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Biological Perspectives

Pathophysiology of Sepsis

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Sepsis remains a critical problem with significant morbidity and mortality even in the modern era of critical care management. Multiple derangements exist in sepsis involving several different organs and systems, although controversies exist over their individual contribution to the disease process. Septic patients have substantial, life-threatening alterations in their coagulation system, and currently, there is an approved therapy with a component of the coagulation system (activated protein C) to treat patients with severe sepsis. Previously, it was believed that sepsis merely represented an exaggerated, hyperinflammatory response with patients dying from inflammation-induced organ injury. More recent data indicate that substantial heterogeneity exists in septic patients' inflammatory response, with some appearing immuno-stimulated, whereas others appear suppressed. Cellular changes continue the theme of heterogeneity. Some cells work too well such as neutrophils that remain activated for an extended time. Other cellular changes become accelerated in a detrimental fashion including lymphocyte apoptosis. Metabolic changes are clearly present, requiring close and individualized monitoring. At this point in time, the literature richly illustrates that no single mediator/system/pathway/pathogen drives the pathophysiology of sepsis. This review will briefly discuss many of the important alterations that account for the pathophysiology of sepsis. ***(Am J Pathol 2007, 170:1435–1444; DOI: 10.2353/ajpath.2007.060872)***

Sepsis has been active as long as infectious agents have been present. Because bacteria predate humans, sepsis probably predates modern man.[1] Despite intense efforts, sepsis remains a serious clinical problem, accounting for thousands of deaths every year. A recent review by Angus et al estimated the 1995 incidence of sepsis in the United States to be 751,000 cases, resulting in 215,000 deaths.[2] The average cost per case of sepsis was $22,100 with total costs of $16.7 billion nationally. A more recent analysis of hospital records indicates that the total number of patients who are dying is actually increasing.[3] This study also confirmed the work of Angus et al[2] that the incidence of sepsis is increasing and projected to continue to grow as the population ages. These studies concluded that "severe sepsis is a common, expensive, and frequently fatal condition, with as many deaths annually as those from acute myocardial infarction."[3] It is important to bear in mind that sepsis mortality is based on 28-day survival, in contrast to most mortality studies, which are based on 5-year survival. Therefore, in addition to its high lethality, sepsis also accounts for a significant number of years of life lost.

Two major consensus conferences have defined sepsis. The first, in 1992, put forth the concept of the Systemic Inflammatory Response Syndrome (SIRS), recognizing that lethally altered pathophysiology could be present without positive blood cultures.[4] The SIRS criteria are listed in Table 1. Some clarification concerning terminology will assist the reader in this review. Sepsis represents SIRS that has been induced by an infection.[5] Severe sepsis is sepsis with dysfunction of a least one organ or organ system, and septic shock is severe sepsis with hypotension.

The 2001 International Sepsis Definitions Conference modified the model of SIRS and developed an expanded view of sepsis after revisiting the literature.[6] This conference developed the concept of a staging system for sepsis based on four separate characteristics designated by the acronym PIRO. P stands for the predisposition, indicating pre-existing co-morbid conditions that would reduce survival. I is the insult or infection, which reflects the clinical knowledge that some pathogenic organisms are more lethal than others. R represents the response to the infectious challenge, including the development of SIRS. The last letter O stands for organ dysfunction and includes organ failure as well as the failure of a system such as the coagulation system.

What are the signs, symptoms, and causes of sepsis? Table 1 defines the changes that are observed in septic patients, but these alterations are extremely nonspecific,

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Table 1. Criteria for the Systemic Inflammatory Response Syndrome, Adapted from the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference[4]

Two or more of the following are required:
1) Body temperature >38°C or <36°C
2) Heart rate >90 beats per minute
3) Respiratory rate >20 breaths per minute or arterial CO_2 tension less than 32 mm Hg or a need for mechanical ventilation
4) White blood count greater than 12,000/mm^3 or <4000/mm^3 or >10% immature forms

Sepsis represents SIRS, which has been induced by an infection.

and an accurate diagnostic test for sepsis would be a welcome addition in the management of patients. The causes of sepsis are multifactorial but can include virtually any infectious organism. Recently, gram-positive infections have been documented to be more frequent than gram-negative infections.[3] Although interactions between pathogens and the Toll-like receptors have been implicated in sepsis, mice genetically deficient in Toll-like receptors still succumb to true models of sepsis.[7] Statements regarding the dominance of endotoxin in the pathogenesis of sepsis have not kept pace with the current published literature.

