Biomarkers in lower respiratory tract infections

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A B S T R A C T
This review aims to provide physicians with an overview of the potential of biomarkers to complement existing clinical severity scores and in conjunction with clinical parameters to improve the diagnosis, risk-stratification and management of lower respiratory tract infections (LRTIs).

The usefulness of biomarkers for diagnosing LRTIs is still unclear. However, the specificity of pneumonia diagnosis is high when high sensitivity C-reactive protein (CRP) and procalcitonin (PCT) are used. PCT, CRP and particularly pro-atrial natriuretic peptide (MR-proANP), pro-vasopressin (CT-proAVP) and proadrenomedullin (proADM) levels can reliably predict LRTIs mortality. These markers do not significantly improve the severity scores predictive values, confirming that biomarkers are meant to complement, rather than supersede, clinician’s judgment and validated severity scores.

Biomarkers, and particularly PCT, are useful tools as antibiotic treatment duration indicators both in pneumonia and exacerbations of chronic obstructive pulmonary disease (COPD).

Even if more data are required to fully appreciate the role of biomarkers in LRTIs management, there is emerging evidence that biomarkers have the potential to improve the daily clinical management of LRTIs.

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1. Do we need biological markers in lower respiratory tract infections?

We can define biological markers (biomarkers) as measurable characteristics that indicate normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention [1]. Ideally, a valuable biomarker should differentiate subjects with active disease from healthy individuals, normalize with therapy, and reproducibly predict clinical outcomes in a specific medical condition.

Unfortunately, up to now, no biomarker proposed in lower respiratory tract infections (LRTIs) completely fulfills this definition. Nevertheless, a number of studies have been carried out or are currently ongoing to evaluate the role of various biomarkers for the differential diagnosis, definition of prognosis, treatment and antibiotic treatment duration in respiratory infections. This is related to the great deal of uncertainty in the LRTIs management. The definition of the presence, the etiology and the severity of LRTI as well as the treatment choice and duration are frequently a real problem for the treating physician. Clinical features are sometimes misleading and not specific varying according to the etiology, bacterial or viral load and virulence, adequacy of host response and presence of concomitant diseases.

There is a clear need for diagnostic and prognostic biomarkers in LRTIs. In this article we intend to critically review the current literature on the possible role of biomarkers in the management of LRTIs from acute bronchitis to severe hospital-acquired pneumonia.

2. Biomarkers and LRTIs diagnosis

The usefulness of biomarkers for diagnosing LRTIs, and identifying particular disease entities amongst LRTIs is still a matter of controversy. Some observational studies indicate that C-reactive protein (CRP) may have some role in identifying patients with pneumonia. Almirall et al. found significantly higher CRP values in confirmed CAP compared to healthy controls and suspected CAP [2]. Flanders et al. evaluated CRP as a possible tool in the differential diagnosis of 168 adults with cough of duration <3 weeks [3]. CRP levels correlated with the presence of pneumonia but not with its severity. At a threshold >40 mg/L CRP had a sensitivity of 70% and specificity of 90% to identify pneumonia. Holm et al. confirmed the low sensitivity and specificity of CRP in the differential diagnosis of LRTIs [4]. In this study CRP sensitivity and specificity, for CAP identification, were 73% and 65%, respectively. The authors concluded that only very high CRP levels (>100 mg/L) can be used...
as indicator for the presence of CAP. Accordingly, Stolz et al. showed that the specificity of CRP at the cut-off value of 100 mg/L to predict radiological confirmed pneumonia reaches 91.2% [5].

Thus, CRP appears to have a limited value as a predictor in the presence of pneumonia and no prospective intervention studies are available.

In some studies procalcitonin (PCT) does not appear to be a significant marker for CAP [6,7]. However, a more recent evaluation of the role of highly sensitive CRP and PCT measurements showed a better discriminatory value of these biomarkers compared to clinical signs [8]. In this study, a more rationale algorithm was applied using a lower PCT threshold compared to the previous studies. PCT had a higher diagnostic accuracy in differentiating CAP from other diagnoses, as compared to high sensitivity CRP and total leukocyte count. Moreover, PCT had a good performance as a predictor of bacteremia.

The utility of PCT levels to improve the early diagnosis of ventilator-associated pneumonia (VAP) has been evaluated in different studies. Due to the use of dissimilar thresholds the results were not consistent [9–11]. Ramirez et al. report a cohort study with sequential measurement of PCT and CRP in well characterized patients with VAP [12]. The results of this study showed that PCT and CRP plasma levels were statistically higher in patients with confirmed VAP. PCT being the more accurate marker. PCT and CRP levels in bronchoalveolar lavage (BAL) did not differentiate between confirmed and not confirmed VAP. The combination of the simplified clinical pulmonary infection score (CPIS) and serum PCT was able to exclude all false-positive diagnosis of VAP thus resulting in 100% specificity.

The soluble triggering receptor expressed by myeloid cell (sTREM) has been proposed as another potentially useful diagnostic tool for CAP and VAP. The first study, dating back from 2004, reports on 148 patients suffering from suspected CAP or VAP and receiving mechanical ventilation [11]. sTREM was assessed in the BAL fluid and its levels were a better predictor for bacterial infection than CIP, TNF-α/FL and IL-1 levels. In the same paper the authors analysed the behavior of PCT and did not find any role for this biomarker in identifying pneumonia. Another group evaluated the presence of sTREM in exhaled ventilator condensate (EVC) and in BAL fluid from 23 patients clinically suspected of having VAP [13]. In contrast with the first report, sTREM-1 was detected in the BAL fluid of all 14 VAP subjects but also in 8 of 9 subjects with no pneumonia, and sTREM levels did not differ in the VAP subjects compared to the non-pneumonia subjects. However, sTREM-1 was detected in the EVC from 11 of 14 subjects with VAP, but from only 1 of 9 subjects without VAP, and was significantly higher in the pneumonia patients. Another study tends to rule out the value of sTREM detection in BAL as a useful tool in VAP diagnosis [14]. In this study, 105 consecutive patients receiving mechanical ventilation and undergoing BAL were enrolled. Of those, 19 patients (18.1%) met definite microbiologic criteria for bacterial or fungal VAP. All the statistical analysis performed showed that measurement of sTREM-1 was inferior to clinical parameters for the diagnosis of VAP.

Phua et al. analysed serum sTREM-1 levels in 150 patients with pneumonia, COPD and asthma exacerbations and 62 healthy controls [15]. The highest level of sTREM-1 was detected in patients with pneumonia, followed by COPD, asthma and controls. Among the patients with pneumonia, COPD and asthma, there was no relationship between sTREM-1 levels and intensive care unit admission, need for invasive ventilation and length of hospital stay. Moreover, the authors stated that serum sTREM has a moderate but insufficient degree of accuracy as a surrogate marker for the need for antibiotics in lower respiratory tract infections.

Another recent study evaluated the usefulness of sTREM-1 in BAL fluid from intensive care unit patients as a potential rapid diagnostic test for VAP [16]. In this retrospective study 207 patients, 90 with confirmed VAP, underwent BAL while receiving mechanical ventilation. Patients were screened daily for VAP using clinical criteria, and BAL was performed on the day of clinical VAP suspicion. sTREM-1 levels were not discriminative for VAP with a ROC curve analysis showing an area under the curve of 0.58 (95% CI 0.50–0.65).

Table 1 summarizes the main published studies on the use of biomarkers in the diagnosis of LRTI's.

3. Biomarkers as prognostic – severity indicators

3.1. Community-acquired pneumonia

Guidelines for the management of adults with CAP suggest the use of severity-based approach. The use of prognostic scores, like CURB and PSI, is indicated to support clinical judgment [17]. A number of studies explored the prognostic value of biomarkers in patients with CAP.

Muller et al. [8] in a retrospective analysis of two published studies [18,19] reported a significant relationship between PCT levels and PSI category, with PCT being markedly elevated in the highest PSI class V. In the interpretation of these results it must be taken into account that many PSI class 5 patients had low PCT values.

Huang et al. [20], report a multicenter, prospective, observational cohort study in a large population of 1651 patients admitted to emergency department for CAP to determine whether procalcitonin can provide prognostic information beyond the Pneumonia Severity Index and CURB-65. In this study procalcitonin levels did not add prognostic information for most pneumonia patients. However, among higher-risk groups as assessed by the Pneumonia Severity Index score, low procalcitonin level reliably predicted lower mortality.

The predictive value of PCT compared to CRP and leukocyte count (WBC), and the clinical CRB-65 score was analysed in a large study of the CAPNETZ competence network [21]. In 1671 patients with proven CAP, PCT, CRP, WBC and CRB-65 were determined at admission and patients were followed-up for 28 days for outcome. The results show that PCT levels at admission are a better predictor of CAP severity and outcome than WBC and CRP levels, with a similar prognostic accuracy as the CRB-65 score. Another interesting result of this study is that a PCT threshold of \( \leq 0.228 \) mg/L identifies low-risk patients within all CRB-65 risk groups.

Another study from the CAPNETZ network explored the role of pro-atrial natriuretic peptide (MR-proANP), pro-vasopressin (CT-proAVP), PCT and CRP for severity assessment and outcome prediction in 589 patients with CAP [22]. In multivariate Cox proportional hazards regression analyses high levels of MR-proANP and CT-proAVP were the strongest predictors of mortality. The authors conclude that MR-proANP and CT-proAVP are predictors of CAP severity and 28-day mortality comparable to the clinical CRB-65 score.

The role of another biomarker, proadrenomedullin (proADM), was evaluated in 302 consecutively admitted adults with CAP [23]. In this study ProADM levels on admission predict the severity and outcome of CAP with a similar prognostic accuracy as the PSI. As previously discussed for PCT, also in this series many patients with PSI risk class V had low ProADM levels, confirming that biomarkers are meant to complement, rather than to supersede, clinician’s judgment and/or validated severity scores.

This is confirmed by the results of a recent multicenter prospective cohort study in 28 community and 45 teaching emergency departments on a total of 1653 patients [24]. In this study both PCT and proADM were evaluated and compared with PSI and CURB-65 scores as predictors of severity and mortality. ProADM performance resulted superior to the PCT one but the prognostic
utility of proADM beyond PSI was limited to high risk subjects. Furthermore, proADM levels do not alter PSI based risk assessment.

Despite the introduction of new biomarkers CRP is still widely used in patients with CAP.

wBruns et al. report a retrospective analysis of the data derived from a prospective, multicenter study involving 289 severe hospitalized CAP, looking to the role of consecutive CRP measurement in follow-up of CAP [25]. CRP was measured at admission, day 3 and day 7. Delayed normalization of CRP was suggestive of inappropriate treatment but was not significantly related to mortality. Baseline CRP levels were influenced by steroids and pneumonia etiology.

The concept of clinical stability is gaining importance in the decision-making process on duration of therapy and hospital discharge. Menéndez et al. investigated the role of different biomarkers, CRP, PCT, IL-6 and IL-10 in the assessment of clinical stability and prediction of absence of complications in CAP patients [26]. Clinical stability was defined as the condition when the following threshold values were achieved for all parameters: temperature \(\leq 37.2^\circ C\), heart rate \(\leq 100\) beats/min, respiratory rate \(\leq 24\) breaths/min, systolic blood pressure \(\geq 90\) mm Hg and oxygen saturation \(\geq 90\%\) or arterial oxygen tension \(\geq 60\) mm Hg when the patient was not receiving supplemental oxygen. The main finding of the study was that a reduction in PCT levels to \(\leq 0.25\) ng/ml and CRP levels to \(\leq 3\) mg/dl together with clinical stability permits to identify patients with a high negative predictive value for low rate of severe complications.

Another paper explored the role of platelets as a possible marker of CAP severity [27]. Platelets have been increasingly recognized as an important component of innate and adaptive immunity and play a crucial role in antimicrobial host defenses and the coagulation system. The study indicates that thrombocytopenia and thrombocytosis are significantly associated with mortality in patients with CAP. At time of hospitalization, abnormalities in platelet count are better predictors of clinical outcomes in patients with CAP when compared to abnormalities in leukocyte count.

### 3.2. Ventilator-acquired pneumonia

Several studies explored the role of biomarkers in monitoring the clinical response of VAP. Povoa et al. evaluated CRP levels, body temperature and WBC after prescription of antibiotics in order to define the clinical resolution of VAP in 47 adult patients [28]. In this study daily CRP concentration measurement was useful in the identification, as early as day 4, of ventilator-associated pneumonia patients with poor outcome, and performed better than body temperature and WBC. Seligman et al. confirmed these results, CRP changes at day 4 were almost twice more accurate than PCT changes in predicting outcome in VAP patients [29]. The value of procalcitonin kinetics as a prognostic marker during VAP was investigated in a prospective, observational study on 63 adult patients [30]. Serum procalcitonin levels were measured on days 1, 3, and 7. Serum procalcitonin concentrations were higher in patients with unfavorable outcomes and a threshold of more than 0.5 ng/ml on Day 7 was the strongest independent marker of unfavorable outcome, superior to WBC and CRP.

These results are not consistent with the recent report of Hillas et al. [31]. Forty-five adults with VAP were prospectively enrolled and CRP and PCT levels were measured on Days 1, 4 and 7. The Acute Physiology and Chronic Health Evaluation (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were used to
assess disease severity. Even if serum PCT levels were significantly higher in non-survivors on Day 1 and Day 7 compared to survivors the authors report a low positive likelihood ratio and the significance of PCT values disappears in a multivariate analysis. In contrast to the results of Seligman [29] CRP and PCT kinetics between Day 1, 4 and 7 were not able to predict survival or development of septic shock. The only predictor of septic shock development in this study was the SOFA score.

3.3. Exacerbation of COPD

Chronic obstructive pulmonary disease (COPD) places a considerable burden on health care systems, and exacerbations constitute a significant proportion of this burden. Acute episodes of exacerbation appear during this chronic course with an increase in the habitual symptoms to which purulent expectoration and fever may be added. The current definition of exacerbation is an increase in respiratory symptoms over baseline that usually requires a change in therapy in a patient with pre-existing COPD [32].

Exacerbations of COPD encompass widely differing clinical conditions from very mild cases, best managed with simple bronchodilator adjustments, to life-threatening situations requiring intensive care admission and mechanical ventilation, representing one of the major contributors to the clinical load of physicians, both in the hospital setting and in the community. Frequency and severity of exacerbations are also the main factors determining COPD prognosis.

Some epidemiological studies have shown that CRP levels are associated with cardiovascular and global mortality in COPD patients [33,34] even if a more recent prospective observational study in a population of moderate to very severe COPD patients tends to rule out the importance of CRP as a survival predictor [35]. The authors report that CRP levels are not associated with survival status and does not add information to the risk assessment provided by other tools such as the multidimensional BODE index.

The role of biomarkers as predictors of outcome in exacerbations of COPD has not been extensively addressed. One interesting study demonstrated that plasma CRP, in the presence of one or more recorded major exacerbation symptoms, is able to reliably differentiate exacerbation of COPD from day-to-day symptom variation but was neither sufficiently sensitive nor specific to be a useful biomarker in the absence of symptom assessment [36]. Moreover, none of the 36 plasma biomarkers assessed was useful in predicting the clinical severity of exacerbation.

Perera et al., in a cohort study involving 73 well characterized COPD patients, found that a high serum C-reactive protein concentration, but not IL-6 or IL-8 levels, 14 days after an index exacerbation was a good predictor of recurrent exacerbations within 50 days [37].

Stolz et al., in a post-hoc analysis of a randomized study, evaluated Copeptin, CRP and PCT as potential prognostic parameters for in-hospital and long-term outcome in patients with exacerbation of COPD [38]. Copeptin, but not CRP and PCT, was predictive of prolonged hospital stay and long-term failure.

The same group reported another study looking to the role of plasma pro-endothelin-1 (proET-1) and proadrenomedullin (proADM) on admission to the hospital as predictors of survival in patients with exacerbations of COPD [39]. In this prospective cohort study including 167 COPD patients proET-1 and proADM levels were markedly increased at exacerbation and decreased significantly in the recovery and stable phases of the disease. Neither proET-1 nor proADM levels correlated consistently with the clinical presentation on hospital admission, however, plasma proADM levels on hospital admission independently predicted 2-year survival in patients with COPD, thus suggesting that this biomarker could be used to predict prognosis during exacerbations.

Table 2 summarizes the main studies on the role of biomarkers in the assessment of prognosis and severity of LRTIs.

4. Biomarkers as treatment and treatment duration indicators

Due to the burden of CAP on morbidity and mortality, health care providers must adopt practices focused on improving outcomes. A key measure in doing so is to optimize antibiotic usage.

During recent decades, increasing evidence strengthened the recommendations of guidelines concerning antibiotic selection, early initiation of therapy and the switch from intravenous to oral therapy. Surprisingly, few well-designed studies exist which evaluate the appropriate use and duration of antibiotic therapy [40].

The same is true if we consider LRTIs as a whole. The first paper addressing the role of biomarkers in defining the appropriateness of antibiotic use in LRTIs was a prospective, cluster-randomized, controlled, single-blinded intervention trial comparing routine use of antimicrobial therapy with procalcitonin-guided antimicrobial treatment for lower respiratory tract infections [18]. In this study 243 patients admitted with suspected lower respiratory tract infections were randomly assigned standard care or procalcitonin-guided treatment. About one third of the included patients suffered from pneumonia and 25% presented for acute exacerbation of COPD (ECOPD). Overall, the use of PCT-guided therapy was associated with a significantly reduction of antibiotic use, mainly in non-CAP patients, without adversely affecting clinical course.

The results of this important study have been recently confirmed by a large multicenter study that explored not only the role of PCT-guided decision on antibiotic use but also the possible role in reducing duration of antibiotic treatment on the basis of PCT kinetics [41]. The study showed that PCT-guided intervention compared with standard guidelines resulted in similar rates of adverse outcomes with lower rates of antibiotic exposure and antibiotic-associated adverse effects. Interestingly, the effects of PCT-guided policy were evident both on overall use and duration of antibiotic use. Indeed in CAP patients the main result was an impressive reduction in duration of therapy. Conversely, in milder respiratory infections, acute bronchitis and ECOPD, initiation of antibiotic therapy was markedly decreased by PCT guidance.

The role of PCT-guided therapy on length of antibiotic treatment has been explored also in VAP. Stolz et al. in a multicentre, randomized, controlled trial, involving 101 patients with VAP addressed the potential benefit of incorporating procalcitonin into the antibiotic reduction strategy in VAP management [42].

Overall, a PCT-guided strategy lead to a significantly increase of average number of antibiotic-free days alive from day 1 to day 28 that resulted 27% higher compared to control group. No difference was recorded in outcome parameters such as number of mechanical ventilation free days alive, number of ICU-free days alive, length of hospital stay and overall mortality suggesting that procalcitonin-guided strategy is safe also in patients with VAP.

Even if numerous studies demonstrated that bacterial infection is involved in approximately 50% of ECOPD [43,44] the role of antimicrobials in ECOPD remains controversial. Anthonisen criteria, sputum purulence and sputum color are advocated as possible clinical markers for the appropriate use of antibiotics [45–48]. Nevertheless, antibiotic use in ECOPD is undoubtedly still excessive, exposing patients to considerable cost and potential adverse effects, and driving antibiotic resistance. A rapid, specific test to identify the patient to be treated with antibiotic would be a major advance.

CRP is not a good marker in terms of both sensitivity and specificity [49]. A recent randomized, controlled trial comparing
Table 2
Summary of the main studies on the use of biomarkers in the assessment of severity and prognosis of LRTIs.

