Mechanisms of sepsis-induced organ dysfunction

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Background: **The past several years have seen remarkable advances in understanding the basic cellular and physiologic mechanisms underlying organ dysfunction and recovery relating to sepsis. Although several new therapeutic approaches have improved outcome in septic patients, the far-reaching potential of these new insights into sepsis-associated mechanisms is only beginning to be realized.**

Aim: **The Brussels Round Table Conference in 2006 convened >30 experts in the field of inflammation and sepsis to review recent advances involving sepsis and to discuss directions that the field is likely to take in the near future.**

Findings: **Current understanding of the pathophysiology underlying sepsis-induced multiple organ dysfunction highlights the multiple cell populations and cell-signaling pathways involved in this complex condition. There is an increasing appreciation of interactions existing between different cells and organs affected by the septic process. The intricate cross-talk provided by temporal changes in mediators, hormones, metabolites, neural signaling, alterations in oxygen delivery and utilization, and by modifications in cell phenotypes underlines the adaptive and even coordinated processes beyond the dysregulated chaos in which sepsis was once perceived. Many pathologic processes previously considered to be detrimental are now viewed as potentially protective. Applying systems approaches to these complex processes will permit better appreciation of the effectiveness or harm of treatments, both present and future, and also will allow development not only of better directed, but also of more appropriately timed, strategies to improve outcomes from this still highly lethal condition. (Crit Care Med 2007; 35:2408–2416)**

Key Words: sepsis; multiple organ failure; pathogenesis

Recent years have seen remarkable advances in our understanding of the basic cellular and physiologic mechanisms underlying organ dysfunction and recovery relating to sepsis. The far-reaching potential of these new insights are only just beginning to be realized as new therapeutic approaches. The Brussels Round Table Conference in 2006, whose discussions are summarized in this article, provided an opportunity to review recent insights into pathophysiologic mechanisms and to discuss likely future directions, both in terms of investigation and treatments. (A full listing of Round Table participants is located in the Appendix.)

Genetics

Various genetic polymorphisms are linked to outcome in sepsis (1, 2). Although relevant studies are often flawed in terms of sample size, categorization of clinical problems (particularly microbiology and site of infection), and accuracy in determining nucleotide substitutions, several have been sufficiently large to provide convincing associations between genetic alterations and outcome (e.g., substitution of G to A in the tumor necrosis factor-α promoter at position 308) (2, 3).

The Toll-like receptor (TLR) family induces cellular activation after engagement with microbial products such as lipopolysaccharide. Certain TLR4 receptor polymorphisms are associated with decreased cellular activation and bronchial reactivity post–lipopolysaccharide exposure (4) and a predisposition to shock with Gram-negative organisms (5).

Increased activation of the transcription factor nuclear factor-κB occurs in sepsis and acute lung injury. As nuclear factor-κB regulates many of the proinflammatory mediators associated with organ dysfunction, associations between enhanced nuclear factor-κB activation and poor outcome are not unexpected (6, 7). Engagement of TLR4 with lipopolysaccharide, or TLR2 with Gram-positive bacterial products such as peptidoglycan, result in enhanced nuclear translocation of nuclear factor-κB after activation of upstream kinases. The interleukin-1 receptor–associated kinase has an amino acid change at position 532 in approximately 25% of white people. Septic patients with this interleukin-1 receptor–associated kinase variant haplotype had increased nuclear factor-κB activation, more time on ventilatory support, greater vasopressor requirements, and an increased mortality rate (8).

Mediators of Cellular Activation in Sepsis

Cytokines. As multiple cell populations are activated by microbial products, it is not surprising that many proinflammatory and anti-inflammatory cytokines are involved in the host response to infection. Several cytokines, including tumor necrosis factor-α and interleukin-1, have been targeted by specific pharmaco-

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logic interventions but without clear effects on clinically important variables (9).

New cytokines involved in the pathophysiology of sepsis continue to be identified. Important roles are occupied by macrophage inhibitory factor and high mobility group box protein type 1 (HMGB1) (10–12). Macrophage inhibitory factor is an early to slightly later-acting proinflammatory mediator involved in lipopolysaccharide-induced signaling. Blockade of macrophage inhibitory factor improves survival in multiple models of sepsis (12). HMGB1 is a late-acting proinflammatory mediator that interacts with multiple receptors, including TLR2, TLR4, and the receptor for advanced glycation end-products (13). Circulating HMGB1 levels remain elevated for prolonged periods in septic patients (11). In experimental models of intra-abdominal sepsis, blockade of HMGB1, even 24 hrs after the initiation of infection, still resulted in improved survival (14). Therapeutic approaches to inhibit the actions of macrophage inhibitory factor and HMGB1 are being explored in early clinical trials.

