Review

Year in review 2007: *Critical Care* – multiple organ failure and sepsis

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Abstract

Several research papers published in *Critical Care* throughout 2007 examined the pathogenesis, diagnosis, treatment and prognosis of sepsis and multiorgan failure. The present review summarizes the findings and implications of the papers published on sepsis and multiorgan failure and places the research in the context of other work in the field.

Introduction

Nine papers exploring sepsis and multiorgan failure were published in *Critical Care* throughout 2007. Four of these articles examined possible pathophysiologic mechanisms underlying sepsis and organ failure. One paper explored the use of biomarkers in community-acquired infections. Three articles reported results of different therapeutic approaches to sepsis, and one article evaluated the longer-term outcomes for sepsis survivors.

Pathogenesis

Organ-specific effects of local infection versus remote infection

In an interesting study from Finland, Vakkala and colleagues systematically explored the epithelial response in the gallbladders of two groups of patients with cholecystitis [1]. The authors compared gallbadders removed during open cholecystectomy from critically ill patients with acute acalculous cholecystitis ($n = 30$), from noncritically ill patients with acute calculous cholecystitis ($n = 21$) and from patients without gallbladder pathology ($n = 9$). The authors suggest this was an opportunity to compare the local effects of infection from obstructed biliary fluid and the remote effects of the systemic inflammatory response.

Compared with normal gallbladders, acute acalculous cholecystitis gallbladders and acute calculous cholecystitis gallbladders showed significantly increased markers of epithelial proliferation and apoptosis. Hypoxia-inducible factor-1α, a marker of the cellular response to ischemia, was increased most dramatically in acute calculous cholecystitis samples but was only intermediately increased in acute acalculous cholecystitis. Because hypoxia-inducible factor-1α can promote epithelial proliferation [2], it is possible that it may be an important part of the signal that augments normal biliary regeneration. In acute acalculous cholecystitis, however, remote infection (50% of patients had sepsis or pneumonia) may have led to decreased perfusion, to ischemia, to impaired regenerative capacity of the gallbladder mucosa and to dysfunction leading to cholecystitis.

Innate immunity in sepsis

Sepsis has a considerable case mortality rate [3,4], but many patients do not die of the initial infectious insult. Patients initially have signs of excess inflammation, with high levels of IL-1β, TNFα, and IL-6. Many patients, however, subsequently show increases in anti-inflammatory mediators, a condition termed compensatory anti-inflammatory response syndrome, leaving patients at risk of nosocomial infections [5,6]. The defensins are part of the innate immune response and display antimicrobial effects against a wide range of pathogens by permeabilizing cell membranes [7]. The defensins also provide stimuli for a variety of immune cells to respond to infection [8]. The role of defensins in sepsis has not been well characterized.

Book and colleagues evaluated *in vivo* and *ex vivo* regulation and expression of human β-defensin 2 (hBD2) in 16 septic

hBD2 = human β-defensin 2; HRQOL = health-related quality of life; ICU = intensive care unit; IL = interleukin; PaO_2/FiO_2 = ratio of arterial oxygen to inspired oxygen fraction; PMX-F = polymixin B immobilized on polystyrene fibers; rhAPC = recombinant human activated protein C; TNF = tumor necrosis factor.

patients in a surgical intensive care unit (ICU), and compared the results with nonseptic ICU patients and with healthy control individuals [9]. While hBD2 mRNA was not detected in whole blood assays from normal control individuals, it was elevated in septic ICU patients and in nonseptic ICU patients. hBD2 protein levels were higher in the plasma of severe sepsis patients than in either of the comparison groups. The time-course of hBD2 protein in plasma did not discriminate survivors from nonsurvivors among the septic patients. In the *ex vivo* whole blood assays, endotoxin stimulated hBD2 mRNA in all groups. The hBD2 induction was much lower in the severely septic patients than in the comparison groups, an effect not mediated by hydrocortisone administration to the septic patients.

