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Immunoparalysis and Adverse Outcomes from Critical Illness

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Children can face a variety of inflammatory challenges ranging from the benign (otitis media) to the life threatening (severe trauma, open heart surgery, and septic shock). The immune system is of vital importance for the successful weathering of these challenges. A massive proinflammatory response without proper controls is pathologic and places patients at risk for organ dysfunction and death. Conversely, an underactive immune system that is unable to detect pathogens, mount an inflammatory response, destroy microbial invaders, or repair damaged tissue places patients at risk for death from secondary infection and persistent organ failure.

In the 1980s and 1990s, multiple therapies targeting proinflammatory mediators and aimed at reducing inflammation reached phase III clinical trials in adults who had severe sepsis and septic shock [1–12]. Nearly all of these studies failed to demonstrate a survival benefit, suggesting that reducing inflammation is not the appropriate therapeutic goal in all cases. Subsequent studies have suggested that late mortality from surgery, sepsis, or trauma can be associated with an acquired immune deficiency state. If prolonged and severe, this state has been termed immunoparalysis. Characterized by markedly impaired innate immune function, immunoparalysis now is recognized as a predictor of morbidity and mortality for children and adults [13–18]. Moreover, the phenomenon often is occult, is not heralded by

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any premorbid phenotype, and commonly occurs in patients previously believed immunocompetent. Although immunoparalysis cannot be detected by analysis of patients' complete blood count or white blood cell differential, methods of immune monitoring exist that can permit the diagnosis to be made in a same-day fashion. Recent investigations offer evidence that immunoparalysis can be reversed with benefit to patients.

To provide a biologic framework, this discussion begins with an overview of the immune system. After this, the phenomenon of immunoparalysis is reviewed in detail with attention to mechanisms of disease, clinical significance, and potential for therapeutic intervention. The overall goal of this review is to highlight the anti-inflammatory end of the spectrum of the immune response as an underappreciated yet highly relevant contributor to outcomes in critically ill patients.

The monocyte and the inflammatory response

The innate immune system

In general terms, the immune system can be divided into the innate and the adaptive arms (Table 1). The innate immune system is understood most easily as the body's first cellular line of defense. It includes members whose primary roles include phagocytosis and intracellular killing (polymorphonuclear cells), cytotoxic killing (natural killer cells), and antigen presentation (dendritic cells). Another innate immune cell, the monocyte, is believed a key determinant of the acute immune response. Its diverse roles (and those of its descendant, the tissue macrophage) include recognition and phagocytosis of pathogens, presentation of digested peptides on its cell surface to

Table 1
Elements of the innate and adaptive immune systems

Innate	Adaptive
Cellular elements	Cellular elements
Phagocytosis	Antibody production
Monocytes/macrophages	B cells/plasma cells
Polymorphonuclear leukocytes	Cytotoxic killing
Dendritic cells	CD8+ T cells
Antigen presentation	Cytokine/chemokine production
Monocytes/macrophages	CD4+ T cells
Dendritic cells	T_H1 cells (proinflammatory)
Cytotoxic killing	T_H2 cells (anti-inflammatory)
Natural killer cells	T_{reg} cells (anti-inflammatory)
Polymorphonuclear leukocytes	
Cytokine/chemokine production	
All of the above	
Noncellular elements	Noncellular elements
Cytokines	Immunoglobulins
Chemokines	Cytokines
Complement	Chemokines