Organ Failure in Sepsis

Herwig Gerlach, MD, PhD, and Susanne Toussaint, MD, DEAA

Corresponding author
Herwig Gerlach, MD, PhD
Vivantes–Klinikum Neukoelln, Klinik für Anaesthesie, operative Intensivmedizin und Schmerztherapie, Rudower Strasse 48, D-12313 Berlin, Germany.
E-mail: herwig.gerlach@vivantes.de

Current Infectious Disease Reports 2007, **9:**374–381
Current Medicine Group LLC ISSN 1523-3847

The development of organ failure determines the course and prognosis of the septic patient. Although several successful clinical trials in recent years have raised the enthusiasm of intensivists, severe sepsis and septic shock still have an increasing incidence with more or less unchanged mortality. Recent sepsis research, including progress made in definitions, epidemiology, pathophysiology, diagnosis, standard and adjunctive therapy, and experimental approaches, is encouraging. This includes genomic information for stratifying subgroups of patients, a broader field of laboratory diagnostics due to clinical studies, and basic research on the cellular mechanisms of inflammation and organ dysfunction. Furthermore, new findings in pathogenesis and therapeutic approaches to organ failure merit attention. In this review, state-of-the-art publications are presented to elucidate the possible impact of sepsis-induced organ failure on clinical routine.

Introduction

Sepsis is an aggressive and multifactorial disease state resulting from the host response to infection. Although a localized and controlled inflammatory reaction helps control infection, a dysregulated response may lead to multiple organ failure, which determines the course and prognosis of the septic patient. Patients usually die of sepsis in the course of different morbidities, and deaths are often attributed to these conditions rather than to sepsis. Despite intensive care, mortality remains as high as 54% for severe sepsis and septic shock [1•]. Regarding specific organ dysfunctions, respiratory failure is the most common organ failure, followed by cardiovascular failure and acute renal failure [2].

As the cellular mechanisms of sepsis become more clearly defined, interventions to interfere with the host response have been attempted. However, results thus far have been largely disappointing, because in septic patients, immunomodulating approaches must orient to patient immunocompetence, inflammatory status, and infectious status. Despite these disappointments, supportive therapies developed within the past few years have shown consistent, positive effects on mortality. Several seminal studies have indicated that early and systematic supportive therapy according to pathophysiologic principles, most notably early goal-directed therapy, low-dose hydrocortisone, and activated protein C, can disrupt dysfunctional cascades, thus favorably influencing the course of the disease. These strategies have helped reduce the incidence of infections, support failing organs, and prevent complications. Multifaceted approaches to patient management, evidence-based methods, and the adoption of incremental goal-oriented strategies are vital to combat this complex, aggressive, and increasingly prevalent condition.

Investigators have made progress. This review provides an overview of publications published since January 2006 on epidemiologic, pathophysiologic, diagnostic, and therapeutic aspects of organ dysfunction in severe sepsis and septic shock.

Cardiovascular Failure

Factors that control the modulation of the immune responses originate not only from the infective organisms but also from the released inflammatory mediators, which act in a paracrine and autocrine manner. In septic shock, the mortality is consequential to refractory hypotension and multiple organ failure (MOF). Detrimental effects of endotoxin, cytokines, and noncytokine mediators play an important role in the development of circulatory collapse [3]. The symptoms of septic shock are based on both myocardial and microcirculatory dysfunction.

Myocardial dysfunction

Abnormalities of cardiac function are quite common in patients with sepsis. However, the pathomechanisms associated with these abnormalities are far from understood, and basic research activities on this topic vary widely. Bacterial peptidoglycan-associated lipoprotein (PAL), an outer membrane protein of gram-negative bacteria, was recently found to be released into the bloodstream in sepsis causing inflammation and death in mice. Zhu et al. [4•] presented an experimental study to assess the effects of PAL on cardiomyocyte function and its signal

transduction in cardiomyocytes. The investigators could demonstrate that PAL uses a specific signal transduction pathway, initiated by Toll-like receptor (TLR) 2 followed by the downstream myeloid differentiation factor 88 (MyD88) pathway. The results suggest that circulating PAL and other TLR2 agonists may contribute to cardiac dysfunction in sepsis.

Soriano et al. [5] investigated the oxidative stress associated with septic shock. The investigators especially focused on the activation of the nuclear enzyme poly(adenosine 5'-diphosphate-ribose) polymerase and used an interesting design. They compared surviving and nonsurviving patients with severe sepsis and septic shock, and took heart sections from patients who died. These sections showed significant myocardial damage with inflammatory infiltration, increased collagen deposition, and mitochondrial damage. Further tests revealed that there was a significant poly(adenosine 5'-diphosphate-ribose) polymerase activation in the hearts with impaired cardiac function [5]. Larche et al. [6] provided further evidence that mitochondrial function plays a major role in septic myocardial failure. They demonstrated that inhibition of mitochondrial permeability transition prevents sepsis-induced cardiac failure and mortality in a rat peritonitis model. In a nice bench-to-bedside review, Protti and Singer [7] examined the latest developments in this exiting field of mitochondrial dysfunction in organ failure.