These findings argue that there are early changes in hBD2 regulation and expression in severe sepsis. These changes occur in concert with known measures of immunodepression (for example, HLA-DR expression on monocytes). While blood levels of hBD2 are elevated in early sepsis, the ability of immune cells to respond to subsequent inflammatory stimuli (for example, endotoxin) with increased expression of hBD2 appears impaired. If these observations are confirmed in larger studies, defensins could be reasonable targets for new therapeutic options in sepsis and/or to prevent subsequent infections in the impaired host.

Platelet exosomes as mediators of cellular injury

Microparticles, small vesicles derived from a primary cell, have been identified in increased numbers in the blood of patients with a variety of diseases [10-12]. A type of platelet-derived vesicle, known as exosomes, has been implicated as a mediator of apoptosis in patients with sepsis [13]. In separate reports from laboratories in Sao Paolo, Brazil, investigators characterize these exosomes more completely and describe their effects on vascular and cardiac function in sepsis [14,15].

Using sera from patients with severe sepsis obtained within 24 hours of onset ($n = 12$), Gambim and colleagues showed there were significant increases in the concentration of exosomes when compared with the concentration found in the sera of healthy control individuals [14]. Differentiating these exosomes from apoptotic bodies was the expression of large amounts of active transmembrane receptors (CD9, CD81 and CD63) and relatively little phosphatidyl serine. These characteristics were reproduced when naïve platelets from healthy donors were exposed to lipopolysaccharide or to the nitric oxide donor diethylamine-NONOate, but not when these platelets were exposed to thrombin, TNFα or UV irradiation alone – suggesting the exosome production is specific for these stimuli. Such exosomes increased generation of reactive oxygen species and induced apoptosis of co-cultured endothelial cells.

Azevedo and colleagues, using similar studies, explored the effects that exosomes have on *ex vivo* cardiac myocyte activity [15]. Similar to the previous study, the concentration of exosomes was found to be significantly higher in septic serum than in serum from normal donors. When exosomes were exposed to either whole rabbit heart or rat papillary muscle explants, there was a transient and reversible reduction in contractile properties. These findings held if the explants were pretreated with endotoxin, separating the myocardial-depressing effects of endotoxemia and of exosomes. The investigators suggested this effect was mediated by nitric oxide since the nitric oxide content of septic exosomes was significantly greater than that of healthy control individuals.

Taken together, the studies of Gambim and colleagues and of Azevedo and colleagues suggest that platelet-specific microvesicles may play a role in endothelial and cardiac dysfunction in sepsis.

Diagnosis

Sepsis biomarkers in community-acquired infections

Clinical characteristics provide minimal discrimination of septic patients by pathophysiologic mechanisms, and there is therefore interest in the role of various biomarkers for the identification of sepsis and patients who may benefit from specific interventions. High-mobility group-box protein 1 is a mediator of later inflammatory events in sepsis, and may be a target for therapeutic intervention [16-18]. Lipopolysaccharide-binding protein is a component of the innate immune system that acutely increases with infection and plays a role in clearance of endotoxin [19]. Procalcitonin is a proinflammatory mediator that has received considerable attention in identifying patients with serious bacterial infections [20].

Gaini and colleagues performed a prospective cohort study among patients admitted to a general medical ward with sepsis in an effort to predict bacteremia using high-mobility group-box protein 1, lipopolysaccharide-binding protein and procalcitonin [21]. The study included information on 154 subjects with suspected sepsis, and approximately one-half of them had severe sepsis or septic shock. As expected, high-mobility group-box protein 1, lipopolysaccharide-binding protein and procalcitonin levels were higher in patients than in healthy control individuals. None of the biomarkers of interest discriminated between survivors and nonsurvivors but all biomarkers were significantly higher in bacteremic patients compared with nonbacteremic patients. Procalcitonin had the greatest area under the curve (0.79), and a sensitivity of 80.7% and a specificity of 67.8% for bacteremia.