Nitric Oxide and Reactive Oxygen Species. Nitric oxide (NO) is involved in smooth muscle relaxation, and increased NO release contributes to sepsis-induced hypotension. However, therapeutic trials indiscriminately blocking NO production or its actions were associated with deleterious physiologic and clinical outcomes (15, 16). NO also has other roles in sepsis, including intracellular signaling involving activation of proinflammatory pathways. New approaches modulating activation of inducible NO synthase, the enzyme responsible for much of the sepsis-induced increase in NO, may offer more beneficial effects in this setting (17).

Reactive oxygen species (ROS) play an important role in producing organ system dysfunction in sepsis and acute lung injury (18). Although nonspecific scavengers of ROS have not been shown to improve outcomes, more specific molecules, such as selenium or mimetics of superoxide dismutase, may be beneficial (19, 20). Like NO, ROS also have an important intracellular role in inducing pathways associated with acute inflammation and organ system dysfunction (21). The source of such intracellular oxygen species remains to be determined, although mitochondria play an important role.

Heat Shock Proteins. Increased amounts of heat shock proteins are produced during sepsis. Several, particularly heat shock protein 90, have a cellular protective effect. Overexpression of heat shock protein 90 and, perhaps, other heat shock proteins decreased mortality and tissue damage in animal models (2, 22).

Immune and Cellular Responses to Sepsis

During sepsis, early activation of immune cells—monocyte/macrophages, lymphocytes, and neutrophils—is followed by down-regulation of their activity (23). This leads to a state of immunoparesis and an increased risk of superinfection. The balance between proinflammatory and anti-inflammatory response is affected locally by surrounding cells that differ between compartments. Circulating monocytes, resident tissue macrophages, and adherent macrophages that have migrated to inflamed cavities display distinct properties in terms of signaling or phagocytosis. Likewise, the responsiveness of neutrophils and lymphocytes obtained from blood differs from cells obtained from inflamed peritoneum and lung (24–26).

This compartmentalization of immune cell populations in sepsis is well highlighted by results from septic mouse models revealing gene expression profiles that were either organ specific, common to more than one organ, or distinctly opposite between organs (27, 28). In light of the above, it has been suggested that *leukocyte reprogramming* is perhaps a more appropriate term, rather than *anergy*, *immunosuppression*, *immunoparesis*, and other such descriptors in current parlance.

Local conditions affect the cellular immune response. Examples include the ten-fold variation in tissue oxygen tension in different organ beds, in levels of local antioxidants such as glutathione, and in tissue concentrations of substrates such as arginine and glutamine. Peripheral blood lymphocytes show reduced capacity to proliferate, monocytes exhibit an attenuated respiratory burst, and neutrophils have reduced phagocytic activity (24, 29, 30). However, responsiveness to certain agonists is often maintained, and production of anti-inflammatory mediators is frequently enhanced.

Cross-talk between compartments is also recognized in sepsis. The lung, kidney, and other organs are affected by distant organ injury. This may be due to leakage of mediators from one inflamed/activated compartment into the systemic circulation. An example is translocation of endotoxin from the gut into portal and lymphatic drainage systems (31). A similar finding has also been made in the lung, where greater amounts of proinflammatory mediators leak into the circulation, depending on the ventilator strategy used (32).

Neuro-immunomodulation. Release of neuromediators that are proinflammatory (e.g., substance P, norepinephrine) or anti-inflammatory (e.g., acetylcholine, epinephrine) will significantly influence the local inflammatory response. Vagal nerve stimulation, activating the "cholinergic anti-inflammatory pathway," can attenuate the hypotensive and inflammatory mediator response induced by a septic insult (33). These protective effects are mediated by acetylcholine and specific nicotine receptors, with the $\alpha 7$ subunit of the nicotinic acetylcholine receptor seeming to be particularly important.

Leukocyte Populations. Adhesion of neutrophils to activated endothelium results from the coordinated activities of selectins, binding ligands, integrins, and members of the immunoglobulin superfamily (34, 35). This process allows neutrophil adhesion and also primes their respiratory burst, phagocytosis, and other actions. After adhesion, leukocytes traverse the endothelium paracellularly or transcellularly and then migrate extravascularly into the tissues, where they are attracted to pathogens by chemotaxis. They bind to microorganisms by recognizing pathogen-associated molecular patterns using receptors that include CD14 and members of the TLR family. After engulfment, phagocytosis occurs by various cytotoxic mechanisms that can be broadly characterized as oxygen dependent (e.g., involving free radicals) or independent (e.g., antimicrobial peptides such as the defensins and proteolytic enzymes such as elastase and cathepsin G).