Sepsis leads to intensive activation of the complement system, which generates powerful anaphylatoxins (eg, C5a) and has recently been associated with septic cardiomyopathy. Niederbirchler et al. [8•] presented an excellent basic research study evaluating cardiac function and cardiomyocyte contractility in rats after cecal ligation and puncture. Significant reductions in left ventricular pressures occurred in vivo, which were prevented by giving blocking antibody to C5a. In contrast, in vitro addition of recombinant rat C5a induced dramatic contractile dysfunction in cardiomyocytes. These data suggest that C5a-dependent pathways cause dysfunction of cardiomyocytes, resulting in compromised cardiac performance. Rozenberg et al. [9] further demonstrated that aging alters endotoxin-induced myocardial dysfunction in a rat model using senescent and young animals. It was shown that the Ca^{2+} myofilament responsiveness is typically reduced in myocardium of young rats, whereas it is unaltered in senescent rats. This may provide a cellular explanation for divergent reports on ventricular diastolic function in septic shock. Furthermore, the investigators speculated that Ca^{2+}-sensitizing agents may be less effective in aged subjects than in younger patients.

New therapeutic approaches have been tested in experimental designs, and two examples published in highly ranked journals should be mentioned here. Carlson et al. [10] examined the effects of antioxidant vitamins on sepsis-related myocardial signaling cascades. They used a rat model and found that sepsis promoted nuclear factor (NF)-κB activation, increased mitochondrial cytochrome C release, increased caspase activity, increased cardiomyocyte secretion of inflammatory cytokines, and impaired left ventricular function. All these effects were inhibited by antioxidant vitamin therapy consisting of vitamins A, C, and E, plus zinc. The investigators concluded that antioxidant therapy may be a potential approach to treat sepsis-related myocardial dysfunction.

In the second study, Ramana et al. [11•] tested the hypothesis that inflammatory signaling and cytokine generation during sepsis depend on the activity of the enzyme aldose reductase, which catalyzes the reduction of lipid peroxidation-derived aldehydes and their glutathione conjugates. The investigators used the aldose reductase inhibitor sorbinil in lipopolysaccharide (LPS)-stimulated cells. Treatment with sorbinil blunted several signaling cascades and induced functional recovery in myocardial fractional shortening as well as contractile function of isolated perfused hearts. Finally, inhibition of aldose reductase increased survival in mice injected with lethal doses of LPS. These two studies nicely demonstrate that novel therapeutic approaches to treat myocardial dysfunction merit further attention.

Most clinical studies on sepsis-induced myocardial dysfunction in recent months have focused on diagnosis by specific markers. B-type natriuretic peptide (BNP), a member of the natriuretic peptide family, is secreted from cardiac myocytes in response to muscle stretch. In recent years, BNP and the N-terminal segment of its prohormone, NT-proBNP, were shown to be very sensitive biochemical markers for cardiac dysfunction in both adults and children. One of the best papers on this topic was presented by Fried et al. [12••], who compared NT-proBNP levels in pediatric patients with acute left ventricular dysfunction to levels in patients with similar hemodynamic status resulting from sepsis. The data revealed that NT-proBNP levels were elevated in pediatric septic patients but were much higher in patients with acute left ventricular dysfunction. Because these two groups overlap, the investigators concluded that excessive elevation in NT-proBNP levels suggest cardiac etiology; however, the use of this marker to differentiate between septic and nonseptic cardiac dysfunction is not suggested. Several additional studies of other markers are underway. At the moment, the routine use of BNP and other natriuretic peptides in sepsis-associated myocardial dysfunction is discouraged. Maeder et al. [13] presented an excellent overview on this topic.

Microcirculatory dysfunction

The severe impairment of microcirculation plays a substantial role in the pathogenesis of organ failure in severe sepsis and septic shock. Therefore, therapeutic strategies to resuscitate the microcirculatory blood flow and improve the functional capillary density are essential to surmount the microcirculatory pathology and avoid tissue hypoxia. Reasonable scientific evidence shows that

early fluid resuscitation directed by defined hemodynamic and metabolic goals as well as application of recombinant human activated protein C (rhAPC) according to guidelines could be recommended.

Trzeciak et al. [14•] performed a clinical investigation of the new technique orthogonal polarization spectral (OPS) imaging in early severe sepsis and septic shock to test the hypotheses that early indices of microcirculatory perfusion would be more severely impaired in sepsis nonsurvivors compared to survivors and that early microcirculatory perfusion indices would correlate with systemic hemodynamic and oxygen transport indices. Their prospective observational study visualized the sublingual microcirculation in septic patients and calculated three microcirculatory perfusion indices: flow velocity score, flow heterogeneity index, and capillary density. These indices were more markedly impaired in nonsurvivors compared with survivors. Moreover, the investigators found a correlation of these indices with the global cardiovascular dysfunction.