These results confirm those from other studies showing an association between high-mobility group-box protein 1, lipopolysaccharide-binding protein and procalcitonin with sepsis and severe sepsis. The biomarkers did not discriminate survivors from nonsurvivors, however, and all biomarkers had only moderate ability to discriminate bacteremic patients from nonbacteremic patients. To be useful in caring for septic

patients, biomarkers should identify patients who should receive different care from those patients without similar biomarker profiles. For example, a recent study suggests that antibiotic duration might be truncated based on procalcitonin levels [22]. Despite reducing the number of days of antibiotic administration, there was a numeric increase in mortality among those patients having truncated courses of antibiotics. The clinical utility of early identification of subsequent growth on blood culture, as shown in the study by Gaini and colleagues, is unclear. Owing to the pronounced effect of antibiotic administration on mortality from sepsis [23,24], a biomarker would need a very high negative predictive value to lead to a decision to withhold antibiotics. Confirming that a septic patient requires antibiotics or will have bacteremia is less useful.

Treatment

Canadian intensivists practices of resuscitation

After ICU-based studies of hemodynamic optimization in critically ill patients failed to definitively show benefit [25,26], Rivers and colleagues demonstrated that an emergency department-based intervention of resuscitation guided by specific hemodynamic goals produced an absolute risk reduction of 16% in hospital mortality for patients with septic shock [27]. The early goal-directed therapy protocol involved a complex interplay of a variety of interventions, including volume resuscitation, central venous saturation monitoring, red cell transfusions and inotropic therapy. As a result, implementation of early goal-directed therapy has a number of barriers and it remains unclear which aspects of the protocol clinicians implement.

McIntyre and colleagues conducted a survey of Canadian intensivists using a clinical vignette to determine self-reported resuscitation practices [28]. Respondents were asked to complete questions about monitoring parameters, resuscitation endpoints and fluid preferences for a vignette of septic shock. A second vignette presented the same patient with optimized blood pressure and intravascular volume but a low central venous saturation. Respondents were asked about triggers for red cell transfusion and the use of inotropes.

Respondents reported that they frequently used oxygen saturation, Foley catheters, an arterial blood pressure line, telemetry and central venous pressure to monitor the therapeutic effort. The measures most commonly indicated as being often or always used as measures of adequate volume resuscitation were the urine output, blood pressure, the heart rate, peripheral perfusion, the central venous pressure, and a sustained rise in central venous pressure after fluid challenge. It was uncommon for respondents to report they often or always used central venous saturation as a monitor of therapeutic response (9.8% of respondents) or as an endpoint of resuscitation (19.4%). The majority of respondents (84.5%) use normal saline for resuscitation often or always, with Ringer's lactate and pentastarch used by approximately one-half of respondents. In the second case, the patient with adequate volume status but inadequate oxygen delivery, <10% of respondents would transfuse red blood cells at a hemoglobin trigger of 100 g/l. More than three-quarters would transfuse red cells in the vignette when hemoglobin was ≤80 g/l. Slightly more than one-half of respondents would use inotropic agents if volume resuscitation and transfusion failed to provide adequate oxygen delivery.

The finding of greatest interest in McIntyre and colleagues' study [28] was the infrequent use of central venous saturation monitoring and higher triggers for red cell transfusion than utilized in the early goal-directed therapy study [27]. While the interpretation of these findings may be limited by the nature of the study (mail-based survey) and the moderate response rate, several hypotheses might be proposed for the results. The early goal-directed therapy study was conducted in an emergency department but the respondents to the survey were not emergency medicine physicians and may not have experience with using such a protocol themselves. The results of the Canadian Transfusion in Critically Ill trial [29] might have also led to reluctance to provide transfusions at higher hemoglobin concentrations. Because of the deleterious effects of transfusion [30], this feature of early goal-directed therapy remains one of the most controversial of the protocol. This survey preceded a randomized trial of the use of hydroxyethyl starch in severe sepsis that showed increased acute renal failure and increased need for renal replacement therapy compared with Ringer's lactate [31]. The effects of this finding on the clinical use of colloids in septic shock and their presence in guidelines for resuscitation [32,33] are unknown.

