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Pathophysiology of Septic Shock: From Bench to Bedside

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Abstract

Our understanding of sepsis and its resultant outcomes remains a paradox. On the one hand, we know more about the pathophysiology of sepsis than ever before. However, this knowledge has not successfully translated to the bedside, as the vast majority of clinical trials for sepsis have been negative. Yet even in the general absence of positive clinical trials, mortality from sepsis has fallen to its lowest point in history, in large part due to educational campaigns that stress timely antibiotics and hemodynamic support. While additional improvements in outcome will assuredly result from further compliance with evidence based practices, a deeper understanding of the science that underlies the host response in sepsis is critical to the development of novel therapeutics. In this review, we outline immunopathologic abnormalities in sepsis, and then look at potential approaches to therapeutically modulate them. Ultimately, an understanding of the science underlying sepsis should allow the critical care community to utilize precision medicine to combat this devastating disease on an individual basis leading to improved outcomes.

Introduction

Sepsis continues to be one of the most challenging and deadly problems in medicine. Unfortunately, thirty years of clinical trials have yet to produce a disease-specific therapy. Mortality from sepsis is decreasing due in large part to efforts such as the Surviving Sepsis Campaign (1) where compliance with evidence based practice has resulted in impressive improvements in outcome (2). However, the overall incidence of sepsis continues to rise and mortality remains unacceptably high.

One of the most challenging elements in changing outcomes is defining sepsis in the first place. Unlike cancer – where staging can be objectively determined based upon microscopic analysis of local or distant spread – sepsis is a syndrome that defies easy characterization, and in its most severe forms can impact every organ in the body. Although sepsis is initiated by an infection, there has long been an understanding that the host response is a vital component in the pathophysiology of sepsis. There is, however, a wide gulf between sepsis definitions that are useful at the bedside and our scientific understanding of the disease.

The definition of sepsis that was used for over 20 years was based upon a 1992 SCCM/ACCP consensus conference that included suspicion of infection and at least two

components of the systemic inflammatory response syndrome (3). Due to shortcomings with the definition (4), a new definition was published in early 2016 (Note for editor: I know this has not been published yet. However it will be published in Feb. 2016, long before this current manuscript is published). While a conceptual advance from the prior definition and one that is driven by data analysis rather than solely expert opinion, this new definition is explicitly designed for the bedside clinician. As such, it has the large upside of being useful to a provider taking care of a septic patient. However, due to an inability to measure a patient's state on a cellular or molecular level, the new definition leaves the biological underpinnings of sepsis to future iterations where the capacity to merge science and clinical care may be possible.

Epidemiology

An inability to strictly define and/or screen for sepsis has clearly influenced our understanding of sepsis epidemiology. Separate terminology and ICD-9 codes for bacteremia, "septicemia," pneumonia, organ dysfunction, etc. have led to widely disparate estimates of the incidence and prevalence of sepsis throughout the world. As an example, official statistics list "septicemia" as causing 38,000 number of deaths per year in the United States (5) while analyses using claims-based data suggest that between 230,000 and 370,000 patients die of the disease annually (6). This is even more complicated worldwide although recent estimates suggest over 5 million people die of sepsis annually (7). In general, sepsis is the most common cause of death in non-cardiac ICUs and likely represents one of the top 3 causes of death in most industrialized countries, with a mortality that ranges from 20–50% depending on study population examined. Patients with COPD, cancer, HIV, and who are on immunosuppressive drugs are at increased risk of developing and dying from sepsis, as are the elderly, neonates, males>females, and blacks>whites (8–11).

Pathophysiology

Our understanding of the pathophysiology of sepsis has greatly evolved over the last 10–15 years, as research has shown it to be much more than a pro-inflammatory cytokine storm (12;13). At the organ system level, sepsis can cause derangements or failure in every organ system. Clinically, this can manifest itself as shock, respiratory failure, thrombocytopenia/ DIC, altered glucose control, altered mental status, acute kidney injury, ileus, polymyopathy, adrenal dysfunction, and/or altered liver function. On a cellular and subcellular level, alterations and/or dysfunction in immune function/signaling, the endothelium, the intestinal epithelium and microbiota, and the coagulation cascade all appear to play a role in the pathophysiology of sepsis. We will highlight key findings in each of these topics below.

Immune dysfunction

Innate Immunity in sepsis

The innate immune system acts as the first responder to an invading pathogen, sensing and reacting to the initial signs of infection. Neutrophils, macrophages, natural killer cells, complement proteins, and others attempt to control the infection in a non-specific manner, while signaling to the adaptive immune system for additional support and regulation.