Termination of neutrophil-mediated inflammation and their subsequent clearance from an inflammatory focus occurs through apoptosis, followed by uptake and removal by macrophages. Neutrophils are constitutively apoptotic, and this program is normally activated within hours of maturation and release from marrow stores. Paradoxically, neutrophil apoptosis is delayed in sepsis as opposed to the accelerated apoptosis described in lymphocytes (23, 36). As apoptosis is fundamental to the resolution of inflammation, a balance must be reached between neutrophil recruitment and removal at

the site of infection, optimizing host defenses yet minimizing host cytotoxicity. The disruption of apoptotic clearance in sepsis will sustain inflammation and enhance injury to lung, liver, and other organs. The extent to which delayed apoptosis contributes to the development of multiple organ dysfunction remains unknown. Better understanding of these programmed cell death pathways will enable timed interventions and, potentially, improved outcomes.

The macrophage has multiple roles in sepsis (37). It can sense foreign molecules and physical stresses in the microenvironment. Stimuli that modulate macrophage activation include microbial products and other events typically seen in tissue injury or stress, such as low oxygen tension, acidosis, extracellular adenosine triphosphate, and proinflammatory molecules, such as HMGB1 and thrombin. The consequent production of cytokines and chemokines by macrophages and other neighboring cells further amplifies the inflammatory response (38).

Kupffer cells play an essential role in clearing bacteria and their products from the portal circulation, although without generating an exaggerated local inflammation. This is in marked contrast to the alveolar macrophage, which seems to be a relatively inactive cell population, and again highlights the different roles and activities of different tissue macrophages (39, 40).

Circulating blood monocytes seem to be "reprogrammed" during sepsis to generate more anti-inflammatory mediators (41). This may prevent excessive, nonspecific, and harmful systemic endothelial and leukocyte activation where it is not desired but may also predispose the host to secondary infection. In addition, as described earlier, the macrophage has a major role in removing immune cells from the site of inflammation to enable resolution.

Endothelium. Endothelial activation plays a major role in the cellular immune response to sepsis (34, 35). Endothelial phenotypes vary markedly across the vascular system, with marked heterogeneity in function both anatomically and in different organs (34). For example, control of leukocyte trafficking is predominantly located in postcapillary venules, whereas regulation of vasomotor tone is mainly arteriolar. In sepsis, endothelial function is influenced by biomechanical forces, such as shear stresses, that lead to release of NO and stimulation of coagulation pathways. There is ample evidence for cross-talk between the endothelium and circulating cells, including erythrocytes, platelets, and leukocytes, and with supporting cells, such as vascular smooth muscle and pericytes, and with underlying parenchymal cells. In sepsis, these lines of communication break down as a result of inflammatory and immune activation, hypoxia, and changes in temperature, pH, and osmolarity.

Structural changes to the endothelium induced by sepsis include contraction, swelling/blebbing, and shedding from the underlying extracellular matrix. The number of circulating endothelial cells seems to be a marker of vascular injury, whereas the number of circulating marrow-derived endothelial progenitor cells reflects the host's repair capacity (42, 43).

There are numerous functional effects of sepsis on the endothelium (34, 35). These include increased expression of cell adhesion molecules and trafficking of leukocytes, activation of clotting pathways, and increased production of mediators that have effects on vascular tone and capillary leak. The most important endothelial function in the context of sepsis is probably the regulation of permeability.

Epithelium. The alveolar epithelium usually forms a tight barrier, resisting passive movement of even small molecules and solutes such as electrolytes. It also produces surfactant to maintain normal stability and can remove excess alveolar fluid. β_2-Adrenergic stimulation seems to be particularly important in enhancing the rate of alveolar fluid clearance; this is now being investigated as a therapeutic tool for acute lung injury. The alveolar epithelial barrier can be injured in sepsis, allowing excess leak of proteinaceous fluid and a decreased rate of fluid clearance (44, 45).

Coagulation. Inflammation-induced activation of coagulation, deposition of fibrin, and inhibition of fibrinolysis can be considered instrumental in containing inflammatory activity to the site of infection (35, 46). However, when this system is insufficiently controlled, it may be detrimental to the host. Disseminated intravascular coagulation is the most severe clinical manifestation of abnormal coagulation variables induced by sepsis. Generation of thrombin and other proteases within the coagulation pathway is a potent proinflammatory stimulus and is effected through activation of protease-activated receptors that induce expression of proinflammatory cytokines and chemokines.