Hemoperfusion with polymixin B

Polymyxin B is a cationic detergent with activity against many aerobic Gram-negative organisms. The cationic detergent disrupts bacterial outer and cytoplasmic membranes but, because of its nephrotoxicity and neurotoxicity, has limited usefulness as a parenteral antibacterial agent [34]. The observation that polymyxin B can adsorb circulating endotoxin – a component of Gram-negative bacteria cell walls – when it is bound to and immobilized with polystyrene fibers (PMX-F) has led to its use as a therapy in severe sepsis, especially in Japan.

Cruz and colleagues [35] performed a systematic review of clinical studies of extracorporeal PMX-F therapy in severe sepsis in an effort to determine its effectiveness. The authors identified 28 publications that were included in the review. These studies included nine randomized controlled trials, seven parallel, nonrandomized controlled trials, and 12 pre–post cohort studies, with a pooled sample size of 1,425 from seven countries. Overall, the quality of included studies was graded as poor. There was variation in the protocol used for PMX-F. When reported, Gram-negative infections were found in 71% of patients.

From the pooled analyses, PMX-F was effective in reducing circulating levels of endotoxin and was associated with an improvement in mean arterial pressure (mean, 26%; absolute mean increase, 19 mmHg). Patients with lower pretreatment mean arterial pressure levels had a greater benefit in blood pressure than those with higher pretreatment blood pressure. This was accompanied by a trend toward decreased doses of vasopressor agents. The PaO_2/FiO_2 ratios also showed a modest improvement. Pooled mortality rates were 61.5% in the conventional therapy group and 33.5% in the PMX-F group. This resulted in a relative risk for PMX-F of 0.53 (95% confidence interval, 0.40 to 0.76). Various sensitivity analyses confirmed the main results. Reported adverse events were rare, and included clotting of the device and erythema.

These results suggest PMX-F may be a promising therapy for severe sepsis. The included patients represent a minority of the patients who have received this therapy, however, as more than 60,000 patients have received PMX-F since the Japanese national health insurance program began supporting this therapy in 1994. The mortality in the conventional therapy arm also exceeds that seen in other studies of patients with severe sepsis [36,37], raising questions about the comparison group and the actual benefit of therapy. The results of this systematic review support evaluation of PMX-F in well-designed multicenter randomized controlled trials with comparison of mortality and cost-effectiveness in the context of best available sepsis care.

Glutamine may attenuate vascular dysfunction in endotoxemia

Glutamine is a nonessential amino acid that may have value as a sepsis therapy through its effects on cytokine release [38,39]. Some of this effect appears to be mediated through increased expression of heat shock protein 70 with glutamine administration [40]. Heat shock proteins are a group of proteins that are induced by a wide range of stimuli and serve to maintain cell homeostasis through a broad range of activities [41,42].

Jing and colleagues hypothesized that glutamine might improve vascular reactivity through its induction of heat shock protein 70 in a rat model of sepsis (lipopolysaccharide infusion) [43]. In the rats receiving 4% glutamine infusions, the mean arterial pressure and vasopressor responsiveness were improved. Glutamine infusion was also associated with reduced levels of proinflammatory cytokines, including TNFα, IL-6 and malondialdehyde. Supporting the role of heat shock proteins, heat shock protein 70 was increased in the heart, the endothelium, the lung and the liver of animals treated with glutamine compared with control animals. While this is an interesting finding, the study used pretreatment with glutamine, limiting its use in patients already identified as having sepsis. Nevertheless, the mechanism of heat shock protein induction is intriguing and could lead to further investigation in humans.

Recovery after sepsis

Most studies of sepsis measure proximate outcomes, such as 28-day mortality or hospital mortality [36]. Fewer studies have examined longer-term mortality after sepsis. Existing data suggest that mortality may be increased over projections expected by age alone for 5 years after sepsis [44]. While morbidity and quality-of-life consequences are even less well studied [45-48], existing data suggest acute organ dysfunction may influence the quality of life in sepsis survivors [49].

