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ASIP Centennial Perspective

A Historical Perspective on Sepsis

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In North America, approximately 700,000 cases of sepsis occur each year, with mortality ranging between 30% and 50%. *The American Journal of Pathology* has featured numerous articles on the topic, revealing mechanistic insights gleaned from both experimental rodent models and human sepsis. Nonetheless, there remains urgent need to determine the basis for sepsis-related complications and how they can be avoided, as well as how they can be most effectively treated once recognized. This historical perspective reviews what we currently understand about the mechanisms of sepsis, as well as the barriers that remain in our treatment strategies. ***(Am J Pathol 2012, 181:2–7; http://dx.doi.org/10.1016/j.ajpath.2012.05.003)***

Over the years, *The American Journal of Pathology* has published a number of articles dealing with mechanisms of experimental sepsis in rodents (eg, endotoxemia and polymicrobial sepsis induced by cecal ligation and puncture [CLP]). Studies in experimental sepsis have addressed the roles of peroxisome proliferator-activated receptors (PPARs)[1] and high mobility group B1 (HMGB1) in septic mice,[2] abnormal levels of ICAM-1 and VCAM-1 in septic lungs,[3] exacerbation of lung inflammatory responses in mice that have recovered from sepsis,[4] the role of matrix metalloproteinases (MMPs) in the septic heart,[5] and the genomic signatures of sepsis in rodents.[6] Such a range of articles suggests considerable research dealing with the pathophysiology of sepsis.

There is no question that sepsis has several features common to both rodents and humans, including excessive systemic production of reactive oxygen species and reactive nitrogen species,[7] a hyperinflammatory state defined by the presence of numerous proinflammatory mediators appearing in plasma (referred to as the systemic inflammatory response syndrome, or SIRS, which occurs also in response to noninfectious insults),[8] and increased expression of adhesion molecules on monocytes, macrophages, and polymorphonuclear neutrophils and on endothelial cells, as well as increased presence of receptors on leukocytes reactive with cytokines and chemokines.[3,9] Such findings suggest enhanced mobilization of leukocytes into tissues and organs, perhaps resulting in progressive development of septic shock and multiorgan failure, and ultimately death. In addition, for both mice and humans, in sepsis there is development of immunosuppression that compromises both acute and longer-term survival.[10–12] In North America there are approximately 700,000 cases of sepsis each year, with a mortality rate ranging between 30% to 50%.[13] Most patients with sepsis are admitted to intensive care units and are on mechanical ventilation, and the annual costs for the treatment of patients with sepsis are estimated to exceed $17 billion.[13,14]

Recent studies have emphasized an aspect of sepsis that had not previously been recognized: medical problems developing after patients and laboratory animals have recovered from sepsis.[15–17] These long-term complications, referred to as lingering consequences, include physical deterioration of skeletal muscle function, cognition impairment, changes in affective behavior, and persistent immunosuppression.[17] What causes these long-term complications is a total mystery. In septic mice, the long-term immunosuppressive state may, at least in part, be reversible by infusion of dendritic cells.[18] Clinical observations suggest that, over time, sepsis induces serious consequences that may require extended medical support. In other words, for some patients who have recovered from sepsis there may nonetheless be progressive, disabling outcomes. There is urgency in the need to determine the basis for these complications and how they can be avoided, as well as how they can most effectively be treated once recognized.

The Disconnect between Outcomes of Studies in Septic Rodents and Outcomes of Clinical Trials in Sepsis

Clinical trials in sepsis have often been based on antagonizing mediators of the systemic inflammatory response,

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in which cytokines and chemokines serve as targets for *in vivo* neutralization. After studies in rodents, investigation progressed to humans with sepsis. Some of the most commonly selected targets in septic mice have been TNF-α and its multiple receptors, including IL-1β, IL-12, IL-18, and HMGB1.[19] Therapeutic strategies in humans have involved use of neutralizing, humanized monoclonal antibodies. In addition, mechanical devices have been developed to remove a variety of cytokines, lipopolysaccharide, or C5a from plasma of septic animals.[20,21] Although there is limited evidence that this technology will significantly and persistently reduce mediator levels in plasma, it is too early to know whether such devices would be clinically efficacious for sepsis in humans.[19] Other targets for neutralization in sepsis have included thrombogenic products, such as activated tissue factor and activated clotting factors V and VIII. Although such interventions showed some efficacy in septic mice, in human clinical trials the interventions were ineffective.[19]