Systemic Pathways Contributing to Organ Dysfunction in Sepsis

Precise mechanisms by which sepsis produces multiple organ dysfunction remain unknown. The circulation is clearly affected at both macrocirculatory and microcirculatory levels, compromising tissue perfusion and normal organ functioning (47). Irrespective of changes in oxygen and substrate provision, the cells themselves may react to a septic insult by modifying their behavior, function, and activity (48). Examples of direct cellular injury implicated in sepsis include peroxidation of lipid membranes, damage or modification to proteins (e.g., enzymes, receptors, transporters), and damage to DNA. Remarkably, despite all the above, minimal evidence of cell death is seen in most affected organs during sepsis (49). This may reflect the relatively slow progression of the disease, allowing cellular phenotypes to adapt more successfully to a reduced oxygen supply and damaging external factors. This is in contrast to more abrupt cardiorespiratory insults, such as cardiac arrest or massive hemorrhage. Such cellular adaptation will also facilitate recovery from the septic process, as many cell types are poorly regenerative and their permanent loss or destruction would hinder restoration of normal organ functioning and long-term survival (48) (Fig. 1).

Vascular Function. In sepsis, hypotension arises from a combination of hypovolemia secondary to external fluid losses and internal fluid redistribution, vasodilatation, and loss of normal vascular tone (hyporeactivity). Factors implicated in this process include 1) excess production of NO and its metabolites, 2) activation of vascular potassium channels, and 3) changes in hormone levels (e.g., cortisol, vasopressin) or the vascular responsiveness to these hormones, either at the level of the receptor (e.g., adrenergic receptor down-regulation) or further downstream (e.g., intracellular calcium signaling) (50, 51).

Although cardiac output is usually elevated in septic patients after adequate fluid resuscitation, myocardial function is often depressed (52). Tissue oxygen delivery is also altered, with diverse effects on different organ beds and heterogenous effects on oxygen consumption. The mi-