In addition to the aforementioned diagnostic qualities of the OPS imaging technology, it also proved useful for therapeutic interventions. De Backer et al. [15•] hypothesized that rhAPC, which had been demonstrated to increase survival in patients with severe sepsis and multiple organ dysfunction, would also improve microcirculatory perfusion in these patients. In 20 patients receiving rhAPC, the proportion of perfused capillaries increased after 4 hours, whereas this increase was not seen in 20 control patients. The improvement in microvascular blood flow was associated with a more rapid resolution of hyperlactatemia. These two studies nicely proved the relevance of microcirculatory dysfunction in septic patients, and hopefully new techniques such as OPS imaging will open new ways to test further therapeutic approaches to improve capillary perfusion.

Respiratory Failure

Although there are a huge number of publications on the topic of acute respiratory failure and acute respiratory distress syndrome, the specific alterations in patients with severe sepsis and septic shock are still poorly understood. Some studies have concentrated on defining variables for a better understanding of predisposition to develop respiratory failure. Mounting evidence suggests that in addition to well-established factors, such as virulence of pathogens or site of infection, individual differences in disease manifestation are a result of the genetic predisposition of the patient. In the near future, knowledge of genetic factors might help identify patients at risk (ie, those with a high likelihood to develop organ dysfunction). The diversity of predisposing risk factors for acute respiratory failure (eg, sepsis, pneumonia, trauma, massive transfusion) and the ill-defined molecular definition of acute lung injury further confound our ability to elucidate these mechanisms.

Winning et al. [16] presented a nice overview on this issue with special reference to diagnosis and therapy of sepsis, and Wurfel [17] published a paper on the microarray-based analysis of ventilator-induced lung injury. Looney and Matthay [18] proposed that a defining feature of sepsis and the related acute respiratory distress syndrome and acute lung injury is damage to the microvascular endothelium leading to altered blood flow, oxygen extraction, and increased permeability to protein and solutes. Thus, the authors concluded that although sepsis often causes clinically apparent injury to multiple organs, the major common denominator of injury is the vascular endothelium. Furthermore, the authors stressed the relevance of physiologic anticoagulant and anti-inflammatory pathways such as the protein C pathway.

A number of small studies have investigated specific aspects of lung injury and sepsis with some novel therapeutic approaches. Baumgarten et al. [19] investigated the role of TLR4 for the pathogenesis of acute lung injury in gram-negative sepsis [19]. Their protocol used TLR4-deficient and control mice. The TLR4-deficient animals had significantly less activation of NF-κB and less expression of proinflammatory cytokines. They concluded that TLR4 plays a key role for regulating the expression of relevant cytokines within the lung during endotoxic shock.

Shu et al. [20] looked for the protective capacity of defensins in rats. They evaluated the effect of an overexpression of a small cationic antimicrobial peptide named β-defensin-2 (BD-2) on lung injury in order to crudely investigate whether the function of BD-2 in the lung attributes to both antimicrobial action and modulation of the immune response. Sepsis was induced either by *Pseudomonas aeruginosa* infection or by cecal ligation and puncture; overexpression of BD-2 was induced by a recombinant adenovirus carrying an expression cassette of rat BD-2. Amounts of *P. aeruginosa* in the lung with BD-2 overexpression were significantly lower than in control animals, and in both sepsis models, BD-2 overexpression reduced alveolar damage, interstitial edema, and neutrophil infiltration. The authors concluded that this pathway may serve as an approach to attenuate lung injury in sepsis. Similar findings were made by Coimbra et al. [21•], who investigated the effect of a phosphodiesterase inhibition using pentoxifylline. LPS-induced lung injury was attenuated, and the proinflammatory cytokine cascade was downregulated, probably because of the marked attenuation of NF-κB binding and activation.

Renal Failure

Acute renal failure (ARF) is a common complication of sepsis in critically ill patients, and sepsis has been identified as the most prevailing factor predisposing to ARF. The reduction in kidney function in sepsis is generally characterized by progressive increases in serum creatinine and urea or the development of oliguria. On

the other hand, predictors of death after ARF must be accurately identified to adjust adequately for comorbidity and severity of illness in quality improvement efforts and prospective clinical trials. Chertow et al. [22••] analyzed data from the Program to Improve Care in Acute Renal Disease (PICARD), a multicenter observational study of ARF. At the time of consultation and upon initiation of dialysis for ARF, sepsis was identified as being associated with mortality in logistic regression models. By incorporating exposures over time, the discriminatory power of predictive models in ARF can be significantly improved. Given the apparent impact of ARF on mortality, it is important to prevent or hasten the resolution of even the mildest forms of ARF.