<table>
<thead>
<tr>
<th>References</th>
<th>Biomarker/disease</th>
<th>Results</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Muller [8]</td>
<td>Serum PCT, high sensitivity CRP, WBC/CAP</td>
<td>545 patients with LRTI (373 with CAP). PCT, in contrast to hsCRP and leukocyte count, increased with increasing severity of CAP, as assessed by the pneumonia severity index. PCT may be useful in the severity assessment of CAP. Multicenter prospective cohort study on 1651 patients admitted to ED for CAP to determine whether PCT can provide prognostic information beyond the Pneumonia Severity Index and CURB-65. Procalcitonin levels did not add prognostic information for most pneumonia patients. However, among higher-risk groups by Pneumonia Severity Index score, low procalcitonin level predicted lower mortality.</td>
<td>Post-hoc analysis of a combination of two different studies</td>
</tr>
<tr>
<td>Huang [20]</td>
<td>Serum PCT/CAP</td>
<td>Multicenter prospective cohort study on 1651 patients. MR-proADM levels correlate with increasing severity of illness and death. High MR-proADM levels offer additional risk-stratification in high risk patients, but otherwise MR-proADM levels do not alter PSI based risk assessment in most patients.</td>
<td>No clear relationship between PCT levels and 30-day mortality</td>
</tr>
<tr>
<td>Kruger [21]</td>
<td>Serum PCT, CRP, WBC/CAP</td>
<td>Multicenter prospective cohort study on 1671 patients with proven CAP. PCT, CRP, WBC and CRB-65 determined on admission, 28 day follow-up for survival. ROC analysis was comparable for PCT and CRB-65 and significantly higher compared with CRP and WBC. PCT identified low-risk patients across CRB classes 0–4.</td>
<td>Low number of both outpatients and severe cases.</td>
</tr>
<tr>
<td>Kruger [22]</td>
<td>MR-proANP, CT-proAVP, PCT and CRP/CAP</td>
<td>589 patients with CAP. In multivariate Cox proportional hazards regression analyses high levels of MR-proANP and CT-proAVP turned out to be the strongest predictors of mortality.</td>
<td>Measurement of MR-proANP and CT-proAVP may be influenced by sex, age and renal function. The timing of biomarkers was not standardised. proADM measurements were done as a predefined secondary endpoint</td>
</tr>
<tr>
<td>Christ-Crain [23]</td>
<td>proADM, PCT, CRP, WBC/CAP</td>
<td>302 consecutively admitted adults with CAP. ProADM levels on admission predict the severity and outcome of CAP with a similar prognostic accuracy as the PSI and a higher prognostic accuracy compared to CRP and WBC.</td>
<td></td>
</tr>
<tr>
<td>Huang [24]</td>
<td>PCT and proADM/CAP</td>
<td>1653 CAP patients. MR-proADM levels correlate with increasing severity of illness and death. High MR-proADM levels offer additional risk-stratification in high risk patients, but otherwise MR-proADM levels do not alter PSI based risk assessment in most patients.</td>
<td>Single point measurement of proADM</td>
</tr>
<tr>
<td>Bruns [25]</td>
<td>CRP in CAP follow-up</td>
<td>289 CAP patients. A delayed normalization of CRP levels is associated with a higher-risk of having received inappropriate antibiotic treatment. CRP levels are influenced by steroids and pneumonia etiology.</td>
<td>Only severe non-ICU patients.</td>
</tr>
<tr>
<td>Menendez [26]</td>
<td>CRP, PCT, IL-6 and IL-10 in the assessment of clinical stability and prediction of absence of complications in CAP</td>
<td>Prospective study on 394 hospitalized patients with CAP. A reduction in PCT levels to &lt;0.25 mg/ml and CRP levels to &lt;3 mg/dl together with clinical stability identifies patients with a high negative predictive value without subsequent severe complications.</td>
<td>Steroids and antibiotic treatment not included in the analysis</td>
</tr>
<tr>
<td>Mirsaedi [27]</td>
<td>Platelets/CAP</td>
<td>Retrospective cohort study of 500 consecutive patients hospitalized with CAP. Thrombocytopenia and thrombocytosis are significantly associated with mortality in patients with CAP</td>
<td>Retrorespective study. Single center, elderly male patients with multiple comorbidities.</td>
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<tr>
<td>Povoa [28]</td>
<td>CRP, WBC/VAP</td>
<td>Prospective observational cohort study on 47 adult patients with VAP. Daily CRP measurements could be used as a marker of VAP resolution, and might be of some help in the clinical decision-making process for the reassessment of patients that fail to improve.</td>
<td>Cohort single center observational pilot study. Distribution of early and late onset VAP not clear. Non pulmonary site of infection and non infectious causes of CRP elevation not reported. Small sample size. No possible analysis of the correlation between survival and treatment.</td>
</tr>
<tr>
<td>Seligman [29]</td>
<td>PCT, CRP/VAP</td>
<td>Prospective observational cohort study on 75 patients with VAP. PCT, CRP and SOFA score were determined on day 0 and day 4. ΔPCT with OR = 4.43 and ΔCRP with OR = 7.40 were significantly associated with survival in a multivariable logistic regression model.</td>
<td>Small sample size. No possible analysis of the correlation between survival and treatment.</td>
</tr>
<tr>
<td>Luyt [30]</td>
<td>PCT, CRP, WBC/VAP</td>
<td>Prospective cohort study on 63 patients with VAP. PCT kinetics as a prognostic marker during VAP. Procalcitonin levels on Days 1, 3, and 7 strong predictors of unfavorable outcome.</td>
<td>Small sample size. Most of patients on prolonged mechanical ventilation (mean 12 days) with severe disease and a high percentage of shock or other organ failures. Small sample size.</td>
</tr>
<tr>
<td>Hillas [31]</td>
<td>PCT, CRP/VAP</td>
<td>Prospective cohort study on 45 patients with VAP. PCT and CRP threshold values and kinetics (day 1,4,7) as predictors of VAP survival and septic shock development. The only factor predicting the development of septic shock was SOFA on Day 1. Neither PCT and CRP threshold values nor their kinetics can predict VAP survival or septic shock development.</td>
<td>Most of the patients were on inhaled steroids, no data on steroids naive patients.</td>
</tr>
<tr>
<td>Hurst [36]</td>
<td>36 plasma biomarkers/ECOPD</td>
<td>Prospective cohort study on 90 patients with COPD. In the presence of one major symptom recorded on that day, CRP ≥ 8 mg/L would be 95% specific for exacerbation and 57% sensitive. A model involving CRP and one major symptom was also significantly better than using all 36 biomarkers in combination, in the absence of symptom assessment. Systemic biomarkers were not helpful in predicting exacerbation severity.</td>
<td>Most of the patients were on inhaled steroids, no data on steroids naive patients.</td>
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5. The future of biomarkers in LRTIs

Taking into account all the limitations of the published studies, there is evidence that the use of biomarkers have the potential to complement existing clinical severity scores and in conjunction with clinical parameters to improve the diagnosis, risk-stratification and management of LRTIs.

Another interesting possible role for biomarkers is the inclusion in the design and conduct of clinical trials both in ECOPD and CAP. Niederman [52] suggests the role of PCT measurement to differentiate bacterial CAP from viral pneumonia and to identify patients with a worse prognosis and a greater severity of illness. PCT could be useful, in clinical trials, as entry criteria to select only true patients. In comparison to CRP and PCT, Copeptin was superior to predict the course of exacerbation in terms of LOS and 6-month failure. The combination of copeptin and previous hospitalization for COPD increased the risk of poor outcome.

Stolz [39] Predetermined post-hoc analysis of a prospective cohort study involving 167 COPD patients. In comparison to CRP and PCT, Copeptin was superior to predict exacerbation independently predicts 2-year survival in patients with COPD.

References


2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference

Mitchell M. Levy, MD, FCCP; Mitchell P. Fink, MD, FCCP; John C. Marshall, MD; Edward Abraham, MD; Derek Angus, MD, MPH, FCCP; Deborah Cook, MD, FCCP; Jonathan Cohen, MD; Steven M. Opal, MD; Jean-Louis Vincent, MD, FCCP, PhD; Graham Ramsay, MD; For the International Sepsis Definitions Conference

**Objective:** In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) convened a “Consensus Conference,” the goals of which were “to provide a conceptual and a practical framework to define the systemic inflammatory response to infection, which is a progressive injurious process that falls under the generalized term ‘sepsis’ and includes sepsis-associated organ dysfunction as well.” The general definitions introduced as a result of that conference have been widely used in practice and have served as the foundation for inclusion criteria for numerous clinical trials of therapeutic interventions. Nevertheless, there has been an impetus from experts in the field to modify these definitions to reflect our current understanding of the pathophysiology of these syndromes.

**Design:** Several North American and European intensive care societies agreed to revisit the definitions for sepsis and related conditions. This conference was sponsored by the SCCM, The European Society of Intensive Care Medicine (ESICM), The American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the Surgical Infection Society (SIS).

**Methods:** The conference was attended by 29 participants from Europe and North America. In advance of the conference, five subgroups were formed to evaluate the following areas: signs and symptoms of sepsis, cell markers, cytokines, microbiologic data, and coagulation parameters. The subgroups corresponded electronically before the conference and met in person during the conference. A spokesperson for each group presented the deliberation of each group to all conference participants during a plenary session. A writing committee was formed at the conference and developed the current article based on executive summary documents generated by each group and the plenary group presentations. The present article serves as the final report of the 2001 International Sepsis Definitions Conference.

**Conclusion:** This document reflects a process whereby a group of experts and opinion leaders revisited the 1992 sepsis guidelines and found that apart from expanding the list of signs and symptoms of sepsis to reflect clinical bedside experience, no evidence exists to support a change to the definitions. This lack of evidence serves to underscore the challenge still present in diagnosing sepsis in 2003 for clinicians and researchers and also provides the basis for introducing PIRO as a hypothesis-generating model for future research. (Crit Care Med 2003; 31:1250–1256)

**Keywords:** sepsis; severe sepsis; septic shock; systemic inflammatory response syndrome; PIRO

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thermal injury, or sterile inflammatory processes, i.e., acute pancreatitis. SIRS is considered to be present when patients have more than one of the following clinical findings: body temperature, >38°C or <36°C; heart rate, >90 min⁻¹; hyperventilation evidenced by a respiratory rate of >20 min⁻¹ or a PaCO₂ of <32 mm Hg; and a white blood cell count of >12,000 cells µL⁻¹ or <4,000 µL⁻¹.

The SIRS concept has been globally adopted by clinicians and investigators. A MEDLINE search dated January 1992–May 2002 yielded almost 800 publications that mention SIRS in the title or the abstract. We did not record all MEDLINE terms used to identify all citations relevant to SIRS. Our goal was not to conduct a systematic review of the literature, which does dictate the need to record the search strategy.

Bone et al. defined sepsis as SIRS plus infection, “severe sepsis” as sepsis associated with organ dysfunction, hypoperfusion, or hypotension, and “septic shock” as sepsis with arterial hypotension, despite adequate fluid resuscitation. These general definitions are now widely used in practice and serve as the basis for numerous clinical trial inclusion criteria. Recent trial data relating to a number of new interventions have created a need to revisit and modify the 1992 definitions to better reflect our understanding of the pathophysiology of these syndromes (2, 3). In addition, many clinicians believe that the 1992 consensus definition does not provide a clear definition of sepsis. A recent European Society of Intensive Care Medicine (ESICM)/SCCM physician attitudinal survey revealed that 71% of respondents cited no common definition of sepsis (4), despite the ACCP/SCCM consensus conference criteria for sepsis, severe sepsis, and septic shock (1).

This gap in clinician understanding and a concurrent increase in clinical trial data provided the support needed for a review of the 1992 definitions of sepsis and related conditions. The 2001 International Sepsis Definitions Conference was sponsored by the SCCM, ESICM, ACCP, American Thoracic Society, and the Surgical Infection Society. Each of the sponsors provided official representation at the conference and during the preparation of this article.

Goals and Methods of Conference

The overall goals of the conference were threefold and began with a view of the strengths and weaknesses of the current definitions of sepsis and related conditions. The second goal focused on the identification of ways to improve the current definitions. The final goal sought to identify methodologies for increasing the accuracy, reliability, and/or clinical utility of the diagnosis of sepsis.

The conference was held in Washington, DC, in December 2001 and included 29 participants from Europe, North America, and the United Kingdom. Before convening, five subgroups were formed to evaluate the signs and symptoms of sepsis, cell markers, cytokines, microbiologic data, and coagulation parameters. Subgroup participants corresponded electronically before meeting in person at the conference. A subgroup spokesperson presented individual deliberations to all conference participants during plenary sessions. A writing committee, formed at the conference, developed this article based on subgroup executive summary documents and the plenary sessions. Additional information was introduced for participant review after the conference during telephone, E-mail, and live discussions. This article serves as the final report of the 2001 International Sepsis Definitions Conference.

Definitions

Establishing working definitions for a syndrome is inherently an imperfect process and one that requires periodic updating on the basis of new insights into pathophysiology or the availability of new diagnostic tests. We point to the example of acute myocardial infarction (AMI) as a disease paradigm to illustrate this point. Generally accepted diagnostic criteria for AMI were formulated by the Joint International Society and Federation of Cardiology/World Health Organization task force in 1979 (5). Although AMI is easily diagnosed when Q-waves are present on the electrocardiogram, non-Q-wave AMI can be distinguished from unstable angina pectoris only by using biochemical markers. Reflecting the contemporary state of knowledge, the World Health Organization biochemical criterion for establishing the diagnosis of AMI was a total creatine kinase concentration greater than twice the upper limit of normal (5). Subsequently, several more sensitive and specific biochemical markers of myocardial cell death were introduced into clinical practice (6–8), and as a result, the diagnostic criteria for AMI have been revised (9).

Unfortunately, a clinically useful set of criteria for diagnosing sepsis and related conditions will necessarily be somewhat arbitrary. There is no “gold standard” (such as the infarcted myocardium) against which the diagnostic criteria can be calibrated. Diagnostic criteria will be judged successful if clinicians regard them as an aid for decision-making at the bedside. The diagnostic scheme requires sufficient sensitivity and specificity to be a clinical aid.

SIRS

The SIRS concept is valid to the extent that a systemic inflammatory response can be triggered by a variety of infectious and noninfectious conditions. Signs of systemic inflammation can and do occur in the absence of infection among patients with burns, pancreatitis, and other disease states. However, the specific criteria proposed in the 1992 consensus definitions are widely considered to be too nonspecific to be of utility in diagnosing a cause for the syndrome or in identifying a distinct pattern of host response (2, 3).

Although the clinical manifestations of systemic inflammation are protean, the biochemical features may be more consistent. Investigators have detected elevated circulating levels of interleukin (IL)-6 (10), adrenomedullin (11), soluble (s)CD14, sELAM-1, MIP-1α (12), extracellular phospholipase A₂ (13), and C-reactive protein (14) in patients meeting the 1992 SIRS criteria. In the future, if supported by further epidemiologic data, it may be possible to use purely biochemical and/or immunologic, rather than clinical, criteria to identify the inflammatory response. It may be that inflammation is present when the circulating concentration of IL-6, procalcitonin (15–17), or C-reactive protein are increased. No large prospective studies currently support such a conclusion.

Sepsis

In contrast to SIRS, it is very important that clinicians and researchers have the tools needed to recognize and diagnose sepsis promptly; effective therapies for infection are widely and readily available. As in 1992, we define sepsis to be the clinical syndrome defined by the presence of both infection and a systemic inflammatory response. In considering whether
the diagnostic criteria for infection or systemic inflammation should be revised, we adhere to several principles. The criteria should be broadly useful both to clinicians caring for patients at the bedside and to researchers designing observational studies and clinical trials to improve the understanding of sepsis and its optimal treatment. The criteria should be sensitive enough to identify most patients with the syndrome, while minimally sacrificing inevitable specificity. The criteria should not be so cumbersome that clinicians will resist a commitment to memory or application. Any laboratory-dependent criteria should use assays that either are widely available now or are likely to be generally available in the near future. The criteria should be applicable to adult, pediatric, and neonatal patients. Infection. We defined infection as a pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms. This definition, essentially the same one used in the 1992 document, is not perfect. For example, colitis caused by Clostridium difficile, results from overgrowth of this organism in the colon, which is certainly not sterile. Furthermore, the clinical manifestations of C. difficile colitis are not caused by the bacteria invading normally sterile tissues but, rather, by the cytopathic effects of an exotoxin secreted by the organism. It is also important to point out that, frequently, infection is strongly suspected without being microbiologically confirmed. Accordingly, sepsis (i.e., infection and the systemic response to it) may only be strongly suspected, without being microbiologically confirmed.

Systemic Inflammation in Response to Infection. Because of the limitations of SIRS discussed above, we included a list of possible signs of systemic inflammation in response to infection (Table 1). Ultimately, this scheme seeks to codify the physical and laboratory findings that prompt an experienced clinician to conclude that an infected patient “looks septic.” Findings indicative of early organ dysfunction may be the first symptoms noted by clinicians when making this assessment. It is for this reason that we included findings such as hemodynamic instability, arterial hypoxemia, oliguria, coagulopathy and altered liver function tests among the list of criteria that can be used to establish the diagnosis of sepsis.

It is important to emphasize that none of the findings in Table 1 is specific for sepsis. A high cardiac output is commonly observed following major surgical procedures or multiple trauma. Arterial hypotension can be caused by many conditions other than sepsis, such as acute left ventricular failure secondary to AMI or hemorrhage. Coagulopathy can be drug-induced and is associated with many different diseases, in addition to sepsis. It is important that as a practitioner “checks off the boxes” to establish the diagnosis of sepsis, only findings that cannot be easily explained by other causes be included. The thresholds chosen in Table 1 merits discussion. We have not chosen thresholds for each of the criteria that are consistently abnormal in degree. The proposition is whether thresholds similar in degree of abnormality confer similar prediction in sepsis.

As a result, the group turned toward the day-to-day “reality” for bedside clinicians. Group consensus concluded that few, if any, patients in the early stages of the inflammatory response to infection are diagnosed with sepsis via four arbitrary criteria. Instead, the clinician goes to the bedside, identifies myriad symptoms, and regardless of an evident infection, declares the patient to “look septic.” If no obvious source of infection exists, the clinician then initiates a search for an infectious origin of the signs and symptoms associated with sepsis. The use of the word “some” reflects the clinical reality at the bedside, rather than an arbitrary list invented for the purpose of clinical trial entry criteria. Should the definition of sepsis reflect reality as seen at the bedside, thereby facilitating a clinical diagnosis, or should the definition enable investigators to develop clear and simple entry criteria for clinical trials? It was the opinion of the group that facilitating a bedside diagnosis should have primacy over research entry criteria.

<table>
<thead>
<tr>
<th>Table 1. Diagnostic criteria for sepsis</th>
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| **Infection** documented or suspected, and some of the following:<sup>a</sup>  
**General variables**  
- Fever (core temperature >38.3°C)  
- Hypothermia (core temperature <36°C)  
- Heart rate >90 min<sup>-1</sup> or >2 sd above the normal value for age  
- Tachypnea  
- Altered mental status  
- Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)  
- Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes  
**Inflammatory variables**  
- Leukocytosis (WBC count >12,000 μL<sup>-1</sup>)  
- Leukopenia (WBC count <4000 μL<sup>-1</sup>)  
- Normal WBC count with >10% immature forms  
- Plasma C-reactive protein >2 sd above the normal value  
- Plasma procalactin >2 sd above the normal value  
**Organ dysfunction variables**  
- Arterial hypotension<sup>b</sup> (SBP <90 mm Hg, MAP <70, or an SBP decrease >40 mm Hg in adults or <2 sd below normal for age)  
- S<sub>VO</sub><sub>2</sub> >70%  
- Cardiac index >3.5 L·min<sup>-1</sup>·M<sup>-2</sup>  
**Coagulation abnormalities**  
- Acute oliguria (urine output <0.5 mL·kg<sup>-1</sup>·hr<sup>-1</sup> or 45 mmol/L for at least 2 hrs)  
- Creatinine increase >0.5 mg/dL  
- Coagulation abnormalities (INR >1.5 or aPTT >60 secs)  
- Thrombocytopenia (platelet count <100,000 μL<sup>-1</sup>)  
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)  
**Respiratory variables**  
- Hypoxemia (<35 mm Hg, or <90% arterial oxygen saturation)  
- Hypercapnia (end tidal CO<sub>2</sub> >43 mm Hg or >8 mmol/L)  
- Hypothermia (core temperature <36°C)  
- Hyperthermia (core temperature >38.5°C or <35°C)  
- Tachypnea (呼吸 rate >20/min)  
- Increased respiratory rate or effort  
- Hypotension (MAP <70, or an SBP decrease >40 mm Hg in adults)  
- S<sub>VO</sub><sub>2</sub> >70%  
- Cardiac index >3.5 L·min<sup>-1</sup>·M<sup>-2</sup>  
**Tissue perfusion variables**  
- Arterial hypotension<sup>b</sup> (SBP <90 mm Hg, MAP <70, or an SBP decrease >40 mm Hg in adults or <2 sd below normal for age)  
- S<sub>VO</sub><sub>2</sub> >70%  
- Cardiac index >3.5 L·min<sup>-1</sup>·M<sup>-2</sup>  
- Acute oliguria (urine output <0.5 mL·kg<sup>-1</sup>·hr<sup>-1</sup> or 45 mmol/L for at least 2 hrs)  
- Creatinine increase >0.5 mg/dL  
- Coagulation abnormalities (INR >1.5 or aPTT >60 secs)  
- Thrombocytopenia (platelet count <100,000 μL<sup>-1</sup>)  
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)  
- Decreased capillary refill or mottling  

<sup>a</sup>WBC, white blood cell; SBP, systolic blood pressure; MAP, mean arterial blood pressure; S<sub>VO</sub><sub>2</sub>, mixed venous oxygen saturation; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

<sup>b</sup>Infection defined as a pathologic process induced by a microorganism; S<sub>VO</sub><sub>2</sub> sat >70% is normal in children (normally, 75–80%), and CI 3.5–5.5 is normal in children; therefore, NEITHER should be used as signs of sepsis in newborns or children; “diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5 or <35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.
Severe Sepsis (Sepsis with Organ Dysfunction)

The definition of severe sepsis remains unchanged and refers to sepsis complicated by organ dysfunction. Severe sepsis is now considered to be the most common cause of death in noncoronary critical care units. Approximately 150,000 people die annually in Europe and >200,000 die annually in the United States (18). Organ dysfunction can be defined using the definitions developed by Marshall et al. (19) or the definitions used for the Sequential Organ Failure Assessment (SOFA) score (20). Organ dysfunction in severe sepsis in the pediatric population can be defined using definitions developed by Wilkinson et al. (21), Proulx et al. (22), and Doughty et al. (23) or the definitions used for the PEMOD and PELOD score (24).

Septic Shock

Septic shock in adults refers to a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. Hypotension is defined by a systolic arterial pressure below 90 mm Hg (or, in children, <2 SD below normal for their age), a MAP <60, or a reduction in systolic blood pressure of >40 mm Hg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension.

Table 2. The PIRO system for staging sepsis

<table>
<thead>
<tr>
<th>Domain</th>
<th>Present</th>
<th>Future</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predisposition</td>
<td>Premorbid illness with reduced probability of short term survival. Cultural or religious beliefs, age, sex.</td>
<td>Genetic polymorphisms in components of inflammatory response (e.g., TIR, TNF, IL-1, CD14); enhanced understanding of specific interactions between pathogens and host diseases.</td>
<td>In the present, premorbid factors impact on the potential attributable morbidity and mortality of an acute insult; deleterious consequences of insult heavily dependent on genetic predisposition (future). Specific therapies directed against inciting insult require demonstration and characterization of that insult.</td>
</tr>
<tr>
<td>Insult infection</td>
<td>Culture and sensitivity of infecting pathogens; detection of disease amenable to source control.</td>
<td>Assay of microbial products (LPS, mannan, bacterial DNA; gene transcript profiles.</td>
<td>Both mortality risk and potential to respond to therapy vary with nonspecific measures of disease severity (e.g., shock); specific mediator-targeted therapy is predicated on presence and activity of mediator. Response to preemptive therapy (e.g., targeting microorganism or early mediator) not possible if damage already present; therapies targeting the injurious cellular process require that it be present.</td>
</tr>
<tr>
<td>Response</td>
<td>SIRS, other signs of sepsis, shock, CRP.</td>
<td>Nonspecific markers of activated inflammation (e.g., PCT or IL-6) or impaired host responsiveness (e.g., HLA-DR); specific detection of target of therapy (e.g., protein C, TNF, PAF).</td>
<td></td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>Organ dysfunction as number of failing organs or composite score (e.g., MODS, SOFA, LODS, PEMOD, PELOD).</td>
<td>Dynamic measures of cellular response to insult—apoptosis, cytopathic hypoxia, cell stress.</td>
<td></td>
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</tbody>
</table>

TLR, Toll-like receptor; TNF, tumor necrosis factor; IL, interleukin; LPS, lipopolysaccharide; SIRS, systemic inflammatory response syndrome; CRP, C-reactive protein; PCT, procalcitonin; HLA-DR, human leukocyte antigen-DR; PAF, platelet-activating factor; MODS, multiple organ dysfunction syndrome; SOFA, sepsis-related organ failure assessment; LODS, logistic organ dysfunction system; PEMOD, pediatric multiple organ dysfunction; PELOD, pediatric logistic organ dysfunction.
such as the premorbid health status of the patient, the reversibility of concomitant diseases, and a host of religious and cultural forces that shape the approach toward therapy. It is also important to appreciate that these multiple predisposing factors could influence both the incidence and the outcome in similar or conflicting ways. They could also pose separate or different risks for each of the different stages of infection, response, and organ dysfunction. For example, immunosuppression may increase a person’s risk of infection, decrease the magnitude of that person’s inflammatory response, and have no direct influence on organ dysfunction. Similarly, a genetic polymorphism such as the TNF-2 allele may result in a more aggressive inflammatory response to an invading organism. This might decrease a person’s risk of infection but increase that person’s risk of an overly exuberant, and potentially harmful, inflammatory response should that patient become infected. We encourage researchers to explore further the complex interaction of the multiple factors that predispose to the onset, stages of progression, and outcome of sepsis.