Activated protein C, an antithrombotic serine protease, has been used as a drug for treatment of sepsis in humans. Recombinant activated human protein C [drotrecogin α (Xigris; Eli Lilly, Indianapolis, IN)] is itself an antithrombotic agent, but has additional effects that are anti-inflammatory.[22] Initial clinical trials with drotrecogin α showed some limited efficacy, slightly improving 28-day-survival in sepsis patients. One adverse effect in treatment with drotrecogin α is an increased risk of hemorrhagic events. Because many humans with sepsis develop consumptive coagulopathy or have other underlying risks for bleeding complications, several limitations have been placed on the use of drotrecogin α for sepsis in humans (eg, platelet counts $>$ 30,000/μL and no history of recent major bleeding events). A few years ago, drotrecogin α was assessed for use in infants and children with severe sepsis (defined as SIRS with organ dysfunction or shock), but the clinical trials were suspended when an increased incidence of intracranial hemorrhage developed in pediatric patients treated with drotrecogin α (U.S. Food and Drug Administration, *http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm152833.htm*, last updated June 19, 2009, last accessed May 22, 2012). Based on a recent (third) clinical trial in septic adults, drotrecogin α was found to be nonefficacious, such that Eli Lilly and the FDA jointly agreed to remove drotrecogin α from the market (U.S. Food and Drug Administration, *http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm277143.htm*, last updated October 25, 2011, last accessed May 22, 2012).[23]

In short, this means that currently there are no FDA-approved drugs specific for the treatment of sepsis in humans.

How, and why, have we experienced such frustrating outcomes after enormous expenditures for basic research and for the conduct of clinical trials in sepsis? In the case of mice with endotoxemia, it has been suggested that this model may not be relevant to the pathophysiology of human sepsis.[19,24,25] There have also been concerns that mouse models use young mice with no comorbidities, which is in marked contrast to adult humans with sepsis, who are often over the age of 60 years and present with comorbidities. Another problem has been inconsistency in experimental protocols across studies as related to fluid resuscitation and use of antibiotics (or lack thereof) in septic mice. In contrast, sepsis patients routinely receive these interventions; they also typically have comorbidities (eg, heart disease, hypertension, diabetes mellitus, and the like) and are on comedications. Furthermore, designs of human clinical trials in sepsis vary substantially with respect to patient selection for enrollment. Such trials almost always use survival at 28 days as the key endpoint (based on FDA criteria).[19,25] Setting the endpoint as survival rates at 28 days ignores the possibility that some interventions significantly improve clinical manifestations over the first 10 days of sepsis. Furthermore, for clinical trials in which nearly two thirds of patients will survive (unless patient selection criteria are more selective) this will translate into individual clinical trials requiring thousands of patients, making such trials extraordinarily expensive.

A Current Perspective on Sepsis Mechanisms

Our current perspective on sepsis mechanisms includes the roles of T and B cells in sepsis, as well as the apparent roles of natural killer (NK) cells[8] and dendritic cells (DCs) and how these cells become dysfunctional in the course of sepsis. We also describe development of apoptosis of T and B cells during sepsis and controversies related to interpretation of data from sepsis models in laboratory animals.

Defects of T and B Cells, NK Cells, and Dendritic Cells in Sepsis

The role of T and B cells in sepsis is not devoid of controversy. Despite extensive evidence suggesting that T and B cells play important protective roles in polymicrobial sepsis, a recent report describes the outcomes after CLP in *Rag1*$^{-/-}$ mice, which lack both B and T cells.[26] The *Rag1*$^{-/-}$ mice have survival curves similar to wild-type mice, and, in general, plasma levels of proinflammatory mediators are similar in *Rag1*$^{-/-}$ and wild-type mice after CLP. Although the initial interpretation is that T and B cells are dispensable in protection against sepsis, there is another explanation. It is possible that these *Rag1* knockout mice, which are profoundly immunodeficient, have orchestrated some type of accommodation during their development and maturation that results in adjustment to the absence of T and B cells, at least in the setting of polymicrobial sepsis.

