Top Ten List in Sepsis*

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Abbreviations: APACHE = acute physiology and chronic health evaluation; BSI = bloodstream infection; CI = cardiac index; cTnl = concentration of troponin I; IL = interleukin; M/R = minocycline and rifampin; ΔPp = change in pulse pressure; TNF = tumor necrosis factor

Pathophysiology


Schröder and colleagues expand our growing knowledge of genetic predisposition to septic shock by examining the relationship of gender to tumor necrosis factor (TNF)-β gene Nco1 polymorphism. Several recent reports indicate that patients who possess the TNF-β2 homozygous genotype for this polymorphism have a higher incidence of severe sepsis, higher TNF-α serum concentrations, and a lower likelihood of survival once sepsis develops. In this prospective study of 201 patients with severe sepsis, the 68 women had a higher survival rate than the men, but no association of survival to different genotypes was found in women. In contrast, the mortality rate was significantly increased in 133 men who were homozygous for TNF-β2 compared to other genotypes. Since previous sepsis studies from the same investigators demonstrated higher interleukin (IL)-10 levels in women and higher TNF-α levels in men, it may be that genetically determined patterns of cytokine response to injury or infection may differ among the sexes and may influence outcome.

Prevention


Catheter-related bloodstream infection (BSI) is the most common cause of nosocomial bacteremia. A meta-analysis1 demonstrated a significant reduction in catheter colonization as well as catheter-related BSI with chlorhexidine and silver sulfadiazine-impregnated central venous catheters compared to standard catheters. In the 12-hospital randomized controlled trial reported by Darouiche and colleagues, triple-lumen catheters impregnated with minocycline and rifampin (M/R) on both the luminal and external surfaces (Cook Bio-Guard Spectrum; Cook Surgical; Bloomington, IN) were compared to catheters impregnated with chlorhexidine and silver sulfadiazine on the external surface (ARROWgard; Arrow International; Reading, PA). M/R catheters had significantly lower rates of colonization (28 of 356 catheters [7.9%] vs 87 of 382 catheters [22.8%], p < 0.001) as well as catheter-related BSI (1 of 356 catheters [0.3%] vs 13 of 382 catheters [3.4%], p < 0.002). A subsequent report2 has confirmed this clinical advantage of M/R-impregnated catheters and demonstrated larger zones of inhibition against common bacteria in vitro. However, an expert3 urges caution in the use of M/R-impregnated catheters because of the theoretical concern for emergence of rifampin resistance. The added cost of these catheters compared to that of unimpregnated catheters is likely to be offset by savings from reduced episodes of BSI.


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The notion that nutritional supplementation, or immunonutrition, can alter the outcome from conditions characterized by infection and inflammation, such as sepsis and ARDS, is controversial. Galban and colleagues conducted a randomized, controlled clinical trial in which they compared a nutritional formula supplemented with arginine, messenger RNA, and omega-3 fatty acids from fish oil (Impact; Novartis Nutrition; Bern, Switzerland) with a high-protein enteral feed without these nutrients, administered to 176 septic patients from six Spanish ICUs. The mortality rate was reduced (19.1% vs 32.2%, p = 0.05), as were acquired bacteremias (7.9% vs 21.8%, p = 0.01) and cases with multiple nosocomial infections (5.6% vs 19.5%, p = 0.01) in the immunonutrition group. Length of stay was not affected. Unexpectedly, most of the mortality benefit was confined to the least sick patients, who had APACHE (acute physiology and chronic health evaluation) II scores of 10 to 15, and there was clearly no treatment benefit for the sickest patients, who had APACHE II scores > 25.

Evaluation


These authors examined the relationship between serum cortisol measurements before and after adrenal gland stimulation with corticotropin and mortality in 189 consecutive adult ICU patients with septic shock. No patient met traditional corticotropin test criteria for adrenal insufficiency. Three groups of patient prognosis were identified: good (baseline cortisol < 34 μg/dL and maximum change > 9 μg/dL), with 28-day mortality rate of 26%; intermediate (baseline cortisol > 34 μg/dL and maximum change > 9 μg/dL, or baseline cortisol < 34 μg/dL and maximum change < 9 μg/dL), with a 28-day mortality rate of 67%; and poor (baseline cortisol > 34 μg/dL and maximum change < 9 μg/dL), with a 28-day mortality of 82%. The authors suggest that the generally poor outcome of patients who have a weak cortisol response to corticotropin injection represents poor adrenal reserve or partial adrenal insufficiency. The striking relationship between baseline cortisol levels and high mortality rate is speculated to represent the consequences of refractory receptor behavior with subsequent continued outpouring of cortisol, but it may merely be a marker of high stress and inflammation.


Identification of biochemical markers of sepsis can be useful to unravel the pathophysiology, identify infection, direct specific therapy to selected patients, and establish prognosis. Muller and coworkers measured serial serum concentrations of calcitonin precursors in 101 consecutive medical ICU patients. Serum levels of calcitonin precursors correlated highly with severity of infection, with greater reliability than C-reactive protein, IL-6, and lactate levels. Calcitonin precursor concentrations > 1 ng/mL had sensitivity of 89% and specificity of 94% for the diagnosis of sepsis. High serum concentrations were associated with poor prognosis (p = 0.01). Other investigators have demonstrated robust discrimination of infected from noninfected patients after cardiac surgery, heart transplantation, trauma, and ARDS. Furthermore, a strong relationship between elevated procalcitonin levels and more organ dysfunction and/or higher mortality rate has also been demonstrated for trauma and pediatric septic shock.