**Infection.** The site, type, and extent of the infection have a significant impact on prognosis. A bilateral bronchopneumonia is a more extensive process than a localized pneumonia, and a generalized fecal peritonitis is a more extensive process than an appendicitis. By studying mortality rates among patients randomized to receive placebo in recent randomized clinical trials of new agents for the adjuvant treatment of sepsis, it is apparent that pneumonia and intra-abdominal infections are associated with a higher risk of mortality than are urinary tract infections. Patients with secondary nosocomial bacteremia experience a higher mortality than those with catheter-related or primary bacteremia (28). Similarly, there is evidence that the endogenous host response to Gram-positive organisms differs from that evoked by Gram-negative organisms (29). Early studies with antibodies directed against endotoxin, for example, suggested that benefit was greatest in patients with Gram-negative infection (30) or endotoxemia (31) but that treatment might be harmful to patients with Gram-positive infection (32).

**Response.** In general, current therapies for sepsis target the host response, rather than the infecting organism. The host response has proven to be difficult to characterize. Putative biologic markers of response severity include circulating levels of procalcitonin (16, 33), IL-6 (34, 35), and many others. When a new mediator is identified, epidemiologic studies will be required to determine whether measurements of the compound can be useful for staging patients. Furthermore, the optimal set of biologic markers for staging sepsis may depend on the nature of the therapeutic decision to be made. For example, an indicator of dysregulation of the coagulation system might be more valuable for making a decision about whether to institute therapy with drotrecogin alfa (activated) (36), whereas a marker of adrenal dysfunction might be more useful for determining whether to institute therapy with hydrocortisone (37).

**Organ Dysfunction.** By analogy with the TNM system, the presence of organ dysfunction in sepsis is similar to the presence of metastatic disease in cancer. Certainly, the severity of organ dysfunction is an important determinant of prognosis in sepsis (19, 38). Whether the severity of organ dysfunction can aid in therapeutic stratification is less clear. Nevertheless, there is some evidence that neutralization of TNF, an early mediator in the inflammatory cascade, is more effective in patients without significant organ dysfunction (39), whereas drotrecogin alpha (activated) may provide more benefit to patients with greater as compared with lesser disease burden (40). The modern organ failure scores can be used to quantitatively describe the degree of organ dysfunction developing over the course of critical illness (41).

The potential utility of the proposed PIRO model lies in being able to discriminate morbidity arising from infection and morbidity arising from the response to infection. Interventions that modulate the response may impact adversely on the ability to contain an infection; conversely, interventions that target the infection are unlikely to be beneficial if the morbidity impact is being driven by the host response. Premorbid conditions establish a baseline risk, independent of the infectious process, while acquired organ dysfunction is an outcome to be prevented.

The PIRO system is proposed as a template for future investigation and is a work in progress, rather than a model to be adopted. Its elaboration will require extensive evaluation of the natural history of sepsis to define those variables that predict not only an adverse outcome but also the potential to respond to therapy. The parameters selected may well vary depending on the aspect of sepsis being studied, being different, for example, if the focus is the antibiotic treatment of pneumonia, the evaluation of a novel inhibitor of tyrosine kinases, or the optimizing of microcirculatory flow in sepsis. The methodologic challenge is at least as great as that faced by oncologists, and the TNM system continues to evolve more than half a century after its introduction.

**CONCLUSIONS**

The 2001 conference participants convened with the belief that the body of bench work since the 1991 sepsis definitions conference may lead to a major change in the definition of sepsis based on biomarkers. After a process of evidenced-based review and considerable debate, the participants determined that the use of biomarkers for diagnosing sepsis is premature. Given the length and focus of this article, we did not expand on how the problem of defining sepsis has hampered progress. We realize that this issue has long been debated in the medical community, and we choose not to elaborate here. The primary issue debated was the importance of an accurate diagnosis of sepsis at the bedside when weighed against...
the development of clear and simple entry criteria for clinical trials. Participants believe that the facilitation of bedside diagnosis should have priority over standardized sepsis entry criteria for clinical trials. A standardized set of signs and symptoms that may aid enrollment into trials. A standardized set of signs and symptoms for the diagnosis of sepsis is presented. The future lies in developing a staging system that will characterize progression of sepsis. A new system, PIRO, is proposed for characterizing and staging the host response to infection.

<table>
<thead>
<tr>
<th>Primary consensus points</th>
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<tr>
<td>● The current concepts of sepsis, severe sepsis, and septic shock seem to be robust definitions and should remain as described 10 yrs ago.</td>
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<tr>
<td>● Current definitions do not allow for precise staging of the host response to infection.</td>
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<tr>
<td>● Signs and symptoms of sepsis are more varied than the initial criteria established in 1991.</td>
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<tr>
<td>● A list of these signs and symptoms, for the diagnosis of sepsis is presented.</td>
</tr>
<tr>
<td>● The future lies in developing a staging system that will characterize progression of sepsis. A new system, PIRO, is proposed for characterizing and staging the host response to infection.</td>
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The fact that no new definitions for sepsis are introduced in this conference report is noteworthy. This document reflects a process whereby a group of experts revisited the 1992 sepsis consensus definitions and found that apart from expanding the list of signs and symptoms of sepsis to reflect clinical bedside experience, no evidence exists to support any change in the definitions. This lack of evidence serves to underscore the challenge for clinicians and researchers still present in diagnosing sepsis in 2003 and also provides the basis for introducing PIRO as a hypothesis-generating model for future research.

**REFERENCES**

20. Ferreira FL, Bota DP, Bross A, et al: Serial evaluation of the SOFA score to predict out-
come in critically ill patients. JAMA 2002; 286:1754–1758
EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

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ABSTRACT

Background Goal-directed therapy has been used for severe sepsis and septic shock in the intensive care unit. This approach involves adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with oxygen demand. The purpose of this study was to evaluate the efficacy of early goal-directed therapy before admission to the intensive care unit.

Methods We randomly assigned patients who arrived at an urban emergency department with severe sepsis or septic shock to receive either six hours of early goal-directed therapy or standard therapy (as a control) before admission to the intensive care unit. Clinicians who subsequently assumed the care of the patients were blinded to the treatment assignment. In-hospital mortality (the primary efficacy outcome), end points with respect to resuscitation, and Acute Physiology and Chronic Health Evaluation (APACHE II) scores were obtained serially for 72 hours and compared between the study groups.

Results Of the 263 enrolled patients, 130 were randomly assigned to early goal-directed therapy and 133 to standard therapy; there were no significant differences between the groups with respect to base-line characteristics. In-hospital mortality was 30.5 percent in the group assigned to early goal-directed therapy, as compared with 46.5 percent in the group assigned to standard therapy (P=0.009). During the interval from 7 to 72 hours, the patients assigned to early goal-directed therapy had a significantly higher mean (±SD) central venous oxygen saturation (70.4±10.7 percent vs. 65.3±11.4 percent), a lower lactate concentration (3.0±4.4 vs. 3.9±4.4 mmol per liter), a lower base deficit (2.0±6.6 vs. 5.1±6.7 mmol per liter), and a higher pH (7.40±0.12 vs. 7.36±0.12) than the patients assigned to standard therapy (P<0.02 for all comparisons). During the same period, mean APACHE II scores were significantly lower, indicating less severe organ dysfunction, in the patients assigned to early goal-directed therapy than in those assigned to standard therapy (13.0±6.3 vs. 15.9±6.4, P<0.001).

Conclusions Early goal-directed therapy provides significant benefits with respect to outcome in patients with severe sepsis and septic shock. (N Engl J Med 2001;345:1368-77.)

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THE systemic inflammatory response syndrome can be self-limited or can progress to severe sepsis and septic shock.1 Along this continuum, circulatory abnormalities (intra-vascular volume depletion, peripheral vasodilatation, myocardial depression, and increased metabolism) lead to an imbalance between systemic oxygen delivery and oxygen demand, resulting in global tissue hypoxia or shock.2 An indicator of serious illness, global tissue hypoxia is a key development preceding multiorgan failure and death.2 The transition to serious illness occurs during the critical “golden hours,” when definitive recognition and treatment provide maximal benefit in terms of outcome. These golden hours may elapse in the emergency department,3 hospital ward,4 or the intensive care unit.5

Early hemodynamic assessment on the basis of physical findings, vital signs, central venous pressure,6 and urinary output7 fails to detect persistent global tissue hypoxia. A more definitive resuscitation strategy involves goal-oriented manipulation of cardiac preload, afterload, and contractility to achieve a balance between systemic oxygen delivery and oxygen demand.2 End points used to confirm the achievement of such a balance (hereafter called resuscitation end points) include normalized values for mixed venous oxygen saturation, arterial lactate concentration, base deficit, and pH.8 Mixed venous oxygen saturation has been shown to be a surrogate for the cardiac index as a target for hemodynamic therapy.9 In cases in which the insertion of a pulmonary-artery catheter is impractical, venous oxygen saturation can be measured in the central circulation.10

Whereas the incidence of septic shock has steadily increased during the past several decades, the associated mortality rates have remained constant or have decreased only slightly.11 Studies of interventions such as immunotherapy,12 hemodynamic optimization,9,13 or pulmonary-artery catheterization14 enrolled patients up to 72 hours after admission to the intensive care unit. The negative results of studies of the use of hemodynamic variables as end points (“hemodynamic...
optimization”), in particular, prompted suggestions that future studies involve patients with similar causes of disease or with global tissue hypoxia (as reflected by elevated lactate concentrations) and that they examine interventions begun at an earlier stage of disease.

We examined whether early goal-directed therapy before admission to the intensive care unit effectively reduces the incidence of multiorgan dysfunction, mortality, and the use of health care resources among patients with severe sepsis or septic shock.

**METHODS**

Approval of Study Design

This prospective, randomized study was approved by the institutional review board for human research and was conducted under the auspices of an independent safety, efficacy, and data monitoring committee.

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**Figure 1. Overview of Patient Enrollment and Hemodynamic Support.**

SIRS denotes systemic inflammatory response syndrome, CVP central venous pressure, MAP mean arterial pressure, ScvO₂ central venous oxygen saturation, SaO₂ arterial oxygen saturation, and VO₂ systemic oxygen consumption. The criteria for a diagnosis of SIRS were temperature greater than or equal to 38°C or less than 36°C, heart rate greater than 90 beats per minute, respiratory rate greater than 20 breaths per minute or partial pressure of arterial carbon dioxide less than 32 mm Hg, and white-cell count greater than 12,000 per cubic millimeter or less than 4000 per cubic millimeter or the presence of more than 10 percent immature band forms.
Eligibility

Eligible adult patients who presented to the emergency department of an 850-bed academic tertiary care hospital with severe sepsis, septic shock, or the sepsis syndrome from March 1997 through March 2000 were assessed for possible enrollment according to the inclusion and exclusion criteria (Fig. 1). The criteria for inclusion were fulfillment of two of four criteria for the systemic inflammatory response syndrome and a systolic blood pressure no higher than 90 mm Hg (after a crystalloid-fluid challenge of 20 to 30 ml per kilogram of body weight over a 30-minute period) or a blood lactate concentration of 4 mmol per liter or more. The criteria for exclusion from the study were an age of less than 18 years, pregnancy, or the presence of an acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, cardiac dysrhythmias (as a primary diagnosis), contraindication to central venous catheterization, active gastrointestinal hemorrhage, seizure, drug overdose, burn injury, trauma, a requirement for immediate surgery, uncur cancer (during chemotherapy), immunosuppression (because of organ transplantation or systemic disease), do-not-resuscitate status, or advanced directives restricting implementation of the protocol.

The clinicians who assessed the patients at this stage were unaware of the patients’ treatment assignments. After written informed consent was obtained (in compliance with the Helsinki Declaration), the patients were randomly assigned either to early goal-directed therapy or to standard (control) therapy in computer-generated blocks of two to eight. The study-group assignments were placed in sealed, opaque, randomly assorted envelopes, which were opened by a hospital staff member who was not one of the study investigators.

Treatment

The patients were treated in a nine-bed unit in the emergency department by an emergency physician, two residents, and three nurses. The study was conducted during the routine treatment of other patients in the emergency department. After arterial and central venous catheterization, patients in the standard-therapy group were treated at the clinicians’ discretion according to a protocol for hemodynamic support (Fig. 1), with critical-care consultation, and were admitted for inpatient care as soon as possible. Blood, urine, and other relevant specimens for culture were obtained in the emergency department before the administration of antibiotics. Antibiotics were given at the discretion of the treating clinicians. Antimicrobial therapy was deemed adequate if the in vitro sensitivities of the identified microorganisms matched the particular antibiotic ordered in the emergency department.

The patients assigned to early goal-directed therapy received a central venous catheter capable of measuring central venous oxygen saturation (Edwards Lifesciences, Irvine, Calif.); it was connected to a computerized spectrophotometer for continuous monitoring. Patients were treated in the emergency department according to a protocol for early goal-directed therapy (Fig. 2) for at least six hours and were transferred to the first available inpatient beds. Monitoring of central venous oxygen saturation was then discontinued. Critical-care clinicians (intensivists, fellows, and residents providing 24-hour in-house coverage) assumed the care of all other patients in the emergency department. Monitoring of central venous oxygen saturation was then discontinued. Critical-care consultants (intensivists, fellows, and residents providing 24-hour in-house coverage) assumed the care of all other patients in the emergency department.

The protocol was as follows. A 500-ml bolus of crystalloid was given every 30 minutes to achieve a central venous pressure of 8 to 12 mm Hg. If the mean arterial pressure was less than 65 mm Hg, vasopressors were given to maintain a mean arterial pressure of at least 65 mm Hg. If the mean arterial pressure was greater than 90 mm Hg, vasodilators were given until it was 90 mm Hg or below. If the central venous oxygen saturation was less than 70 percent, red cells were transfused to achieve a hematocrit of at least 30 percent. After the central venous pressure, mean arterial pressure, and hematocrit were thus optimized, if the central venous oxygen saturation was less than 70 percent, dobutamine administration was started at a dose of 2.5 µg per kilogram of body weight per minute, a dose that was increased by 2.5 µg per kilogram per minute every 30 minutes until the central venous oxygen saturation was 70 percent or higher or until a maximal dose of 20 µg per kilogram per minute was given. Dobutamine was decreased in dose or discontinued if the mean arterial pressure was less than 65 mm Hg or if the heart rate was above 120 beats per minute. To decrease oxygen consumption, patients in whom hemodynamic optimization could not be achieved received mechanical ventilation and sedatives.

Outcome Measures

The patients’ temperature, heart rate, urine output, blood pressure, and central venous pressure were measured continuously for the first 6 hours of treatment and assessed every 12 hours for 72 hours. Arterial and venous blood gas values (including central venous oxygen saturation measured by in vitro co-oximetry; Nova Biomedical, Waltham, Mass.), lactate concentrations, and coagulation-related variables and clinical variables required for determination of the Acute Physiology and Chronic Health Evaluation (APACHE II) score (on a scale from 0 to 71, with higher scores indicating more severe organ dysfunction), the Simplified Acute Physiology Score II (SAPS II, on a scale from 0 to 174, with higher scores indicating more severe organ dysfunction), and the Multiple Organ Dysfunction Score (MODS, on a scale from 0 to 24, with higher scores indicating more severe organ dysfunction) were obtained at base line (0 hours) and at 3, 6, 12, 24, 36, 48, 60, and 72 hours. The results of laboratory tests required only for purposes of the study were made known only to the study investigators. Patients were followed for 60 days or until death. The consumption of health care resources (indicated by the duration of vasopressor therapy and mechanical ventilation and the length of the hospital stay) was also examined.

Statistical Analysis

In-hospital mortality was the primary efficacy end point. Secondary end points were the resuscitation end points, organ-dysfunction scores, coagulation-related variables, administered treatments, and the consumption of health care resources. Assuming a rate of refusal or exclusion of 10 percent, a two-sided type I error rate of 5 percent, and a power of 80 percent, we calculated that a sample size of 260 patients was required to permit the detection of a 15 percent reduction in in-hospital mortality. Kaplan–Meier estimates of mortality, along with risk ratios and 95 percent confidence intervals, were used to describe the relative risk of death. Differences between the two groups at base line were tested with the use of Student’s t-test, the chi-square test, or Wilcoxon’s rank-sum test. Incremental analyses of the area under the curve were performed to quantify differences during the interval from base line to six hours after the start of treatment. For the data at six hours, analysis of covariance was used with the base-line values as the covariates. Mixed models were used to assess the effect of treatment on prespecified secondary variables during the interval from 7 to 72 hours after the start of treatment. An independent, 12-member external safety, efficacy, and data monitoring committee reviewed interim analyses of the data after one third and two thirds of the patients had been enrolled and at both times recommended that the trial be continued. To adjust for the two interim analyses, the alpha spending function of DeMets and Lan was used to determine that a P value of 0.04 or less would be considered to indicate statistical significance.

RESULTS

Base-Line Characteristics

We evaluated 288 patients; 8.7 percent were excluded or did not consent to participate. The 263 patients enrolled were randomly assigned to undergo either standard therapy or early goal-directed therapy; 236 patients completed the initial six-hour study period.

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All 263 were included in the intention-to-treat analyses. The patients assigned to standard therapy stayed a significantly shorter time in the emergency department than those assigned to early goal-directed therapy (mean [±SD], 6.3±3.2 vs. 8.0±2.1 hours; P<0.001). There was no significant difference between the groups in any of the base-line characteristics, including the adequacy and duration of antibiotic therapy (Table 1). Vital signs, resuscitation end points, organ-dysfunction scores, and coagulation-related variables were also similar in the two study groups at base line (Table 2).

Twenty-seven patients did not complete the initial six-hour study period (14 assigned to standard therapy and 13 assigned to early goal-directed therapy), for the following reasons: discontinuation of aggressive medical treatment (in 5 patients in each group), discontinuation of aggressive surgical treatment (in 2 patients in each group), a need for immediate surgery (in 4 patients assigned to standard therapy and in 3 assigned to early goal-directed therapy), a need for interventional urologic, cardiologic, or angiographic procedures (in 2 patients in each group), and refusal to continue participation (in 1 patient in each group) (P=0.99 for all comparisons). There were no significant differences between the patients who completed
**Table 1. Base-Line Characteristics of the Patients.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>STANDARD THERAPY (N=133)</th>
<th>EARLY GOAL-DIRECTED THERAPY (N=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64.4±17.1</td>
<td>67.1±17.4</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>49.6</td>
<td>49.2</td>
</tr>
<tr>
<td>Male</td>
<td>50.4</td>
<td>50.8</td>
</tr>
<tr>
<td>Time from arrival at emergency department to enrollment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (hr)</td>
<td>1.5±1.7</td>
<td>1.3±1.5</td>
</tr>
<tr>
<td>Median (min)</td>
<td>50.5</td>
<td>59.0</td>
</tr>
<tr>
<td>Entry criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>36.6±2.3</td>
<td>35.9±3.2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>114±27</td>
<td>117±31</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>109±34</td>
<td>106±36</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>30.2±10.6</td>
<td>31.8±15.8</td>
</tr>
<tr>
<td>Partial pressure of carbon dioxide (mm Hg)</td>
<td>20.6±15.1</td>
<td>31.5±15.7</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>14,200±9,600</td>
<td>13,600±8,300</td>
</tr>
<tr>
<td>Lactate (mmol/liter)</td>
<td>6.9±4.5</td>
<td>7.7±4.7</td>
</tr>
<tr>
<td>Base-line laboratory values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anion gap (mmol/liter)</td>
<td>21.4±8.5</td>
<td>21.7±7.6</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>2.6±2.0</td>
<td>2.6±2.0</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>45.4±33.0</td>
<td>47.1±31.3</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>19.9±3.0</td>
<td>13.2±17.7</td>
</tr>
<tr>
<td>γ-Glutamyltransferase (U/liter)</td>
<td>123±130</td>
<td>117±159</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.8±0.7</td>
<td>2.8±0.7</td>
</tr>
<tr>
<td>Chronic coexisting conditions (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td>38.7</td>
<td>38.5</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>30.2</td>
<td>36.7</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>23.5</td>
<td>26.5</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease or emphysema</td>
<td>13.4</td>
<td>18.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>31.9</td>
<td>30.8</td>
</tr>
<tr>
<td>Human immunodeficiency virus infection</td>
<td>1.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>66.4</td>
<td>68.4</td>
</tr>
<tr>
<td>Liver disease</td>
<td>23.5</td>
<td>23.1</td>
</tr>
<tr>
<td>History of cancer</td>
<td>10.1</td>
<td>12.8</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>31.9</td>
<td>34.2</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>21.9</td>
<td>21.4</td>
</tr>
<tr>
<td>Smoking</td>
<td>31.1</td>
<td>29.9</td>
</tr>
<tr>
<td>Diagnosis (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical condition</td>
<td>93.3</td>
<td>90.6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>39.5</td>
<td>38.5</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>27.7</td>
<td>25.6</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>4.2</td>
<td>3.4</td>
</tr>
<tr>
<td>Other</td>
<td>21.9</td>
<td>23.1</td>
</tr>
<tr>
<td>Surgical condition</td>
<td>6.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Intraabdominal process</td>
<td>5.9</td>
<td>7.7</td>
</tr>
<tr>
<td>Abscess of the arms or legs</td>
<td>0.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Types and features of sepsis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>48.7</td>
<td>45.3</td>
</tr>
<tr>
<td>Septic shock</td>
<td>51.3</td>
<td>54.7</td>
</tr>
<tr>
<td>Sepsis syndrome</td>
<td>71.4</td>
<td>75.2</td>
</tr>
<tr>
<td>Culture positive</td>
<td>76.5</td>
<td>76.1</td>
</tr>
<tr>
<td>Culture negative</td>
<td>23.5</td>
<td>23.9</td>
</tr>
<tr>
<td>Blood culture positive</td>
<td>36.1</td>
<td>34.2</td>
</tr>
<tr>
<td>Antibiotic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics given in the first 6 hr (%)</td>
<td>92.4</td>
<td>86.3</td>
</tr>
<tr>
<td>Antibiotics adequate (%)</td>
<td>94.3</td>
<td>96.7</td>
</tr>
<tr>
<td>Duration (days)</td>
<td>11.3±15.8</td>
<td>11.7±16.2</td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. There were no significant differences between groups in any of the variables. To convert the values for creatinine to micromoles per liter, multiply by 88.4; to convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357; and to convert the values for total bilirubin to micromoles per liter, multiply by 17.1.