Published evidence suggests that apoptosis-dependent deletion of both B and T cells occurs early in sepsis, especially in humans. A recent study using autopsy specimens and focusing exclusively on sepsis in humans demonstrated extensive apoptosis of both T and B cells, which was accompanied by evidence of profound immunosuppression.[10] Analysis of lipopolysaccharide-stimulated cells obtained from spleen and lung of patients with

sepsis revealed greatly diminished *in vitro* production of TNF-α, IFN-γ, IL-6, and IL-10, with levels generally $<10\%$ of those in cell culture supernatant fluids from lipopolysaccharide-stimulated cells obtained from age-matched patients without sepsis. Flow cytometry revealed increased expression on splenocytes of receptors and ligands that are T-cell regulators (eg, programmed cell death protein 1 [PD-1] and its ligands). There were also increased numbers of T-suppressor cells (T-regulatory cells) in tissues. As expected, there was extensive tissue depletion of $CD4^+$, $CD8^+$, and HLA-DR^+ cells. Collectively, these studies indicate a loss of T and B cells, due to apoptosis, and the expression of receptors and ligands that inhibit T-cell-dependent immune responses. Attempts have been made in mice to reverse the immunosuppressive state in sepsis, using synthetic inhibitors of apoptosis, which we describe below.

B Cells

B cells are reported to enhance early innate immune responses in CLP mice.[27] It was postulated that under these circumstances B cells are protective in an IFN-γ-dependent manner. Recently, however, a different protective mechanism for B cells in sepsis has been suggested. A newly recognized subclass of splenic B cells, termed innate response activator B (IRA-B) cells, has been shown to be protective in the setting of polymicrobial sepsis (induced by CLP).[28] These B cells locally produce GM-CSF, which may in some manner preserve innate immune functions (eg, phagocytosis, chemotaxis, and the like) of tissue neutrophils that otherwise lose these protective functions as the sepsis state develops. To what extent these B-cell findings in mice are relevant to sepsis in humans remains to be determined.

T Cells

Development and progression of sepsis is associated with a variety of derangements in the innate immune and adaptive immune systems, such as increased T and B cell apoptosis, diminished Th1 cell function, reduced T cell receptor (TCR) function, and increased presence of T-suppressor (T-regulatory cells) cells in tissues.[10,29] The T-cell system is clearly central to the ability of the immune system to neutralize products, whether intrinsic or extrinsic, that trigger the dangerous cascade of events that develop during sepsis. In addition, there is abundant evidence that sepsis via generation of the complement anaphylatoxin C5a also compromises innate immune responses of phagocytes (eg, chemotaxis and phagocytosis), alongside defective responses of these cells to various TLR agonists.[30] It seems clear that a sepsis-induced cascade of events leads to immunosuppression. As will be briefly discussed, interventions under consideration are designed to i) reduce apoptosis of T and B cells and replace apoptotic T cells or in some manner restore T cell function, ii) restore innate immune functions of defective phagocytic cells, and iii) restore DC functions.

NK Cells

NK cells are defined by surface markers ($CD3^-$, $NKp46^+$, $CD56^+$) that reflect their cytotoxic properties and also by production of cytokines, including IFN-γ. NK cells may yield protective effects in sepsis, but they may also contribute to some of the harmful consequences of sepsis.[31,32] NK cells play a major role in host defenses against residential viruses, such as herpesvirus and cytomegalovirus. These viruses often emerge as a result of sepsis-induced immunosuppression. There is additional evidence that NK cells are important for *in vivo* containment of organisms such as *Streptococcus pneumoniae*, *Escherichia coli*, *Toxoplasma gondii*, and *Listeria monocytogenes*. In a way, one could posit that NK cells function in a manner similar to that of Th17 cells in containing the infectious agents (eg, bacteria, fungi) that tend to emerge in immunocompromised individuals.[32] In the early phases of septic shock, NK cells may contribute to an overactive immune response and development of systemic inflammation, which appear to be detrimental to survival. In the later phases of sepsis, however, NK cells may provide protection against development of secondary bacterial infections as the immunosuppressive condition intensifies. In the face of such contrasting effects, there is no consensus on whether NK cells should be therapeutically manipulated in sepsis.

