Commentary

From bench to bedside: bacterial growth and cytokines

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Abstract

The recognition that neutrophils, macrophages, and other components of the inflammatory cascade participate in the generation and progression of acute lung injury/acute respiratory distress syndrome has resulted in the use of anti-inflammatory agents in an attempt to attenuate this inflammatory response and to prevent further progression of the acute lung injury. The recent finding that cytokines, in part mediators of this 'overwhelming' inflammatory reaction, may also stimulate bacterial growth, impair bacterial clearance, and promote the subsequent development of nosocomial infections may have important implications to the management of the acute lung injury/acute respiratory distress syndrome patient.

Keywords acute respiratory distress syndrome, bacterial growth, cytokines infection, inflammation

On page 24 of this issue of *Critical Care*, Meduri introduces a new layer of complexity to our understanding of the inflammatory response in acute respiratory distress syndrome (ARDS). He postulates that cytokines secreted by the host during ARDS may favor the growth of some strains of bacteria and consequently explain the association between exaggerated and protracted systemic inflammation and the development of nosocomial infections [1]. Evidence for this novel theory comes from *in vitro* studies evaluating the extracellular and intracellular responses of clinically relevant bacterial species to graded concentrations of pro-inflammatory cytokines [2]. These studies demonstrate a U-shaped bacterial growth response curve. Bacterial growth was enhanced at both extremes of this curve, suggesting that insufficient or dysregulated inflammation may play an active role in stimulating bacterial growth and/or impairment of bacterial clearance, with the subsequent development of nosocomial infections. This new finding has important implications for our understanding and management of patients with ARDS.

Immune response and acute lung injury/ARDS

Over the past two decades, the recognition that neutrophils, macrophages, and other components of the inflammatory cascade participate in the generation and progression of acute lung injury (ALI) and ARDS has resulted in the use of anti-inflammatory agents as pharmacological probes to define this syndrome. Furthermore, preclinical models of endotoxin-induced sepsis demonstrated a survival benefit if pro-inflammatory cytokines were neutralized [3], leading to a number of studies in which this therapy was used in patients with ARDS. The U-shaped bacterial growth curve may be a partial explanation for the lack of efficacy of these trials as decreasing cytokine activity may be beneficial, or may be harmful, depending on the specific location on the dose response curve.

For an effective host response to be mounted against infection, the cellular components of the innate and acquired immune system need bidirectional communication. Cytokines are an important group of molecules through which this

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; NF-κB = nuclear factor-κB.

process is initiated. The interaction between cytokines and bacteria may be an important factor in the development of organ injury and death from severe infections, although numerous host and local factors, including inflammatory cells, profoundly influence the role of a specific cytokine. It has recently been proposed that patients with sepsis or a systemic inflammatory response have an 'immunoparalysis' and are, in fact, immunosuppressed [4,5].

The use of growth factors or cytokines to augment the host response to infection has been proposed in the critically ill. A small preclinical trial with granulocyte colony stimulating factor showed favorable mortality results in patients with community acquired pneumonia and sepsis [6]. Although a recent phase III trial did not detect a mortality difference between the treatment and the placebo group in a *post hoc* analysis, Nelson and colleagues [7] documented faster radiological resolution of pneumonias, which was associated with a decreased incidence of ARDS. Further evidence for the role of augmentative cytokine therapy comes from clinical data using interferon to upregulate HLA-DR expression and consequently increase the lipopolysaccharide-induced tumor necrosis factor-α responses *ex vivo*, and from improved clinical outcome in eight out of nine septic patients [4].