†Values sum to more than 100% because patients could have more than one condition.
the initial six-hour study period and those who did not in any of the base-line characteristics or base-line vital signs, resuscitation end points, organ-dysfunction scores, or coagulation-related variables (data not shown).

Vital Signs and Resuscitation End Points

During the initial six hours after the start of therapy, there was no significant difference between the two study groups in the mean heart rate ($P=0.25$) or central venous pressure ($P=0.22$) (Table 2). During this period, the mean arterial pressure was significantly lower in the group assigned to standard therapy than in the group assigned to early goal-directed therapy ($P<0.001$), but in both groups the goal of 65 mm Hg or higher was met by all the patients. The goal of 70 percent or higher for central venous oxygen saturation was met by 60.2 percent of the patients in the standard-therapy group, as compared with 94.9 percent of those in the early-therapy group ($P<0.001$). The combined hemodynamic goals for central venous pressure, mean arterial pressure, and urine output (with adjustment for patients with end-stage renal failure) were achieved in 86.1 percent of the standard-therapy group, as compared with 94.9 percent of the early-therapy group ($P<0.001$). During this period, the patients assigned to standard therapy had a significantly lower central venous oxygen saturation ($P<0.001$) and a greater base deficit ($P=0.006$) than those assigned to early goal-directed therapy; the two
groups had similar lactate concentrations (P=0.62) and similar pH values (P=0.26).

During the period from 7 to 72 hours after the start of treatment, the patients assigned to standard therapy had a significantly higher heart rate (P=0.04) and a significantly lower mean arterial pressure (P<0.001) than the patients assigned to early goal-directed therapy; the two groups had a similar central venous pressure (P=0.68). During this period, those assigned to standard therapy also had a significantly lower central venous oxygen saturation than those assigned to early goal-directed therapy (P<0.001), as well as a higher lactate concentration (P=0.02), a greater base deficit (P<0.001), and a lower pH (P<0.001).

Organ Dysfunction and Coagulation Variables

During the period from 7 to 72 hours, the APACHE II score, SAPS II, and MODS were significantly higher in the patients assigned to standard therapy than in the patients assigned to early goal-directed therapy (P<0.001 for all comparisons) (Table 2). During this period, the prothrombin time was significantly greater in the patients assigned to standard therapy than in those assigned to early goal-directed therapy (P=0.001), as was the concentration of fibrin-split products (P<0.001) and the concentration of D-dimer (P=0.006). The two groups had a similar partial-thromboplastin time (P=0.06), fibrinogen concentration (P=0.21), and platelet count (P=0.51) (Table 2).

Mortality

In-hospital mortality rates were significantly higher in the standard-therapy group than in the early-therapy group (P=0.009), as was the mortality at 28 days (P=0.01) and 60 days (P=0.03) (Table 3). The difference between the groups in mortality at 60 days primarily reflected the difference in in-hospital mortality. Similar results were obtained after data from the 27 patients who did not complete the initial six-hour study period were excluded from the analysis (data not shown). The rate of in-hospital death due to sudden cardiovascular collapse was significantly higher in the standard-therapy group than in the early-therapy group (P=0.02); the rate of death due to multiorgan failure was similar in the two groups (P=0.27).

Administered Treatments

During the initial six hours, the patients assigned to early goal-directed therapy received significantly more fluid than those assigned to standard therapy (P<0.001) and more frequently received red-cell transfusion (P<0.001) and inotropic support (P<0.001), whereas similar proportions of patients in the two groups required vasopressors (P=0.62) and mechanical ventilation (P=0.90) (Table 4). During the period from 7 to 72 hours, however, the patients assigned to standard therapy received significantly more fluid than those assigned to early goal-directed therapy (P=0.01) and more often received red-cell transfusion (P<0.001) and vasopressors (P=0.03) and underwent mechanical ventilation (P<0.001) and pulmonary-artery catheterization (P=0.04); the rate of use of inotropic agents was similar in the two groups (P=0.14) (Table 4). During the overall period from baseline to 72 hours after the start of treatment, there was no significant difference between the two groups in the total volume of fluid administered (P=0.73) or the rate of use of inotropic agents (P=0.15), although a greater proportion of the patients assigned to standard therapy than of those assigned to early goal-direct-

---

**TABLE 3. Kaplan–Meier Estimates of Mortality and Causes of In-Hospital Death.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>STANDARD THERAPY (N=133)</th>
<th>EARLY GOAL-DIRECTED THERAPY (N=130)</th>
<th>RELATIVE RISK (95% CI) P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>59 (46.5)</td>
<td>38 (30.5)</td>
<td>0.58 (0.38–0.87) 0.009</td>
</tr>
<tr>
<td>Patients with severe sepsis</td>
<td>19 (30.0)</td>
<td>9 (14.9)</td>
<td>0.46 (0.21–1.03) 0.06</td>
</tr>
<tr>
<td>Patients with septic shock</td>
<td>40 (56.8)</td>
<td>29 (42.3)</td>
<td>0.60 (0.36–0.98) 0.04</td>
</tr>
<tr>
<td>Patients with sepsis syndrome</td>
<td>44 (45.4)</td>
<td>35 (35.1)</td>
<td>0.66 (0.42–1.04) 0.07</td>
</tr>
<tr>
<td>28-Day mortality†</td>
<td>61 (49.2)</td>
<td>40 (33.3)</td>
<td>0.58 (0.39–0.87) 0.01</td>
</tr>
<tr>
<td>60-Day mortality†</td>
<td>70 (56.9)</td>
<td>50 (44.3)</td>
<td>0.67 (0.46–0.96) 0.03</td>
</tr>
<tr>
<td>Causes of in-hospital death‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudden cardiovascular collapse</td>
<td>25/119 (21.0)</td>
<td>12/117 (10.3)</td>
<td>—</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>26/119 (21.8)</td>
<td>19/117 (16.2)</td>
<td>—</td>
</tr>
</tbody>
</table>

*CI denotes confidence interval. Dashes indicate that the relative risk is not applicable.
†Percentages were calculated by the Kaplan–Meier product-limit method.
‡The denominators indicate the numbers of patients in each group who completed the initial six-hour study period.
Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock

TABLE 4. TREATMENTS ADMINISTERED.*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hours after the Start of Therapy</th>
<th>0–6</th>
<th>7–72</th>
<th>0–72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fluids (ml)</td>
<td></td>
<td>3499±2438</td>
<td>10,602±6,216</td>
<td>13,358±7,729</td>
</tr>
<tr>
<td>Standard therapy</td>
<td>EGDT</td>
<td>4981±2984</td>
<td>8,625±5,162</td>
<td>13,443±6,390</td>
</tr>
<tr>
<td>P value</td>
<td>0.001</td>
<td>0.01</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Red-cell transfusion (%)</td>
<td></td>
<td>18.5</td>
<td>32.8</td>
<td>44.5</td>
</tr>
<tr>
<td>Standard therapy</td>
<td>EGDT</td>
<td>64.1</td>
<td>11.1</td>
<td>68.4</td>
</tr>
<tr>
<td>P value</td>
<td>0.001</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Any vasopressor (%)†</td>
<td></td>
<td>30.3</td>
<td>42.9</td>
<td>51.3</td>
</tr>
<tr>
<td>Standard therapy</td>
<td>EGDT</td>
<td>27.4</td>
<td>29.1</td>
<td>36.8</td>
</tr>
<tr>
<td>P value</td>
<td>0.62</td>
<td>0.03</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Inotropic agent (dobutamine) (%)</td>
<td></td>
<td>0.8</td>
<td>8.4</td>
<td>9.2</td>
</tr>
<tr>
<td>Standard therapy</td>
<td>EGDT</td>
<td>13.7</td>
<td>14.5</td>
<td>15.4</td>
</tr>
<tr>
<td>P value</td>
<td>0.001</td>
<td>0.14</td>
<td>0.15</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation (%)</td>
<td></td>
<td>53.8</td>
<td>16.8</td>
<td>70.6</td>
</tr>
<tr>
<td>Standard therapy</td>
<td>EGDT</td>
<td>53.0</td>
<td>2.6</td>
<td>55.6</td>
</tr>
<tr>
<td>P value</td>
<td>0.90</td>
<td>&lt;0.001</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Pulmonary-artery catheterization (%)‡</td>
<td></td>
<td>3.4</td>
<td>28.6</td>
<td>31.9</td>
</tr>
<tr>
<td>Standard therapy</td>
<td>EGDT</td>
<td>0</td>
<td>18.0</td>
<td>18.0</td>
</tr>
<tr>
<td>P value</td>
<td>0.12</td>
<td>0.04</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

*Plus–minus values are means ±SD. Because some patients received a specific treatment both during the period from 0 to 6 hours and during the period from 7 to 72 hours, the cumulative totals for those two periods do not necessarily equal the values for the period from 0 to 72 hours. EGDT denotes early goal-directed therapy.

†Administered vasopressors included norepinephrine, epinephrine, dopamine, and phenylephrine hydrochloride.

‡All pulmonary-artery catheters were inserted while patients were in the intensive care unit.

Early goal-directed therapy received vasopressors (P=0.02) and mechanical ventilation (P=0.02) and underwent pulmonary-artery catheterization (P=0.01), and a smaller proportion required red-cell transfusion (P<0.001). Though similar between the groups at base line (P=0.91), the mean hematocrit during this 72-hour period was significantly lower in the standard-therapy group than in the early-therapy group (P<0.001). Despite the transfusion of red cells, it was significantly lower than the value obtained at base line in each group (P<0.001 for both comparisons) (Table 2).

Consumption of Health Care Resources

There were no significant differences between the two groups in the mean duration of vasopressor therapy (2.4±4.2 vs. 1.9±3.1 days, P=0.49), the mean duration of mechanical ventilation (9.0±13.1 vs. 9.0±11.4 days, P=0.38), or the mean length of stay in the hospital (13.0±13.7 vs. 13.2±13.8 days, P=0.54). However, of the patients who survived to hospital discharge, those assigned to standard therapy had stayed a significantly longer time in the hospital than those assigned to early goal-directed therapy (18.4±15.0 vs. 14.6±14.5 days, P=0.04).

Discussion

Severe sepsis and septic shock are common and are associated with substantial mortality and substantial consumption of health care resources. There are an estimated 751,000 cases (3.0 cases per 1000 population) of sepsis or septic shock in the United States each year, and they are responsible for as many deaths each year as acute myocardial infarction (215,000, or 9.3 percent of all deaths).29 In elderly persons, the incidence of sepsis or septic shock and the related mortality rates are substantially higher than those in younger persons. The projected growth of the elderly population in the United States will contribute to an increase in incidence of 1.5 percent per year, yielding an estimated 934,000 and 1,110,000 cases by the years 2010 and 2020, respectively.29 The present annual cost of this disease is estimated to be $16.7 billion.29

The transition from the systemic inflammatory response syndrome to severe sepsis and septic shock involves a myriad of pathogenic changes, including circulatory abnormalities that result in global tissue hypoxia.1,2 These pathogenic changes have been the therapeutic target of previous outcome studies.12 Although this transition occurs over time, both out of the hospital and in the hospital, in outcome studies interventions have usually been initiated after admission to the intensive care unit.12 In studies of goal-directed hemodynamic optimization, in particular, there was no benefit in terms of outcome with respect to normal and supranormal hemodynamic end points, as well as those guided by mixed venous oxygen saturation.9,13 In contrast, even though we enrolled patients with lower central venous oxygen saturation and lower central venous pressure than those studied by Gattinoni et al.9 and with a higher lactate concentration than those studied by Hayes et al.,13 we found significant benefits with respect to outcome when goal-directed therapy was applied at an earlier stage of disease. In patients with septic shock, for example, Hayes et al. observed a higher in-hospital mortality rate with aggressive hemodynamic optimization in the intensive care unit (71 percent) than with control therapy (52 percent), whereas we observed a lower mortality rate in patients with septic shock assigned to early goal-directed therapy (42.3 percent) than in those assigned to standard therapy (56.8 percent).

The benefits of early goal-directed therapy in terms of outcome are multifactorial. The incidence of death due to sudden cardiovascular collapse in the standard-therapy group was approximately double that in the group assigned to early goal-directed therapy, suggesting that an abrupt transition to severe disease is an important cause of early death. The early identification...
of patients with insidious illness (global tissue hypoxia accompanied by stable vital signs) makes possible the early implementation of goal-directed therapy. If sudden cardiovascular collapse can be prevented, the subsequent need for vasoressors, mechanical ventilation, and pulmonary-artery catheterization (and their associated risks) diminishes. In addition to being a stimulus of the systemic inflammatory response syndrome, global tissue hypoxia independently contributes to endothelial activation and disruption of the homeostatic balance among coagulation, vascular permeability, and vascular tone. These are key mechanisms leading to microcirculatory failure, refractory tissue hypoxia, and organ dysfunction. When early therapy is not comprehensive, the progression to severe hypoxia, and organ dysfunction diminishes. In addition to being a stimulus of the systemic inflammatory response syndrome, global tissue hypoxia independently contributes to endothelial activation and disruption of the homeostatic balance among coagulation, vascular permeability, and vascular tone. These are key mechanisms leading to microcirculatory failure, refractory tissue hypoxia, and organ dysfunction. When early therapy is not comprehensive, the progression to severe hypoxia, and organ dysfunction. When early therapy is not comprehensive, the progression to severe hypoxia, and organ dysfunction diminishes. In addition to being a stimulus of the systemic inflammatory response syndrome, global tissue hypoxia independently contributes to endothelial activation and disruption of the homeostatic balance among coagulation, vascular permeability, and vascular tone. These are key mechanisms leading to microcirculatory failure, refractory tissue hypoxia, and organ dysfunction. When early therapy is not comprehensive, the progression to severe hypoxia, and organ dysfunction. When early therapy is not comprehensive, the progression to severe hypoxia, and organ dysfunction. Though not numerically equivalent, these ranges of values are pathologically equivalent and are associated with high mortality. Among all the patients in the current study in whom the goals with respect to central venous pressure, mean arterial pressure, and urine output during the first six hours were met, 39.8 percent of those assigned to standard therapy were still in this oxygen-dependent phase of resuscitation at six hours, as compared with 5.1 percent of those assigned to early goal-directed therapy. The combined 56.5 percent in-hospital mortality of this 39.8 percent of patients, who were at high risk for hemodynamic compromise, is consistent with the results of previous studies in the intensive care unit.

In an open, randomized, partially blinded trial, there are unavoidable interactions during the initial period of the study. As the study progressed, the patients in the standard-therapy group may have received some form of goal-directed therapy, reducing the treatment effect. This reduction may have been offset by the slight but inherent bias resulting from the direct influence of the investigators on the care of the patients in the treatment group. The potential period of bias was 9.9±19.5 percent of the overall hospital stay in the standard-therapy group and 7.2±12.0 percent of that in the group assigned to early goal-directed therapy (P=0.20). This interval was minimal in comparison with those in previous studies because the clinicians who assumed responsibility for the remainder of hospitalization were completely blinded to the randomization order.

We conclude that goal-directed therapy provided at the earliest stages of severe sepsis and septic shock, though accounting for only a brief period in comparison with the overall hospital stay, has significant short-term and long-term benefits. These benefits arise from the early identification of patients at high risk for cardiovascular collapse and from early therapeutic intervention to restore a balance between oxygen delivery and oxygen demand. In the future, investigators conducting outcome trials in patients with sepsis should consider the quality and timing of the resuscitation before enrollment as an important outcome variable.

APPENDIX


REFERENCES


Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008*

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Design: Modified Delphi method with a consensus conference of 55 international experts, several subsequent meetings of subgroups and key individuals, teleconferences, and electronic-based discussion among subgroups and among the entire committee. This process was conducted independently of any industry funding.

Methods: We used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations. A strong recommendation (1) indicates that an intervention’s desirable effects clearly outweigh its undesirable effects (risk, burden, cost) or clearly do not. Weak recommendations (2) indicate that the tradeoff between desirable and undesirable effects is less clear. The grade of strong or weak is considered of greater clinical importance than a difference in letter level of quality of evidence. In areas without complete agreement, a formal process of resolution was developed and applied. Recommendations are grouped into those directly targeting severe sepsis, recommendations targeting general care of the critically ill patient that are considered high priority in severe sepsis, and pediatric considerations.

Results: Key recommendations, listed by category, include early goal-directed resuscitation of the septic patient during the first 6 hrs after recognition (1C); blood cultures before antibiotic therapy (1C); imaging studies performed promptly to confirm potential source of infection (1C); administration of broad-spectrum antibiotic therapy within 1 hr of diagnosis of septic shock (1B) and severe sepsis without septic shock (10); reassessment of antibiotic therapy with microbiology and clinical data to narrow coverage, when appropriate (1C); a usual 7–10 days of antibiotic therapy guided by clinical response (1C); source control with attention to the balance of risks and benefits of the chosen method (1C); administration of either crystallloid or colloid fluid resuscitation (1B); fluid challenge to restore mean circulating filling pressure (1C); reduction in rate of fluid administration with rising filling pressures and no improvement in tissue perfusion (1D); vasopressor preference for norepinephrine or dopamine to maintain an initial target of mean arterial pressure >65 mm Hg (1C); dobutamine inotropic therapy when cardiac output remains low despite fluid resuscitation and combined inotropic/vasopressor therapy (1C); stress-dose steroid therapy given only in septic shock after blood pressure is identified to be poorly responsive to fluid and vasopressor therapy (2C); recombinant activated protein C in patients with severe sepsis and clinical assessment of high risk for death (2B except 2C for postoperative patients). In the absence of tissue hypoperfusion, coronary artery disease, or acute hemorrhage, target a hemoglobin of 7–9 g/dl (1B); a low tidal volume (1B) and limitation of inspiratory plateau pressure strategy (1C) for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS); application of at least a minimal amount of positive end-expiratory pressure in acute lung injury (1C); head of bed elevation in mechanically ventilated patients unless contraindicated (1B); avoiding routine use of pulmonary artery catheters in ALI/ARDS (1A); to decrease days of mechanical ventilation and ICU length of stay, a conservative fluid strategy for patients with established ALI/ARDS who are not in shock (1C); protocols for weaning and sedation/intubation (1B); using either intermittent bolus sedation or continuous infusion sedation with daily interruptions or lightening (1B); avoidance of neuro muscular blockers, if at all possible (1B); institution of glycemic control (1B), targeting a blood glucose <150 mg/dl after initial stabilization (2C); equivalence of continuous veno-veno hemofiltration or intermittent hemodialysis (2B); prophylaxis for deep vein thrombosis (1A); use of stress ulcer prophylaxis to prevent upper gastrointestinal bleeding using H2 blockers (1A) or proton pump inhibitors (1B); and consideration of limitation of support where appropriate (1D). Recommendations specific to pediatric severe sepsis include greater use of physical examination therapeutic end points (2C); dopamine as the first drug of choice for hypotension (2C); steroids only in children with suspected or proven adrenal insufficiency (2C); and a recommendation against the use of recombinant activated protein C in children (1B).

Conclusions: There was strong agreement among a large cohort of international experts regarding many level 1 recommendations for the best current care of patients with severe sepsis. Evidenced-based recommendations regarding the acute management of sepsis and septic shock are the first step toward improved outcomes for this important group of critically ill patients.

Key Words: sepsis; severe sepsis; septic shock; sepsis syndrome; infection; Grades of Recommendation, Assessment, Development and Evaluation criteria; GRADE; guidelines; evidence-based medicine; Surviving Sepsis Campaign; sepsis bundles


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Severe sepsis (acute organ dysfunction secondary to infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation) are major healthcare problems, affecting millions of individuals around the world each year, killing one in four (and often more), and increasing in incidence (1–5). Similar to polytrauma, acute myocardial infarction, or stroke, the speed and appropriateness of therapy administered in the initial hours after severe sepsis develops are likely to influence outcome. In 2004, an international group of experts in the diagnosis and management of infection and sepsis, representing 11 organizations, published the first internationally accepted guidelines that the bedside clinician could use to improve outcomes in severe sepsis and septic shock (6, 7). These guidelines represented phase II of the Surviving Sepsis Campaign (SSC), an international effort to increase awareness and improve outcomes in severe sepsis. Joined by additional organizations, the group met again in 2006 and 2007 to update the guidelines document using a new evidence-based methodology system for assessing quality of evidence and strength of recommendations (8–11).

These recommendations are intended to provide guidance for the clinician caring for a patient with severe sepsis or septic shock. Recommendations from these guidelines cannot replace the clinician’s decision-making capability when he or she is provided with a patient’s unique set of clinical variables. Most of these recommendations are appropriate for the severe sepsis patient in both the intensive care unit (ICU) and non-ICU settings. In fact, the committee believes that currently, the greatest outcome improvement can be made through education and process change for those caring for severe sepsis patients in the non-ICU setting and across the spectrum of acute care. It should also be noted that resource limitations in some institutions and countries may prevent physicians from accomplishing particular recommendations.