This thesis was nicely presented by Venkataraman and Kellum [23•] in an excellent review on the prevention of ARF in critically ill patients. In this review, the authors categorized preventive strategies for ARF into nonpharmacologic, pharmacologic, and dialytic strategies. They concluded that nonpharmacologic strategies such as hydration, maintaining renal perfusion pressure, decompression in case of abdominal compartment syndrome, and the avoidance of nephrotoxic interventions are probably more effective than drugs to prevent ARF. The role of prophylactic use of dialysis is still unproven.

The relevance of adequate fluid resuscitation in severe sepsis was also stressed by Bagshaw and Bellomo [24]. Evolving evidence implies that the choice, timing, and amount of fluid used for resuscitation in severe sepsis may directly impact kidney function. However, the precise role of fluid resuscitation in hyperdynamic sepsis complicated by ARF is still uncertain and merits further rigorous evaluation. Not only incidence of ARF, but also recovery after ARF is an important clinical determinant of patient morbidity. This field of clinical research is rather empty, and again Bagshaw [25•] drew attention to this issue by reviewing the recent literature in a very interesting paper. He noted that studies of recovery after ARF often have fundamental, important disparities in study design, study population, specifics on the provision of renal replacement therapies, and timing for ascertainment of recovery prognosis. These disparities greatly limit the overall generalizability of the studies and present challenges for clinicians attempting to make predictions for renal recovery after ARF. Thorough analysis revealed that older age, female sex, comorbid illnesses (especially chronic kidney disease), and late initiation of renal replacement therapy have been coupled with nonrecovery. Overall, however, the prognosis is generally good, and most patients will be independent of replacement therapy within 90 days. Bagshaw [25•] concluded that questions on the role of various interventions require characterization in randomized controlled trials to determine how they may influence renal prognosis.

Probably one of the best studies on therapy of ARF in critically ill patients including those with severe sepsis and septic shock was presented by Vinsonneau et al. [26••]. In this prospective, randomized, multicenter trial, the investigators compared the effect of intermittent hemodialysis (IHD) and continuous venovenous hemodiafiltration on the survival rates of patients with multiple organ dysfunction syndrome including ARF. The rate of survival did not differ, and the only significant difference was found in the incidence of hypothermia, which was higher in the continuous venovenous hemodiafiltration group. Hence, it was concluded that almost all patients with ARF as part of a multiple organ dysfunction syndrome can be treated with IHD. Most recently, Gupta et al. [27] investigated the role of protein C in renal dysfunction after polymicrobial sepsis. Their study explored the consequences of protein C suppression on the kidney in an animal model and found a rapid drop in protein C after sepsis. Treatment of septic animals with activated protein C reduces blood urea, renal pathology, and chemokine expression, thus suggesting that activated protein C treatment may be effective in reducing inflammatory and apoptotic insult during sepsis-induced ARF, which is also a possible option for clinical trials.

Hemostatic Dysfunction

The question "Do coagulation abnormalities contribute to sepsis-associated organ failure?" presented by Abraham [28] seems rather rhetorical. Activation of the coagulation system during sepsis and inflammation is known to result in the deposition of fibrin within intra- and extravascular spaces. It has also been implicated in the pathogenesis of pulmonary bacterial infections, and the tissue factor (TF) factor VIIa (FVIIa)–dependent pathway is probably crucial in this context. In his editorial, Abraham referred to the excellent research paper by Rijneveld et al. [29], who investigated the role of the TF-FVIIa complex in the host response against bacterial pneumonia. In patients with unilateral community-acquired pneumonia, elevated concentrations of FVIIa, soluble TF, and thrombin-antithrombin complexes were found in bronchoalveolar lavage fluid. Similarly, a mouse model revealed activation of this pathway. Most interestingly, the investigators could demonstrate that inhibition of TF attenuated the procoagulant response, but did not alter host defense, as reflected by unchanged survival and bacterial growth.

In addition to papers on the pathomechanisms of sepsis-associated coagulopathy, several studies have examined the clinical relevance of this pathway. Voves et al. [30] evaluated the score for disseminated intravascular coagulation (DIC) in sepsis patients and found a significant association with mortality. They concluded that the DIC score is useful to identify patients with coagulation activation, predicting fatality and disease severity. This mainly depends on the prolongation of the prothrombin time and platelet counts. The relevance of low platelets was also described in the overview by Nguyen and Carcillo [31•]. They stressed that new-onset thrombocytopenia in

critically ill patients is an indicator of thrombotic microangiopathy, and that resolution of thrombocytopenia should be the goal for directed use of therapy. The protein C pathway could be one option.