In contrast, agents that block tumor necrosis factor-α, interleukin-1, and endotoxin have been shown to attenuate nuclear factor-κB (NF-κB) activation, inflammation, and organ dysfunction. However, no agent has been shown to be efficacious in human studies [8]. These studies, however, did not look at the incidence of nosocomial pneumonia as an outcome in patients with ARDS. From a biological standpoint, it may be that blocking a single mediator, especially after the initiating insult, is insufficient to inhibit NF-κB activation in complex clinical conditions. This is primarily because of the redundancy of proximal mediators with the potential to activate NF-κB. Furthermore, none of these molecules appears to be both a critical and essential pathway for activation of NF-κB [8].

From bench to bedside?

But can we extrapolate Meduri's experiments to the bedside? There are certainly a number of caveats. Firstly, these studies were carried out *in vitro*. If we have learned anything from clinical trials in sepsis/inflammation it is that the transfer of information from the bench to the bedside can be fraught with difficulty. The intricate relationship between innate and adaptive response shapes patient outcome, and this is rarely determined by a single factor. There are, in fact, many more levels of complexity; with multiple cytokines and multiple U-shaped curves that interact, it may be impossible to predict whether a specific anti-cytokine therapy will benefit or harm a given patient, especially as the cytokine profiles change during the course of the disease.

Secondly, even if these concepts are correct *in vivo*, the impact of nosocomial pneumonias on the mortality of patients with ALI/ARDS in not entirely clear. Despite the fact that at postmortem almost two-thirds of non-survivors have histological evidence of pneumonia [9], Sutherland *et al*. found that the incidence of nosocomial pneumonia in patients with ARDS was only 15% (antibiotic use may have inhibited bacterial growth in this study) [10]. Two prospective studies in France reported a much higher incidence (55–60%) [11,12]. In all three studies, however, the presence or absence of ventilator-associated pneumonia had little or no effect on mortality. In contrast, Headley *et al*. reported that the rate of nosocomial infection per day of mechanical ventilation was 1% in survivors and 8% in non-survivors [2]. The impact of nosocomial infections on mortality is hence not entirely clear.

Even if nosocomial infections do not directly determine outcome in this population of patients, they may play a key role in the loss of pulmonary compartmentalization of the inflammatory response, and consequently the development and progression of multi-organ dysfunction syndrome [13]. Data presented by Meduri suggest that bacterial growth and impaired clearance is secondary to a dysregulated inflammatory response [1] and is not the inciting event leading to loss of pulmonary compartmentalization. Ranieri and Slutsky, however, showed that an injurious ventilatory strategy increases the level of serum inflammatory mediators [14] and that this increase is related to an increased incidence of organ dysfunction [15]. It has been postulated that loss of pulmonary compartmentalization may explain these findings. Whether this may be, in part, amplified by concurrent nosocomial pulmonary infections and the U-shaped dose response to cytokines is yet to be determined.

Moreover, treating cytokines in isolation of the underlying pathophysiology may not alter important clinical outcomes. Compelling evidence looking at different ventilatory strategies in the management of patients with ARDS has demonstrated that protective ventilatory strategies that attenuate the pulmonary and systemic inflammatory responses, by addressing the underlying pathophysiology of ventilator-induced lung injury in patients with ARDS, improve outcome [14–16]. Evidence from both animal and clinical studies suggest that cyclic stretch induces changes in pro-inflammatory and anti-inflammatory gene expression [14,17]. It consequently follows that mechanical forces may be immunomodulatory. If this is the case, mechanical ventilation primarily used in the treatment of respiratory failure and responsible for ventilator-induced lung injury may now become a therapeutic tool in the immunomodulatory management of ventilated patients with ARDS.

Conclusion

This is an exciting time for intensivists involved in the care of patients with ARDS/ALI. The rate-limiting step in developing novel therapies for acute inflammatory diseases of the lung is not delineating the molecular mechanisms of lung injury, but

understanding how the pieces of the puzzle fit together. To this end, Meduri has made a significant contribution to our understanding of the mechanisms underlying nosocomial infections in patients with ARDS. The challenge now is in the generation of meaningful questions that will pave the way towards novel strategies in the management of this patient population.

Competing interests

None declared.

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