S E C H E M E 1. Diagnostic criteria for sepsis

Infection, documented or suspected, and some of the following:

**General variables**
- Fever (>38.3°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90 min⁻¹ or >2 SD above the normal value for age
- Tachypnea
- Altered mental status

**Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)

**Hyperglycemia** (plasma glucose >140 mg/dL or 7.7 mmol/L in the absence of diabetes

**Inflammatory variables**
- Leukocytosis (WBC count >12,000 µL⁻¹)
- Leukopenia (WBC count <4000 µL⁻¹)
- Normal WBC count with >10% immature forms
- Plasma C-reactive protein >2 SD above the normal value
- Plasma procalcitonin >2 SD above the normal value

**Hemodynamic variables**
- Arterial hypotension (SBP <90 mm Hg; MAP <70 mm Hg; or an SBP decrease >40 mm Hg in adults or <2 SD below normal for age)

**Organ dysfunction variables**
- Arterial hypoxemia (PaO₂/FIO₂ <300)
- Acute oliguria (urine output <0.5 mL/kg hr or 45 mmol/L for at least 2 hrs, despite adequate fluid resuscitation)
- Creatinine increase >0.5 mg/dL or 44.2 µmol/L
- Coagulation abnormalities (INR >1.5 or a PTT >60 secs)
- Ileus (absent bowel sounds)
- Thrombocytopenia (platelet count, <100,000 µL⁻¹)
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 µmol/L)

**Tissue perfusion variables**
- Hyperlactatemia (> upper limit of lab normal)
- Decreased capillary refill or mottling

**Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulses.

**Scheme 1.**

**Severe sepsis =** sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)

**Sepsis-induced hypotension**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>Lactate greater than the upper limits of normal laboratory results</td>
<td></td>
</tr>
<tr>
<td>Urine output &lt;0.5 mL/kg hr for &gt;2 hrs, despite adequate fluid resuscitation</td>
<td></td>
</tr>
<tr>
<td>ALI with PaO₂/FIO₂ &lt;250 in the absence of pneumonia as infection source</td>
<td></td>
</tr>
<tr>
<td>ALI with PaO₂/FIO₂ &lt;200 in the presence of pneumonia as infection source</td>
<td></td>
</tr>
<tr>
<td>Creatinine &gt;2.0 mg/dL (176.8 µmol/L)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin &gt;2 mg/dL (34.2 µmol/L)</td>
<td></td>
</tr>
<tr>
<td>Platelet count &lt;100,000</td>
<td></td>
</tr>
<tr>
<td>Coagulopathy (INR &gt;1.5)</td>
<td></td>
</tr>
</tbody>
</table>

**ALI, acute lung injury; INR, international normalized ratio.**

**Methods**

Sepsis is defined as infection plus systemic manifestations of infection (Scheme 1) (12). Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion. The threshold for this dysfunction has varied somewhat from one severe sepsis research study to another. An example of typical thresholds identification of severe sepsis is shown in Scheme 2 (12, 13). Sepsis-induced hypotension is defined as a systolic blood pressure (SBP) <90 mm Hg or mean arterial pressure <70 mm Hg or a SBP decrease >40 mm Hg or <2 SD below normal for age in the absence of other causes of hypotension. Septic shock is defined as sepsis-induced hypotension persisting de-
spite adequate fluid resuscitation. Sepsis-induced tissue hypoperfusion is defined as either septic shock, an elevated lactate, or oliguria.

The current clinical practice guidelines build on the first and second editions from 2001 (discussed subsequently) and 2004 (6, 7, 14). The 2001 publication incorporated a MEDLINE search for clinical trials in the preceding 10 yrs, supplemented by a manual search of other relevant journals (14). The 2004 publication incorporated the evidence available through the end of 2003. The current publication is based on an updated search into 2007 (see following methods and rules).

The 2001 guidelines were coordinated by the International Sepsis Forum; the 2004 guidelines were funded by unrestricted educational grants from industry and administered through the Society of Critical Care Medicine (SCCM), the European Society of Intensive Care Medicine (ESICM), and the International Sepsis Forum. Two of the SSC administering organizations receive unrestricted industry funding to support SSC activities (ESICM and SCCM), but none of this funding was used to support the 2006/2007 committee meetings.

It is important to distinguish between the process of guidelines revision and the SSC. The SSC is partially funded by unrestricted educational industry grants, including those from Edwards LifeSciences, Eli Lilly and Company, and Philips Medical Systems. SSC also received funding from the Coalition for Critical Care Excellence of the Society of Critical Care Medicine. The great majority of industry funding has come from Eli Lilly and Company.

Current industry funding for the SSC is directed to the performance improvement initiative. No industry funding was used in the guidelines revision process.

For both the 2004 and the 2006/2007 efforts, there were no members of the committee from industry, no industry input into guidelines development, and no industry presence at any of the meetings. Industry awareness or comment on the recommendations was not allowed. No member of the guideline committee received any honoraria for any role in the 2004 or 2006/2007 guidelines process. The committee considered the issue of recusement of individual committee members during deliberation and decision making in areas where committee members had either financial or academic competing interests; however, consensus as to threshold for exclusion could not be reached. Alternatively, the committee agreed to ensure full disclosure and transparency of all committee members’ potential conflicts at time of publication. (See disclosures at the end of this document.)

The guidelines process included a modified Delphi method, a consensus conference, several subsequent meetings of subgroups and key individuals, teleconferences and electronic-based discussions among subgroups and members of the entire committee, and two follow-up nominal group meetings in 2007.

Subgroups were formed, each charged with updating recommendations in specific areas, including corticosteroids, blood products, activated protein C, renal replacement therapy, antibiotics, source control, and glucose control. Each subgroup was responsible for updating the evidence (into 2007, with major additional elements of information incorporated into the evolving manuscript throughout 2006 and 2007). A separate search was performed for each clearly defined question. The committee chair worked with subgroup heads to identify pertinent search terms that always included, at a minimum, sepsis, severe sepsis, septic shock, and sepsis syndrome crossed against the general topic area of the subgroup as well as pertinent key words of the specific question posed. All questions of the previous guidelines publications were searched, as were pertinent new questions generated by general topic-related search or recent trials. Quality of evidence was judged by predefined Grades of Recommendation, Assessment, Development and Evaluation (GRADE) criteria (discussed subsequently). Significant education of committee members on the GRADE system was performed via e-mail before the first committee meeting and at the first meeting. Rules were distributed concerning assessing the body of evidence, and GRADE experts were available for questions throughout the process. Subgroups agreed electronically on draft proposals that were presented to committee meetings for general discussion. In January 2006, the entire group met during the 35th SCCM Critical Care Congress in San Francisco, California. The results of that discussion were incorporated into the next version of recommendations and again discussed using electronic mail. Recommendations were finalized during nominal group meetings (composed of a subset of the committee members) at the 2007 SCCM (Orlando, FL) and 2007 International Symposium on Intensive Care and Emergency Medicine (Brussels) meetings with recirculation of deliberations and decisions to the entire group for comment or approval. At the discretion of the chair and following adequate discussion, competing proposals for wording of recommendations or assigning strength of evidence were resolved by formal voting. On occasions, voting was performed to give the committee a sense of distribution of opinions to facilitate additional discussion. The manuscript was edited for style and form by the writing committee with final approval by section leads for their respective group assignment and then by the entire committee.

The development of guidelines and grading of recommendations for the 2004 guideline development process were based on a system proposed by Sackett (15) in 1989, during one of the first American College of Chest Physicians (ACCP) conferences on the use of antithrombotic therapies. The revised guidelines recommendations are based on the GRADE system, a structured system for rating quality of evidence and grading strength of recommendation in clinical practice (8–11). The SSC Steering Committee and individual authors collaborated with GRADE representatives to apply the GRADE system to the SSC guidelines revision process. The members of GRADE group were directly involved, either in person or via e-mail, in all discussions and deliberations among the guidelines committee members as to grading decisions. Subsequently, the SSC authors used written material prepared by the GRADE group and conferred with GRADE group members who were available at the first committee meeting and subsequent nominal group meetings. GRADE representatives were also used as a resource throughout subgroup deliberation.

The GRADE system is based on a sequential assessment of the quality of evidence, followed by assessment of the balance between benefits vs. risks, burden, and cost, and, based on the preceding, development and grading of a management recommendations (9–11). Keeping the rating of quality of evidence and strength of recommendation explicitly separate constitutes a crucial and defining feature of the GRADE approach. This system classifies quality of evidence as high (grade A), mod-
erate (grade B), low (grade C), or very low (grade D). Randomized trials begin as high-quality evidence but may be downgraded due to limitations in implementation, inconsistency or imprecision of the results, indirectness of the evidence, and possible reporting bias (Table 1). Examples of indirectness of the evidence include population studied, interventions used, outcomes measured, and how these relate to the question of interest. Observational (nonrandomized) studies begin as low-quality evidence, but the quality level may be upgraded on the basis of large magnitude of effect. An example of this is the quality of evidence for early administration of antibiotics.

The GRADE system classifies recommendations as strong (grade 1) or weak (grade 2). The grade of strong or weak is considered of greater clinical importance than a difference in letter level of quality of evidence. The committee assessed whether the desirable effects of adherence will outweigh the undesirable effects, and the strength of a recommendation reflects the group’s degree of confidence in that assessment (Table 2). A strong recommendation in favor of an intervention reflects that the desirable effects of adherence to a recommendation (beneficial health outcomes, less burden on staff and patients, and cost savings) will clearly outweigh the undesirable effects (harms, more burden, and greater costs). A weak recommendation in favor of an intervention indicates that the desirable effects of adherence to a recommendation probably will outweigh the undesirable effects, but the panel is not confident about these tradeoffs—either because some of the evidence is low quality (and thus there remains uncertainty regarding the benefits and risks) or the benefits and downsides are closely balanced. While the degree of confidence is a continuum and there is no precise threshold between a strong and a weak recommendation, the presence of important concerns about one or more of the preceding factors makes a weak recommendation more likely. A strong recommendation is worded as “we recommend” and a weak recommendation as “we suggest.”

The implications of calling a recommendation strong are that most well-informed patients would accept that intervention and that most clinicians should use it in most situations. There may be circumstances in which a strong recommendation cannot or should not be followed for an individual patient because of that patient’s preferences or clinical characteristics that make the recommendation less applicable. Being a strong recommendation does not automatically imply standard of care. For example, the strong recommendation for administering antibiotics within 1 hr of the diagnosis of severe sepsis, although desirable, is not currently standard of care as verified by current practice (M Levy, personal communication, from first 8,000 patients entered internationally into the SSC performance improvement database). The implication of a weak recommendation is that although a majority of well-informed patients would accept it (but a substantial proportion would not), clinicians should consider its use according to particular circumstances.

Differences of opinion among committee members about interpretation of evidence, wording of proposals, or strength of recommendations were resolved using a specifically developed set of rules. We will describe this process in detail in a separate publication. In summary, the main approach for converting diverse opinions into a recommendation was as follows: 1) to give a recommendation a direction (for or against the given action), a majority of votes were to be in favor of that direction, with ≤20% preferring the opposite direction (there was a neutral vote allowed as well); 2) to call a given recommendation strong rather than weak, ≥70% “strong” votes were required; 3) if <70% of votes indicated “strong” preference, the recommendation was assigned a weak category of strength. We used a combination of modified Delphi process and nominal (expert) group techniques to ensure both depth and breadth of review. The entire review group (together with their parent organizations as required) participated in the larger, iterative, modified Delphi process. The smaller working group meetings, which took place in person, functioned as the nominal groups. If a clear consensus could not be obtained by polling within the nominal group meetings, the larger group was specifically asked to use the polling process. This was only required for corticosteroids

Table 1. Determination of the quality of evidence

<table>
<thead>
<tr>
<th>Factors that may decrease the strength of evidence</th>
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<tbody>
<tr>
<td>A. Poor quality of planning and implementation of available RCTs, suggesting high likelihood of bias</td>
</tr>
<tr>
<td>B. Inconsistency of results (including problems with subgroup analyses)</td>
</tr>
<tr>
<td>C. Indirectness of evidence (differing population, intervention, control, outcomes, comparison)</td>
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<tr>
<td>D. Imprecision of results</td>
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<tr>
<td>E. High likelihood of reporting bias</td>
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</tbody>
</table>

Table 2. Factors determining strong vs. weak recommendation

<table>
<thead>
<tr>
<th>What Should Be Considered</th>
<th>Recommended Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of evidence</td>
<td>The lower the quality of evidence, the less likely a strong recommendation</td>
</tr>
<tr>
<td>Relative importance of the outcomes</td>
<td>If values and preferences vary widely, a strong recommendation becomes less likely</td>
</tr>
<tr>
<td>Baseline risks of outcomes</td>
<td>The higher the risk, the greater the magnitude of benefit</td>
</tr>
<tr>
<td>Magnitude of relative risk, including benefits, harms, and burden</td>
<td>Larger relative risk reductions or larger increases in relative risk of harm make a strong recommendation more or less likely, respectively</td>
</tr>
<tr>
<td>Absolute magnitude of the effect</td>
<td>The larger the absolute benefits and harms, the greater or lesser likelihood, respectively, of a strong recommendation</td>
</tr>
<tr>
<td>Precision of the estimates of the effects</td>
<td>The greater the precision, the more likely a strong recommendation</td>
</tr>
<tr>
<td>Costs</td>
<td>The higher the cost of treatment, the less likely a strong recommendation</td>
</tr>
</tbody>
</table>
and glycemic control. The larger group had the opportunity to review all outputs. In this way the entire review combined intense focused discussion (nominal group) with broader review and monitoring using the Delphi process.

Note: Refer to Tables 3–5 for condensed adult recommendations.

I. MANAGEMENT OF SEVERE SEPSIS

A. Initial Resuscitation

1. We recommend the protocolized resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration >4 mmol/L). This protocol should be initiated as soon as hypoperfusion is recognized and should not be delayed pending ICU admission. During the first 6 hrs of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as one part of a treatment protocol:

- Central venous pressure 8–12 mm Hg
- Mean arterial pressure (MAP) ≥65 mm Hg
- Urine output ≥0.5 mL·kg⁻¹·hr⁻¹
- Central venous (superior vena cava) or mixed venous oxygen saturation ≥70% or ≥65%, respectively (grade 1C)

Rationale. Early goal-directed resuscitation has been shown to improve survival for emergency department patients presenting with septic shock in a randomized, controlled, single-center study (16). Resuscitation directed toward the previously mentioned goals for the initial 6-hr period of the resuscitation was able to reduce 28-day mortality rate. The consensus panel judged use of central venous and mixed venous oxygen saturation targets to be equivalent. Either intermittent or continuous measurements of oxygen saturation were judged to be acceptable. Although blood lactate concentration may lack precision as a measure of tissue metabolic status, elevated levels in sepsis support aggressive resuscitation. In mechanically ventilated patients or patients with known preexisting decreased ventricular compliance, a higher target central venous pressure of 12–15 mm Hg is recommended to account for the impediment to filling (17). Similar consideration may be warranted in circumstances of increased abdominal pressure or diastolic dysfunction (18). Elevated central venous pressures may also be seen with preexisting clinically significant pulmonary artery hypertension. Although the cause of tachycardia in septic patients may be multifactorial, a decrease in elevated pulse rate with fluid resuscitation is often a useful marker of improving intravascular filling. Recently published observational studies have demonstrated an association between good clinical outcome in septic shock and MAP ≥65 mm Hg as well as central venous oxygen saturation (SvO₂, measured in superior vena cava, either intermittently or continuously) of ≥70% (19). Many recent studies support the value of early protocolized resuscitation in severe sepsis and sepsis-induced tissue hypoperfusion (20–25). Studies of patients with shock indicate that mixed venous oxygen saturation (SvO₂) runs 5–7% lower than central venous oxygen saturation (ScvO₂) (26) and that an early goal-directed resuscitation protocol can be established in a nonresearch general practice venue (27).

Table 3. Initial resuscitation and infection issues

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Initial resuscitation (first 6 hrs)

- Begin resuscitation immediately in patients with hypotension or elevated serum lactate >4 mmol/L; do not delay pending ICU admission (1C)
- Resuscitation goals (1C)
  - CVP 8–12 mm Hg
  - Mean arterial pressure ≥ 65 mm Hg
  - Urine output ≥0.5 mL·kg⁻¹·hr⁻¹
  - Central venous (superior vena cava) oxygen saturation ≥70% or mixed venous ≥65%
- If venous oxygen saturation target is not achieved (2C)
  - Consider further fluid
  - Transfuse packed red blood cells if required to hematocrit of ≥30% and/or
  - Start dobutamine infusion, maximum 20 µg·kg⁻¹·min⁻¹

Diagnosis

- Obtain appropriate cultures before starting antibiotics provided this does not significantly delay antimicrobial administration (1C)
- Obtain two or more BCs
- One or more BCs should be percutaneous
- One BC from each vascular access device in place >48 hrs
- Culture other sites as clinically indicated
- Perform imaging studies promptly to confirm and sample any source of infection, if safe to do so (1C)

Antibiotic therapy

- Begin intravenous antibiotics as early as possible and always within the first hour of recognizing severe sepsis (1D) and septic shock (1B)
- Broad-spectrum: one or more agents active against likely bacterial/fungal pathogens and with good penetration into presumed source (1B)
- Reassess antimicrobial regimen daily to optimize efficacy, prevent resistance, avoid toxicity, and minimize costs (1C)
- Consider combination therapy in Pseudomonas infections (2D)
- Consider combination empiric therapy in neutropenic patients (2D)
- Combination therapy ≤3–5 days and de-escalation following susceptibilities (2D)
- Duration of therapy typically limited to 7–10 days; longer if response is slow or there are undrivable foci of infection or immunologic deficiencies (1D)
- Stop antimicrobial therapy if cause is found to be noninfectious (1D)

Source identification and control

- A specific anatomic site of infection should be established as rapidly as possible (1C) and within first 6 hrs of presentation (1D)
- Formally evaluate patient for a focus of infection amenable to source control measures (e.g. abscess drainage, tissue debridement) (1C)
- Implement source control measures as soon as possible following successful initial resuscitation (1C) (exception: infected pancreatic necrosis, where surgical intervention is best delayed) (2B)
- Choose source control measure with maximum efficacy and minimal physiologic upset (1D)
- Remove intravascular access devices if potentially infected (1C)

GRADE, Grades of Recommendation, Assessment, Development and Evaluation; ICU, intensive care unit; CVP, central venous pressure; BC, blood culture.

“A higher target CVP of 12–15 mm Hg is recommended in the presence of mechanical ventilation or preexisting decreased ventricular compliance.”

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Table 4. Hemodynamic support and adjunctive therapy

Strength of recommendation and quality of evidence have been assessed using the GRADE criteria, presented in parentheses after each guideline.

- Indicates a strong recommendation, or “we recommend”
- Indicates a weak recommendation, or “we suggest”

**Fluid therapy**
- Fluid-resuscitate using crystalloids or colloids (1B)
- Target a CVP of ≥6 mm Hg (≥12 mm Hg if mechanically ventilated) (1C)
- Use a fluid challenge technique while associated with a hemodynamic improvement (1D)
- Give fluid challenges of 1000 mL of crystalloids or 300–500 mL of colloids over 30 mins. More rapid and larger volumes may be required in sepsis-induced tissue hypoperfusion (1D)
- Rate of fluid administration should be reduced if cardiac filling pressures increase without concurrent hemodynamic improvement (1D)

**Vasopressors**
- Maintain MAP ≥65 mm Hg (1C)
- Norepinephrine and dopamine centrally administered are the initial vasopressors of choice (1C)
- Epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (2C). Vasopressin 0.03 units/min may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone
- Use epinephrine as the first alternative agent in septic shock when blood pressure is poorly responsive to norepinephrine or dopamine (2B).
- Do not use low-dose dopamine for renal protection (1A)
- In patients requiring vasopressors, insert an arterial catheter as soon as practical (1D)

**Inotropic therapy**
- Use dobutamine in patients with myocardial dysfunction as supported by elevated cardiac filling pressures and low cardiac output (1C)
- Do not increase cardiac index to predetermined supranormal levels (1B)

**Steroids**
- Consider intravenous hydrocortisone for adult septic shock when hypotension responds poorly to adequate fluid resuscitation and vasopressors (2C)
- ACTH stimulation test is not recommended to identify the subset of adults with septic shock who should receive hydrocortisone (2B)
- Hydrocortisone is preferred to dexamethasone (2B)
- Fluidcortisone (50 µg orally once a day) may be included if an alternative to hydrocortisone is being used that lacks significant mineralocorticoid activity. Fludrocortisone if optional if hydrocortisone is used (2C)
- Steroid therapy may be weaned once vasopressors are no longer required (2D)
- Hydrocortisone dose should be ≤300 mg/day (1A)
- Do not use corticosteroids to treat sepsis in the absence of shock unless the patient’s endocrine or corticosteroid history warrants it (1D)

**Recombinant human activated protein C**
- Consider rhAPC in adult patients with sepsis-induced organ dysfunction with clinical assessment of high risk of death (typically APACHE II ≥25 or multiple organ failure) if there are no contraindications (2B, 2C for postoperative patients).
- Adult patients with severe sepsis and low risk of death (typically, APACHE II <20 or one organ failure) should not receive rhAPC (1A)

**Rationale.** The protocol used in the study cited previously targeted an increase in ScvO₂ to ≥70% (16). This was achieved by sequential institution of initial fluid resuscitation, packed red blood cells, and then dobutamine. This protocol was associated with an improvement in survival. Based on bedside clinical assessment and personal preference, a clinician may deem either blood transfusion (if hematocrit is <30%) or dobutamine the best initial choice to increase oxygen delivery and thereby elevate ScvO₂ when fluid resuscitation is believed to be already adequate. The design of the aforementioned trial did not allow assessment of the relative contribution of these two components (i.e., increasing oxygen content or increasing cardiac output) of the protocol on achievement of improved outcome.

**B. Diagnosis**

1. We recommend obtaining appropriate cultures before antimicrobial therapy is initiated if such cultures do not cause significant delay in antibiotic administration. To optimize identification of causative organisms, we recommend at least two blood cultures be obtained before antibiotics with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently (<48 hrs) inserted. Cultures of other sites (preferably quantitative where appropriate), such as urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids that may be the source of infection should also be obtained before antibiotic therapy if not associated with significant delay in antibiotic administration (grade 1C).