Several publications reported on the efficiency of promoting the protein C pathway. Shorr et al. [32] demonstrated that baseline and day 1 protein C levels in patients with severe sepsis were independent predictors of sepsis outcome. Because the patients were analyzed post hoc from a large randomized trial on the use of rhAPC, the investigators could also show that increased protein C levels in the treatment group were associated with improved survival. Nadel et al. [33••] published a large randomized clinical trial on rhAPC in children with severe sepsis. The study used the Composite Time to Complete Organ Failure Resolution score, which revealed no difference between treatment and control group. Furthermore, rhAPC treatment did not result in improved survival. Finally, the authors noted that treatment did not cause a higher rate of serious bleedings, except in children younger than 60 days old. Schellongowski et al. [34] presented a small observational study in adult patients, for which they used a plasma-derived protein C concentrate rather than rhAPC. So far, this substance has been used mostly in children with purpura fulminans. In this study, treatment with protein C concentrate increased the median protein C activity in patients from 29% to 184% and resolved coagulopathy assessed by a DIC score in most patients. Although this was an uncontrolled trial, the substance might be another useful option, at least in the rare subgroup of patients with purpura fulminans.

Finally, there have been some interesting reports on the "crosstalk" between coagulation and host response. Asakura et al. [35] showed that immunoglobulin preparations attenuated organ dysfunction and hemostatic abnormality in LPS-induced DIC in rats. Especially a marked glomerular fibrin deposition induced by LPS was reduced in the treatment group, which was interpreted as consequence of a suppression of cytokine production.

On the other hand, application of rhAPC in patients with septic shock was demonstrated to exert antiapoptotic effects in the paper by Bilbault et al. [36•]. In this nonrandomized study, researchers investigated the variation of Bax/Bcl-2 and Bax/Bcl-xl ratios in circulating mononuclear cells of septic shock patients, and the data revealed that rhAPC treatment reduced apoptosis in circulating cells from blood samples. The authors concluded that the beneficial effects of rhAPC treatment on organ dysfunction in human sepsis are dependent not only on its anticoagulant activity but also on an antiapoptotic activity through antiapoptotic gene expression regulation. This may represent a new way to select patients who could benefit from rhAPC during severe infections, as suggested by Carlet [37].

Hepatosplanchnic Dysfunction

Insufficient blood flow in the hepatosplanchnic tract during sepsis is believed to be a common denominator in many patients who eventually develop MOF. The precise nature of this area, especially regarding the distributive alterations, has been largely unknown for many decades. Several studies were published that investigated splanchnic blood flow during adrenergic vasopressor therapy in septic shock. Most of these studies, however, were performed on septic patients, only allowing the use of indirect methods to estimate splanchnic blood flow.

Boerma et al. [38•] used OPS imaging in patients with abdominal sepsis to test the hypothesis that septic shock is characterized by a dissociation between the splanchnic microcirculation and the systemic circulation. Sublingual and intestinal OPS imaging revealed that in the initial phase of the disease, there is a complete dispersion of flow, not only between macro- and microcirculation but also between sublingual and intestinal microvascular flow. After 3 days, a correlation appeared to be restored, mainly due to a normalization of flow in both regions. Krejci et al. [39••] compared the effects of the three vasopressor agents epinephrine, norepinephrine, and phenylephrine on systemic, regional, and microcirculatory blood flow during severe sepsis, using direct ultrasound transit time flowmetry in a pig model. All three vasopressors failed to increase microcirculatory blood flow in most abdominal organs despite increased perfusion pressure. Even more, norepinephrine and epinephrine increased systemic blood flow, but appeared to divert blood flow away from the splanchnic circulation with decreased microcirculation in the jejunal mucosa and pancreas. These important data give more insight into the complex mechanisms of hepatosplanchnic dysfunction in severe sepsis.

A Brazilian group had two interesting publications looking for the occurrence and relevance of organ failure including hepatic failure induced by bloodstream infections either by *Pseudomonas aeruginosa* [40] or enterococci [41]. Among other organ dysfunctions, hepatic failure was demonstrated to be associated with fatal outcome. Interestingly, no difference was seen between vancomycin-susceptible and vancomycin-resistant enterococcal bloodstream infections. Experimental trials are still trying to elucidate the cause of liver failure in sepsis. Croner et al. [42] investigated the liver microcirculation disturbances in rats using intravital microscopy. They found that in liver sinusoids and postsinusoidal venules, hepatic adherence of platelets to the vascular endothelium occurred only 1 hour after induction of endotoxemia; after 3 to 5 hours, adherence was also observed for leukocytes. The authors concluded that the early involvement of platelets in the initiation of leukocyte-endothelial interaction was probable. These microcirculatory disturbances result in hepatocellular damage as a result of organ hypoxia and cytotoxic cellular damage.

Neurologic and Neurocognitive Dysfunction

So far, the area of neurologic and neurocognitive dysfunction in severe sepsis has not been appreciated adequately, although the sequelae are often evident even after years. Many studies have examined the pathophysiology, diagnosis, and possible treatment of the critical illness neuromuscular syndromes (CINM). Increasingly, CINM is recognized in intensive care unit (ICU) patients after several days of mechanical ventilation and organ failure, and it is now the most common peripheral neuromuscular disorder encountered in the ICU. Most recently, De Jonghe et al. [43•] presented an excellent review on this topic. The authors nicely described the risk factors for CINM according to the "level of suspicion," because confirmatory studies for suspected causes are still missing. The highest level of suspicion is the severity and duration of systemic inflammatory response syndrome or MOF. The main cause of MOF in ICU is severe sepsis or septic shock. Sepsis is therefore a strong risk factor for CINM, although it does not appear clearly in many multivariate analyses.