Opinions on the causes and potential therapies for sepsis have evolved over time, and this review will focus on some of the current thoughts concerning the basic mechanisms of the septic process. This brief review does not represent an exhaustive listing of all possibilities, and I hope no offense will be taken by those investigators whose area of work is not cited.

Dysregulated Coagulation

Normal hemostasis exists as a finely tuned balance where the blood typically remains liquid to allow free flow within the vessels yet clots appropriately to control bleeding. Under normal conditions the clotting cascade is extremely complex.[8] During inflammatory situations such as sepsis, significant alterations occur at multiple levels within both the coagulation system and the cells that regulate this system[9] (Figure 1). Septic patients frequently manifest disseminated intravascular coagulation (DIC) with consumption of platelets and prolongation of clotting times. In addition, the altered hemostasis allows blood to clot when it should not, clogging blood vessels and reducing blood flow. Because the liver produces fixed quantities of procoagulant factors, and the bone marrow releases a defined number of white blood cells into the circulation, local effects modulate the systemic coagulopathy. In other words, although the coagulopathy is systemic, the bleeding typically occurs in select sites, where dysfunctional vasculature provides the necessary environment for bleeding to occur at that site. The interaction between the clotting system, circulating white blood cells and platelets, and the endothelium adds another layer to an already multifaceted picture. Although several of these abnormalities have been documented in septic patients, the underlying cause of the coagulopathy almost certainly remains multifactorial.

Abnormalities in the coagulation system resulting from systemic illnesses, which cause local disturbances in hemostasis, and the thrombotic potential of cancer patients have been described since the time of Virchow. Virchow's classic triad consists of changes in coagulability, endothelial cell injury, and abnormal blood flow. In septic patients, all three of these classic alterations are present and culminate in reduced blood flow to vital organs. Septic patients frequently have poor tissue perfusion in addition to inappropriate use of oxygen with resulting cytopathic hypoxia.[10] The coagulation abnormalities in septic patients are profound and have led to a successful, Food and Drug Administration-approved therapeutic intervention: activated protein C (APC, marketed under the name Xigris; Eli Lilly & Co., Indianapolis, IN).[11] The approval of APC was controversial, with half of the Food and Drug Administration panel voting to require a confirmatory trial.[12]

The successful clinical trials with APC for the treatment of sepsis were initiated following studies in the baboon model of *Escherichia coli* sepsis.[13] There are very few compounds that have successfully made the transition from preclinical sepsis trials to a viable therapeutic option. Approval of APC for the treatment of septic patients clearly demonstrates that alterations in the coagulation system are important in sepsis mortality. Despite the success, the mechanism of action, beyond the coagulation system, has not been fully defined. It has been postulated that APC has anti-inflammatory properties that help to explain the beneficial effects. However, the question of whether excessive inflammation plays a critical role in sepsis mortality has yet to be definitively answered.

Although APC improves survival in patients with severe sepsis, it is clearly not a panacea for all patients. Analysis of the initial data showed that the most beneficial effects were observed in patients with the worst prognosis. Follow-up studies demonstrated that patients at low risk for death had no improvement in survival and had a significantly increased risk of bleeding if treated with activated protein C.[14]

Aberrant Mediator Production

The inflammatory response represents an important, central component of sepsis because elements of the response drive the physiological alterations that become manifest as the systemic inflammatory response syndrome. An appropriate inflammatory response eliminates the invading microorganisms without causing damage to tissues, organs, or other systems.

Hyperinflammatory Response

Several years ago, many basic science investigators and clinicians believed that the problem of sepsis was directly related to the exuberant production of proinflammatory molecules. The problem seemed rather simple: inflam-