**Rationale.** Although sampling should not delay timely administration of antibiotics in patients with severe sepsis (e.g., lumbar puncture in suspected meningitis), obtaining appropriate cultures before administration of antibiotics is essential to confirm infection and the responsible pathogens and to allow de-escalation of antibiotic therapy after receipt of the susceptibility profile. Samples can be refrigerated or frozen if processing cannot be performed immediately. Immediate transport to a microbiological lab is necessary. Because rapid sterilization of blood cultures can occur within a few hours after the first antibiotic dose, obtaining those cultures before starting therapy is essential if the causative organ-
Table 5. Other supportive therapy of severe sepsis

Strength of recommendation and quality of evidence have been assessed using the GRADE criteria, presented in parentheses after each guideline:
- Indicates a strong recommendation, or “we recommend”
- Indicates a weak recommendation, or “we suggest”

**Blood product administration**
- Give red blood cells when hemoglobin decreases to <7.0 g/dL (<70 g/L) to target a hemoglobin of 7.0–9.0 g/dL in adults (1B). A higher hemoglobin level may be required in special circumstances (e.g., myocardial ischaemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease, or lactic acidosis).
- Do not use erythropoietin to treat sepsis-related anemia. Erythropoietin may be used for other accepted reasons (1B).
- Do not use fresh frozen plasma to correct laboratory clotting abnormalities unless there is bleeding or planned invasive procedures (2D).
- Do not use antithrombin therapy (1B).
- Administer platelets when (2D)
  - Counts are ≤5000/mm^3 (5 × 10^9/L) regardless of bleeding.
  - Counts are 5000–30,000/mm^3 (5–30 × 10^9/L) and there is significant bleeding risk.
  - Higher platelet counts (≥50,000/mm^3 [50 × 10^9/L]) are required for surgery or invasive procedures.

**Mechanical ventilation of sepsis-induced ALI/ARDS**
- Target a tidal volume of 6 mL/kg (predicted) body weight in patients with ALI/ARDS (1B).
- Target an initial upper limit plateau pressure ≤30 cm H₂O. Consider chest wall compliance when assessing plateau pressure (1C).
- Allow Paco₂ to increase above normal, if needed, to minimize plateau pressures and tidal volumes (1C).
- Set PEEP to avoid extensive lung collapse at end-expiration (1C).
- Consider using the prone position for ARDS patients requiring potentially injurious levels of P/F or plateau pressure, provided they are not put at risk from positional changes (2C).
- Maintain mechanically ventilated patients in a semirecumbent position (head of the bed raised to 45°) unless contraindicated (1B), between 30° and 45° (2C).
- Noninvasive ventilation may be considered in the minority of ALI/ARDS patients with mild to moderate hypoxic respiratory failure. The patients need to be hemodynamically stable, comfortable, easily arousable, able to protect/clear their airway, and expected to recover rapidly (2B).
- Use a weaning protocol and an SBT regularly to evaluate the potential for discontinuing mechanical ventilation (1A).
- SBT options include a low level of pressure support with continuous positive airway pressure 5 cm H₂O or a T-piece.
- Before the SBT, patients should be a aroused
  - be hemodynamically stable without vasopressors
  - have no new potentially serious conditions
  - have low ventilatory and end-expiratory pressure requirement
  - require P/F levels that can be safely delivered with a face mask or nasal cannula.
- Do not use a pulmonary artery catheter for the routine monitoring of patients with ALI/ARDS (1A).
- Use a conservative fluid strategy for patients with established ALI who do not have evidence of tissue hypoperfusion (1C).

**Sedation, analgesia, and neuromuscular blockade in sepsis**
- Use sedation protocols with a sedation goal for critically ill mechanically ventilated patients (1B).
- Use either intermittent bolus sedation or continuous infusion sedation to predetermined end points (sedation scales), with daily interruption/lightening to produce awakening. Re-titrare if necessary (1B).
- Avoid neuromuscular blockers where possible. Monitor depth of block with train-of-four when using continuous infusions (1B).

**Glucose control**
- Use intravenous insulin to control hyperglycemia in patients with severe sepsis following stabilization in the ICU (1B).
  - Aim to keep blood glucose <150 mg/dL (8.3 mmol/L) using a validated protocol for insulin dose adjustment (2C).
  - Interpret with caution low glucose levels obtained with point of care testing, as these techniques may overestimate arterial blood or plasma glucose values (1B).

**Renal replacement**
- Intermittent hemodialysis and CVVH are considered equivalent (2B).
- CVVH offers easier management in hemodynamically unstable patients (2D).

**Bicarbonate therapy**
- Do not use bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements when treating hypoperfusion-induced lactic acidemia with pH ≤7.15 (1B).

**Deep vein thrombosis prophylaxis**
- Use either low-dose UFH or LMWH, unless contraindicated (1A).
- Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated (1A).
  - Consider using the prone position for ARDS patients requiring potentially injurious levels of P/F or plateau pressure, provided they are not at risk from positional changes (2C).
  - Use CVVH offers easier management in hemodynamically unstable patients (2D).
- Use a combination of pharmacologic and mechanical therapy for patients who are at very high risk for deep vein thrombosis (2C).
  - In patients at very high risk, LMWH should be used rather than UFH (2C).

**Stress ulcer prophylaxis**
- Use a combination of pharmacologic and mechanical therapy for patients who are at very high risk for deep vein thrombosis (2C).
- In patients at very high risk, LMWH should be used rather than UFH (2C).

**Consideration for limitation of support**
- Discuss advance care planning with patients and families. Describe likely outcomes and set realistic expectations (1D).

- **Bicarbonate therapy**
  - Do not use bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements when treating hypoperfusion-induced lactic acidemia with pH ≤7.15 (1B).
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- **Deep vein thrombosis prophylaxis**
  - Use either low-dose UFH or LMWH, unless contraindicated (1A).
  - Use a mechanical prophylactic device, such as compression stockings or an intermittent compression device, when heparin is contraindicated (1A).
  - Consider using the prone position for ARDS patients requiring potentially injurious levels of P/F or plateau pressure, provided they are not at risk from positional changes (2C).
  - Use CVVH offers easier management in hemodynamically unstable patients (2D).
- **Stress ulcer prophylaxis**
  - Use a combination of pharmacologic and mechanical therapy for patients who are at very high risk for deep vein thrombosis (2C).
  - In patients at very high risk, LMWH should be used rather than UFH (2C).

- **Consideration for limitation of support**
  - Discuss advance care planning with patients and families. Describe likely outcomes and set realistic expectations (1D).
C. Antibiotic Therapy

1. We recommend that intravenous antibiotic therapy be started as early as possible and within the first hour of recognition of septic shock (1B) and severe sepsis without septic shock (1D). Appropriate cultures should be obtained before initiating antibiotic therapy but should not prevent prompt administration of antimicrobial therapy (grade 1D).

Rationale. Establishing vascular access and initiating aggressive fluid resuscitation are the first priority when managing patients with severe sepsis or septic shock. However, prompt infusion of antimicrobial agents should also be a priority and may require additional vascular access ports (42, 43). In the presence of septic shock, each hour delay in achieving administration of effective antibiotics is associated with a measurable increase in mortality (42). If antimicrobial agents cannot be mixed and delivered promptly from the pharmacy, establishing a supply of premixed antibiotics for such urgent situations is an appropriate strategy for ensuring prompt administration. In choosing the antimicrobial regimen, clinicians should be aware that some antimicrobial agents have the advantage of bolus administration, while others require a lengthy infusion. Thus, if vascular access is limited and many different agents must be infused, bolus drugs may offer an advantage.

2a. We recommend that initial empirical anti-infective therapy include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal) and that penetrate in adequate concentrations into the presumed source of sepsis (grade 1B).

Rationale. The choice of empirical antibiotics depends on complex issues related to the patient’s history, including drug intolerances, underlying disease, the clinical syndrome, and susceptibility patterns of pathogens in the community, in the hospital, and that previously have been documented to colonize or infect the patient. There is an especially wide range of potential pathogens for neutropenic patients.

Recently used antibiotics should generally be avoided. When choosing empirical therapy, clinicians should be cognizant of the virulence and growing prevalence of oxacillin (methicillin-resistant *Staphylococcus aureus* (ORSA or MRSA) in some communities and healthcare settings (especially in the United States). If the prevalence is significant, and in consideration of the virulence of this organism, empirical therapy adequate for this pathogen would be warranted. Clinicians should also consider whether candidemia is a likely pathogen when choosing initial therapy. When deemed warranted, the selection of empirical antifungal therapy (e.g., fluconazole, amphotericin B, or echinocandin) will be tailored to the local pattern of the most prevalent *Candida* species and any prior administration of azoles drugs (44). Risk factors for candidemia should also be considered when choosing initial therapy.

Because patients with severe sepsis or septic shock have little margin for error in the choice of therapy, the initial selection of antimicrobial therapy should be broad enough to cover all likely pathogens. There is ample evidence that failure to initiate appropriate therapy (i.e., therapy with activity against the pathogen that is subsequently identified as the causative agent) correlates with increased morbidity and mortality (45–48).

Patients with severe sepsis or septic shock warrant broad-spectrum therapy until the causative organism and its antibiotic susceptibilities are defined. Restriction of antibiotics as a strategy to reduce the development of antimicrobial resistance or to reduce cost is not an appropriate initial strategy in this patient population.

All patients should receive a full loading dose of each antimicrobial. However, patients with sepsis or septic shock often have abnormal renal or hepatic function and may have abnormal volumes of distribution due to aggressive fluid resuscitation. Drug serum concentration monitoring can be useful in an ICU setting for those drugs that can be measured promptly. An experienced physician or clinical pharmacist should be consulted to ensure that serum concentrations are attained that maximize efficacy and minimize toxicity (49–52).

2b. We recommend that the antimicrobial regimen be reassessed daily to optimize activity, to prevent the development of resistance, to reduce toxicity, and to reduce costs (grade 1C).

Rationale. Although restriction of antibiotics as a strategy to reduce the development of antimicrobial resistance or to reduce cost is not an appropriate initial strategy in this patient population, once the causative pathogen has been identified, it may become apparent that none of the empirical drugs offers optimal therapy; that is, there may be another drug proven to produce superior clinical out-
come that should therefore replace empirical agents.

Narrowing the spectrum of antibiotic coverage and reducing the duration of antibiotic therapy will reduce the likelihood that the patient will develop superinfection with pathogenic or resistant organisms, such as *Candida* species, *Clostridium difficile*, or vancomycin-resistant *Enterococcus faecium*. However, the desire to minimize superinfections and other complications should not take precedence over the need to give the patient an adequate course of therapy to cure the infection that caused the severe sepsis or septic shock.

2c. We suggest combination therapy for patients with known or suspected *Pseudomonas* infections as a cause of severe sepsis (grade 2D).

2d. We suggest combination empirical therapy for neutropenic patients with severe sepsis (grade 2D).

2e. When used empirically in patients with severe sepsis, we suggest that combination therapy should not be administered for >3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2D).

**Rationale.** Although no study or meta-analysis has convincingly demonstrated that combination therapy produces a superior clinical outcome for individual pathogens in a particular patient group, combination therapies do produce *in vitro* synergy against pathogens in some models (although such synergy is difficult to define and predict). In some clinical scenarios, such as the two preceding, combination therapies are biologically plausible and are likely clinically useful even if evidence has not demonstrated improved clinical outcome (53–56). Combination therapy for suspected known *Pseudomonas* pending sensitivities increases the likelihood that at least one drug is effective against that strain and clinician's expertise.

3. We recommend that the duration of therapy typically be 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, or immunologic deficiencies, including neutropenia (grade 1D).

4. We recommend that if the presenting clinical syndrome is determined to be due to a noninfectious cause, antimicrobial therapy be stopped promptly to minimize the likelihood that the patient will become infected with an antibiotic-resistant pathogen or will develop a drug-related adverse effect (grade 1D).

**Rationale.** Clinicians should be cognizant that blood cultures will be negative in >50% of cases of severe sepsis or septic shock, yet many of these cases are very likely caused by bacteria or fungi. Thus, the decisions to continue, narrow, or stop antimicrobial therapy must be made on the basis of clinician judgment and clinical information.

**D. Source Control**

1a. We recommend that a specific anatomic diagnosis of infection requiring consideration for emergent source control (e.g., necrotizing fasciitis, diffuse peritonitis, cholangitis, intestinal infarction) be sought and diagnosed or excluded as rapidly as possible (grade 1C) and within the first 6 hrs following presentation (grade 1D).

1b. We further recommend that all patients presenting with severe sepsis be evaluated for the presence of a focus on infection amenable to source control measures, specifically the drainage of an abscess or local focus on infection, the debridement of infected necrotic tissue, the removal of a potentially infected device, or the definitive control of a source of ongoing microbial contamination (grade 1C). (Appendix A provides examples of potential sites needing source control.)

2. We suggest that when infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred (grade 2B).

3. We recommend that when source control is required, the effective intervention associated with the least physiologic insult be employed (e.g., percutaneous rather than surgical drainage of an abscess (grade 1D).

4. We recommend that when intravascular access devices are a possible source of severe sepsis or septic shock, they be promptly removed after other vascular access has been established (grade 1C).

**Rationale.** The principals of source control in the management of sepsis include a rapid diagnosis of the specific site of infection and identification of a focus on infection amenable to source control measures (specifically the drainage of an abscess, debridement of infected necrotic tissue, removal of a potentially infected device, and definitive control of a source of ongoing microbial contamination) (58). Foci of infection readily amenable to source control measures include an intra-abdominal abscess or gastrointestinal perforation, cholangitis or pylonephritis, intestinal ischemia or necrotizing soft tissue infection, and other deep space infection, such as an empyema or septic arthritis. Such infectious foci should be controlled as soon as possible following successful initial resuscitation (59), accomplishing the source control objective with the least physiologic upset possible (e.g., percutaneous rather than surgical drainage of an abscess [60], endoscopic rather than surgical drainage of biliary tree), and removing intravascular access devices that are potentially the source of severe sepsis or septic shock promptly after establishing other vascular access (61, 62). A randomized, controlled trial comparing early vs. delayed surgical intervention for peripancreatic necrosis showed better outcomes with a delayed approach (63). However, areas of uncertainty exist, such as definitive documentation of infection and appropriate length of delay. The selection of optimal source control methods must weigh benefits and risks of the specific intervention as well as risks of transfer (64). Source control interventions may cause further complications, such as bleeding, fistulas, or inadvertent organ injury. Surgical intervention should be considered when lesser interventional approaches are inadequate or when diagnostic uncertainty persists despite radiologic evaluation. Specific clinical situations require consideration of available choices, patient’s preferences, and clinician’s expertise.

**E. Fluid Therapy**

1. We recommend fluid resuscitation with either natural/artificial colloids or crystalloids. There is no evidence-based support for one type of fluid over another (grade 1B).

**Rationale.** The SAFE study indicated that albumin administration was safe and equally as effective as crystalloid (65). There was an insignificant decrease in mortality rates with the use of colloid in a subset
analysis of septic patients ($p = .09$). Previous meta-analyses of small studies of ICU patients had demonstrated no difference between crystalloid and colloid fluid resuscitation (66–68). Although administration of hydroxyethyl starch may increase the risk of acute renal failure in patients with sepsis, variable findings preclude definitive recommendations (69, 70). As the volume of distribution is much larger for crystalloids than for colloids, resuscitation with crystalloids requires more fluid to achieve the same end points and results in more edema. Crystalloids are less expensive.

2. We recommend that fluid resuscitation initially target a central venous pressure of $\geq 8$ mm Hg (12 mm Hg in mechanically ventilated patients). Further fluid therapy is often required (grade 1C).

3a. We recommend that a fluid challenge technique be applied wherein fluid administration is continued as long as the hemodynamic improvement (e.g., arterial pressure, heart rate, urine output) continues (grade 1D).

3b. We recommend that fluid challenge in patients with suspected hypovolemia be started with $\geq 1000$ mL of crystalloids or $300–500$ mL of colloids over 30 mins. More rapid administration and greater amounts of fluid may be needed in patients with sepsis-induced tissue hypoperfusion (see Initial Resuscitation recommendations) (grade 1D).

3c. We recommend that the rate of fluid administration be reduced substantially when cardiac filling pressures (central venous pressure or pulmonary artery balloon-occluded pressure) increase without concurrent hemodynamic improvement (grade 1D).

**Rationale.** Fluid challenge must be clearly separated from simple fluid administration; it is a technique in which large amounts of fluids are administered over a limited period of time under close monitoring to evaluate the patient’s response and avoid the development of pulmonary edema. The degree of intravascular volume deficit in patients with severe sepsis varies. With venodilation and ongoing capillary leak, most patients require continuing aggressive fluid resuscitation during the first 24 hrs of management. Input is typically much greater than output, and input/output ratio is of no utility to judge fluid resuscitation needs during this time period.

### F. Vasopressors

1. We recommend that mean arterial pressure (MAP) be maintained $\geq 65$ mm Hg (grade 1C).

**Rationale.** Vasopressor therapy is required to sustain life and maintain perfusion in the face of life-threatening hypotension, even when hypovolemia has not yet been resolved. Below a certain mean arterial pressure, autoregulation in various vascular beds can be lost, and perfusion can become linearly dependent on pressure. Thus, some patients may require vasopressor therapy to achieve a minimal perfusion pressure and maintain adequate flow (71, 72). The titration of norepinephrine to as low as $MAP \geq 65$ mm Hg has been shown to preserve tissue perfusion (72). In addition, preexisting comorbidities should be considered as to most appropriate MAP target. For example, a MAP of $65$ mm Hg might be too low in a patient with severe uncontrolled hypertension, and in a young previously normotensive, a lower MAP might be adequate. Supplementing end points, such as blood pressure, with assessment of regional and global perfusion, such as blood lactate concentrations and urine output, is important. Adequate fluid resuscitation is a fundamental aspect of the hemodynamic management of patients with septic shock and should ideally be achieved before vasopressors and inotropes are used, but using vasopressors early as an emergency measure in patients with severe shock is frequently necessary. When that occurs, great effort should be directed to weaning vasopressors with continuing fluid resuscitation.

2. We recommend either norepinephrine or dopamine as the first choice vasopressor agent to correct hypotension in septic shock (administered through a central catheter as soon as one is available) (grade 1C).

3a. We suggest that epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (grade 2C). Vasopressin 0.03 units/min may be added to norepinephrine subsequently with anticipation of an effect equivalent to that of norepinephrine alone.

3b. We suggest that epinephrine be the first chosen alternative agent in septic shock that is poorly responsive to norepinephrine or dopamine (grade 2B).

**Rationale.** There is no high-quality primary evidence to recommend one catecholamine over another. Much literature exists that contrasts the physiologic effects of choice of vasopressor and combined inotrope/vasopressors in septic shock (73–85). Human and animal studies suggest some advantages of norepinephrine and dopamine over epinephrine (the latter with the potential for tachycardia as well as disadvantageous effects on splanchnic circulation and hyperlactemia) and phenylephrine (decrease in stroke volume). There is, however, no clinical evidence that epinephrine results in worse outcomes, and it should be the first chosen alternative to dopamine or norepinephrine. Phenylephrine is the adrenergic agent least likely to produce tachycardia but as a pure vasopressor would be expected to decrease stroke volume. Dopamine increases mean arterial pressure and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases mean arterial pressure due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine. Either may be used as a first-line agent to correct hypotension in sepsis. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function but causes more tachycardia and may be more arrhythmogenic (86). It may also influence the endocrine response via the hypothalamic-pituitary axis and have immunosuppressive effects.

Vasopressin levels in septic shock have been reported to be lower than anticipated for a shock state (87). Low doses of vasopressin may be effective in raising blood pressure in patients refractory to other vasopressors and may have other potential physiologic benefits (88–93). Terlipressin has similar effects but is long lasting (94). Studies show that vasopressin concentrations are elevated in early septic shock, but with continued shock the concentration decreases to normal range in the majority of patients between 24 and 48 hrs (95). This has been called relative vasopressin deficiency because in the presence of hypotension, vasopressin would be expected to be elevated. The significance of this finding is unknown. The recent VASST trial, a randomized, controlled trial comparing norepinephrine alone to norepinephrine plus vaso-
pressin at 0.03 units/min, showed no difference in outcome in the intent to treat population. An a priori defined subgroup analysis showed that the survival of patients receiving <15 μg/min norepinephrine at the time of randomization was better with vasopressin. However, the pretrial rationale for this stratification was based on exploring potential benefit in the ≥15 μg norepinephrine requirement population. Higher doses of vasopressin have been associated with cardiac, digital, and splanchnic ischemia and should be reserved for situations where alternative vasopressors have failed (96). Cardiac output measurement to allow maintenance of a normal or elevated flow is desirable when these pure vasopressors are instituted.

5. We recommend that low-dose dopamine not be used for renal protection (grade 1A).

Rationale. A large randomized trial and meta-analysis comparing low-dose dopamine to placebo found no difference in either primary outcomes (peak serum creatinine, need for renal replacement, urine output, time to recovery of normal renal function) or secondary outcomes (survival to either ICU or hospital discharge, ICU stay, hospital stay, arrhythmias) (97, 98). Thus, the available data do not support administration of low doses of dopamine solely to maintain renal function.

6. We recommend that all patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (grade 1D).

Rationale. In shock states, estimation of blood pressure using a cuff is commonly inaccurate; use of an arterial cannula provides a more appropriate and reproducible measurement of arterial pressure. These catheters also allow continuous analysis so that decisions regarding therapy can be based on immediate and reproducible blood pressure information.

G. Inotropic Therapy

1. We recommend that a dobutamine infusion be administered in the presence of myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output (grade 1C).

2. We recommend against the use of a strategy to increase cardiac index to predetermined supranormal levels (grade 1B).

Rationale. Dobutamine is the first-choice inotrope for patients with measured or suspected low cardiac output in the presence of adequate left ventricular filling pressure (or clinical assessment of adequate fluid resuscitation) and adequate mean arterial pressure. Septic patients who remain hypotensive after fluid resuscitation may have low, normal, or increased cardiac outputs. Therefore, treatment with a combined inotrope/vasopressor, such as norepinephrine or dopamine, is recommended if cardiac output is not measured. When the capability exists for monitoring cardiac output in addition to blood pressure, a vasopressor, such as norepinephrine, may be used separately to target specific levels of mean arterial pressure and cardiac output. Two large prospective clinical trials that included critically ill ICU patients who had severe sepsis failed to demonstrate benefit from increasing oxygen delivery to supranormal targets by use of dobutamine (99, 100). These studies did not specifically target patients with severe sepsis and did not target the first 6 hrs of resuscitation. The first 6 hrs of resuscitation of sepsis-induced hypoperfusion need to be treated separately from the later stages of severe sepsis (see Initial Resuscitation recommendations).