The innate system senses pathogens and injury through toll-like receptors (TLR's). These receptors recognize carbohydrate and lipid molecules that commonly exist on the surface of pathogens -- pathogen associated molecular patterns (PAMPS) (14). In addition, they recognize patterns associated with injury, derived from necrotic cells and mitochondria, called danger associated molecular patterns (DAMPs). Once PAMPs and DAMPs are engaged, cytokine/chemokine signaling and release of reactive oxygen species (ROS) ensues. While signaling through this pathway is undoubtedly important, a study utilizing TLR4/MD2 antagonist within 24 hours of sepsis showed no benefit over placebo in septic patients (15).

Recognition of a pathogen (or danger) signal subsequently leads to the release of cytokine and chemokine signaling molecules such as IL-1, TNF- α , IL-2, IL-6, IL-8, IL-10, IFN- γ , and PAF. Both pro- and anti-inflammatory cytokines are increased following the onset of sepsis, and survival has been inversely correlated to both IL-6 and IL-10 levels. In addition, IL-17 has recently also been strongly implicated in sepsis pathophysiology, with antibody neutralization of IL-17 in mouse models showing decreased organ damage and improved survival (16). Finally, microRNA's also play a major role in feedback inhibition of TLR/MyD88 signaling, which may explain some of the genetic variation in the sepsis response and potentially be a target for future intervention (17).

Alterations in innate cell function clearly play a critical role in the pathophysiology of sepsis. Neutrophil function has been implicated in both beneficial and detrimental roles. Neutrophil recruitment and bacterial clearance in the peritoneum separates mice predicted to die and mice predicted to live after cecal ligation and puncture (CLP), and neutrophils play a key role in the early host response to sepsis (18). However, delayed neutrophil apoptosis and prolonged neutrophil response is associated with increased organ injury including ARDS and decreased survival (19). ROS released by neutrophils are part of the positive feedback propagation of the inflammatory response and have been shown to cause both endothelial and mitochondrial dysfunction that contributes to the multi-organ failure process. Neutrophils also release networks of extracellular DNA called neutrophil extracellular traps that both assist in pathogen clearance and signal within the inflammation and coagulation cascades (20;21).

Monocyte and macrophage dysfunction have also been shown to be altered in sepsis. Both programmed cell death receptor 1 (PD-1) and adenosine receptors have been implicated as playing an important role. There is improved bacterial clearance and survival in PD-1 knockout mice, related at least in part to macrophage PD-1 expression as protection from sepsis lethality is diminished when macrophages are depleted in knockout animals (22). Antagonists to the adenosine A2B receptor on macrophages also reduce inflammatory markers, augment bacterial killing, and improve survival after CLP (23). Finally, decreased HLA-DR expression in monocytes (a marker of cellular exhaustion) has been shown to be an independent predictor of nosocomial infection in patients with sepsis (24).

Adaptive immunity in sepsis

While sepsis typically increases white blood cell count in patients, this is due to an increase from the innate system in the form of circulating neutrophils. In contrast, the lymphocyte

population markedly declines in sepsis, with the largest decreases in CD4+ T cells and B cells in both septic patients and pre-clinical models of sepsis (25–27). The process begins early, with decreases in weight and cell count of the thymus by three hours. The functional significance of these losses has been confirmed by multiple groups in multiple models of sepsis which demonstrate that prevention of apoptosis via BCL-2 overexpression, blocking Fas signaling, or treatment with Caspase inhibitors leads to an improvement in survival (28–30).

While lymphocyte depletion is one possible reason for the immune suppression and vulnerability to nosocomial infections seen in patients after sepsis, another complementary possibility is that remaining cells are dysfunctional. After the onset of sepsis, lymphocytes express markers of T-cell exhaustion, with increased expression of co-inhibitory markers such as PD-1 and cytotoxic T-lymphocyte antigen-4 (CTLA-4) in both patients and pre-clinical models of sepsis as well as a shift toward a more T-helper type 2 (TH2) immune suppressive cytokine profile. Further, there is increased T regulatory cell (T_{reg}) activity which is immune suppressive in nature. These findings have been associated with changes in mortality after sepsis. Anti-CTLA 4 has been shown to improve survival in septic mice in a dose dependent fashion (31). Anti-PD-1 and anti-PD-L1 given to mice after septic challenge also improves survival rates after primary and secondary fungal infections (32).

