes a less active VDR and may affect the host's ability to use vitamin D for antimicrobial activities or inflammatory regulation, it has been postulated that higher circulating vitamin D levels could overcome this hypofunctionality. In fact there are several mechanisms by which activated vitamin D binding to the VDR could modulate viral lower respiratory tract disease, including downregulation of the Toll-like receptor 4<sup>29</sup> to which RSV binds, suppression of T cell proliferation,<sup>30</sup> tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) synthesis<sup>29</sup> or stimulation of the production of an antimicrobial host protein.<sup>31</sup>

Therefore, increasing vitamin D levels into an "optimal range" in COPD may be of benefit on several levels; it may reduce bacterial load at exacerbation and airway bacterial colonisation, influence susceptibility to virus infection or even reduce the rate of FEV<sub>1</sub> decline. Certainly as the authors of this article suggest, the next step in establishing the importance of vitamin D deficiency in COPD is to study supplementation in adequately powered clinical trials using relevant clinical outcomes. However, there is much still to be learnt about the role of vitamin D in COPD, and the mechanisms by which increasing vitamin D levels into the normal range would influence the natural

history of COPD is far from being determined.

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# ECMO in adults for severe respiratory failure finally comes of age: just in time?

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The idea of employing cardiopulmonary bypass technology as a means of oxygenating (extracorporeal membrane oxygenation (ECMO)) or removing carbon dioxide (ECCO<sub>2</sub>R) in patients with acute respira-

tory failure (ARF) was first assessed in randomised controlled trials in the 1970s and 1980s.<sup>1 2</sup> Poor rates of survival and major complications, particularly massive haemorrhage, led to most intensivists believing that ECMO was inappropriate in adults. A small number of centres worldwide—including that in Leicester, UK—continued to refine the use of ECMO in small numbers of adult patients whom it proved impossible to oxygenate by conventional means. Following the publi-

cation of their case series with improved results,<sup>3</sup> Peek and colleagues embarked upon a randomised controlled trial of conventional ventilation or ECMO in patients with severe ARF (CESAR), the results of which have just been reported.<sup>4</sup>

Patients (n=766) were screened for inclusion over a 5-year period and those with potentially reversible severe ARF (defined as a Murray score >3 or uncontrolled hypercapnia (pH <7.20); n=188) were entered in the trial. Many had multiorgan failure. The mean PaO<sub>2</sub>/FIO<sub>2</sub> ratio at study entry was 10 kPa, with a positive end-expiratory pressure of 14 cm H<sub>2</sub>O. Exclusion criteria included irreversible disease, the receipt of high-pressure high-inspired oxygen ventilation for >7 days and contraindications to anticoagulation. Patients were randomised to receive conventional treatment at the referring hospital or an approved tertiary centre where they received mechanical ventilation alone (which could include

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