H. Corticosteroids

1. We suggest that intravenous hydrocortisone be given only to adult septic shock patients after it has been confirmed that their blood pressure is poorly responsive to fluid resuscitation and vasopressor therapy (grade 2C).

Rationale. One French multicenter, randomized controlled trial (RCT) of patients in vasopressor-unresponsive septic shock (hypotension despite fluid resuscitation and vasopressors) showed a significant shock reversal and reduction of mortality rate in patients with relative adrenal insufficiency (defined as postadrenocorticotropic hormone [ACTH] cortisol increase ≥9 μg/dl) (101). Two additional smaller RCTs also showed significant effects on shock reversal with steroid therapy (102, 103). However, a recent large, European multicenter trial (CORTICUS), which has been presented in abstract form but not yet published, failed to show a mortality benefit with steroid therapy of septic shock (104). CORTICUS did show a faster resolution of septic shock in patients who received steroids. The use of the ACTH test (responders and nonresponders) did not predict the faster resolution of shock. Importantly, unlike the French trial, which only enrolled shock patients with blood pressure unresponsive to vasopressor therapy, the CORTICUS study included patients with septic shock, regardless of how the blood pressure responded to vasopressors. Although corticosteroids do appear to promote shock reversal, the lack of a clear improvement in mortality—coupled with known side effects of steroids, such as increased risk of infection and myopathy—generally tempered enthusiasm for their broad use. Thus, there was broad agreement that the recommendation should be downgraded from the previous guidelines (Appendix B). There was considerable discussion and consideration by the committee on the option of encouraging use in those patients whose blood pressure was unresponsive to fluids and vasopressors, while strongly discouraging use in subjects whose shock responded well to fluids and pressors. However, this more complex set of recommendations was rejected in favor of the preceding single recommendation (Appendix B).

2. We suggest that the ACTH stimulation test not be used to identify the subset of adults with septic shock who should receive hydrocortisone (grade 2B).

Rationale. Although one study suggested those who did not respond to ACTH with a brisk surge in cortisol (failure to achieve or >9 μg/dl increase in cortisol 30–60 mins after ACTH administration) were more likely to benefit from steroids than those who did respond, the overall trial population appeared to benefit regardless of ACTH result, and the observation of a potential interaction between steroid use and ACTH test was not statistically significant (101). Furthermore, there was no evidence of this distinction between responders and nonresponders in a recent multicenter trial (104). Commonly used cortisol immunoassays measure total cortisol (protein-bound and free) while free cortisol is the pertinent measurement. The relationship between free and total cortisol varies with serum protein concentration. When compared with a reference method (mass spectrometry), cortisol immunoassays may over- or underestimate the actual cortisol level, affecting the assignment of patients to responders or nonresponders (105).
Although the clinical significance is not clear, it is now recognized that etomidate, when used for induction for intubation, will suppress the hypothalamic-pituitary-adrenal axis (106).

3. We suggest that patients with septic shock should not receive dexamethasone if hydrocortisone is available (grade 2B).

**Rationale.** Although often proposed for use until an ACTH stimulation test can be administered, we no longer suggest an ACTH test in this clinical situation (see the preceding point 3). Furthermore, dexamethasone can lead to immediate and prolonged suppression of the hypothalamic-pituitary-adrenal axis after administration (107).

4. We suggest the daily addition of oral fludrocortisone (50 μg) if hydrocortisone is not available and the steroid that is substituted has no significant mineralocorticoid activity. Fludrocortisone is considered optional if hydrocortisone is used (grade 2C).

**Rationale.** One study added 50 μg of fludrocortisone orally (101). Since hydrocortisone has intrinsic mineralocorticoid activity, there is controversy as to whether fludrocortisone should be added.

5. We suggest that clinicians wean the patient from steroid therapy when vasopressors are no longer required (grade 2D).

**Rationale.** There has been no comparative study between a fixed-duration and clinically guided regimen or between tapering and abrupt cessation of steroids. Three RCTs used a fixed-duration protocol for treatment (101, 103, 104), and in two RCTs, therapy was decreased after shock resolution (102, 108). In four RCTs steroids were tapered over several days (102–104, 108), and in two RCTs (101, 109) steroids were withdrawn abruptly. One crossover study showed hemodynamic and immunologic rebound effects after abrupt cessation of corticosteroids (110). It remains uncertain whether outcome is affected by tapering of steroids.

6. We recommend that doses of corticosteroids comparable to >300 mg of hydrocortisone daily not be used in severe sepsis or septic shock for the purpose of treating septic shock (grade 1A).

**Rationale.** Two randomized prospective clinical trials and a meta-analyses concluded that for therapy of severe sepsis or septic shock, high-dose corticosteroid therapy is ineffective or harmful (111–113). Reasons to maintain higher doses of corticosteroid for medical conditions other than septic shock may exist.

7. We recommend that corticosteroids not be administered for the treatment of sepsis in the absence of shock. There is, however, no contraindication to continuing maintenance steroid therapy or to using stress-dose steroids if the patient’s endocrine or corticosteroid administration history warrants (grade 1D).

**Rationale.** No studies exist that specifically target severe sepsis in the absence of shock and offer support for use of stress doses of steroids in this patient population. Steroids may be indicated in the presence of a history of steroid therapy or adrenal dysfunction. A recent preliminary study of stress-dose level steroids in community-acquired pneumonia is encouraging but needs confirmation (114).

I. Recombinant Human Activated Protein C (rhAPC)

1. We suggest that adult patients with sepsis-induced organ dysfunction associated with a clinical assessment of high risk of death, most of whom will have Acute Physiology and Chronic Health Evaluation (APACHE) II ≥25 or multiple organ failure, receive rhAPC if there are no contraindications (grade 2B except for patients within 30 days of surgery, for whom it is grade 2C). Relative contraindications should also be considered in decision making.

2. We recommend that adult patients with severe sepsis and low risk of death, most of whom will have APACHE II <20 or one organ failure, do not receive rhAPC (grade 1A).

**Rationale.** The evidence concerning use of rhAPC in adults is primarily based on two RCTs: PROWESS (1,690 adult patients, stopped early for efficacy) (115) and ADDRESS (stopped early for futility) (116). Additional safety information comes from an open-label observational study, ENHANCE (117). The ENHANCE trial also suggested that early administration of rhAPC was associated with better outcomes.

PROWESS involved 1,690 patients and documented 6.1% in absolute total mortality reduction with a relative risk reduction of 19.4%, 95% confidence interval 6.6–30.5%, and number needed to treat 16 (115). Controversy associated with the results focused on a number of subgroup analyses. Subgroup analyses have the potential to mislead due to the absence of an intent to treat, sampling bias, and selection error (118). The analyses suggested increasing absolute and relative risk reduction with greater risk of death using both higher APACHE II scores and greater number of organ failures (119). This led to drug approval for patients with high risk of death (such as APACHE II ≥25) and more than one organ failure in Europe.

The ADDRESS trial involved 2,613 patients judged to have a low risk of death at the time of enrollment. The 28-day mortality rate from all causes was 17% on placebo vs. 18.5% on APC, relative risk 1.08, 95% confidence interval 0.92–1.28 (116). Again, debate focused on subgroup analyses; analyses were restricted to small subgroups of patients with APACHE II score >25 or more than one organ failure, which failed to show benefit. However, these patient groups also had a lower mortality than in PROWESS.

Relative risk reduction of death was numerically lower in the subgroup of patients with recent surgery (n = 502) in the PROWESS trial (30.7% placebo vs. 27.8% APC) (119) when compared with the overall study population (30.8% placebo vs. 24.7% APC) (115). In the ADDRESS trial, patients with recent surgery and single organ dysfunction who received APC had significantly higher 28-day mortality rates (20.7% vs. 14.1%, p = .03, n = 635) (116).

Serious adverse events did not differ in the studies (115–117) with the exception of serious bleeding, which occurred more often in the patients treated with APC: 2% vs. 3.5% (PROWESS; p = .06) (115); 2.2% vs. 3.9% (ADDRESS; p < .01) (116); 6.5% (ENHANCE, open label) (117). The pediatric trial and implications are discussed in the pediatric consideration section of this article. (Appendix C provides absolute contraindications to use of rhAPC and prescribing information for relative contraindications.)

Intracranial hemorrhage (ICH) occurred in the PROWESS trial in 0.1% (placebo) and 0.2% (APC) (not significant) (106); in the ADDRESS trial 0.4% (placebo) vs. 0.5% (APC) (not significant) (116); and in ENHANCE 1.5% (108). Registry studies of rhAPC report higher bleeding rates than randomized controlled trials, suggesting that the risk of bleeding in actual practice may be greater.
than reported in PROWESS and AD-RESS (120, 121).

The two RCTs in adult patients were methodologically strong and precise and provided direct evidence regarding death rates. The conclusions are limited, however, by inconsistency that is not adequately resolved by subgroup analyses (thus the designation of moderate-quality evidence). Results, however, consistently fail to show benefit for the subgroup of patients at lower risk of death and consistently show increases in serious bleeding. The RCT in pediatric severe sepsis failed to show benefit and has no important limitations. Thus, for low-risk and pediatric patients, we rate the evidence as high quality.

For adult use there is probable mortality reduction in patients with clinical assessment of high risk of death, most of whom will have APACHE II ≥25 or multiple organ failure. There is likely no benefit in patients with low risk of death, most of whom will have APACHE II ≤20 or single organ dysfunction. The effects in patients with more than one organ failure but APACHE II ≤25 are unclear, and in that circumstance one may use clinical assessment of the risk of death and number of organ failures to support decision. There is a certain increased risk of bleeding with administration of rhAPC, which may be higher in surgical patients and in the context of invasive procedures. Decision on utilization depends on assessing likelihood of mortality reduction vs. increases in bleeding and cost. (Appendix D provides the nominal committee vote on recommendation for rhAPC.) A European regulatory mandated RCT of rhAPC vs. placebo in patients with septic shock is now ongoing (122).

J. Blood Product Administration

1. Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, cyanotic heart disease, or lactic acidosis (see recommendations for initial resuscitation), we recommend that red blood cell transfusion occur when hemoglobin decreases to <7.0 g/dL (<70 g/L) to target a hemoglobin of 7.0–9.0 g/dL (70–90 g/L) in adults (grade 1B).

Rationale. Although the optimum hemoglobin for patients with severe sepsis has not been specifically investigated, the Transfusion Requirements in Critical Care trial suggested that a hemoglobin of 7–9 g/dL (70–90 g/L) when compared with 10–12 g/dL (100–200 g/L) was not associated with increased mortality in adults (123). Red blood cell transfusion in septic patients increases oxygen delivery but does not usually increase oxygen consumption (124–126). This transfusion threshold of 7 g/dL (70 g/L) contrasts with the early goal-directed resuscitation protocol that uses a target hematocrit of 30% in patients with low ScvO2 (measured in superior vena cava) during the first 6 hrs of resuscitation of septic shock.

2. We recommend that erythropoietin not be used as a specific treatment of anemia associated with severe sepsis but may be used when septic patients have other accepted reasons for administration of erythropoietin, such as renal failure-induced compromise of red blood cell production (grade 1B).

Rationale. No specific information regarding erythropoietin use in septic patients is available, but clinical trials in critically ill patients show some decrease in red cell transfusion requirement with no effect on clinical outcome (127, 128). The effect of erythropoietin in severe sepsis and septic shock would not be expected to be more beneficial than in other critical conditions. Patients with severe sepsis and septic shock may have coexisting conditions that do warrant use of erythropoietin.

3. We suggest that fresh frozen plasma not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (grade 2D).

Rationale. Although clinical studies have not assessed the impact of transfusion of fresh frozen plasma on outcomes in critically ill patients, professional organizations have recommended fresh frozen plasma for coagulopathy when there is a documented deficiency of coagulation factors (increased prothrombin time, international normalized ratio, or partial thromboplastin time) and the presence of active bleeding or before surgical or invasive procedures (129–131). In addition, transfusion of fresh frozen plasma in nonbleeding patients with mild abnormalities of prothrombin time usually fails to correct the prothrombin time (132). There are no studies to suggest that correction of more severe coagulation abnormalities benefits patients who are not bleeding.

4. We recommend against antithrombin administration for the treatment of severe sepsis and septic shock (grade 1B).

Rationale. A phase III clinical trial of high-dose antithrombin did not demonstrate any beneficial effect on 28-day all-cause mortality in adults with severe sepsis and septic shock. High-dose antithrombin was associated with an increased risk of bleeding when administered with heparin (133). Although a post hoc subgroup analysis of patients with severe sepsis and high risk of death showed better survival in patients receiving antithrombin, antithrombin cannot be recommended until further clinical trials are performed (134).

5. In patients with severe sepsis, we suggest that platelets be administered when counts are <5000/mm³ (5 × 10⁹/L) regardless of apparent bleeding. Platelet transfusion may be considered when counts are 5000–30,000/mm³ (5–30 × 10⁹/L) and there is a significant risk of bleeding. Higher platelet counts (≥50,000/mm³ [50 × 10⁹/L]) are typically required for surgery or invasive procedures (grade 2D).

Rationale. Guidelines for transfusion of platelets are derived from consensus opinion and experience in patients undergoing chemotherapy. Recommendations take into account the etiology of thrombocytopenia, platelet dysfunction, risk of bleeding, and presence of concomitant disorders (129, 131).

II. SUPPORTIVE THERAPY OF SEVERE SEPSIS

A. Mechanical Ventilation of Sepsis-Induced Acute Lung Injury (ALI)/Acute Respiratory Distress Syndrome (ARDS)

1. We recommend that clinicians target a tidal volume of 6 mL/kg (predicted) body weight in patients with ALI/ARDS (grade 1B).

2. We recommend that plateau pressures be measured in patients with ALI/ARDS and that the initial upper limit goal for plateau pressures in a passively inflated patient be ≤30 cm H₂O. Chest wall compliance should be considered in the assessment of plateau pressure (grade 1C).
Rationale. Over the past 10 yrs, several multicenter randomized trials have been performed to evaluate the effects of limiting inspiratory pressure through moderation of tidal volume (135–139). These studies showed differing results that may have been caused by differences between airway pressures in the treatment and control groups (135, 140). The largest trial of a volume- and pressure-limited strategy showed a 9% decrease of all-cause mortality in patients with ALI or ARDS ventilated with tidal volumes of 6 mL/kg of predicted body weight (PBW), as opposed to 12 mL/kg, and aiming for a plateau pressure ≤30 cm H2O (135). The use of lung-protective strategies for patients with ALI is supported by clinical trials and has been widely accepted, but the precise choice of tidal volume for an individual patient with ALI may require adjustment for such factors as the plateau pressure achieved, the level of positive end-expiratory pressure chosen, the compliance of the thoracoabdominal compartment, and the vigor of the patient’s breathing effort. Some clinicians believe it may be safe to ventilate with tidal volumes >6 mL/kg PBW as long as the plateau pressure can be maintained ≤30 cm H2O (141, 142). The validity of this ceiling value will depend on breathing effort, as those who are actively inspiring generate higher transalveolar pressures for a given plateau pressure than those who are passively inflated. Conversely, patients with very stiff chest walls may require plateau pressures >30 cm H2O to meet vital clinical objectives. One retrospective study suggested that tidal volumes should be lowered even with plateau pressures ≤30 cm H2O (143). An additional observational study suggested that knowledge of the plateau pressures was associated with lower plateau pressures; however, in that trial plateau pressure was not independently associated with mortality rates across a wide range of plateau pressures that bracketed 30 cm H2O (144). The largest clinical trial employing a lung-protective strategy coupled limited pressure with limited tidal volumes to demonstrate a mortality benefit (135).

High tidal volumes that are coupled with high plateau pressures should be avoided in ALI/ARDS. Clinicians should use as a starting point the objective of reducing tidal volume over 1–2 hrs from its initial value toward the goal of a “low” tidal volume (≤6 mL/kg PBW) achieved in conjunction with an end-inspiratory plateau pressure ≤30 cm H2O. If plateau pressure remains >30 after reduction of tidal volume to 6 mL/kg PBW, tidal volume should be reduced further to as low as 4 mL/kg PBW. (Appendix E provides ARDSNet ventilator management and formulas to calculate predicted body weight.)

No single mode of ventilation (pressure control, volume control, airway pressure release ventilation, high-frequency ventilation) has been consistently shown advantageous when compared with any other that respects the same principles of lung protection.

3. We recommend that hypercapnia (allowing PICO₂ to increase above its premorbid baseline, so-called permissive hypercapnia) be allowed in patients with ALI/ARDS if needed to minimize plateau pressures and tidal volumes (grade 1C).

Rationale. An acutely elevated PICO₂ may have physiologic consequences that include vasodilation as well as an increased heart rate, blood pressure, and cardiac output. Allowing modest hypercapnia in conjunction with limiting tidal volume and minute ventilation has been demonstrated to be safe in small, nonrandomized series (145, 146). Patients treated in larger trials that have the goal of limiting tidal volumes and airway pressures have demonstrated improved outcomes, but permissive hypercapnia was not a primary treatment goal in these studies (135). The use of hypercapnia is limited in patients with preexisting metabolic acidosis and is contraindicated in patients with increased intracranial pressure. Sodium bicarbonate or tromethamine (THAM) infusion may be considered in selected patients to facilitate use of permissive hypercapnia (147, 148).

4. We recommend that positive end-expiratory pressure (PEEP) be set so as to avoid extensive lung collapse at end-expiration (grade 1C).

Rationale. Raising PEEP in ALI/ARDS keeps lung units open to participate in gas exchange. This will increase PICO₂ when PEEP is applied through either an endotracheal tube or a face mask (149–151). In animal experiments, avoidance of end-expiratory alveolar collapse helps minimize ventilator-induced lung injury when relatively high plateau pressures are in use. One large multicenter trial of the protocol-driven use of higher PEEP in conjunction with low tidal volumes did not show benefit or harm when compared with lower PEEP levels (152). Neither the control nor experimental group in that study, however, was clearly exposed to hazardous plateau pressures. A recent multicenter Spanish trial compared a high PEEP, low-moderate tidal volume approach to one that used conventional tidal volumes and the least PEEP achieving adequate oxygenation. A marked survival advantage favored the former approach in high-acuity patients with ARDS (153). Two options are recommended for PEEP titration. One option is to titrate PEEP (and tidal volume) according to bedside measurements of thoracopulmonary compliance with the objective of obtaining the best compliance, reflecting a favorable balance of lung recruitment and overdistension (154). The second option is to titrate PEEP based on severity of oxygenation deficit and guided by the PICO₂ required to maintain adequate oxygenation (135) (Appendix D). Whichever the indicator—compliance or oxygenation—recruiting maneuvers are reasonable to employ in the process of PEEP selection. Blood pressure and oxygenation should be monitored and recruitment discontinued if deterioration in these variables is observed. A PEEP >5 cm H₂O is usually required to avoid lung collapse (155).

5. We suggest prone positioning in ARDS patients requiring potentially injurious levels of FICO₂ or plateau pressure who are not at high risk for adverse consequences of positional changes in facilities that have experience with such practices (grade 2C).

Rationale. Several small studies and one larger study have shown that a majority of patients with ALI/ARDS respond to the prone position with improved oxygenation (156–159). One large multicenter trial of prone positioning for approximately 7 hrs/day did not show improvement in mortality rates in patients with ALI/ARDS; however, a post hoc analysis suggested improvement in those patients with the most severe hypoxemia by PICO₂/FICO₂ ratio, in those exposed to high tidal volumes, and in those who improved CO₂ exchange as a result of proning (159). A second large trial of prone positioning, conducted for an average of approximately 8 hrs/day for 4 days in adults with hypoxemic respiratory failure of low-moderate acuity, confirmed improvement in oxygenation but also failed to show a survival advantage (160). However, a randomized study that extended the length of time for
pronating each day to a mean of 17 hrs for a mean of 10 days supported benefit of proning, with randomization to supine position an independent risk factor for mortality by multivariate analysis (161). Prone positioning may be associated with potentially life-threatening complications, including accidental dislodgment of the endotracheal tube and central venous catheters, but these complications can usually be avoided with proper precautions.

6a. Unless contraindicated, we recommend that mechanically ventilated patients be maintained with the head of the bed elevated to limit aspiration risk and to prevent the development of ventilator-associated pneumonia (grade 1B).

6b. We suggest that the head of bed be elevated approximately 30–45° (grade 2C).

Rationale. The semirecumbent position has been demonstrated to decrease the incidence of ventilator-associated pneumonia (VAP) (162). Enteral feeding increased the risk of developing VAP; 50% of the patients who were fed enterally in the supine position developed VAP (163). However, the bed position was only monitored once a day, and patients who did not achieve the desired bed elevation were not included in the analysis (163). A recent study did not show a difference in incidence of VAP between patients maintained in supine and semirecumbent positions (164). In this study, patients in the semirecumbent position did not consistently achieve the desired head of the bed elevation, and the head of bed elevation in the supine group approached that of the semirecumbent group by day 7 (164). When necessary, patients may be laid flat for procedures, hemodynamic measurements, and during episodes of hypotension. Patients should not be fed enterally with the head of the bed at 0°.

7. We suggest that noninvasive mask ventilation (NIV) only be considered in that minority of ALI/ARDS patients with mild-moderate hypoxic respiratory failure (responsive to relatively low levels of pressure support and PEEP) with stable hemodynamics who can be made comfortable and are easily arousable; who are able to protect the airway and spontaneously clear the airway of secretions; and who are anticipated to recover rapidly from the precipitating insult. A low threshold for airway intubation should be maintained (grade 2B).

Rationale. Obviating the need for airway intubation confers multiple advantages: better communication, lower incidence of infection, reduced requirements for sedation. Two RCTs demonstrate improved outcome with the use of NIV when it can be employed successfully (162, 165). Unfortunately, only a small percentage of patients with life-threatening hypoxemia can be managed in this way.

8. We recommend that a weaning protocol be in place and that mechanically ventilated patients with severe sepsis undergo spontaneous breathing trials regularly to evaluate the ability to discontinue mechanical ventilation when they satisfy the following criteria: a) They are arousable; b) they are hemodynamically stable (without vasopressor agents); c) they have no new potentially serious conditions; d) they have low ventilatory and end-expiratory pressure requirements; and e) their FiO₂ requirements could be safely delivered with a face mask or nasal cannula. If the spontaneous breathing trial is successful, consideration should be given for extubation (Appendix E). Spontaneous breathing trial options include a low level of pressure support, continuous positive airway pressure (~5 cm H₂O), or a T-piece (grade 1A).