T-helper (T_H) cells shift toward a TH2 subset in sepsis. Subsets of these including T_{H9} , T_{H17} , T_{H22} , T_{HF} , and different types of T_{reg} have recently been identified and are potentially important in the pathophysiology of sepsis (33). T_{H17} cells link the adaptive and innate systems, augmenting neutrophil responses and are increased in patients who survive sepsis (34). A similar correlation has been shown in T_{reg} cells where higher levels have been found in survivors 24 hours after sepsis than in non-survivors.

Three other T cell subsets, all with innate-like behavior, also are believed to have a role in sepsis pathophysiology: natural killer T (NKT) cells, mucosal-associated invariant T (MAIT) cells, and $\gamma\delta$ T cells. NKT cells are potent producers of IFN- γ and other pro-inflammatory cytokines and have cytotoxic effector function. They promote the dysregulated septic inflammatory response and are associated with increased mortality in elderly septic patients (35–37). $\gamma\delta$ T cells interact with the epithelium of mucosal organs and help regulate macrophages. $\gamma\delta$ cell counts fall in sepsis, in a manner that correlates with the severity of injury (38;39). MAIT cells rapidly secrete IL-17 and IFN- γ after an infection. Patients with severe sepsis have significantly reduced MAIT counts which correlates with the development of subsequent nosocomial infections (40).

CD8+ T cells also appear to play a significant role in the pathophysiology of sepsis. While CD8+ T cells are generally thought of as effector cytotoxic cells, they can also play an innate like role. CD8+ T cells are decreased in patients with septic shock, and altered memory CD8+ T cell response after sepsis results in increased susceptibility to nosocomial organisms (41). Samples from septic patients have also shown increased CD8+ T cell expression of PD-1 and decreased IFN- γ and IL-2 secretion compared to non-septic critically-ill controls (42). In mice, CD8 +T cell loss and dysfunction results in impaired responses to secondary infection by *LCMV* and *Listeria monocytogenes* (43).

B lymphocytes are most well known for differentiating into antibody secreting plasma cells, but also have been shown to have both antigen presenting and innate-like immune sensing properties. Patients with septic shock have decreased peripheral B cells. CD80 and CD86 are part of the B cell antigen presentation process. Septic patients have increased CD86 expression, with non-survivors having an elevated CD19CD80+ phenotype compared to survivors (44). In addition, innate response activator B cells have been shown to be critical in septic mice as animals that lack these cells fail to clear bacteria and have significantly increased mortality after sepsis (45).

The inflammatory reflex

Neuro-immune regulation, also called “the inflammatory reflex,” refers to vagal nerve fibers that regulate the immune response (46). In this pathway, afferent nerve fibers are triggered by mediators of inflammation or injury, then efferent fibers send a signal via the vagus nerve that results in acetylcholine release from the spleen (47). Cholinergic receptors on macrophage are engaged and release of pro-inflammatory cytokines is suppressed. In mouse models, disruption of this pathway via vagotomy increases systemic inflammation after sepsis while stimulation of this pathway suppresses the inflammatory response. Theoretically, implantation of nerve stimulators could therefore lead to the ability to modulate the immune system in sepsis.

The endothelium

The endothelium provides a selective barrier that regulates the movement of water, solutes, and cellular components of the blood to the tissues. The endothelial surface has an active role in both vascular tone/permeability and in modulating the immune response. While endothelial cells are generally not thought of as immune cells, they express immune receptors, including TLRs. These TLR’s can activate inflammatory pathways mediated by NF κ B and the MAP kinases. TLR signaling also alters endothelial cell permeability and expression of coagulation pathway signaling, contributing to the coagulopathy, increased vascular permeability, and organ dysfunction seen in septic patients. Studies have identified several molecules that are altered in sepsis that may help restore barrier function in sepsis, including modulation of C5a, HMGB-1, VEGF receptor 2, angiopoietin-1, and sphingosine 1 phosphate receptor 1 (48–50).

The gut

For over 30 years, the gut has been hypothesized to be the motor of critical illness (51–53). Although originally thought to be related to translocation of intact bacteria into the systemic circulation, this has not been supported by existing evidence. Nonetheless, sepsis has been demonstrated to alter the gut in a number of ways that might impact progression of disease and mortality.