Longo and colleagues performed a cohort study in nine Canadian ICUs to determine the health-related quality of life (HRQOL) for up to 7 months after sepsis, and compared these outcomes for patients who did and did not receive recombinant human activated protein C (rhAPC) [50]. Over 4 years, the investigators identified ICU patients with severe sepsis and at least two organ failures. Decisions regarding the use of rhAPC were at the discretion of the clinical team. Subjects completed the Short Form-36 at 28 days and at 3, 5, and 7 months, and kept a diary to track resource utilization. Subjects were recruited in blocks of nine per site, with three rhAPC patients and six non-rhAPC patients comprising each block to reduce imbalances in rhAPC patients and non-rhAPC patients at each site.

A total of 164 patients meeting the inclusion criteria were screened, and 100 patients provided consent and comprised the study cohort. During the 6-month follow-up, mortality among initial sepsis survivors tended to be lower among those receiving rhAPC than among those patients not treated (absolute risk reduction, 11.8%). Patients treated with rhAPC had shorter initial hospital stays, but the ICU length of stay and the need for transfer to a chronic care facility after hospitalization were not different between the groups.

Seven months after admission for sepsis, the HRQOL was significantly lower in severe sepsis survivors than among age-matched control individuals. This difference was most evident in physical subscores, but was seen across all measured dimensions. After adjusting for age, patients treated with rhAPC had better scores in the physical components of HRQOL than those not treated with rhAPC. This difference was not observed among the mental component scores. Of those participants previously employed, patients treated with rhAPC tended to return to work sooner than those patients not receiving rhAPC.

These data suggest that survivors of sepsis continue to suffer from impairments in HRQOL for months, especially among physical domains. This is similar to the effects of other critical illnesses on the recovery of HRQOL [51-53]. Furthermore, rhAPC appears to hasten the recovery of quality of life among survivors. These are encouraging findings after concerns were expressed that rhAPC did not affect the discharge destination of treated patients treated in the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial

[54]. If confirmed, these data argue that the analyses showing the cost-effectiveness of rhAPC [55-60] may, in fact, underestimate the benefit of treatment.

Inclusion of measures of morbidity among survivors, such as the HRQOL, in subsequent studies of severe sepsis would provide more robust estimates of benefit. Readers are advised, however, that several of the authors are current or former Eli Lilly employees. Additionally, the study sample is smaller than initially intended. Risk adjustment was only made for age and for prior HRQOL scores, and may therefore not have accounted for residual confounding due to selection bias in the administration of rhAPC. It would have been useful to perform a propensity score-matching process to account for differences between those patients given rhAPC and those not given rhAPC.

Competing interests

Jim O'Brien: University grant monies: Davis/Bremer Medical Research Award Non-industry grant monies: NHLBI HL075076; NIH Clinical Research Loan Repayment Program Industry grant monies: Sub-I on studies of rhAPC, iseganan, PAF-ase, LY315920, Zemplat®, ARDS Network. SubI on M01 RR0051 (NIH and Lilly). PI for aerosolized amikacin (Aerogen) Consultant/Speakers' Bureau: Gave lecture on ARDS to Lilly; Received honorarium from Lilly for talk on tidal volume, unrestricted educational grant from Lilly to present talk at SCCM (2005), consultant to Medical Simulation Corporation, Co-author on manuscript with Lilly employees

Authors' contributions

JMO'B and NAA contributed equally to this manuscript.

