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

Very interestingly, IL-1 β 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 VAP⁸ there remains widespread high variability

in the use of bronchoscopic sampling across ICUs throughout Europe.¹⁹

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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REFERENCES

1. Ibrahim EH, Tracy L, Hill C, *et al.* The occurrence of ventilator-associated pneumonia in a community hospital: risk factors and clinical outcomes. *Chest* 2001;**120**:555–61.
2. Heyland DK, Cook DJ, Griffith L, *et al.* The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. *Am J Respir Crit Care Med* 1999;**159**:1249–56.
3. American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;**171**:388–416.
4. Fabregas N, Ewig S, Torres A, *et al.* Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. *Thorax* 1999;**54**:867–73.
5. Luyt CE, Chastre J, Fagon JY. Value of the clinical pulmonary infection score for the identification and management of ventilator-associated pneumonia. *Intensive Care Med* 2004;**30**:844–52.
6. Miller PR, Johnson JCI, Karchmer T, *et al.* National nosocomial infection surveillance system: from benchmark to bedside in trauma patients. *J Trauma* 2006;**60**:98–103.
7. Rea-Neto A, Youssef NC, Tuche F, *et al.* Diagnosis of ventilator-associated pneumonia: a systematic review of the literature. *Crit Care* 2008;**12**:R56.
8. Conway-Morris A, Kefala K, Simpson AJ, *et al.* Evaluation of the effect of diagnostic methodology on the reported incidence of ventilator-associated pneumonia. *Thorax* 2009;**64**:516–22.
9. Souweine B, Veber B, Bedos JP, *et al.* Diagnostic accuracy of protected specimen brush and bronchoalveolar lavage in nosocomial pneumonia: impact of previous antimicrobial treatments. *Crit Care Med* 1998;**26**:236–44.
10. Baker AM, Bowton DL, Haponik EF. Decision making in nosocomial pneumonia: an analytic approach to the interpretation of quantitative bronchoscopic cultures. *Chest* 1995;**107**:85–95.
11. Robert R, Grollier G, Frat JP, *et al.* Colonization of lower respiratory tract with anaerobic bacteria in mechanically ventilated patients. *Intensive Care Med* 2003;**29**:1062–8.
12. Daubin C, Parienti JJ, Vincent S, *et al.* Epidemiology and clinical outcome of virus-positive respiratory samples in ventilated patients: a prospective cohort study. *Crit Care* 2006;**10**:R142.
13. Delisle MS, Williamson DR, Perreault MM, *et al.* The clinical significance of *Candida* colonization of respiratory tract secretions in critically ill patients. *J Crit Care* 2008;**23**:11–17.
14. Browne G, Troughton J, McMullan R, *et al.* Comparison between mortality and airway colonization vs. noncolonization with *Candida* species in critically ill adults. *J Crit Care* 2009;**24**:155.
15. Conway Morris A, Kefala K, Wilkinson TS, *et al.* Diagnostic importance of pulmonary interleukin-1 β and interleukin-8 in ventilator-associated pneumonia. *Thorax* 2010;**65**:201–7.
16. <<http://helics.univ-lyon1.fr/home.htm>> (accessed 31 Oct 2009).
17. Health Protection Agency. Standard operating procedure, investigation of bronchoalveolar lavage and associated samples. Version 5.1. *Standards Unit, Evaluation and Standards Laboratory, Specialist and Reference Microbiology Division, Health Protection Agency*. Issued 2/6/2003.
18. Horonenko G, Hoyt JC, Robbins RA, *et al.* Soluble triggering receptor expressed on myeloid cell-1 is increased in patients with ventilator-associated pneumonia: a preliminary report. *Chest* 2007;**132**:58–63.
19. Koulenti D, Lisboa T, Brun-Buisson C, *et al.* Spectrum of practice in the diagnosis of nosocomial pneumonia in patients requiring mechanical ventilation in European intensive care units. *Crit Care Med* 2009;**37**:2360–8.