Although there is not strong evidence to support translocation of bacteria, an alternate potential is the gut-lymph hypothesis (54). This theory postulates that the gut releases toxic mediators that travel through the mesenteric lymphatics to the lung, where they can cause

remote injury (55). There is significant pre-clinical data to support the importance of the gut-lymph hypothesis in critical illness. For instance, when the mesenteric lymph duct is ligated, lung injury and neutrophil activation are decreased or prevented and mortality is also decreased or abolished (56). Further, when mesenteric lymph from rats subjected to trauma/hemorrhage are injected into unmanipulated rats, the animals receiving the injection develop a lung injury similar to shock rats. Notably, mice with gut-specific deletion of Mttp (a protein required for chylomicron assembly) have improved survival following sepsis from pneumonia (57), although interestingly aged animals with the identical genetic knockout have lower survival when subjected to the same insult (58).

Gut epithelial integrity is also compromised in sepsis. In pre-clinical studies, sepsis increases apoptosis, decreases proliferation, decreases villus length and increases permeability (59;60). Preventing gut epithelial apoptosis by overexpression of the anti-apoptotic protein Bcl-2 improves survival in murine models of CLP and pneumonia, and improving gut integrity by either intestine-specific or systemic EGF also improves survival in animals subjected to the same insults (61–63).

Increasing recognition has also been paid recently to the role of the microbiome in the pathogenesis of sepsis. There are 100 trillion bacterial cells in a human -- ten times more cells than the host has (64). There is increasing evidence that bacteria which reside within the gut are neither inherently “good” or “bad” but alter their relationship with the host depending on its health. Specifically, bacteria can sense host stress and surrounding bacterial density and alter their virulence in response. As an example, *Pseudomonas* injected into the cecum of mice undergoing a sham operation and subsequently removed can be injected into the peritoneum of a different animal without causing harm. However, if *Pseudomonas* is injected in the cecum of mice given a non-lethal partial hepatectomy and subsequently removed and injected into the peritoneum of a different animal, the resulting mortality is 100%, consistent with the conclusion that bacteria change their virulence based upon the host environment (65). This suggests that simply treating patients with antibiotics without attention to microbial virulence may not be sufficient for treating septic patients and that altering the microflora with antibiotics may be paradoxically harmful. Thus a potential approach to sepsis care in the future is to prevent bacteria from becoming virulent or reprogramming them to a non-virulent phenotype. A pre-clinical example of this approach involves the administration of a non-antibiotic, high-molecular-weight polymer to mice which prevents mortality from typically virulent organisms by altering their phenotype (66).

From Bench to Bedside: what can be learned from the past and looking toward the future

Despite the fact that there currently are no approved agents on the market other than antibiotics that are aimed at treating sepsis, improved supportive care and early administration of antibiotics via sepsis bundles has led to a decrease in overall sepsis mortality. Unfortunately, associated with this improvement in short-term outcomes, a new disease has emerged as survivors of the early inflammatory surge now frequently face chronic critical illness- a state of persistent catabolic inflammation and vulnerability to

nosocomial infections (67). Previously, most sepsis trials were directed at the early pro-inflammatory mediators. With recognition of the continuum of acute inflammation to chronic critical illness, more targeted approaches are being postulated; thus, a patient with newly diagnosed septic shock may not benefit from the same therapy that a patient on day 3 would benefit from, which, in turn, might be different from a therapy a patient on day 32 would benefit from (68).

Starting in the 1960's, there have been numerous immunomodulating agents used in clinical trials, all without success despite seemingly sound scientific rationales for testing the agents and positive pre-clinical data. This has challenged researchers to re-examine the underlying translational hypotheses and trial design. Transplantation and cancer researchers successfully modulate the immune system for therapeutic benefit, so what makes sepsis different? Outside of the more rapid time frame of sepsis (which should not be a rate-limiting step), one major issue has been the absence of well-defined patient selection into trials based upon biology. For instance, a cancer researcher will typically test a drug on a specific tumor type based upon stage and genetic mutations as opposed to simply treating "cancer". Sepsis trials, however, have historically had very broad entry criteria enrolling patients of widely different ages, genetics, co-morbidities, infectious sources and through a continuum of early inflammatory surge and late catabolism/immune paralysis. While some of the agents used in the past likely did help a fraction of the patients whose immune status was ideal for the agent, the signal was likely drowned out by others who were not helped, or possibly harmed with the same agent. A future state in which adaptive trial designs based upon mechanistic endpoints that enroll patients based upon specific biology -- biomarkers, fingerprints from genomics, transcriptomics, proteomics, metabolomics, microbiomics, etc. -- holds the promise that scientific advances made at the bench will be able to be translated to the bedside, leading to improved patient outcomes.

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