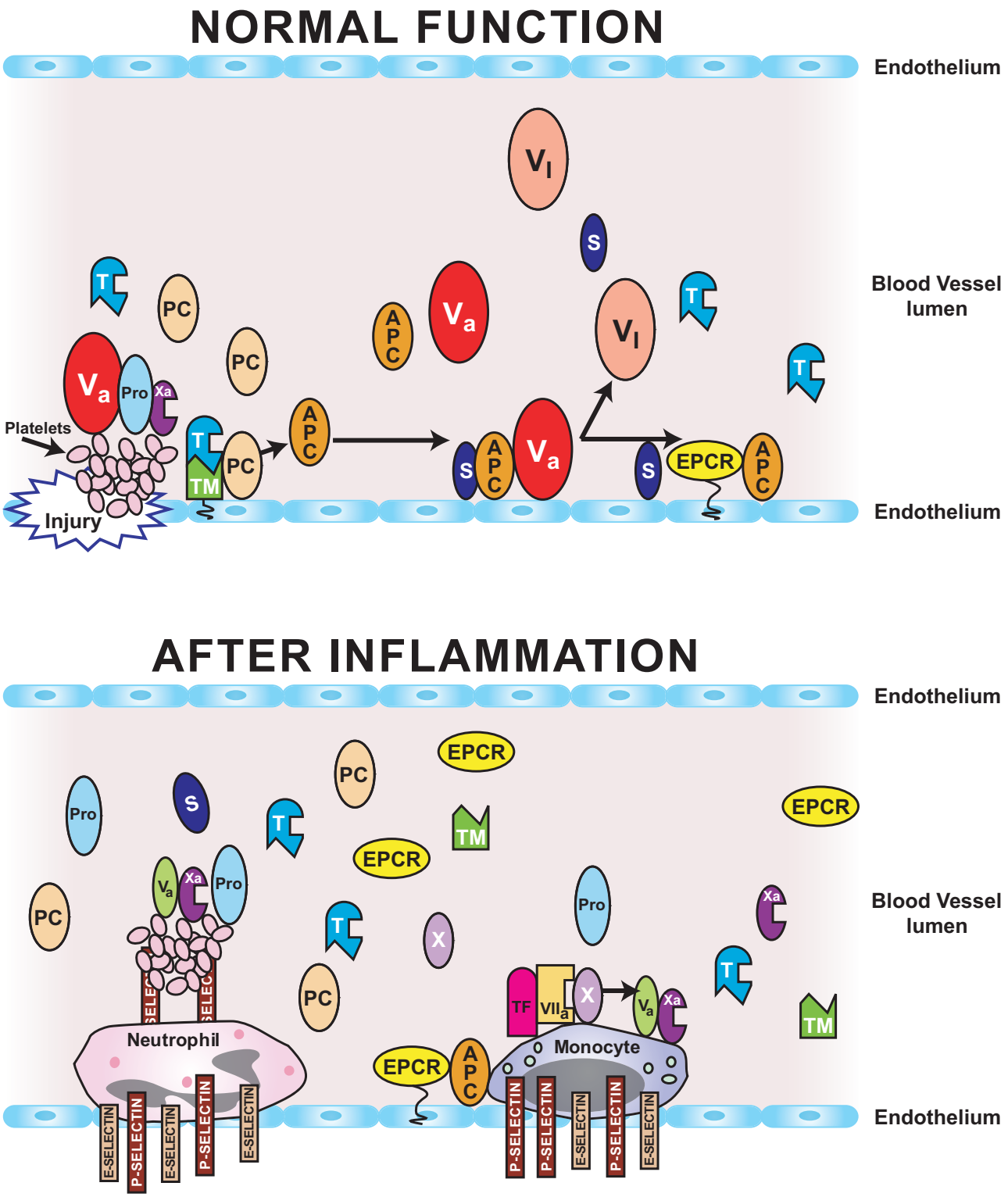

Figure 1. Control of coagulation in normal and inflamed vasculature. Top panel: Normal function. Vascular injury, indicated on the lower portion of the blood vessel wall, initiates prothrombin (Pro) activation, which subsequently induces thrombin (T) formation. Prothrombin activation involves the formation of complexes between factor V_a and factor X_a. Thrombin then binds to thrombomodulin (TM) on the luminal side of the endothelial cell wall, and the thrombin-TM complex converts protein C to APC. APC then binds to protein S (S) on endothelial cell surfaces. The complex composed of protein S and APC then converts factor V_a into an inactive complex (V_I). Protein S and APC also interact with the endothelial cell protein C receptor (EPCR). Bottom panel: After inflammation. During inflammation, specific mediators cause the disappearance of thrombomodulin from the endothelial cell surface. The endothelial cell leukocyte adhesion molecules P-selectin and E-selectin are synthesized and expressed on the surfaces of endothelial cells or platelets. Tissue factor (TF) is expressed on monocytes where it binds to factor VII_a. The TF-VII_a complex converts factor X to factor X_a, which then complexes with factor V_a to generate thrombin from prothrombin. Very little APC is formed, and that which is formed does not function well because of low levels of protein S. Consequently, factor V_a is not activated, and the prothrombin activation complexes are stabilized. Modified from Br J Haematol, 131, Esmon CT, The interactions between inflammation and coagulation, 417–430, Copyright (2005),[9] with permission from Blackwell Publishing.