Dendritic Cells

It has been known for some time that DCs are protective in mice with polymicrobial sepsis (induced by CLP) and that sepsis causes depletion of splenic and myeloid DCs, whereas the remaining DCs have been rendered functionally deficient and show poor production of IL-12—all of which predicts poor survival.[4,33,34] It also appears that CLP induces depletion of DCs via interaction of TLR2 and TLR4 with their relevant ligands.[35] Although DCs serve as a major source of antigen presentation to T cells, they also produce IL-12 and IL-10 and express on their surfaces MHCII and CD86 (an immune costimulatory molecule). Moldawer and colleagues[33] have suggested that DCs function to bridge innate and acquired immune systems. Finally, infusion of bone marrow-derived DCs into mice with polymicrobial sepsis markedly improves survival, consistent with protective functions of DCs in sepsis.[18,33–35] This raises the question of whether infusion of DCs into sepsis patients may represent a strategy to reverse the state of immunosuppression (although problems related to histocompatibility present substantial obstacles).

Mechanisms of Apoptosis of T and B Cells in Sepsis

As we have indicated above, there is strong evidence that the immunosuppressive outcomes of sepsis can be linked at least in part to apoptosis of the lymphoid system (T and B cells in humans, together with thymocytes in rodents). In the case of apoptosis of thymocytes in CLP rats, this is linked to the trigger, C5a, interacting with its

receptor, C5aR, on thymocytes to induce apoptosis. In this example of apoptosis, there appears to be a dominant role for activation of the intrinsic (mitochondrial) pathway of apoptosis.[36] In polymicrobial sepsis, there is also apoptosis of gastrointestinal epithelial cells, possibly setting the stage for translocation of Gram-negative bacteria and their breakdown products into the draining lymphatic system and hence into the bloodstream. Other studies suggest that the pathways leading to apoptosis during sepsis involve both the extrinsic pathway (Fas/Fas-ligand and TNF/TNF-receptors) and the intrinsic (mitochondrial) pathway.[36–38] Naturally occurring inhibitors of apoptosis (Bcl-2) as well as synthetic inhibitors of caspases have been used in the setting of polymicrobial sepsis in mice. Although *Myd88*$^{-/-}$ mice (with deletion of an adaptor protein common to many TLRs) exhibit diminished apoptosis of T and B cells after CLP, overall survival is reduced.[39]

Some evidence[40] exists that apoptotic pathways are also involved in cell proliferation and related functions, which raises a concern that excessive inhibition of caspase pathways may, on balance, be harmful. The other constraining feature related to inhibition of apoptosis in the setting of sepsis is the fact that, by the time they are admitted to an intensive care unit, most patients with sepsis are already significantly lymphopenic.[41] This suggests that, for interventions aimed at suppressing apoptosis and intended to be applied at the time of admission of patients with sepsis to the intensive care unit, it may be too late for effective reversal of the apoptotic state. Accordingly, it has been suggested that the use of immunostimulants (eg, IL-7) might be able to revive the immune system (although this remains to be demonstrated in humans with sepsis).[42]

Controversies Related to Sepsis Research

The development of the so-called cytokine storm during sepsis (triggered after endotoxemia or in polymicrobial sepsis induced by CLP in rodents and the subject of some controversy) has been interpreted to represent a hyperinflammatory response caused by the inability to regulate activation of the immune system. Consistent with this view has been emerging evidence that several other changes developing during sepsis could indicate a hy-