In addition to CINM, encephalopathy with clinical symptoms such as delirium may be overlooked during severe sepsis while attention is devoted to reversing life-threatening imbalances in organ function. A nice overview paper was written by Stevens and Pronovost [44]. They stress that, in recent years, measurable progress has been made in developing and validating tools to identify encephalopathy in the ICU setting, and encephalopathy has now been recognized as an independent predictor of short-term outcomes. Respiratory disease, infection, fever, hypotension (ie, symptoms that occur frequently during severe sepsis), were identified as independent predictors in the ICU setting. A special subchapter of this paper points to the special problem of "septic encephalopathy" reporting the latest findings in literature. However, the neuropathogenesis of encephalopathy must still be explored with hypothesis-driven studies in animals and humans.

Finally, two review articles have elucidated the area of long-term neurocognitive function after critical illness. Milbrandt and Angus [45•] focused on pathogenesis of neurocognitive dysfunction, especially on two mechanisms that appeared to have the greatest merit: neurotransmitter abnormalities and occult diffuse brain injury. Hopkins and Jackson [46] concentrated on long-term neurocognitive dysfunctions. Both papers nicely describe the wide field of research, which recently has helped to better understand pathomechanisms, symptoms, diagnostic tools, preventive measures, and possible therapeutic options. Moreover, it should be noted that the economic burden for long-term treatment of these syndromes is probably enormous, and activities to reduce the incidence definitely merit further attention.

Conclusions

Multiple organ dysfunction or MOF is the culmination of tissue injuries in severe sepsis. Sepsis and septic shock are still the leading causes of death in noncardiology ICUs despite recent advances in clinical and basic research. Although the pathophysiology of MOF is only speculative, the current consensus points to the inflammatory response by mediators, ischemic-reperfusion injury, oxygen free radicals, and gut-related bacteremia, acting alone or most likely in concert to cause end-organ failure.

The management of sepsis in hospitals is significantly better today than it was 10 years ago. However, sepsis-associated mortality rates due to multiple organ dysfunctions still remain unacceptably high, and new strategies to improve patient outcomes must be embraced further. The recent improvement in outcomes of patients with severe sepsis and septic shock has been characterized by the successive introduction of multiple interventions and therapies and is an ongoing process. Large clinical trials especially in the past 2 to 3 years now allow the clinician to perform a partially evidence-based therapeutic strategy to approach single and/or multiple organ dysfunctions. It is believed that the current wave of clinical trial data relating to a number of new interventions should be viewed in the context of this trend towards ever-improving management of the condition.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.• Engel C, Brunkhorst FM, Bone HG, et al.: **Epidemiology of sepsis in Germany: results from a national prospective multicenter study.** *Intensive Care Med* 2007, **33:**606–618.

Excellent study with a randomized design to exclude biases such as hospital size and seasonal variations.

2. Karlsson S, Varpula M, Roukonen E, et al.: **Incidence, treatment and outcome of severe sepsis in ICU-treated adults in Finland: the Finnsepsis study.** *Intensive Care Med* 2007, **33:**435–443.

3. Jean-Baptiste E: **Cellular mechanisms in sepsis.** *J Intensive Care Med* 2007, **22:**63–72.

4.• Zhu X, Bagchi A, Zhao H, et al.: **Toll-like receptor 2 activation by bacterial peptidoglycan-associated lipoprotein activates cardiomyocyte inflammation and contractile dysfunction.** *Crit Care Med* 2007, **35:**886–892.

Thoroughly designed animal study with important new findings on the pathomechanisms of septic cardiomyopathy.

5. Soriano FG, Nogueira AC, Caldini EG, et al.: **Potential role of poly(adenosine 5'-diphosphate-ribose) polymerase activation in the pathogenesis of myocardial contractile dysfunction associated with human septic shock.** *Crit Care Med* 2006, **34:**1073–1079.

6. Larche J, Lancel S, Hassoun SM, et al.: **Inhibition of mitochondrial permeability transition prevents sepsis-induced myocardial dysfunction and mortality.** *J Am Coll Cardiol* 2006, **48:**377–385.

7. Protti A, Singer M: **Bench-to-bedside review: Potential strategies to protect or reverse mitochondrial dysfunction in sepsis-induced organ failure.** *Crit Care* 2006, **10:**228–234.