References

1. Vakkala M, Laurila JJ, Saarnio J, Koivukangas V, Syrjala H, Karttunen T, Soini Y, Ala-Kokko TI: **Cellular turnover and expression of hypoxic-inducible factor in acute acalculous and calculous cholecystitis.** *Crit Care* 2007, **11:**R116.
2. Ke Q, Costa M: **Hypoxia-inducible factor-1 (HIF-1).** *Mol Pharmacol* 2006, **70:**1469-1480.
3. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D: **Sepsis in European intensive care units: results of the SOAP study.** *Crit Care Med* 2006, **34:**344-353.
4. Engel C, Brunkhorst FM, Bone HG, Brunkhorst R, Gerlach H, Grond S, Gruendling M, Huhle G, Jaschinski U, John S, Mayer K, Oppert M, Olthoff D, Quintel M, Ragaller M, Rossaint R, Stuber F, Weiler N, Welte T, Bogatsch H, Hartog C, Loeffler M, Reinhart K: **Epidemiology of sepsis in Germany: results from a national prospective multicenter study.** *Intensive Care Med* 2007, **33:** 606-618.
5. Hotchkiss RS, Karl IE: **The pathophysiology and treatment of sepsis.** *N Engl J Med* 2003, **348:**138-150.
6. Sriskandan S, Altmann DM: **The immunology of sepsis.** *J Pathol* 2008, **214:**211-223.
7. Boman HG: **Antibacterial peptides: basic facts and emerging concepts.** *J Intern Med* 2003, **254:**197-215.
8. Yang D, Biragyn A, Kwak LW, Oppenheim JJ: **Mammalian defensins in immunity: more than just microbicidal.** *Trends Immunol* 2002, **23:**291-296.
9. Book M, Chen Q, Lehmann LE, Klaschik S, Weber S, Schewe JC, Luepertz M, Hoeft A, Stuber F: **Inducibility of the endogenous antibiotic peptide beta-defensin 2 is impaired in patients with severe sepsis.** *Crit Care* 2007, **11:**R19.
10. Brodsky SV, Zhang F, Nasjletti A, Goligorsky MS: **Endothelium-derived microparticles impair endothelial function in vitro.** *Am J Physiol Heart Circ Physiol* 2004, **286:**H1910-H1915.
11. Meziani F, Tesse A, Andriantsitohaina R: **Microparticles are vectors of paradoxical information in vascular cells including the endothelium: role in health and diseases.** *Pharmacol Rep* 2008, **60:**75-84.
12. Piccin A, Murphy WG, Smith OP: **Circulating microparticles: pathophysiology and clinical implications.** *Blood Rev* 2007, **21:** 157-171.
13. Janiszewski M, Do Carmo AO, Pedro MA, Silva E, Knobel E, Laurindo FR: **Platelet-derived exosomes of septic individuals possess proapoptotic NAD(P)H oxidase activity: a novel vascular redox pathway.** *Crit Care Med* 2004, **32:**818-825.
14. Gambim MH, do Carmo AO, Marti L, Verissimo-Filho S, Lopes LR, Janiszewski M: **Platelet-derived exosomes induce endothelial cell apoptosis through peroxynitrite generation: experimental evidence for a novel mechanism of septic vascular dysfunction.** *Crit Care* 2007, **11:**R107.
15. Azevedo LC, Janiszewski M, Soriano FG, Laurindo FR: **Redox mechanisms of vascular cell dysfunction in sepsis.** *Endocr Metab Immune Disord Drug Targets* 2006, **6:**159-164.
16. Wang H, Bloom O, Zhang M, Vishnubhakat JM, Ombrellino M, Che J, Frazier A, Yang H, Ivanova S, Borovikova L, Manogue KR, Faist E, Abraham E, Andersson J, Andersson U, Molina PE, Abumrad NN, Sama A, Tracey KJ: **HMG-1 as a late mediator of endotoxin lethality in mice.** *Science* 1999, **285:**248-251.
17. Parrish W, Ulloa L: **High-mobility group box-1 isoforms as potential therapeutic targets in sepsis.** *Methods Mol Biol* 2007, **361:**145-162.
18. Wang H, Li W, Goldstein R, Tracey KJ, Sama AE: **HMGB1 as a potential therapeutic target.** *Novartis Found Symp* 2007, **280:** 73-85.
19. Zweigner J, Schumann RR, Weber JR: **The role of lipopolysaccharide-binding protein in modulating the innate immune response.** *Microbes Infect* 2006, **8:**946-952.
20. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C: **High serum procalcitonin concentrations in patients with sepsis and infection.** *Lancet* 1993, **341:**515-518.
21. Gaini S, Koldkjaer OG, Moller HJ, Pedersen C, Pedersen SS: **A comparison of high-mobility group-box 1 protein, lipopolysaccharide-binding protein and procalcitonin in severe community-acquired infections and bacteraemia: a prospective study.** *Crit Care* 2007, **11:**R76.
22. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J: **Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial.** *Am J Respir Crit Care Med* 2008, **177:**498-505.
23. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH: **The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting.** *Chest* 2000, **118:**146-155.
24. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, Suppes R, Feinstein D, Zanotti S, Taiberg L, Gurka D, Kumar A, Cheang M: **Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock.** *Crit Care Med* 2006, **34:**1589-1596.
25. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R: **A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO_2 Collaborative Group.** *N Engl J Med* 1995, **333:**1025-1032.
26. Heyland DK, Cook DJ, King D, Kernerman P, Brun-Buisson C: **Maximizing oxygen delivery in critically ill patients: a methodologic appraisal of the evidence.** *Crit Care Med* 1996, **24:**517-524.
27. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M: **Early goal-directed therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345:**1368-1377.
28. McIntyre LA, Hebert PC, Fergusson D, Cook DJ, Aziz A: **A survey of Canadian intensivists' resuscitation practices in early septic shock.** *Crit Care* 2007, **11:**R74.
29. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E: **A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group.** *N Engl J Med* 1999, **340:**409-417.