Cardiac function is a key determinant of outcome from septic shock; however, the development of myocardial injury and its impact on outcome have received little attention until recently. Ver Elst and colleagues measured troponin I and troponin T serially and assessed left ventricular function using two-dimensional transesophageal echocardiography in 46 patients with septic shock. Increased plasma concentration of troponin I (cTnI) and plasma concentration of troponin T were found in 50% and 36% of patients, respectively, at one or more time points. cTnI-positive patients were older, had higher APACHE II scores, had worse survival, and more commonly had systemic hypertension or previous myocardial infarction. cTnI and plasma concentration of troponin T levels were highly associated with left ventricular dysfunction (p = 0.001). Interestingly, continuous ECG monitoring in all patients and autopsy in 12 nonsurvivors did not disclose the occurrence of acute ischemia during the first 48 h of observation. Other investigators have demonstrated higher cTnI levels among septic patients who received vasopressor therapy, but did not clarify whether the vasopressors contribute directly to injury or are merely markers for more severe shock.
MANAGEMENT


In a prospective cohort study of 492 medical and surgical ICU patients with BSI, 147 patients (29.9%) received inadequate antimicrobial treatment. The hospital mortality rate for those who received inadequate antimicrobial treatment was higher (61.9%) than for patients who received appropriate antibiotics (28.4%; relative risk, 2.18; p < 0.001). Inadequate antibiotic treatment was an independent determinant of hospital mortality. BSI caused by antibiotic-resistant Gram-positive organisms and Candida species accounted for the majority of cases of inadequate antibiotic administration in this series. Correct antibiotic selection is one of the few interventions proven to improve the outcome of sepsis and bacteremia.


Achieving adequate left ventricular preload through IV administration of fluids is a basic component of resuscitation in patients with septic shock, yet measurements that are commonly used to guide volume administration, such as pulmonary artery occlusion pressure and central venous pressure, are imprecise. The authors investigated whether changes in arterial pressure during positive-pressure ventilation could be correlated to the effects of volume expansion on cardiac index (CI) during septic shock. They examined the change in pulse pressure (ΔPp) [(maximum pulse pressure − minimum pulse pressure)/(mean of maximum and minimum pulse pressure)] and the change in systolic pressure over the course of a respiratory cycle in 40 patients. A positive response to volume expansion, defined as an increase of ≥15% in CI, was observed in 16 patients. The respiration-induced ΔPp at baseline of > 13% allowed discrimination between responders and non-responders with a sensitivity of 94% and a specificity of 96%. ΔPp and change in systolic pressure were much more robust predictors of response to volume expansion than central venous pressure or pulmonary artery occlusion pressure. This technique offers promise as a technique that can be performed using available technology in patients with septic shock receiving mechanical ventilation. Furthermore, repeated measurements can be made. The influence of changing lung mechanics or adjustments in ventilator settings on reproducibility requires further study.


It is well established that treatment with high-dose corticosteroids has no beneficial actions in patients with septic shock; however, recent case series and uncontrolled studies suggest physiologic doses of corticosteroids administered over days to weeks may hasten recovery from septic shock. In the study by Briegel et al, 40 patients with hyperdynamic (defined as a CI > 4 L/min/m²) septic shock were randomized to receive placebo or hydrocortisone infusion (100-mg loading dose followed by 0.18 mg/kg/h) for 6 days followed by scheduled tapering of the dose. Hydrocortisone infusion was associated with significantly (p = 0.005) reduced time to cessation of vasopressor support, from a median of 7 days for placebo to 2 days for hydrocortisone. The investigators also observed a trend favoring earlier resolution of organ dysfunction but no difference in mortality. A second recent prospective, randomized, placebo-controlled single-center clinical trial by Bollaert et al also demonstrated more rapid recovery from septic shock when hydrocortisone (100 mg IV tid for 5 days, then tapered) was administered to patients who had been in shock an average of 6 days prior to enrollment. We await the final results of the recently concluded European multicenter clinical trial designed to evaluate the physiologic dose of hydrocortisone in patients with septic shock.


The past several decades have produced many disappointments in the search for an agent that modifies the inflammatory response to sepsis and improves survival. Recent attention has also focused on thrombotic microvascular events as a target for intervention. Recombinant human activated protein C, or drotrecogin alfa (activated), has anti-inflammatory, as well as antithrombotic and profibrinolytic properties. In this multicenter, randomized, controlled trial of 1,690 patients with severe sepsis, a 96-h infusion of activated protein C was associated with a significant reduction in 28-day mortality when compared to placebo infusion (24.7% vs 30.8%, p = 0.005). A consistent treatment effect was observed for important predefined subgroups, including patients with and without pretreatment protein C.
deficiency. Blood levels of biological markers of inflammation (IL-6) and a procoagulant state (D-dimer) were reduced with activated protein C infusion. There was a trend for higher rates of serious bleeding among patients who received activated protein C (3.5% vs 2.0% in the placebo group, p = 0.06), occurring primarily during infusion. This important study demonstrates safety and efficacy of a novel agent for treatment of severe sepsis beyond traditional therapeutic measures. Further work is needed to examine the effects of the drug for patient populations not examined in this study, as well as to test additional related products.

REFERENCES