Table 2. Clinical Trials with TNF Inhibitors

Year	No. of Patients	Inhibitor	Outcome
1995	42	Humanized antibody	Safety study. Treatment resulted in a reduction in circulating cytokines[20]
1993	80	Murine antibody	Safety study. Increased IL-6 predicted mortality[21]
2006	81	Sheep antibody	No reduction in 28-day mortality, decreased circulating TNF and IL-6[22]
1998	92	Chimeric antibody	No reduction in mortality or circulating cytokines[23]
1996	122	Antibody fragment	No improvement in survival, but patients with high baseline IL-6 levels appeared to benefit[24]
1996	141	p75-soluble receptor	Higher mortality with highest dose of receptor[25]
1997	498	p55-soluble receptor	Trend towards reduced mortality, but not significant[26]
1996	564	Monoclonal antibody	More rapid reversal of shock, but no significant improvement in 28-day mortality[27]
2001	944	Antibody fragment	Patients stratified by plasma IL-6 levels, no improvement in survival[28]
1995	994	Monoclonal antibody	Significant reduction in mortality at day 3 but not day 28[29]
2001	1342	p55-soluble receptor	No improvement in survival or the incidence of organ dysfunction[30]
1998	1879	Monoclonal antibody	No improvement in survival[31]
2004	2634	F(ab′)2 monoclonal antibody	Patients stratified by IL-6 levels, TNF inhibition resulted in improved survival[32]

The table is arranged by increasing numbers of patients enrolled in the trial. A meta-analysis of all of the trials together indicates that there is a survival advantage when using the TNF inhibitors.[33]

mation was excessive. The solution was easy: blunt inflammation, and save lives. This concept was driven by four pieces of information. First, septic patients with increased levels of specific mediators such as tumor necrosis factor (TNF) are at increased risk for death.[15] Second, injection of TNF molecules into experimental animals results in widespread inflammatory alterations[16] and tissue injury[17] similar to that observed in septic patients. Third, experimental animals injected with lethal doses of endotoxin display elevated levels of the same mediators. Finally, inhibition of these specific mediators improves survival in endotoxin shock models.[18] Together, these observations launched a series of clinical trials aimed at blocking TNF or interleukin (IL)-1. The results of these clinical trials are summarized, as recently reviewed[19] (Tables 2 and 3).

Although these individual trials did not show significant or dramatic improvements in survival, a meta-analysis of all TNF inhibitors did demonstrate overall improvement.[33] Despite these failed endeavors, exploration of new mediators of organ injury should still be explored. Among the potential candidates are high mobility group 1,[38] triggering receptor expressed on myeloid cells (TREM),[39] and vascular endothelial growth factor.[40] Exciting recent work has also emerged on the role of the complement system in sepsis, undoubtedly providing another fruitful area for investigation.[41]

Table 3. Clinical Trials Using the Interleukin-1 Receptor Antagonist to Treat Sepsis

Year	No. of Patients	Outcome
1995	26	Reduction in surrogate activation markers[34]
1994	99	Dose-related reduction in APACHE score[35]
1997	696	No improvement in survival[36]
1994	893	No reduction in 28-day mortality[37]

None of the trials demonstrated an improvement in survival.

A frequent explanation put forth for the previous inhibitor trial failures was that the anti-inflammatory agents were not administered quickly enough. The classic endotoxin model of "sepsis" drove much of this thinking. In this model, lethal doses of endotoxin are injected intraperitoneally or intravenously into an experimental animal. Endotoxin induces a massive, rapid release of several proinflammatory molecules, including cytokines in both humans and experimental animals.[42] However, subsequent work has shown that models of sepsis that more closely reproduce the clinical situation, such as that caused by cecal ligation and puncture, induce a proinflammatory response that is substantially lower in magnitude and longer in duration than that observed after acute exposure to endotoxin.[43,44] In addition, human clinical trials aimed at giving global immunosuppression with high-dose glucocorticoids failed to yield any improvement in survival. Although the cecal ligation and puncture model of sepsis has become widely used, it may not represent the best preclinical model because most septic patients have a pulmonary source of infection (pneumonia) rather than peritoneal. Controversy remains about the best animal model for the study of sepsis.[45]