30. Raghavan M, Marik PE: **Anemia, allogenic blood transfusion, and immunomodulation in the critically ill.** *Chest* 2005, **127:** 295-307.
31. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, Moerer O, Gruendling M, Oppert M, Grond S, Olthoff D, Jaschinski U, John S, Rossaint R, Welte T, Schaefer M, Kern P, Kuhnt E, Kiehntopf M, Hartog C, Natanson C, Loeffler M, Reinhart K; German Competence Network Sepsis (SepNet): **Intensive insulin therapy and pentastarch resuscitation in severe sepsis.** *N Engl J Med* 2008, **358:**125-139.
32. **Evidence-based colloid use in the critically ill: American Thoracic Society Consensus Statement.** *Am J Respir Crit Care Med* 2004, **170:**1247-1259.
33. Barron ME, Wilkes MM, Navickis RJ: **A systematic review of the comparative safety of colloids.** *Arch Surg* 2004, **139:**552-563.
34. Ouderkirk JP, Nord JA, Turett GS, Kislak JW: **Polymyxin B nephrotoxicity and efficacy against nosocomial infections caused by multiresistant gram-negative bacteria.** *Antimicrob Agents Chemother* 2003, **47:**2659-2662.
35. Cruz DN, Perazella MA, Bellomo R, de Cal M, Polanco N, Corradi V, Lentini P, Nalesso F, Ueno T, Ranieri VM, Ronco C: **Effectiveness of polymyxin B-immobilized fiber column in sepsis: a systematic review.** *Crit Care* 2007, **11:**R47.
36. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ Jr, Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study group: **Efficacy and safety of recombinant human activated protein C for severe sepsis.** *N Engl J Med* 2001, **344:**699-709.
37. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D, Briegel J; CORTICUS Study Group: **Hydrocortisone therapy for patients with septic shock.** *N Engl J Med* 2008, **358:**111-124.
38. Wischmeyer PE, Lynch J, Liedel J, Wolfson R, Riehm J, Gottlieb L, Kahana M: **Glutamine administration reduces Gram-negative bacteremia in severely burned patients: a prospective, randomized, double-blind trial versus isonitrogenous control.** *Crit Care Med* 2001, **29:**2075-2080.
39. Wischmeyer PE, Kahana M, Wolfson R, Ren H, Musch MM, Chang EB: **Glutamine reduces cytokine release, organ damage, and mortality in a rat model of endotoxemia.** *Shock* 2001, **16:**398-402.
40. Singleton KD, Serkova N, Banerjee A, Meng X, Gamboni-Robertson F, Wischmeyer PE: **Glutamine attenuates endotoxin-induced lung metabolic dysfunction: potential role of enhanced heat shock protein 70.** *Nutrition* 2005, **21:**214-223.
41. Lindquist S, Craig EA: **The heat-shock proteins.** *Annu Rev Genet* 1988, **22:**631-677.
42. Ang D, Liberek K, Skowyra D, Zylicz M, Georgopoulos C: **Biological role and regulation of the universally conserved heat shock proteins.** *J Biol Chem* 1991, **266:**24233-24236.
43. Jing L, Wu Q, Wang F: **Glutamine induces heat-shock protein and protects against *Escherichia coli* lipopolysaccharide-induced vascular hyporeactivity in rats.** *Crit Care* 2007, **11:** R34.
44. Quartin AA, Schein RM, Kett DH, Peduzzi PN: **Magnitude and duration of the effect of sepsis on survival. Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group.** *JAMA* 1997, **277:**1058-1063.