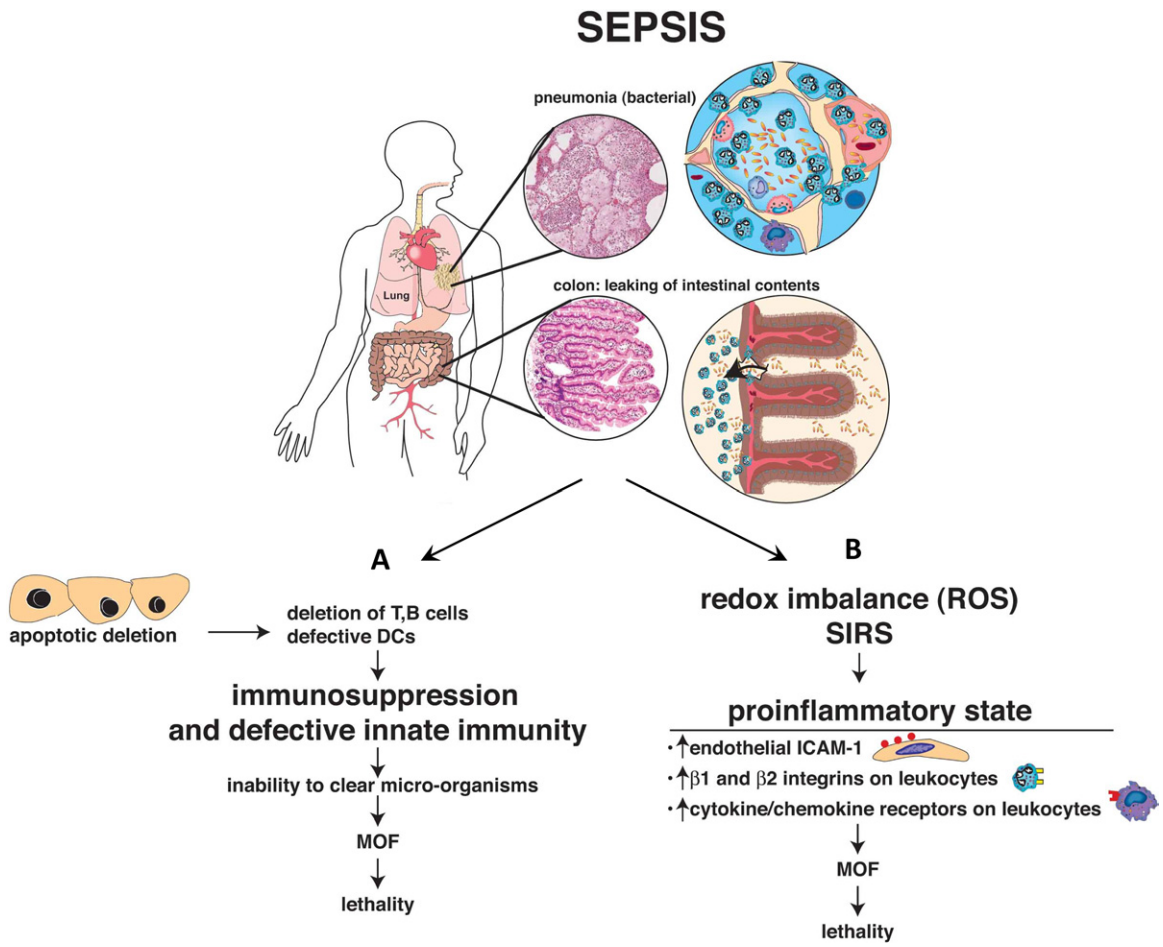

Figure 1. Onset of sepsis beginning either as bacterial pneumonia or as peritonitis associated with extramural leaking of intestinal contents. **A:** Subsequent events include apoptotic deletion of T and B cells, defective DCs, and onset of immunosuppression, together with defective innate immunity. These events lead to loss of the ability to clear bacteria, resulting in development of multiorgan failure (MOF) and death. **B:** Development of sepsis can also lead to redox imbalance in a variety of cells (leukocytes) and organs due to buildup of reactive oxygen species (ROS). This is followed by an inflammatory response (SIRS), including a sustained immune response and other immune activation states in endothelial cells and leukocytes, ultimately associated with MOF and death.

perinflammatory state: increased levels of endothelial cell adhesion molecules (ICAM-1) for leukocytes[3] and increased up-regulation of adhesion molecules on blood leukocytes (β_1 and β_2 integrins), as well as increased expression on leukocytes or chemokine and cytokine receptors,[9] all of which would imply a gain of function for these cells and intensification of the inflammatory response.