In traditional thinking, a mediator must be elevated and detectable to be implicated in the pathogenesis of disease. In septic patients with poor survival, TNF was elevated, and this provided a portion of the rationale on why it should be blocked.[15] However, it must be borne in mind that cytokines may have significant effects at the local level such that detectable plasma levels may not be necessary for the cytokine blockade to be effective. This was shown dramatically in a recent clinical trial of neonatal-onset multisystem inflammatory disease where chil-

dren treated with the IL-1 receptor antagonist demonstrated a remarkable improvement in both objective and subjective criteria.[46] This dramatic improvement occurred even though IL-1 was not detectable in the plasma. As one index of improvement, IL-6 levels were significantly decreased with IL-1 receptor antagonist treatment.

Blunted Inflammatory Response

Another viewpoint would argue that septic patients failed to control the bacterial infection and died as a result of immunosuppression rather than immunostimulation. Recent work has shown that intensive care unit patients have reduced production of both TNF and IL-6 in response to endotoxin stimulation.[47,48] Another study demonstrated that although TNF was reduced, IL-10 production was not impaired in patients with sepsis.[49] These studies would indicate that the proinflammatory response could not be initiated, whereas the anti-inflammatory response continued unabated, producing the equivalent of a blunted inflammatory response. Patients with severe burns and sepsis exhibit defects in their T lymphocytes because the cells fail to proliferate in response to mitogenic stimuli and also fail to produce IL-2 or -12.[50,51] Because blocking the inflammatory response with specific inhibitors was not tremendously effective (see Tables 2 and 3), the possibility was raised that the patients required immunostimulation. However, in the clinical trial using granulocyte colony-stimulating factor to treat 701 patients with pneumonia and severe sepsis, there was no improvement in survival.[52] In a smaller study with 58 patients, granulocyte macrophage colony-stimulating factor also did not improve survival but did decrease length of hospitalization and improve other clinical parameters.[53] The blunted monocyte response observed in septic patients has been reversed with interferon-γ, and systemic therapy successfully cleared sepsis in eight of nine patients.[54] A larger clinical trial with 416 trauma patients indicated that interferon-γ therapy did not reduce infections or overall mortality but did reduce deaths due to infections.[55]

Unknown Inflammatory Response

The previous data would indicate that the inflammatory response in septic patients is complex and not as neatly defined as enhanced or decreased. Because of this heterogenous response, some patients will benefit from blunting their inflammation, whereas others would be better served by augmenting their inflammatory response. Tailoring the therapy to the individual patient occurs with many diseases, and sepsis should not be an exception. Work with the preclinical model of sepsis has indicated that blunting inflammation only improves survival in those animals at a high risk of dying.[56] Clinical evidence favoring a tailored response comes from sepsis trials demonstrating that low-dose glucocorticoid therapy is most effective in those patients with an impaired adrenal response.[57]

Roger Bone observed, "We should spend more time learning how to achieve an accurate diagnosis and less time searching for a magic bullet."[58] In this context, different plasma markers have been proposed as diagnostic markers for the presence of sepsis as well as the severity of sepsis. These molecules may not actually participate in the cell or organ injury but may serve as markers for the presence and severity of sepsis. It must be acknowledged that controversy exists in this area. Some investigators believe that IL-6 serves as a marker of injury,[59] whereas others believe that IL-6 may be responsible for the altered pathophysiology.

Defining the precise inflammatory response also represents a significant issue, one frequently debated within my own laboratory. Measuring plasma levels of cytokines is probably not sufficient to determine whether a patient or experimental animal is hyperinflammatory or hypoinflammatory. If only the proinflammatory mediators are measured, then the patient will appear hyperinflammatory. Conversely, if only cytokine antagonists or anti-inflammatory mediators are measured, a person appears to be hypoinflammatory. In fact, both proinflammatory and anti-inflammatory mediators may be circulating at the same time in the plasma.[44] Better methods for determining the precise immunological status may be achieved via either a multiplex format for cytokine measurements[60] or an evaluation of cellular function.[54]

Cellular Dysfunction

Many cellular aspects become dysfunctional in sepsis and may be characterized as either excessive activation or depressed function. Excessive activation refers to cells that are primed such that they respond in a very vigorous manner to a second stimulus. An example of excessive activation would be neutrophils generating excess toxic products that cause damage to nearby cells.[61] An example of depressed function would be neutrophil failure to phagocytize and clear invading pathogens.