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

J K Quint, J A Wedzicha

Academic Unit of Respiratory Medicine, University College London, UK

Correspondence to Dr JK Quint, University College London, Department of Academic Respiratory Medicine, Royal Free Hospital, Rowland Hill Street, London NW3 2QG, UK; j.quint@medsch.ucl.ac.uk

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.¹

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.² 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.³ 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.⁴

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,^{3–5} 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 (FEV₁) and that vitamin D levels decrease with increasing disease severity.⁶ 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,⁷ with deficiency associated with lower FEV₁. 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,^{8–9} 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 FEV₁. 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.¹⁰ This is also likely to be important in COPD; we know that patients with more severe COPD spend less time outdoors¹¹ 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,¹² and some of the SNPs in the DBP influence circulating vitamin D levels.¹³ Many polymorphisms also exist in the VDR gene, and the influence of these polymorphisms on VDR protein function may influence immunomodulatory responses.¹⁴ 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.¹⁵

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 FEV₁ decline,¹⁶ 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.¹⁷ Viral host defence is complex, involving both innate and acquired immunity; however, we may be closer to establishing markers of viral COPD exacerbations.¹⁸ Vitamin D modulates macrophage response by preventing the release of too many cytokines and chemokines,^{19–20} and it also prevents macrophage maturation.^{21–22} Multiple studies have linked vitamin D deficiency with TB,^{23–25} though supplementation studies have shown mixed results.^{26–27} 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.²⁸ 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 4²⁹ to which RSV binds, suppression of T cell proliferation,³⁰ tumour necrosis factor α (TNF α) synthesis²⁹ or stimulation of the production of an antimicrobial host protein.³¹

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 FEV₁ 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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REFERENCES