If such a hypothesis is correct, then the use of approaches aimed at neutralizing proinflammatory mediators or adhesion molecules on endothelial cells (ICAM-1) or leukocytes (β_1 and β_2 integrins) in sepsis patients would seem reasonable. However, in view of the well-known state of immunosuppression that develops in sepsis, such strategies would have to be very judiciously used in humans. Another problem is the redundancy and overlapping responses in inflammatory mediators. Numerous clinical trials in humans targeted at neutralizing proinflammatory mediators or their receptors have failed (see review by Marshall[19]). The widespread interest in the Toll-like receptor (TLR) system playing a role in sepsis led to recent clinical trials using a potent antagonist to TLR4, eritoran, but these trials were prematurely terminated in 1500 patients because of lack of evidence for efficacy (K. Matsuyama, Bloomberg News 2011, *http://www.bloomberg.com/news*, posted January 25, 2011, last accessed May 22, 2012).

There may be a tendency to dismiss these many clinical trials as misguided or inadequately designed, or because of great overlap and redundancy in functions of inflammatory mediators and receptors, which would be an indication that the inflammatory and innate immune systems are difficult targets for interventions in human sepsis. If so, attempts to correct the immunosuppressive state might represent an alternative approach. For now, no ex cathedra conclusions about design of new clinical trials in sepsis are possible. It could also be that the systemic inflammatory response represents a protective reaction in sepsis, reflecting an inflammatory response that has been triggered after an inability of the organism to adequately cope with and to clear offending infectious agents and/or their products. If there is any truth to this concept, then a different clinical approach for the treatment of sepsis patients may hold promise, namely, interventions with immunostimulants such as IL-15 and/or IL-7, which might restore the incapacitated immune response caused by sepsis. There is some evidence in septic mice suggesting that treatment with IL-7 may be protective and may enhance the IL-17/Th17 axis.[41] Interventions with IL-7 and/or IL-15 may have some capacity to reverse the immunosuppressive state in septic mice. Until appropriate clinical trials in sepsis commence, however, the question of the reversibility of immune suppression cannot be answered. Another suggested strategy is to block receptors or ligands, such as PD-1, that suppress T cell activation.[43] Nonetheless, given the numerous receptors and ligands that negatively regulate the immune response and that are up-regulated in patients with sepsis,[10] selection of a single target of this type for blockade may not be efficacious.

Where Do We Go from Here?

Animal models of sepsis and clinical observations in sepsis patients suggest three issues related to our current understanding of sepsis and possible interventions.

1. Progressive onset of immunosuppression relates to apoptosis of T and B cells, as well as loss of innate immune functions of leukocytes. The T-cell defects might be reversed by use of immunostimulants (eg, IL-7, IL-15) (Figure 1A).
2. An excessive inflammatory response associated with excessive levels in tissues of reactive oxygen species, along with the systemic inflammatory response, results in multiorgan damage. The containment of a hyperinflammatory response is difficult, because of the multitude of proinflammatory mediators and receptors that have overlapping functions. This dilemma reflects our poor understanding of the responses in sepsis and the pressing need for new therapeutic approaches (Figure 1B).
3. The delayed onset of complications of sepsis poses major problems for recovered patients after sepsis. Because we do not know the causes of these postrecovery complications, we are in no position to institute therapies. Such lingering complications may contribute to defects in cognition, immune competence, and skeletal muscle function.[17] The basis for these delayed and persistent complications is not known.

As we have emphasized above, sepsis is a major medical condition associated with severe morbidity and high mortality. It is an especially costly medical problem. Although improvements in supportive care of patients with sepsis (eg, more effective and less damaging mechanical ventilation, improved fluid resuscitation, and broad-spectrum antibiotic coverage) have improved survival rates, sepsis remains a condition with high mortality. Despite many clinical trials, to date no FDA-approved drug is available for use in sepsis, a lack that underscores the importance of future sepsis research.

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