One of the current areas of active investigation concerning cellular function is the induction of cellular apoptosis or necrosis. The signaling mechanisms and molecules that induce apoptosis are currently being described in great detail by a number of investigators. One must carefully evaluate the literature with regards to apoptosis because some detection methodologies suffer from a high rate of false-positive reactions with subsequent controversy concerning the findings.[62,63] Apoptosis and necrosis in the field of sepsis have been reviewed quite nicely in the recent past.[64,65] Apoptosis may contribute to the pathogenesis of sepsis by delayed removal of those cells that should be removed, ie, neutrophils, and early removal of those cells that should not be removed, ie, lymphocytes.

Lymphocyte Apoptosis

Lymphocytes are critical cells in the response to sepsis, and the interactions between the innate and adaptive immune system are becoming increasingly important.

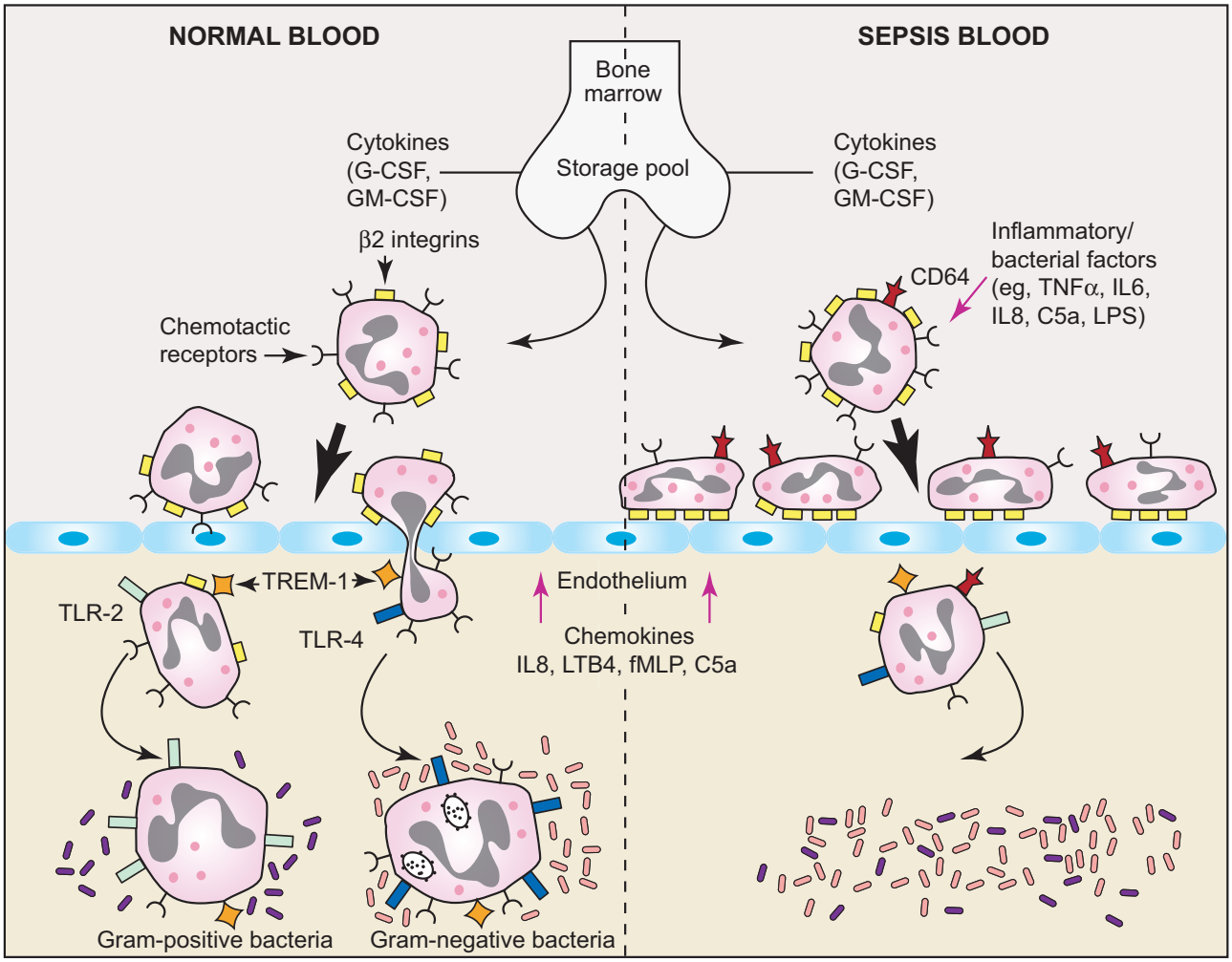

Figure 2. Proposed model for dysregulation of neutrophil recruitment to bacterial infection in nonpulmonary tissue under normal conditions (left) and in sepsis (right). Colony stimulating factors [granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF)] induce the release of neutrophils from the bone marrow. Under normal conditions, large numbers of the peripheral blood neutrophils enter sites of bacterial infection by first adhering to activated endothelial cells and then migrating along a gradient of chemotactic factors. These chemotactic factors are produced at the local site of infection. Neutrophils use Toll-like receptors (TLR-2 or TLR-4) to interact with pathogen-associated molecular patterns on bacteria to phagocytize and eliminate the pathogens. In contrast, neutrophils from septic patients have increased expression of surface integrins, which promote firm adhesion to endothelial cells. As a consequence, the neutrophils remain bound more tightly to the endothelial cells and fail to migrate appropriately into the site of the bacterial infection. Redrawn from The Lancet, 368, Brown KA, Brain SD, Pearson JD, Edgeworth JD, Lewis SM, Treacher DF, Neutrophils in development of multiple organ failure in sepsis, 157–169, Copyright (2006),[69] with permission from Elsevier.

Pioneering studies by Hotchkiss et al have defined that septic patients have significant apoptosis of lymphocytes.[62] These apoptotic lymphocytes were observed in virtually all lymphoid organs including the obvious locations, such as the spleen and thymus, but also in the gastric associated lymphatic tissue and essentially wherever collections of lymphocytes exist. These murine experiments were extended in a very interesting study when these investigators performed rapid autopsies in the intensive care unit on patients who died from sepsis.