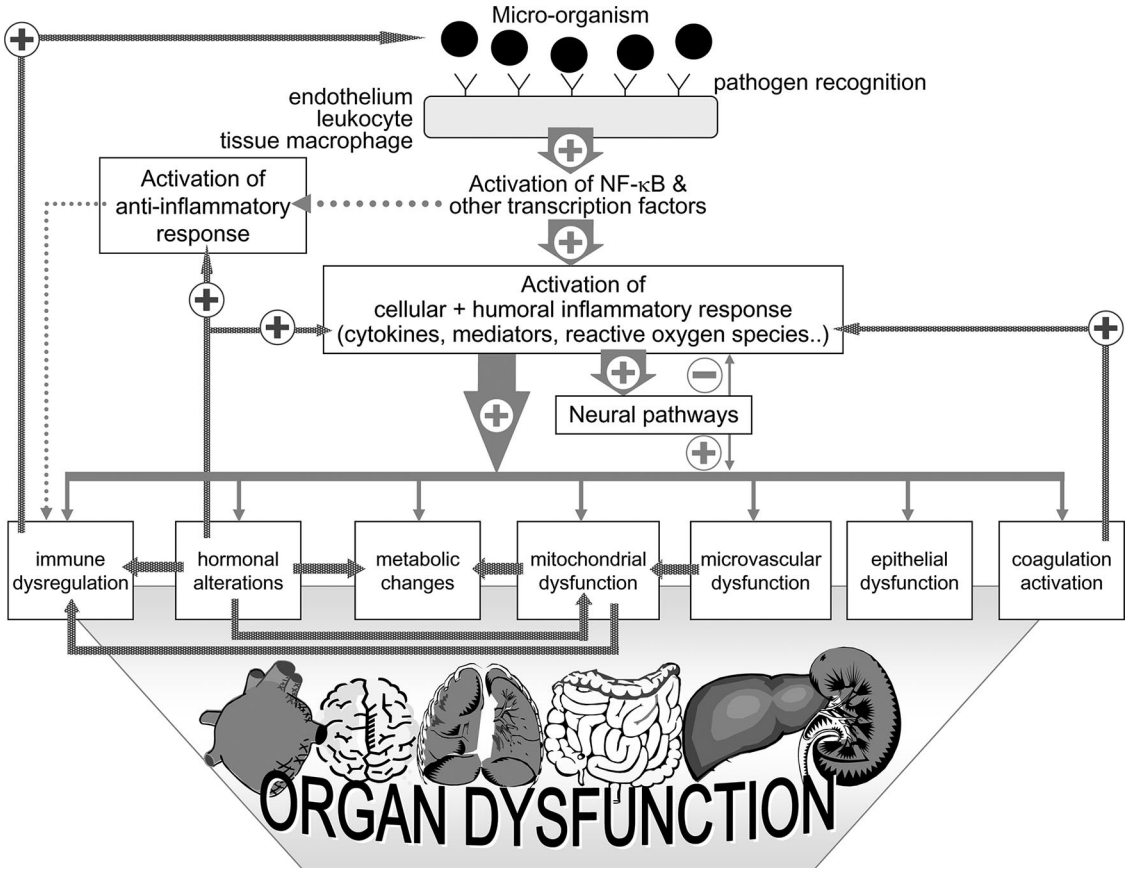

Figure 1. Systemic pathways contributing to organ dysfunction in sepsis. *NF-κB,* nuclear factor-κB.

crovasculature is compromised in sepsis, both before and after seemingly adequate volume resuscitation. In humans, this has been directly shown in the sublingual circulation (47), although how these changes relate to other organ beds remains to be determined.

The severity of shock and a requirement for high-dose catecholamines are both important prognostic indicators. Because early correction of hypotension and tissue hypoperfusion has a major impact on survival (53), the role of the circulation in causing organ dysfunction is vital, at least in the initial phases of the disease.

Regional changes in blood flow are well described in sepsis. There is a disproportionate increase in metabolic requirements of the hepatosplanchnic area that often exceeds the increase in splanchnic blood flow (54). Variable effects have been reported on gut blood flow, and studies suggest redistribution of blood away from the mucosa and microvilli (55). Coronary perfusion does not seem to be affected, despite coexisting myocardial depression (56). Renal hypoperfusion is implicated in the pathogenesis of renal failure, although most of the evidence is derived from studies using under-resuscitated animal models (57). Indirect evidence for changes in afferent and efferent arteriolar tone within the kidney is drawn from the improved urine output seen with vasopressin (acting on the efferent arteriole) as compared with norepinephrine (acting primarily on the afferent arteriole) (58).

There is an ongoing debate regarding the contributions of microvascular dysfunction and bioenergetic derangements toward the development of multiple organ failure. Both can be combined within a paradigm that supports both findings. Microvascular shunting can lead to regional areas of tissue hypoxia and reduced generation of adenosine triphosphate (59). In addition, decreased mitochondrial respiration can be related to decreased expression of mitochondrial protein, hormonal influences, and direct inhibition/damage from reactive nitrogen and oxygen species, despite adequate oxygenation (cellular dysoxia) (48). If metabolic activity continues in excess of energy provision, adenosine triphosphate levels will fall below the threshold that stimulates cell death pathways. However, as cell death is an uncommon phenomenon in sepsis (41), this implies a metabolic shutdown akin to hibernation that could explain the functional yet minimal morphologic derangements seen in multiple organ failure. The increased venous oxygen saturations seen in resuscitated sepsis could be explained by a combination of shunting and decreased mitochondrial utilization, whereas the maintained or elevated tissue oxygen tensions recorded in various organ beds (60, 61) may represent a reduction in metabolic activity to match, or even exceed, the reduction in energy supply related to decreased oxygen delivery or mitochondrial dysfunction.

Metabolic Alterations. Considerable attention has been paid to the role of hyperglycemia in the pathogenesis of organ failure since the finding that intensive insulin therapy with tight glycemic control resulted in survival benefit and prevention of further organ failure (62). Was the gain achieved mainly through prevention of hyperglycemia or from provision of additional insulin? The acute toxicity of high glucose levels may be

related to cellular glucose overload and resulting oxidative stress, particularly affecting cells whose uptake of glucose is insulin independent, such as hepatocytes, neurons, gut mucosal, renal tubular, immune, and endothelial cells (63). Such cell populations rely on the glucose transporters (GLUTs)-1, -2, and -3, as opposed to cells whose glucose uptake is insulin dependent via the GLUT-4 transporter, such as heart, skeletal muscle, and adipose tissue. These latter cells are relatively protected from glucose toxicity by down-regulation of the GLUT-4 receptor. By contrast, proinflammatory cytokines and hypoxia up-regulate expression and membrane localization of GLUT-1 and GLUT-3.

