Double-Edged Sword

Musculoskeletal Infection Provoked Acute Phase Response in Children

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KEYWORDS

• Musculoskeletal infection • Septic arthritis • Osteomyelitis • Pyomyositis
• Acute phase response

KEY POINTS

- The acute phase response is the physiologic reaction to tissue injury, such as musculoskeletal infection, trauma, and orthopedic surgery.
- Although trauma and orthopedic surgery are temporally isolated injuries, musculoskeletal infection is a continuous injury that leads to exuberant activation of the acute phase response that persists until the infection resolves.
- The acute phase response to musculoskeletal infection is paradoxic, as it is not only necessary to combat infection and repair damaged tissue, but also responsible for many of the associated complications.
- Given the interplay between musculoskeletal infection and the acute phase response, measuring positive and negatively regulated acute phase reactants has been useful in diagnosing and monitoring patients with musculoskeletal infection.
- Future strategies that modulate the acute phase response have the potential to improve treatment and prevent complications associated with musculoskeletal infection.

INTRODUCTION

Musculoskeletal infection represents a challenging disease process for orthopedic surgeons that poses significant health care costs and carries a high potential for morbidity and mortality. The most common pathogens of the musculoskeletal system express virulence factors that lead to a tropism, *or selectivity*, for damaged and regenerating tissue.[1] As developing and regenerative tissue share many overlapping features (eg, growth factors and angiogenesis), there is an increased prevalence of infection in children as compared with adults,

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even in the absence of injury.[2] Only recently in orthopedics, the burden and mortality of musculoskeletal infection has been surpassed by other pathologies. In the pre-antibiotic era, the mortality rate of acute hematogenous osteomyelitis in children was upward of 50% due to overwhelming sepsis and metastatic abscesses.[3,4] The advent of antibiotics and the capacity to perform debridement of infected tissue has tremendously impacted the outcome of these patients and in the modern era mortality rates from pediatric musculoskeletal infection in the United States have dropped significantly.

Nevertheless, although most pediatric musculoskeletal infections are effectively treated and resolve without complications, severe infections continue to cause devastating complications.[5] For example, without timely treatment, septic arthritis of the hip and severe osteomyelitis may lead to avascular necrosis, pathologic fracture, growth arrest, and even amputation.[6–8] Disseminated infections have the potential to cause venous and arterial thromboembolic disease and septic shock.[9,10] In extreme infections, such as necrotizing fasciitis, mortality rates in epidemiologic studies have been recorded as high as 76%.[11,12] Moreover, the incidence of musculoskeletal infection has increased in recent years due to a number of factors, including the rising prevalence of diseases such as diabetes and obesity, which impair the immune system.[13,14]

In addition, the pharmacologic basis of antibiotic therapy is overwhelmingly based on disrupting microbial genetic machinery, such as cell wall and protein synthesis.[15] As microbial genetics evolve, drug-resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), are increasingly common and often more difficult to treat.[16,17] Without the development of novel antibiotics capable of countering these organisms' genetic adaptations, the tremendous gains against musculoskeletal infection of the past century may be short-lived.

ACUTE PHASE RESPONSE: THE DOUBLE-EDGED SWORD IN ORTHOPEDICS

Damage to musculoskeletal tissue initiates a cascade of reactions that is collectively referred to as the acute phase response (Fig. 1). This dramatic physiologic response has far-reaching effects, affecting the activity of nearly all organ systems through coagulation, inflammatory, and regenerative processes. The acute phase response typically occurs over a 6-week process following an isolated injury, such as trauma or elective surgery (Fig. 2).[18] (The acute phase response in response to a total knee arthroplasty is used in this review as a point of reference of an elective surgical procedure. It is a procedure familiar to most orthopedic surgeons and stimulates a well-described acute phase response to the brink of developing acute phase response–related complications.)

The acute phase response is a critical mechanism for humans to survive and recover from injury. An insufficient response leads to hemorrhage, infection, and impaired tissue regeneration. *A decreased acute phase response may be observed in patients with cirrhosis, as the liver is the principal effector organ of the acute phase response.*[19,20] On the other hand, an excessive or prolonged acute phase response (see Fig. 2A, B) is a major cause of systemic complications observed in orthopedics (Fig. 3A), ranging from the relatively benign (nausea/pain) to more severe (coagulopathy, venous thromboembolism [VTE], systemic inflammatory response syndrome [SIRS]) and most severe (multiorgan failure [MOF] and death). As such, close monitoring of the acute phase response is the cornerstone concept of "damage control orthopedics."[21] Given that both trauma and orthopedic surgery elicit an acute phase response, the principle of damage control orthopedics is to perform more invasive surgical management such that their cumulative response does not push a patient into the threshold of more severe complications, such as SIRS, shock, MOF, or death (Fig. 3B, C). Furthermore, although this response has "acute" in the name, it is activated in the context of both acute and chronic inflammatory conditions. Chronic baseline activation of the acute phase response causes degeneration of musculoskeletal tissue in conditions such as osteoporosis.[22] Additionally, elevated baseline activity of the acute phase response amplifies the response to an elective or traumatic injury, increasing the risk of complications in those patients.[23] Therefore, the acute phase response as a whole may be viewed as a "double-edged sword," because a well-coordinated acute phase response is essential for survival and recovery from tissue injury, but an excessive response may lead to devastating complications.

When infectious pathogens invade the body, bacterial proliferation and virulence factor expression cause damage to surrounding tissues. However, injury caused by a developing infection is dramatically different from isolated surgery or trauma in that it is continuous (Fig. 4). As the infection propagates, tissue injury persists until it is resolved by the immune system, antibiotics, and/or surgical debridement