[66] It was necessary to perform the autopsies rapidly to collect tissue that did not display substantial postmortem autolysis. Lymphocyte apoptosis may be the cause of the reduced lymphocyte function in septic patients previously described (failure to produce cytokines[50,51]). In septic patients, there is a combination of apoptotic and necrotic cell death. The importance of apoptosis in the pathophysiology of sepsis has been demonstrated in multiple studies.[65] It has been shown transfer of apoptotic splenocytes will worsen survival in a mouse model of sepsis, whereas transfer of necrotic splenocytes improves survival.[67]

Neutrophil Hyperactivity

Neutrophils are critical components of the innate immune response to infectious challenges. Neutropenic patients, regardless of the cause of the neutropenia, and patients with neutrophil dysfunction are at increased risk for the development of infectious complications.[68] There is no question that an appropriate, robust neutrophil response benefits the patient and helps to eradicate an infectious focus. The difficulty lies in attempting to define an appropriate response versus a hyperactive response,[69] as illustrated in Figure 2. Patients who have suffered trau-

matic injury are at increased risk for the development of multisystem organ failure, and neutrophils recovered from such patients demonstrate increased chemotactic responses to CXC chemokines.[70] However, neutrophils isolated from septic patients demonstrate decreased chemotaxis toward IL-8 and depressed expression of CXCR2.[71] These results were further explored in a article showing that high CXCR2 function correlates with the development of organ injury, ie, acute respiratory distress syndrome, whereas low function predisposes to pneumonia and sepsis.[72] These studies aptly demonstrate the heterogeneity of the septic response in that some patients have an excessive response, whereas others have a blunted response.

Modulating the recruitment of neutrophils to the site of inflammation has potential benefits, but this should be via specific modulation rather than global inhibition of neutrophil function. Recently, a class of immunomodulatory compounds termed pepducins, which are cell-penetrating lipopeptides, have been used to target CXC chemokine receptors.[73] These compounds were able to block neutrophil chemotaxis to CXC chemokines without affecting neutrophil responses to other stimulants such as the formyl peptides. These compounds were used in the murine model of cecal ligation and puncture-induced sepsis, where they were able to significantly improve survival.