45. Graf J, Koch M, Dujardin R, Kersten A, Janssens U: **Health-related quality of life before, 1 month after, and 9 months after intensive care in medical cardiovascular and pulmonary patients.** *Crit Care Med* 2003, **31:**2163-2169.
46. Granja C, Dias C, Costa-Pereira A, Sarmento A: **Quality of life of survivors from severe sepsis and septic shock may be similar to that of others who survive critical illness.** *Crit Care* 2004, **8:** R91-R98.
47. Korosec JH, Jagodic K, Podbregar M: **Long-term outcome and quality of life of patients treated in surgical intensive care: a comparison between sepsis and trauma.** *Crit Care* 2006, **10:** R134.
48. Erickson SE, Martin GS: **Effect of sepsis therapies on health-related quality of life.** *Crit Care* 2008, **12:**109.
49. Garcia LF, Peres BD, De Cubber M, Vincent JL: **Long-term outcome in ICU patients: what about quality of life?** *Intensive Care Med* 2003, **29:**1286-1293.
50. Longo CJ, Heyland DK, Fisher HN, Fowler RA, Martin CM, Day AG: **A long-term follow-up study investigating health-related quality of life and resource use in survivors of severe sepsis: comparison of recombinant human activated protein C with standard care.** *Crit Care* 2007, **11:**R128.
51. Herridge MS: **Long-term outcomes after critical illness: past, present, future.** *Curr Opin Crit Care* 2007, **13:**473-475.
52. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, Cooper AB, Guest CB, Mazer CD, Mehta S, Stewart TE, Barr A, Cook D, Slutsky AS; Canadian Critical Care Trials Group: **One-year outcomes in survivors of the acute respiratory distress syndrome.** *N Engl J Med* 2003, **348:** 683-693.
53. Herridge MS: **Long-term outcomes after critical illness.** *Curr Opin Crit Care* 2002, **8:**331-336.
54. Banks SM, Gerstenberger E, Eichacker PQ, Natanson C: **Long-term cost effectiveness of drotrecogin alfa (activated): an unanswered question.** *Crit Care Med* 2003, **31:**308-309.
55. Angus DC, Linde-Zwirble WT, Clermont G, Ball DE, Basson BR, Ely EW, Laterre PF, Vincent JL, Bernard G, van Hout B: **Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis.** *Crit Care Med* 2003, **31:**1-11.
56. Davies A, Ridley S, Hutton J, Chinn C, Barber B, Angus DC: **Cost effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in the United Kingdom.** *Anaesthesia* 2005, **60:** 155-162.
57. Neilson AR, Burchardi H, Chinn C, Clouth J, Schneider H, Angus D: **Cost-effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in Germany.** *J Crit Care* 2003, **18:** 217-227.
58. Frampton JE, Foster RH: **Drotrecogin alfa (activated): a pharmacoeconomic review of its use in severe sepsis.** *Pharmacoeconomics* 2004, **22:**445-476.
59. Green C, Dinnes J, Takeda AL, Cuthbertson BH: **Evaluation of the cost-effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in the United Kingdom.** *Int J Technol Assess Health Care* 2006, **22:**90-100.
60. Manns BJ, Lee H, Doig CJ, Johnson D, Donaldson C: **An economic evaluation of activated protein C treatment for severe sepsis.** *N Engl J Med* 2002, **347:**993-1000.