Hyperglycemia causes severe oxidative damage to mitochondria. Such mitochondrial injury was particularly apparent in hepatocytes taken postmortem from septic nonsurvivors, whereas muscle mitochondria were essentially spared, likely due to GLUT-4 down-regulation (64). Hyperglycemia also produces a variety of metabolic and nonmetabolic effects, including alterations in the circulating lipid profile, endothelial dysfunction, and decreased neutrophil function, including phagocytosis and opsonic activity (63). Some or all of these changes may negatively affect organ function and survival.

Additional metabolic derangements are well recognized in sepsis (65, 66), although these may represent, at least in part, a teleological response to injury and decreased food intake. Therapeutic interventions such as catecholamines may further perturb the metabolic picture by enhancing insulin resistance and increasing lipolysis (67).

A large proportion of whole body energy expenditure in sepsis is used on protein metabolism (68). With the common accompaniment of decreased food intake, skeletal muscle breakdown increases considerably in sepsis. This is particularly true for alanine and glutamine, the latter being a primary fuel substrate for immune cells. Glutamine also plays a central role in nucleotide synthesis, in amino acid metabolism, and in the interface between amino acids and carbohydrate metabolism (69).

Organ-Specific Mechanisms of Dysfunction

One of the many fascinating paradoxes of sepsis is its variable effect on the body's organs. Why a similar infection will stimulate a systemic inflammatory process that affects some organs but not others, and induce distinct profiles in different patients, is still a matter of conjecture. Some organs can escape relatively unscathed, whereas others are affected both early and severely.

Lung. The lung is involved early in the inflammatory process, with ingress of activated neutrophils, interstitial edema, loss of surfactant, and fibrinous alveolar exudates (70). Later, the pathology is characterized by mononuclear cell infiltrates, proliferation of type II pneumocytes, and interstitial fibrosis. Iatrogenic influences cannot be underestimated because ventilator-induced lung injury, oxygen toxicity, and the large volumes of fluid used for circulatory resuscitation amplify the degree of lung dysfunction and arguably alter its pathology (71). Mortality rates from acute lung injury have decreased, likely related to more adroit management of mechanical ventilation, use of fluid, and advances in supportive care (72).

Postmortem studies show the epithelium to be more severely affected than the endothelium, with many areas of exposed alveolar basement membrane (73). The cause of this injury remains unclear, but necrotic and apoptotic cell death are likely to be involved (74), with shear stresses induced by alveolar recruitment and derecruitment playing an important role (75).

Apoptosis can be initiated by receptor-mediated and mitochondrial pathways (76). The former involves a family of "death" receptors triggered by protein ligands either on the surface of effector cells or in the soluble phase in surrounding extracellular fluid. Fas (CD95) is one such membrane receptor protein that mediates apoptosis via activation of caspases (intracellular proteases), resulting in cleavage of DNA (77). Soluble FasL is significantly increased in bronchoalveolar fluid taken from patients at high risk of developing acute lung injury (78). Of note, soluble FasL levels did not increase further after the onset of clinical lung injury. The accumulation of soluble FasL is thought to create a proinflammatory phenotype in alveolar macrophages and newly recruited mononuclear cells. Despite such findings, many questions remain about the mechanistic importance of apoptosis in clinical settings that are significant risk factors for acute lung injury, including sepsis. Indeed, apoptotic pathways within the lung may be critical to the repair phase by clearing proliferating type II pneumocytes and fibroblasts (79).

Another recent area of interest in the pathogenesis of lung injury has been the role of ROS. Apart from direct cytotoxic effects, ROS have important effects on the inflammatory response mediated via changes in oxidant/antioxidant balance, redox signaling, and iron-mediated catalytic reactions (80, 81). Iron availability also regulates activity of the nuclear transcription factor hypoxia inducible factor that responds to low oxygen tensions by up-regulating expression of numerous genes, including those encoding for vascular endothelial growth factor, erythropoietin, and inducible heme oxygenase-1 (82). Catabolism of heme by heme oxygenase-1 produces carbon monoxide, bilirubin, and free iron. Although heme oxygenase-1 is usually considered cytoprotective, it can produce lung injury in animal models relevant to critical illness via mechanisms related to formation of low molecular mass, redox-active iron (83). In rats subjected to iron overload, heme oxygenase-1 was up-regulated faster in lung than in other organs (84).

Brain. Septic patients present with clinical features of encephalopathy, including agitation, confusion, and coma. In autopsy studies, various cerebral lesions are found, including ischemia, hemorrhage (26%), microthrombi (9%), microabscesses (9%), and multifocal necrotizing leukoencephalopathy (9%) (85). How much of this change represents the dying process and any subsequent delay in sampling remains uncertain. The prevalence and features of brain lesions in the antemortem period and in survivors of sepsis remain to be explored.