Another significant issue concerns inappropriate apoptosis of neutrophils in the septic patients. Neutrophils in the circulation typically have a very short lifespan of approximately 24 hours. However, patients with sepsis have a delay in their neutrophil apoptosis, causing them to persist longer in the bloodstream. This is due to prolonged activation of nuclear factor κB and reduced caspase 3 levels.[74] As a result, the septic patient has increased numbers of activated cells with the potential to cause organ injury. However, it must be borne in mind that these activated neutrophils are also the precise defenders that are critical in the innate immune response to clear an infection.[75]

Endothelial Cell Failure and Apoptosis in Other Cells

Endothelial cells reside at the critical interface between the blood and tissue. Intact endothelial cells exhibit anticoagulant properties through elaboration of anticoagulant molecules such as protein C. These cells also serve as a barrier between blood products and procoagulant molecules, such as heparin, residing in the extracellular matrix. Endothelial disruption comes about because of increased expression of adhesion molecules on the endothelial cells, resulting in attachment of white blood cells. It has also become increasingly clear that abundant cross talk exists between the coagulation system and the inflammation system in sepsis.[76]

Endothelial cells will undergo apoptosis in response to several mediators *in vitro*, including some infectious agents. However, endothelial cells are relatively resistant to the effects of endotoxin, and several investigators have failed to demonstrate convincing evidence of endothelial cell apoptosis during sepsis.[62] Although it is strongly suspected that endothelial cells are dysfunctional in septic patients, clear-cut documentation during *in vivo* settings has been difficult to obtain. Other cells within the body also fail to function normally, and it has been demonstrated that increased apoptosis of dendritic cells, macrophages/monocytes, and mucosal epithelial cells, among other cells, are present in septic patients.[65]

Metabolic Alterations

Glycemic Control

Intensive insulin therapy has been shown to improve mortality among critically ill patients in a prospective randomized clinical trial involving 1548 patients.[77] The reduced mortality was particularly impressive in those septic patients with a proven focus of infection. There were additional beneficial effects to maintaining strict glucose control including reduced infections, reduced acute renal failure, and decreased muscle wasting and anemia. Consequently, current recommendations for patients in the trauma unit call for strict glycemic control.[78] Patients who are critically ill exhibit insulin resistance and hyperglycemia, a condition that has been termed the diabetes of stress. These high blood glucose levels have been shown to decrease the function of polymorphonuclear neutrophils, including diminished bactericidal activity.[79] Further analysis of the patients with strict glycemic control indicated that there seems to be substantial protection of the endothelial cells.[80] This was manifested by significantly reduced circulating levels of intracellular adhesion molecule-1 on the endothelial cells. However, it should be noted that strict glycemic control is not without controversy.[81] There are issues with potential hypoglycemia[82] as well as the costs associated with close monitoring.

Low-Dose Steroids

Previous work has demonstrated that high-dose glucocorticoids aimed at blunting the inflammatory response do not provide an improvement in outcome, as recently reviewed.[83] In fact, high-dose steroids have been associated with increased mortality in at least one study. Evidence exists that some patients with sepsis have adrenal failure, and these patients benefit from having replacement doses of glucocorticoids administered over a prolonged time.[57] The steroids were not used at a dose necessary to blunt the inflammatory response but were given as replacement therapy for a failing organ, in this case, the adrenal gland.

Early Goal-Directed Therapy

An important study by Rivers et al demonstrated that early administration of fluids and blood products to septic patients in the emergency room will significantly improve survival.[84] This study was important because the types of

fluids and the total volume of fluids did not change; it was only when the fluids were given. The use of more sophisticated monitoring techniques in the emergency room allowed better determination of the resuscitation status of the patient.

Conclusion

Numerous immunopathologic alterations account for the morbidity and mortality of sepsis. Active research by several investigators continues to define the principal alterations in sepsis, though significant challenges remain before this devastating process is understood and conquered. Numerous controversies swirl in the sepsis arena. Critical questions that remained unanswered in 2007 concerning the pathogenesis of sepsis include the following: 1) What is the precise role of coagulopathy in the organ injury and mortality of sepsis? 2) Are septic patients hyperinflammatory or immuno-comprimised? 3) Is there a magic bullet that can be used to improve survival of septic patients? 4) What cellular alterations drive substantial organ injury? 5) How should the metabolic and physiological alterations be appropriately managed? Although advances have been made, much work remains. Understanding the altered pathophysiology will help to guide the management of sepsis.[85]

Acknowledgments

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