Immunoparalysis in Pediatric Critical Care

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KEYWORDS

• Immunoparalysis • Pediatric • Critical care • Immune • Sepsis • Trauma
• Cardiopulmonary bypass

KEY POINTS

- The proinflammatory surge that accompanies the onset of pediatric critical illness often occurs concurrently with a compensatory anti-inflammatory response.
- When severe and persistent, this anti-inflammatory response has been termed immunoparalysis and is associated with increased risks for nosocomial infection and mortality across a wide variety of pediatric intensive care unit (PICU) diagnoses.
- Immunoparalysis is quantifiable by tests that measure monocyte human leukocyte antigen (HLA)-DR expression, ex vivo stimulated cytokine production capacities, and cell counts.
- Promising therapies exist that have the potential to reverse immunoparalysis and improve outcomes in the PICU.
- Standardized immune monitoring regimens are needed to guide clinical management and inform enrollment into clinical trials aimed at restoring immune function in the PICU.

INTRODUCTION

Although the diagnoses that result in pediatric critical illness can vary (eg, sepsis, trauma, cardiopulmonary bypass [CPB]), the initial insult is often proinflammatory in nature.

It has long been understood that the degree of hyperinflammation associated with these diagnoses predicts adverse outcomes, with greater inflammation being linked to organ failure and mortality.[1–3] Mounting evidence suggests, however, that a

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compensatory anti-inflammatory response syndrome (CARS) often occurs concurrently with the systemic inflammatory response syndrome (SIRS) (Fig. 1). This anti-inflammatory response, when severe and persistent, has been termed immunoparalysis and it represents a form of acquired immune deficiency that is itself associated with adverse outcomes in the pediatric intensive care unit (PICU). Immunoparalysis can affect multiple arms of the immune system and is often occult, with no physical examination or routine clinical laboratory evidence of its presence. Specialized testing, however, can identify patients with critical illness-induced immune suppression and a growing body of evidence suggests that immunoparalysis is reversible with the potential for beneficial effects on clinical outcomes.

To place the concept of immunoparalysis in context, this article begins with an overview of the immune system. Following this, the laboratory characteristics of immunoparalysis are reviewed along with detailed discussions of its clinical implications across multiple forms of pediatric critical illness. The treatment of immunoparalysis through immunostimulatory strategies is also reviewed. The overall goal is to highlight the need for immunologic balance in children with critical illness and to identify immunoparalysis as an important contributor to clinical outcomes in the PICU.

THE IMMUNOLOGY OF INFLAMMATION

The Innate Immune System

In general terms, the immune system can be divided into the innate and the adaptive arms (Box 1). The innate immune system is the body's first cellular line of defense. It includes cell types such as monocytes, macrophages, polymorphonuclear cells, natural killer (NK) cells, and dendritic cells. Innate immune cells are key drivers of the initial acute immune response. Their diverse roles include recognition and phagocytosis of pathogens, presentation of antigens to adaptive immune cells, and secretion of mediators that modulate the overall immune response. A characteristic feature of innate immune cells is their ability to consistently respond to pathogens regardless of prior

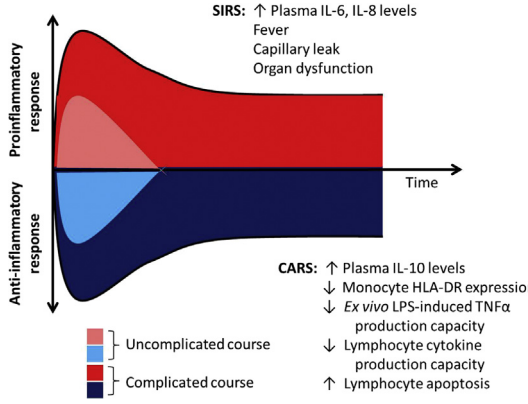

Fig. 1. The dynamic nature of the immune response to critical illness. Severe and persistent inflammation is associated with the classic symptoms of SIRS with fever, capillary leak, and organ dysfunction. CARS can occur concurrently with systemic inflammation. This can also be pathogenic when severe and prolonged, with associated increases in risk of nosocomial infection and death. More modest and transient deviations from immunologic homeostasis are typically associated with uncomplicated recovery. Both SIRS and CARS can be quantified through specific laboratory testing. HLA, human leukocyte antigen; IL, interleukin; LPS, lipopolysaccharide; TNF, tumor necrosis factor.