The brain senses the presence of microorganisms and inflammation through different pathways (86). There may be direct diffusion of microorganisms and inflammatory mediators into cerebral structures due to disruption of the blood–brain barrier, endothelial activation and leakage enabling release or passive diffusion of cytokines and bacterial products, such as lipopolysaccharide, and input via afferent sensory fibers of the vagus. The brain can then mount a strong modulatory response via three efferent pathways: the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system, and the cholinergic anti-inflammatory pathway. Thus, the effect of sepsis on the brain will affect other organs through stimulating a

neuroendocrine response and by disturbing the normally well-balanced interplay between the central nervous system and the immune system, resulting in altered immunologic function. A host of immunomodulatory neurotransmitters and neuroendocrine mediators are released in sepsis, including sensory neuropeptides, calcitonin gene-related peptide, substance P, corticotropin-releasing factor, and α-melanocyte-stimulating hormone (87).

The neuroendocrine system regulates the stress response in a coordinated manner under normal conditions (87). Early release of catecholamines, corticotropin-releasing factor, vasopressin, and oxytocin is followed by secretion of pituitary adrenocorticotropic hormone, then prolactin and growth hormone. The consequent release of hormones from target organs (e.g., glucocorticoids from the adrenal gland, renin from the kidney, and glucagon from the pancreas) follows shortly after. In sepsis, this normal response is disrupted. For example, NO expressed within the brain can induce apoptosis in neurons and microglial cells, although this seems to be particularly targeted to neuroendocrine and autonomic nuclei (88). As with the lung, apoptosis would seem to be harmful on first inspection; however, there is evolving evidence that production of proapoptotic factors such as neuronal cytochrome C may offer protection in sepsis (89).

Hepatosplanchnic System. The hepatosplanchnic system is not only directly affected by the septic process but, like the brain and lung, can also affect distant organs. Lymphatic drainage and alterations in intestinal epithelial permeability allow both direct and indirect systemic absorption of proinflammatory mediators and toxins from luminal microbes (90, 91). Furthermore, enterocytes themselves can generate proinflammatory cytokines, including HMGB1 (92). Sepsis-induced disruption of the epithelial barrier occurs widely throughout the body, from gut to kidney, lung to brain (90). NO and its metabolite peroxynitrite are involved in the regulation of tight junction protein expression and function, and this may involve modulation of activity of the membrane pump, Na^+,K^+–adenosine triphosphatase (93).

The portal system drains directly into the liver. A third of the liver's blood supply also comes directly from the systemic circulation. Thus, it is centrally placed to detect the presence of microbes or microbial products either from the gut or systemically (94). It is the primary site for clearance of bacterial endotoxin, and its production of proinflammatory cytokines can result in distant effects, particularly on the lung, which is the first organ bed to receive its effluent. The liver is also heavily involved in the production of acute phase proteins. Perhaps because of its regular exposure to microbial products, the liver seems remarkably well protected from acute septic insults. This may be related to its high levels of protective antioxidants (95) and to its large reserve capacity. Clinical features of liver dysfunction generally occur later in the septic process and, if present, portend a worse outcome (96).

Kidney. Whereas sepsis-induced acute renal failure was formerly considered a hemodynamic disease induced by ischemia, recent research suggests the perhaps greater importance of other etiologies, including inflammation, cellular mechanisms, and coagulation (97). These concepts are considered to fit well with the typical paucity of histologic abnormalities seen in biopsy studies (49) and with the finding that renal perfusion, at least globally, is usually adequate or even increased (57). Regional redistribution of blood flow may occur, but again, data in resuscitated, hyperdynamic septic models suggest otherwise (98). The kidney may be particularly vulnerable to cytokine-induced injury (97). Proinflammatory cytokines can be produced by renal mesangial, tubular, and endothelial cells, although in isolated kidney models, their increased expression was not related to deterioration in physiologic function. Local NO production is increased, and this results in enhanced renal blood flow, particularly to the medulla (99). Other ROS are also generated within the kidney and may contribute to oxidative injury. Epithelial barrier dysfunction and endothelial dysfunction are described in septic models. Although apoptosis and necrosis are found in ischemic models of acute tubular necrosis, the significance of renal cell death in sepsis is far less clear. Activation of the coagulation pathway, with subsequent deposition of fibrin, may also play a role in inducing renal injury (100).