8.• Niederbirchler AD, Hoesel LM, Westfall MV, et al.: **An essential role for complement C5a in the pathogenesis of septic cardiac dysfunction.** *J Exp Med* 2006, **203:**53–61.
First class paper on the role of complement C5a in the pathogenesis of septic cardiomyopathy.
9. Rozenberg S, Besse S, Brisson H, et al.: **Endotoxin-induced myocardial dysfunction in senescent rats.** *Crit Care* 2006, **10:**124–132.
10. Carlson D, Maass DL, White DJ, et al.: **Antioxidant vitamin therapy alters sepsis-related apoptotic myocardial activity and inflammatory responses.** *Am J Physiol Heart Circ Physiol* 2006, **291:**H2779–H2789.
11.• Ramana KV, Willis MS, White MD, et al.: **Endotoxin-induced cardiomyopathy and systemic inflammation in mice is prevented by aldolase reductase inhibition.** *Circulation* 2006, **114:**1838–1846.
Perfectly designed study using isolated cells, perfused hearts, and animals to demonstrate the potential benefit of an aldolase reductase inhibitor.
12.•• Fried I, Bar-Oz B, Algur N, et al.: **Comparison of N-terminal pro-B-type natriuretic peptide levels in critically ill children with sepsis versus acute left ventricular dysfunction.** *Pediatrics* 2006, **118:**1165–1168.
This paper is very important to better understand the relevance of NT-proBNP. It was demonstrated that NT-proBNP is only useful to diagnose primary cardiac dysfunction, whereas it should not be used for analysis of septic cardiomyopathy.
13. Maeder M, Fehr T, Rickli H, Ammann P: **Sepsis-associated myocardial dysfunction. Diagnostic and prognostic impact of cardiac troponins and natriuretic peptides.** *Chest* 2006, **129:**1349–1366.
14.• Trzeciak S, Dellinger RP, Parrillo JE, et al.: **Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival.** *Ann Emerg Med* 2007, **49:**88–98.
First paper that demonstrates association between microcirculatory perfusion and outcome, measured by a new technique.
15.• De Backer D, Verdant C, Chierego M, et al.: **Effects of drotrecogin alfa activated on microcirculatory alterations in patients with severe sepsis.** *Crit Care Med* 2006, **34:**1918–1924.
Clinical study demonstrating the direct effect of rhAPC on microcirculation.
16. Winning J, Claus RA, Huse K, Bauer M: **Molecular biology on the ICU. From understanding to treating sepsis.** *Minerva Anestesiol* 2006, **72:**255–267.
17. Wurfel MM: **Microarray-based analysis of ventilator-induced lung injury.** *Proc Am Thorac Soc* 2007, **4:**77–84.
18. Looney MR, Matthay MA: **Bench-to-bedside review: The role of activated protein C in maintaining endothelial tight junction function and its relationship to organ injury.** *Crit Care* 2006, **10:**239–244.
19. Baumgarten G, Knuefermann P, Wrigge H, et al.: **Role of Toll-like receptor 4 for the pathogenesis of acute lung injury in Gram-negative sepsis.** *Eur J Anaesthesiol* 2006, **23:**1041–1048.
20. Shu Q, Shi Z, Zhao Z, et al.: **Protection against Pseudomonas aeruginosa pneumonia and sepsis-induced lung injury by overexpression of beta-defensin-2 in rats.** *Shock* 2006, **26:**365–371.
21.• Coimbra R, Melbostad H, Loomis W, et al.: **LPS-induced acute lung injury is attenuated by phosphodiesterase inhibition: effects on proinflammatory mediators, metalloproteinases, NF-kappaB, and ICAM-1 expression.** *J Trauma* 2006, **60:**115–125.
Nicely designed experimental study testing phosphodiesterase inhibition as a new therapeutic approach.
22.•• Chertow GM, Soroko SH, Paganini EP, et al.: **Mortality after acute renal failure: models for prognostic stratification and risk adjustment.** *Kidney Int* 2006, **70:**1120–1126.
Excellent post hoc analysis of the PICARD data. Several models were tested to evaluate the predictive power of risk indicators for acute renal failure. High clinical relevance.
23.• Venkataraman R, Kellum JA: **Prevention of acute renal failure.** *Chest* 2007, **131:**300–308.
Important review demonstrating that nonpharmacological measures are more relevant than drugs to prevent renal dysfunction.
24. Bagshaw AM, Bellomo R: **Fluid resuscitation and the septic kidney.** *Curr Opin Crit Care* 2006, **12:**527–530.
25.• Bagshaw SM: **Epidemiology of renal recovery after acute renal failure.** *Curr Opin Crit Care* 2006, **12:**544–550.
Clinically relevant topic that is rarely reported in literature.
26.•• Vinsonneau C, Camus C, Combes A, et al.: **Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomised trial.** *Lancet* 2006, **368:**379–385.
One of the most important clinical trials in 2006. Showed that IHD does not have increased risk in patients with multiple organ dysfunctions including acute renal failure.
27. Gupta A, Berg DT, Gerlitz B, et al.: **Role of protein C in renal dysfunction after polymicrobial sepsis.** *J Am Soc Nephrol* 2007, **18:**860–867.
28. Abraham E: **Do coagulation abnormalities contribute to sepsis associated organ failure?** *Crit Care Med* 2006, **34:**1842–1844.
29. Rijneveld AW, Weijer S, Bresser P, et al.: **Local activation of the tissue factor-factor VIIa pathway in patients with pneumonia and the effect of inhibition of this pathway in murine pneumococcal pneumonia.** *Crit Care Med* 2006, **34:**1725–1730.
30. Voves C, Wuillemin WA, Zeerleder S: **International Society on Thrombosis and Haemostasis score for overt disseminated intravascular coagulation predicts organ dysfunction and fatality in sepsis patients.** *Blood Coagul Fibrinolysis* 2006, **17:**445–451.
31.• Nguyen TC, Carcillo JA: **Bench-to-bedside review: Thrombocytopenia-associated multiple organ failure—a newly appreciated syndrome in the critically ill.** *Crit Care* 2006, **10:**235–242.
Nice paper for those who are interested in pathophysiology of septic coagulopathy. Easy to follow, excellent figures.
32. Shorr AF, Bernard GR, Dhainaut JF, et al.: **Protein C concentrations in severe sepsis: an early directional change in plasma levels predicts outcome.** *Crit Care* 2006, **10:**92–99.
33.•• Nadel S, Goldstein B, Williams MD, et al.: **Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial.** *Lancet* 2007, **369:**836–843.
The first large randomized controlled trial with rhAPC in children. Although it showed no benefit, the information about side effects is crucial.
34. Schellongowski P, Bauer E, Holzinger U, et al.: **Treatment of adult patients with sepsis-induced coagulopathy and purpura fulminans using a plasma-derived protein C concentrate (Ceprotin).** *Vox Sang* 2006, **90:**294–301.
35. Asakura H, Takahashi Y, Kubo A, et al.: **Immunoglobulin preparations attenuate organ dysfunction and hemostatic abnormality by suppressing the production of cytokines in lipopolysaccharide-induced disseminated intravascular coagulation in rats.** *Crit Care Med* 2006, **34:**2421–2425.
36.• Bilbault P, Lavaux T, Launoy A, et al.: **Influence of drotrecogin alpha (activated) infusion on the variation of Bax/Bcl-2 and Bax/Bcl-xl ratios in circulating mononuclear cells: A cohort study in septic shock patients.** *Crit Care Med* 2007, **35:**69–75.
Excellent paper on the "crosstalk" between coagulation and host response.
37. Carlet J: **Prescribing indications based on successful clinical trials in sepsis: A difficult exercise.** *Crit Care Med* 2006, **34:**525–529.
38.• Boerma EC, van der Voort PH, Spronk PE, Ince C: **Relationship between sublingual and intestinal microcirculatory perfusion in patients with abdominal sepsis.** *Crit Care Med* 2007, **35:**1055–1060.
The investigators were able to demonstrate the disparity between macro- and microcirculation, as well as between different areas of microcirculation.

