stockings or an intermittent compression device should be used. Recovery is also assisted by prevention of skin breakdown, nosocomial infections, and stress ulcers.

The role of tight control of the blood glucose concentration in recovery from critical illness has been addressed in numerous controlled trials. Meta-analyses of these trials have concluded that use of insulin to lower blood glucose levels to 100–120 mg/dL is potentially harmful and does not improve survival rates. Most experts now recommend using insulin only if it is needed to maintain the blood glucose concentration below ~180 mg/dL. Patients receiving intravenous insulin must be monitored frequently (every 1–2 h) for hypoglycemia.

OTHER MEASURES

Despite aggressive management, many patients with severe sepsis or septic shock die. Numerous interventions have been tested for their ability to improve survival rates among patients with severe sepsis. The list includes endotoxin-neutralizing proteins, inhibitors of cyclooxygenase or nitric oxide synthase, anticoagulants, polyclonal immunoglobulins, glucocorticoids, a phospholipid emulsion, and antagonists to TNF-α, IL-1, platelet-activating factor, and bradykinin. Unfortunately, none of these agents has improved rates of survival among patients with severe sepsis/septic shock in more than one large-scale, randomized, placebo-controlled clinical trial. Many factors have contributed to this lack of reproducibility, including (1) heterogeneity of the patient populations studied, the primary infection sites, the preexisting illnesses, and the inciting microbes; and (2) the nature of the "standard" therapy also used. A dramatic example of this problem was seen in a trial of tissue factor pathway inhibitor. Whereas the drug appeared to improve survival rates after 722 patients had been studied (p = .006), it did not do so in the next 1032 patients, and the overall result was negative. This inconsistency argues that the results of a clinical trial may not apply to individual patients, even within a carefully selected patient population. It also suggests that, at a minimum, a sepsis intervention should show a significant survival benefit in more than one placebo-controlled, randomized clinical trial before it is accepted as routine clinical practice. In one attempt to reduce patient heterogeneity in clinical trials, experts have called for changes that would restrict these trials to patients who have similar underlying diseases (e.g., major trauma) and inciting infections (e.g., pneumonia). Other investigators have proposed using specific biomarkers, such as IL-6 levels in blood or the expression of HLA-DR on peripheral-blood monocytes, to identify the patients most likely to benefit from certain interventions.

Recombinant activated protein C (aPC) was the first immunomodulatory drug to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with severe sepsis or septic shock. Approval was based on the results of a single randomized controlled trial in which the drug was given within 24 h of the patient's first sepsis-related organ dysfunction; the 28-day survival rate was significantly higher among aPC recipients who were very sick (APACHE II score, ≥25) before infusion of the protein than among placebo-treated controls. Subsequent trials failed to show a benefit of aPC treatment in patients who were less sick (APACHE II score, <25) or in children, and, a decade after its licensure by the FDA, the drug was withdrawn from the market when a European trial failed to confirm its efficacy in adults with sepsis. Agents in ongoing or planned clinical trials include intravenous immunoglobulin, a polymyxin B hemofiltration column, and granulocyte-macrophage colony-stimulating factor, which has been reported to restore monocyte immunocompetence in patients with sepsis-associated immunosuppression.

A careful retrospective analysis found that the apparent efficacy of all sepsis therapeutics studied to date has been greatest among the patients at greatest risk of dying before treatment; conversely, use of many of these drugs has been associated with increased mortality rates among patients who are less ill. It is possible that neutralizing one of many different mediators may help patients who are very sick, whereas disrupting the mediator balance may be harmful to patients whose adaptive defense mechanisms are working well. This analysis suggests that if more aggressive early resuscitation improves survival rates among sicker patients, it will become more difficult to obtain additional benefit from other therapies; that is, if an intervention improves patients' risk status, moving them into a "less severe illness" category, it will be harder to show that adding another agent to the therapeutic regimen is beneficial.

THE SURVIVING SEPSIS CAMPAIGN

An international consortium has advocated "bundling" of multiple therapeutic maneuvers into a unified algorithmic approach that will become the standard of care for severe sepsis. In theory, such a strategy would improve care by mandating measures that seem to bring maximal benefit, such as the rapid administration of appropriate antimicrobial therapy, fluids, and blood pressure support. Caution may be engendered by the fact that three of the key elements of the initial algorithm were eventually withdrawn for lack of evidence; moreover, the benefit of the current sepsis bundles has not been established in randomized controlled clinical trials.

PROGNOSIS

Approximately 20–35% of patients with severe sepsis and 40–60% of patients with septic shock die within 30 days. Others die within the ensuing 6 months. Late deaths often result from poorly controlled infection, immunosuppression, complications of intensive care, failure of multiple organs, or the patient's underlying disease. Case–fatality rates are similar for culture-positive and culture-negative severe sepsis. Prognostic stratification systems such as APACHE II indicate that factoring in the patient's age, underlying condition, and various physiologic variables can yield useful estimates of the risk of dying of severe sepsis. Age and prior health status are probably the most important risk factors (Fig. 325-1). In patients with no known preexisting morbidity, the case–fatality rate remains <10% until the fourth decade of life, after which it gradually increases to >35% in the very elderly. Death is significantly more likely in severely septic patients with preexisting illness. Septic shock is also a strong predictor of

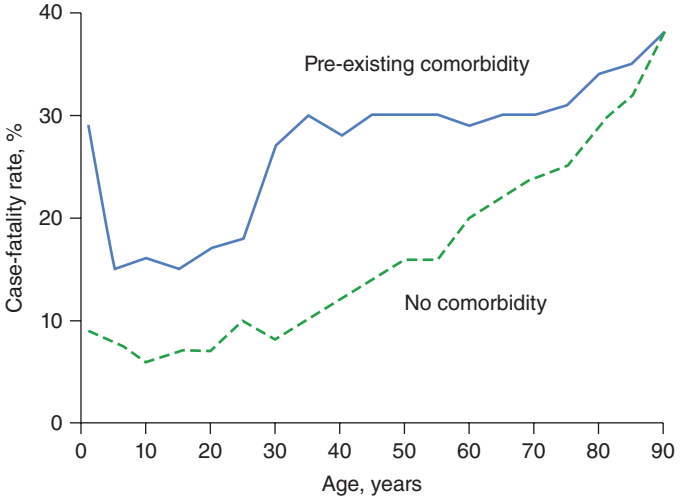

FIGURE 325-1 Influence of age and prior health status on outcome of severe sepsis. With modern therapy, fewer than 10% of previously healthy young individuals (below 35 years of age) die with severe sepsis; the case–fatality rate then increases slowly through middle and old age. The most commonly identified etiologic agents in patients who die are *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*. Individuals with preexisting comorbidities are at greater risk of dying of severe sepsis at any age. The etiologic agents in these cases are likely to be *S. aureus*, *Pseudomonas aeruginosa*, various Enterobacteriaceae, enterococci, or fungi. *(Adapted from DC Angus et al: Crit Care Med 29:1303, 2001.)*