Heart. Myocardial depression is a common accompaniment of sepsis, even in patients with elevated cardiac outputs. There is systolic and diastolic dysfunction affecting both ventricles (101). A characteristic pattern of ventricular dilation and decreased ejection fraction is seen. These are actually greater in survivors and typically resolve after 7–14 days (102). The cause of sepsis-induced myocardial dysfunction was traditionally considered to be related to hypoperfusion, but this hypothesis has now been largely dismissed. However, cardiomyocyte injury, as evidenced by elevated circulating levels of troponins, does occur in sepsis, although this is probably not ischemic in origin (103).

Circulating myocardial depressant factors are also described (104). Candidates include tumor necrosis factor-α, interleukin-1β, interleukin-6, lysozyme C, bacterial DNA and RNA, and NO. At the cellular level, derangements in calcium physiology (105) and overproduction of NO (106) are two nonexclusive potential mechanisms resulting in myocardial depression. Although an overt increase in cardiomyocyte apoptosis is not recognized in spontaneous disease or live infection models, preapoptotic signaling may play a role in myocardial depression (107).

Primum Non Nocere

It is increasingly recognized that sepsis should not be viewed simply as an uncontrolled, chaotic, and damaging process but rather as a sophisticated, intricate, and multisystem condition that incorporates many protective and damaging pathways. A strong argument can be advanced that multiple organ failure represents an adaptive response to a prolonged and severe inflammatory insult that enables the organs to recover adequate function to enable long-term recovery (48). An important corollary of this concept is the recognition that many of our current treatments may interfere with the body's attempts to adapt and that this may carry potentially detrimental consequences (108). Examples range from sedatives to antibiotics, blood transfusion to inotropes, and ventilators to temperature control that carry hormonal, immune, metabolic, and bioenergetic effects that may have far-ranging sequelae not always apparent at the end of the needle. The negative outcomes seen in randomized trials assessing growth hormone, thyroxine, soluble tumor necrosis factor receptors, and NO synthase blockade therapies emphasize the point that what seemed at the time to be a theoretically sound basis for a specific intervention can backfire badly.

Summary

Current understanding of the pathophysiology underlying sepsis-induced multiple organ dysfunction highlights the multiple cell populations and cell-signaling pathways involved in this complex condition. We are gaining an increasing appreciation of the interactions that exist between different cells and organs affected by the septic process. The intricate cross-talk provided by temporal changes in mediators, hormones, metabolites, neural signaling, alterations in oxygen delivery and utilization, and by modifications in cell phenotypes underlines the adaptive and even coordinated processes beyond the dysregulated chaos in which sepsis was once perceived. Indeed, many pathologic processes previously considered to be detrimental are now viewed as protective. Applying systems approaches to these complex processes involved in sepsis will permit better appreciation of the effectiveness or harm of treatments, both present and future, and also will allow development not only of better directed but also of more appropriately timed strategies to improve outcomes from this still highly lethal condition. Many potentially useful therapies have fallen by the wayside, often due to a lack of appreciation of when and how they should be used. It is unlikely that a single magic bullet will exist. However, a combination approach that can be individualized, titrated, and correctly timed must be the logical progression.

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APPENDIX

Participants in the 2006 Brussels Round Table Conference included: William C. Aird (Boston, MA), Djillali Annane (Garches, France), Geoff Bellingan (London, UK), Timothy R. Billiar (Pittsburgh, PA), Thierry Calandra (Lausanne, Switzerland), Jean-Marc Cavaillon (Paris, France), Christopher J. Czura (Manhasset, NY), Daniel De Backer (Brussels, Belgium), Clifford S. Deutschman (Philadelphia, PA), Timothy Evans (London, UK), Mitchell Fink (Pittsburgh, PA), Richard Griffiths (Liverpool, UK), Can Ince (Amsterdam, The Netherlands), John C. Kellum (Pittsburgh, PA), Geoff Laurent (London, UK), John C. Marshall (Toronto, Canada), Thomas R. Martin (Seattle, WA), Sadis Matalon (Birmingham, AL), Michael A. Matthay (San Francisco, CA), Christian Meisel (Berlin, Germany), Jean-Paul Mira (Paris, France), Salvador Moncada (London, UK), Steven Opal (Pawtucket, RI), Joseph E. Parrillo (Camden, NJ), Jérôme Pugin (Geneva, Switzerland), Greet Van Den Berghe (Leuven, Belgium), Tom Van Der Poll (Amsterdam, Netherlands), Jean-Louis Vincent (Brussels, Belgium), and Jan Wernerman (Stockholm, Sweden).