39.•• Krejci V, Hiltebrand LB, Sigurdsson GH: **Effects of epinephrine, norepinephrine, and phenylephrine on microcirculatory blood flow in the gastrointestinal tract in sepsis.** *Crit Care Med* 2006, **34:**1456–1463.

Cutting edge paper on the pharmacodynamics of vasopressor therapy. It was demonstrated that improvement of systemic circulation does not correlate with the splanchnic perfusion. Catecholamines may even impair intestinal blood flow although blood pressure is increasing.

40. Marra AR, Bar K, Bearman GM, et al.: **Systemic inflammatory response syndrome in adult patients with nosocomial bloodstream infection due to Pseudomonas aeruginosa.** *J Infect* 2006, **53:**30–35.

41. Bar K, Wisplinghoff H, Wenzel RP, et al.: **Systemic inflammatory response syndrome in adult patients with nosocomial bloodstream infections due to enterococci.** *BMC Infect Dis* 2006, **6:**145–152.

42. Croner RS, Hoerer E, Kulu Y, et al.: **Hepatic platelet and leukocyte adherence during endotoxemia.** *Crit Care* 2006, **10:**15–20.

43.• De Jonghe B, Lacherade JC, Durand MC, Sharshar T: **Critical illness neuromuscular syndromes.** *Crit Care Clin* 2007, **23:**55–69.

Excellent review on critical illness polyneuropathy. Especially the risk factors are analyzed in a sophisticated manner. Should be read by every ICU physician.

44. Stevens RD, Pronovost PJ: **The spectrum of encephalopathy in critical illness.** *Semin Neurol* 2006, **26:**440–451.

45.• Milbrandt EB, Angus DC: **Bench-to-bedside review: Critical illness-associated cognitive dysfunction—mechanisms, markers, and emerging therapeutics.** *Crit Care* 2006, **10:**238–246.

Nicely designed review which gives a perfect overview on the different aspects of neurocognitive dysfunctions.

46. Hopkins RO, Jackson JC: **Long-term neurocognitive function after critical illness.** *Chest* 2006, **130:**869–878.