- Janssens W, Lehouck A, Carremans C, *et al.* Vitamin D beyond bones in chronic obstructive pulmonary disease: time to act. *Am J Respir Crit Care Med* 2009;**179**:630–6.
- Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol* 2008;**8**:685–98.
- Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;**357**:266–81.
- Waterhouse JC, Perez TH, Albert PJ. Reversing bacteria-induced vitamin D receptor dysfunction is key to autoimmune disease. *Ann NY Acad Sci* 2009;**1173**:757–65.
- Norman AW, Bouillon R, Whiting SJ, *et al.* 13th Workshop consensus for vitamin D nutritional guidelines. *J Steroid Biochem Mol Biol* 2007;**103**:204–5.
- Janssens W, Bouillon R, Claes B, *et al.* Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. *Thorax* 2010;**65**:215–20.
- Black PN, Scragg R. Relationship between serum 25-hydroxyvitamin D and pulmonary function in the third national health and nutrition examination survey. *Chest* 2005;**128**:3792–8.
- Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, *et al.* Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. *Am J Clin Nutr* 2007;**85**:788–95.
- Hyppönen E, Sovio E, Wjst M, *et al.* Infant vitamin D supplementation and allergic conditions in adulthood: Northern Finland birth cohort 1966. *Ann NY Acad Sci* 2004;**1037**:84–95.
- Brehm JM, Celedón JC, Soto-Quiros ME, *et al.* Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med* 2009;**179**:765–71.
- Donaldson GC, Wilkinson TMA, Hurst JR, *et al.* Exacerbations and time spent outdoors in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;**171**:446–52.
- Schellenberg D, Pare PD, Weir TD, *et al.* Vitamin D binding protein variants and the risk of COPD. *Am J Respir Crit Care Med* 1998;**157**:957–61.
- Lauridsen AL, Vestergaard P, Hermann AP, *et al.* Plasma concentrations of 25-hydroxy-vitamin D and 1,25-dihydroxy-vitamin D are related to the phenotype of Gc (vitamin D-binding protein): a cross-sectional study on 595 early postmenopausal women. *Calcif Tissue Int* 2005;**77**:15–22.
- Uitterlinden AG, Fang Y, Van Meurs JB, *et al.* Genetics and biology of vitamin D receptor polymorphisms. *Gene* 2004;**338**:143–56.
- Hopkinson NS, Li KW, Kehoe A, *et al.* Vitamin D receptor genotypes influence quadriceps strength in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2008;**87**:385–90.
- Donaldson GC, Seemungal TAR, Bhowmik A, *et al.* Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;**57**:847–52.
- Hope-Simpson RE. The role of season in the epidemiology of influenza. *J Hyg (Lond)* 1981;**86**:35–47.
- Quint JK, Donaldson GC, Goldring JJP, *et al.* Serum IP-10 as a biomarker of human rhinovirus infection at exacerbation of COPD. *Chest*. Published Online First: 16 October 2009. doi:10.1378/chest.09.1541.
- Hewison M, Zehnder D, Chakraverty R, *et al.* Vitamin D and barrier function: a novel role for extra-renal 1 alpha-hydroxylase. *Mol Cell Endocrinol* 2004;**215**:31–8.
- Helming L, Böse J, Ehrchen J, *et al.* 1alpha,25-Dihydroxyvitamin D3 is a potent suppressor of interferon gamma-mediated macrophage activation. *Blood* 2005;**106**:4351–8.
- Abu-Amer Y, Bar-Shavit Z. Impaired bone marrow-derived macrophage differentiation in vitamin D deficiency. *Cell Immunol* 1993;**151**:356–68.
- Cohen MS, Mesler DE, Snipes RG, *et al.* 1,25-Dihydroxyvitamin D3 activates secretion of hydrogen peroxide by human monocytes. *J Immunol* 1986;**136**:1049–53.
- Grange JM, Davies PD, Brown RC, *et al.* A study of vitamin D levels in Indonesian patients with untreated pulmonary tuberculosis. *Tubercle* 1985;**66**:187–91.
- Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. *Int J Epidemiol* 2008;**37**:113–19.
- Gibney KB, MacGregor L, Leder K, *et al.* Vitamin D deficiency is associated with tuberculosis and latent tuberculosis infection in immigrants from Sub-Saharan Africa. *Clin Infect Dis* 2008;**46**:443–6.
- Martineau AR, Wilkinson RJ, Wilkinson KA, *et al.* A single dose of vitamin D enhances immunity to mycobacteria. *Am J Respir Crit Care Med* 2007;**176**:208–13.
- Wejse C, Gomes VF, Rabna P, *et al.* Vitamin D as supplementary treatment for tuberculosis: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2009;**179**:843–50.
- Roth DE, Jones AB, Prosser C, *et al.* Vitamin D receptor polymorphisms and the risk of acute lower respiratory tract infection in early childhood. *J Infect Dis* 2008;**197**:676–80.
- Sadeghi K, Wessner B, Laggner U, *et al.* Vitamin D3 down-regulates monocyte TLR expression and triggers hyporesponsiveness to pathogen associated molecular patterns. *Eur J Immunol* 2006;**36**:361–70.
- Bhalla AK, Amento EP, Krane SM. Differential effects of 1,25 dihydroxyvitamin D3 on human lymphocytes and monocyte/macrophages: inhibition of interleukin 2 and augmentation of interleukin1 production. *Cell Immunol* 1986;**98**:311–22.
- Liu PT, Stenger S, Li H, *et al.* Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* 2006;**311**:1770–3.

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

S J Finney, J J Cordingley, M J D Griffiths, T W Evans

The idea of employing cardiopulmonary bypass technology as a means of oxygenating (extracorporeal membrane oxygenation (ECMO)) or removing carbon dioxide (ECCO₂R) in patients with acute respira-

tory failure (ARF) was first assessed in randomised controlled trials in the 1970s and 1980s.^{1 2} 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,³ 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.⁴

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 PaO₂/FIO₂ ratio at study entry was 10 kPa, with a positive end-expiratory pressure of 14 cm H₂O. 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

Adult Intensive Care Unit, Royal Brompton Hospital, London, UK

Correspondence to Professor T W Evans, Adult Intensive Care Unit, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK; t.evans@rbh.nthames.nhs.uk