Rationale. Recent studies demonstrate that daily spontaneous breathing trials in appropriately selected patients reduce the duration of mechanical ventilation (166–169). Successful completion of spontaneous breathing trials leads to a high likelihood of successful discontinuation of mechanical ventilation.

9. We recommend against the routine use of the pulmonary artery catheter for patients with ALI/ARDS (grade 1A).

Rationale. While insertion of a pulmonary artery catheter may provide useful information on a patient’s volume status and cardiac function, potential benefits of such information may be confounded by differences in interpretation of results (170–172), lack of correlation of pulmonary artery occlusion pressures with clinical response (173), and absence of a proven strategy to use catheter results to improve patient outcomes (174). Two multicenter randomized trials, one in patients with shock or acute lung injury (175) and one in patients with acute lung injury (176), failed to show benefit with the routine use of pulmonary artery catheters in patients with acute lung injury. In addition, other studies in different types of critically ill patients have failed to show definitive benefit with routine use of the pulmonary artery catheter (177–179). Well-selected patients remain appropriate candidates for pulmonary artery catheter insertion when the answers to important management decisions depend on information only obtainable from direct measurements made within the pulmonary artery.

10. To decrease days of mechanical ventilation and ICU length of stay we recommend a conservative fluid strategy for patients with established acute lung injury who do not have evidence of tissue hypoperfusion (grade 1C).

Rationale. Mechanisms for the development of pulmonary edema in patients with acute lung injury include increased capillary permeability, increased hydrostatic pressure, and decreased oncotic pressure (180, 181). Small prospective studies in patients with critical illness and acute lung injury have suggested that less weight gain is associated with improved oxygenation (182) and fewer days of mechanical ventilation (183, 184). Use of a fluid-conservative strategy directed at minimizing fluid infusion and weight gain in patients with acute lung injury based on either a central venous catheter or a pulmonary artery catheter along with clinical variables to guide treatment strategies led to fewer days of mechanical ventilation and reduced length of ICU stay without altering the incidence of renal failure or mortality rates (185). Of note, this strategy was only used in patients with established acute lung injury, some of whom had shock present. Active attempts to reduce fluid volume were conducted only during periods free from shock.

B. Sedation, Analgesia, and Neuromuscular Blockade in Sepsis

1. We recommend sedation protocols with a sedation goal when sedation of critically ill mechanically ventilated patients with sepsis is required (grade 1B).

Rationale. A growing body of evidence indicates that the use of protocols for
sedation of critically ill ventilated patients can reduce the duration of mechanical ventilation and ICU and hospital length of stay (186–188). A randomized, controlled clinical trial found that protocol use reduced duration of mechanical ventilation, lengths of stay, and tracheostomy rates (186).

A report describing the implementation of protocols, including sedation and analgesia, using a short-cycle improvement methodology in the management of critically ill patients demonstrated a decrease in the cost per patient-day and a decrease of ICU length of stay (187). Furthermore, a prospective before-and-after study on the implementation of a sedation protocol demonstrated enhanced quality of sedation with reduced drug costs. Although this protocol also may have contributed to a longer duration of mechanical ventilation, ICU discharge was not delayed (188). Despite the lack of evidence regarding the use of subjective methods of evaluation of sedation in septic patients, the use of a sedation goal has been shown to decrease the duration of mechanical ventilation in critically ill patients (186). Several subjective sedation scales have been described in the medical literature. Currently, however, there is not a clearly superior sedation evaluation methodology against which these sedation scales can be evaluated (189). The benefits of sedation protocols appear to outweigh the risks.

2. We recommend intermittent bolus sedation or continuous infusion sedation to predetermined end points (e.g., sedation scales) with daily interruption/lightening of continuous infusion sedation with awakening and retitration if necessary for sedation administration to septic mechanically ventilated patients (grade 1B).

**Rationale.** Although not specifically studied in patients with sepsis, the administration of intermittent sedation, daily interruption, and retitration or systemic titration to a predefined end point have been demonstrated to decrease the duration of mechanical ventilation (186, 189, 190). Patients receiving neuromuscular blocking agents (NMBAs) must be individually assessed regarding discontinuation of sedative drugs because neuromuscular blocking drugs must also be discontinued in that situation. The use of intermittent vs. continuous methods for the delivery of sedation in critically ill patients has been examined. An observational study of mechanically ventilated patients showed that patients receiving continuous sedation had significantly longer durations of mechanical ventilation and ICU and hospital length of stay (191).

Similarly, a prospective, controlled study in 128 mechanically ventilated adults receiving continuous intravenous sedation demonstrated that a daily interruption in the continuous sedative infusion until the patient was awake decreased the duration of mechanical ventilation and ICU length of stay (192). Although the patients did receive continuous sedative infusions in this study, the daily interruption and awakening allowed for titration of sedation, in effect making the dosing intermittent. Systematic (protocolized) titration to a predefined end point has also been shown to alter outcome (186). Additionally, a randomized prospective blinded observational study demonstrated that although myocardial ischemia is common in critically ill ventilated patients, daily sedative interruption is not associated with an increased occurrence of myocardial ischemia (193). Thus, the benefits of daily interruption of sedation appear to outweigh the risks. These benefits include potentially shorter duration of mechanical ventilation and ICU stay, better assessment of neurologic function, and reduced costs.

3. We recommend that NMBAs be avoided if possible in the septic patient due to the risk of prolonged neuromuscular blockade following discontinuation. If NMBAs must be maintained, either intermittent bolus as required or continuous infusion with monitoring the depth of blockade with train-of-four monitoring should be used (grade 1B).

**Rationale.** Although NMBAs are often administered to critically ill patients, their role in the ICU is not well defined. No evidence exists that maintaining neuromuscular blockade in this patient population reduces mortality or major morbidity. In addition, no studies have been published that specifically address the use of NMBAs in septic patients.

The most common indication for NMBAs in the ICU is to facilitate mechanical ventilation (194). When appropriately used, NMBAs may improve chest wall compliance, prevent respiratory dysynchrony, and reduce peak airway pressures (195). Muscle paralysis may also reduce oxygen consumption by decreasing the work of breathing and respiratory muscle blood flow (196). However, a randomized, placebo-controlled clinical trial in patients with severe sepsis demonstrated that oxygen delivery, oxygen consumption, and gastric intramucosal pH were not improved during profound neuromuscular blockade (197).

An association between NMBAs and myopathies and neuropathies has been suggested by case studies and prospective observational studies in the critical care population (195, 198–201). The mechanisms by which NMBAs produced or contribute to myopathies and neuropathies in critically ill patients are presently unknown. There appears to be an added association with the concurrent use of NMBAs and steroids. Although no studies exist specific to the septic patient population, it seems clinically prudent based on existing knowledge that NMBAs not be administered unless there is a clear indication for neuromuscular blockade that cannot be safely achieved with appropriate sedation and analgesia (195).

Only one prospective, randomized clinical trial has evaluated peripheral nerve stimulation vs. standard clinical assessment in ICU patients. Rudis et al. (202) randomized 77 critically ill patients requiring neuromuscular blockade in the ICU to receive dosing of vecuronium based on train-of-four stimulation or clinical assessment (control). The peripheral nerve stimulation group received less drug and recovered neuromuscular function and spontaneous ventilation faster than the control group. Nonrandomized observational studies have suggested that peripheral nerve monitoring reduces or has no effect on clinical recovery from NMBAs in the ICU (203, 204).

Benefits to neuromuscular monitoring, including faster recovery of neuromuscular function and shorter intubation times, appear to exist. A potential for cost savings (reduced total dose of NMBAs and shorter intubation times) also may exist, although this has not been studied formally.

**C. Glucose Control**

1. We recommend that following initial stabilization, patients with severe sepsis and hyperglycemia who are admitted to the ICU receive intravenous insulin therapy to reduce blood glucose levels (grade 1B).

2. We suggest use of a validated protocol for insulin dose adjustments and tar-
We recommend that all patients receiving intravenous insulin receive a glucose calorie source and that blood glucose values be monitored every 1–2 hours until glucose values and insulin infusion rates are stable and then every 4 hours thereafter (grade 2C).

4. We recommend that low glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution, as such measurements may overestimate arterial blood or plasma glucose values (grade 1B).

**Rationale.** The consensus on glucose control in severe sepsis was achieved at the first committee meeting and subsequently approved by the entire committee. (Appendix G presents the committee vote.) One large randomized single-center trial in a predominantly cardiac surgical ICU demonstrated a reduction in ICU mortality with intensive intravenous insulin (Leuven protocol) targeting blood glucose to 80–110 mg/dL for all patients, a relative 43% and absolute 3.4% mortality reduction; for those with >5 days in the ICU, a 48% relative and 9.6% absolute mortality reduction (205). A reduction in organ dysfunction and ICU length of stay (LOS) (from a median of 12 to 12 days) was also observed in the subset with ICU LOS >5 days. A second randomized trial of intensive insulin therapy using the Leuven protocol enrolled medical ICU patients with an anticipated ICU LOS of >3 days in three medical ICUs (206). Overall mortality was not reduced, but ICU and hospital LOS were reduced associated with earlier weaning from mechanical ventilation and less acute kidney injury. In patients with a medical ICU LOS >3 days, hospital mortality was reduced with intensive insulin therapy (43% vs. 52.5%; p = .009). However, investigators were unsuccessful in predicting ICU LOS, and 433 patients (36%) had an ICU LOS of <3 days. Furthermore, use of the Leuven protocol in the medical ICU resulted in a nearly three-fold higher rate of hypoglycemia than in the original experience (18% vs. 6.2% of patients) (205, 206).

One large before-and-after observational trial showed a 29% relative and 6.1% absolute reduction in mortality and a 10.8% reduction in median ICU LOS (207). In a subgroup of 53 patients with septic shock, there was an absolute mortality reduction of 27% and a relative reduction of 45% (p = .02). Two additional observational studies reported an association of mean glucose levels with reductions in mortality, polyneuropathy, acute renal failure, nosocomial bactere mia, and number of transfusions, and they suggested that a glucose threshold for improved mortality lies somewhere between 145 and 180 mg/dL (208, 209). However, a large observational study (n = 7,049) suggested that both a lower mean glucose and less variation of blood glucose may be important (210). A meta-analysis of 35 trials on insulin therapy in critically ill patients, including 12 randomized trials, demonstrated a 15% reduction in short-term mortality (relative risk 0.85, 95% confidence interval 0.75–0.97) but did not include any studies of insulin therapy in medical ICUs (211).

Two additional multicenter RCTs of intensive insulin therapy, one focusing on patients with severe sepsis (VISEP) and the second on medical and surgical ICU patients, failed to demonstrate improvement in mortality but are not yet published (212, 213). Both were stopped earlier than planned because of high rates of hypoglycemia and adverse events in the intensive insulin groups. A large RCT that is planned to compare targeting 80–110 mg/dL (4.5–6.0 mmol/L) vs. 140–180 mg/dL (8–10 mmol/L) and recruit >6,000 patients (Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation, or NICE-SUGAR) is ongoing (214).

Several factors may affect the accuracy and reproducibility of point-of-care testing of blood capillary blood glucose, including the type and model of the device used, user expertise, and patient factors, including hematocrit (false elevation with anemia), PaO₂, and drugs (215). One report showed overestimation of arterial plasma glucose values by capillary point-of-care testing sufficient to result in different protocol-specified insulin dose titration. The disagreement between protocol-recommended insulin doses was largest when glucose values were low (216). A recent review of 12 published insulin infusion protocols for critically ill patients showed wide variability in insulin dose recommendations and variable glucose control during simulation (217). This lack of consensus about optimal dosing of intravenous insulin may reflect variability in patient factors (severity of illness, surgical vs. medical settings) or practice patterns (e.g., approaches to feeding, intravenous dextrose) in the environments in which these protocols were developed and tested. Alternatively, some protocols may be more effective than others. This conclusion is supported by the wide variability in hypoglycemia rates reported with protocols (205–207, 212, 213). Thus, the use of a validated and safe intensive insulin protocol is important not only for clinical care but also for the conduct of clinical trials to avoid hypoglycemia, adverse events, and premature termination of these trials before the efficacy signal, if any, can be determined.

The finding of reduced morbidity and mortality within the longer ICU length of stay subsets along with acceptable cost weighed heavily on our recommendation to attempt glucose control after initial stabilization of the patient with hyperglycemia and severe sepsis. However, the mortality benefit and safety of intensive insulin therapy (goal to normalize blood glucose) have been questioned by two recent trials, and we recommend maintaining glucose levels <150 mg/dL until recent and ongoing trials are published or completed. Further study of protocols that have been validated to be safe and effective for controlling blood glucose concentrations and blood glucose variation in the severe sepsis population is needed.

**D. Renal Replacement**

1. We suggest that continuous renal replacement therapies and intermittent hemodialysis are equivalent in patients with severe sepsis and acute renal failure (grade 2B).

2. We suggest the use of continuous therapies to facilitate management of fluid balance in hemodynamically unstable septic patients (grade 2D).

**Rationale.** Although numerous non-randomized studies have reported a non-significant trend toward improved survival using continuous methods (218–225), two meta-analyses (226, 227) reported the absence of significant difference in hospital mortality between patients who receive continuous and intermittent renal replacement therapies. This absence of apparent benefit of one modality over the other persists even when the analysis is restricted to only randomized studies (227). To date, five prospective randomized studies have been published (228–232). Four of them found no significant difference in mortality (229–232). One study found significantly higher
mortality in the continuous treatment group (228), but imbalanced randomization had led to a higher baseline severity of illness in this group. When a multivariable model was used to adjust for severity of illness, no difference in mortality was apparent between the groups (228). Most studies comparing modes of renal replacement in the critically ill have included a small number of patients and some major weaknesses (randomization failure, modifications of therapeutic protocol during the study period, combination of different types of continuous renal replacement therapies, small number of heterogenous groups of patients enrolled). The most recent and largest randomized study (232) enrolled 360 patients and found no significant difference in survival between the two groups. Moreover, there is no current evidence to support the use of continuous therapies in sepsis independent of renal replacement needs.

Concerning the hemodynamic tolerance of each method, no current evidence exists to support a better tolerance with continuous treatments. Only two prospective studies (230, 233) have reported a better hemodynamic tolerance with continuous treatment, with no improvement in regional perfusion (233) and no survival benefit (230). Four other prospective studies did not find any significant difference in mean arterial pressure or drop in systolic pressure between the two methods (229, 231, 232, 234). Concerning fluid balance management, two studies reported a significant improvement in goal achievement with continuous methods (228, 230). In summary, current evidence is insufficient to draw strong conclusions regarding the mode of replacement therapy for acute renal failure in septic patients.

Four randomized controlled trials have addressed whether the dose of continuous renal replacement affects outcomes in patients with acute renal failure (235–238). Three found improved mortality in patients receiving higher doses of renal replacement (235, 237, 238), while one (236) did not. None of these trials was conducted specifically in patients with sepsis. Although the weight of current evidence suggests that higher doses of renal replacement may be associated with improved outcomes, these results may not be easily generalizable. The results of two very large multicenter randomized trials comparing the dose of renal replacement (ATN in the United States and RENAL in Australia and New Zealand) will be available in 2008 and will greatly inform practice.

E. Bicarbonate Therapy

1. We recommend against the use of sodium bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH \( \leq 7.15 \) (grade 1B).

**Rationale.** No evidence supports the use of bicarbonate therapy in the treatment of hypoperfusion-induced lactic acidemia associated with sepsis. Two randomized, blinded, crossover studies that compared equimolar saline and bicarbonate in patients with lactic acidosis failed to reveal any difference in hemodynamic variables or vasopressor requirements (239, 240). The number of patients with pH < 7.15 in these studies was small. Bicarbonate administration has been associated with sodium and fluid overload, an increase in lactate and \( \text{PCO}_2 \), and a decrease in serum ionized calcium, but the relevance of these variables to outcome is uncertain. The effect of bicarbonate administration on hemodynamics and vasopressor requirements at lower pH as well as the effect on clinical outcomes at any pH is unknown. No studies have examined the effect of bicarbonate administration on outcomes.

F. Deep Vein Thrombosis Prophylaxis

1. We recommend that patients with severe sepsis receive deep vein thrombosis (DVT) prophylaxis with either a) low-dose unfractionated heparin (UFH) administered twice or three times per day; or b) daily low-molecular weight heparin (LMWH) unless there are contraindications (i.e., thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage) (grade 1A).

2. We recommend that septic patients who have a contraindication for heparin use receive mechanical prophylactic device, such as graduated compression stockings or intermittent compression devices, unless contraindicated (grade 1A).

3. We suggest that in very high-risk patients, such as those who have severe sepsis and history of DVT, trauma, or orthopedic surgery, a combination of pharmacologic and mechanical therapy be used unless contraindicated or not practical (grade 2C).

4. We suggest that in patients at very high risk, LMWH be used rather than UFH as LMWH is proven superior in other high-risk patients (grade 2C).

**Rationale.** ICU patients are at risk for DVT (241). Significant evidence exists for benefit of DVT prophylaxis in ICU patients in general. No reasons suggest that severe sepsis patients would be different from the general patient population.

Nine randomized placebo-controlled clinical trials of DVT prophylaxis in general populations of acutely ill patients exist (242–250). All nine trials showed reduction in DVT or pulmonary embolism. The prevalence of infection/sepsis was 17% in all studies in which this was ascertainable, with a 52% prevalence of infection/sepsis patients in the study that included ICU patients only. Benefit of DVT prophylaxis is also supported by meta-analyses (251, 252). With that in mind, DVT prophylaxis would appear to have a high grade for quality of evidence (A). Because the risk of administration to the patient is small, the gravity of the potential result of not administering is great, and the cost is low, the grading of the strength of the recommendation is strong. The evidence supports equivalency of LMWH and UFH in general medical populations. A recent meta-analysis comparing UFH twice daily and three times daily demonstrated that UFH three times daily produced better efficacy and twice daily produced less bleeding (253). Practitioners should use underlying risk for VTE and bleeding to individualize choice of twice daily vs. three times daily.

The cost of LMWH is greater and the frequency of injection is less. UFH is preferred over LMWH in patients with moderate to severe renal dysfunction.

Mechanical methods (intermittent compression devices and graduated compression stockings) are recommended when anticoagulation is contraindicated or as an adjunct to anticoagulation in very high-risk patients (254–256). In very high-risk patients, LMWH is preferred over UFH (257–259). Patients receiving heparin should be monitored for development of heparin-induced thrombocytopenia.

G. Stress Ulcer Prophylaxis

1. We recommend that stress ulcer prophylaxis using H2 blocker (grade 1A) or proton pump inhibitor (grade 1B) be given to patients with severe sepsis...
to prevent upper gastrointestinal (GI) bleed. The benefit of prevention of upper GI bleed must be weighed against the potential effect of an increased stomach pH on development of ventilator-associated pneumonia.

**Rationale.** Although no study has been performed specifically in patients with severe sepsis, trials confirming the benefit of stress ulcer prophylaxis in reducing upper GI bleeds in general ICU populations would suggest that 20% to 25% of patients enrolled in these types of trials have sepsis (260–263). This benefit should be applicable to patients with severe sepsis and septic shock. In addition, the conditions shown to benefit from stress ulcer prophylaxis (coagulopathy, mechanical ventilation, hypotension) are frequently present in patients with severe sepsis and septic shock (264, 265).

Although there are individual trials that have not shown benefit from stress ulcer prophylaxis, numerous trials and a meta-analysis show reduction in clinically significant upper GI bleeding, which we consider significant even in the absence of proven mortality benefit (266–269). The benefit of prevention of upper GI bleed must be weighed against the potential effect of increased stomach pH on greater incidence of ventilator-associated pneumonia (270). Those severe sepsis patients with the greatest risk of upper GI bleeding are likely to benefit most from stress ulcer prophylaxis. The rationale for preferring suppression of acid production over sulcrafate was based on the study of 1,200 patients by Cook et al. (271, 272) comparing H2 blockers and sulcrafate and a meta-analysis. Two studies support equivalency between H2 blockers and proton pump inhibitors. One study included very ill ICU patients; the second study was larger and demonstrated noninferiority of omeprazole suspension for clinically significant stress ulcer bleeding (273, 274). No data relating to utility of enteral feeding in stress ulcer prophylaxis exist. Patients should be periodically evaluated for continued need for prophylaxis.

**H. Selective Digestive Tract Decontamination (SDD)**

The guidelines group was evenly split on the issue of SDD, with equal numbers weakly in favor and against recommending the use of SDD (Appendix H). The committee therefore chose not to make a recommendation for the use of SDD specifically in severe sepsis at this time. The final consensus on use of SDD in severe sepsis was achieved at the last nominal committee meeting and subsequently approved by the entire committee (Appendix H provides the committee vote).

**Rationale.** The cumulative conclusion from the literature demonstrates that prophylactic use of SDD (enteral nonabsorbable antimicrobials and short-course intravenous antibiotics) reduces infections, mainly pneumonia, and mortality in the general population of critically ill and trauma patients (275–286) without promoting emergence of resistant Gram-negative bacteria. Post hoc subgroup analyses (287, 288) of two prospective blinded studies (289, 290) suggest that SDD reduces nosocomial (secondary) infections in ICU patients admitted with primary infections (286) and may reduce mortality (288). No studies of SDD specifically focused on patients with severe sepsis or septic shock. The use of SDD in severe sepsis patients would be targeted toward preventing secondary infection. As the main effect of SDD is in preventing ventilator-associated pneumonia (VAP), studies comparing SDD with nonantimicrobial interventions, such as ventilator bundles for reducing VAP, are needed. Further investigation is required to determine the comparative efficacy of these two interventions, separately or in combination. Although studies incorporating enteral vancomycin in the regimen appear to be safe (291–293), concerns persist about the potential for emergence of resistant Gram-positive infections.

**I. Consideration for Limitation of Support**

1. We recommend that antibiotics be administered within 1 hr of the identification of severe sepsis, after appropriate cultures have been obtained (grade 1D).

Early antibiotic therapy is as critical for children with severe sepsis as it is for adults.

**B. Mechanical Ventilation**

No graded recommendations.

Due to low functional residual capacity, young infants and neonates with severe sepsis may require early intubation (300). Drugs used for intubation have important side effects in these patients; for example, concerns have been raised about the safety of using etomidate in children with meningococcal sepsis because of adrenal suppression effect (301). The principles of lung-protective strategies are applied to children as they are to adults.

**C. Fluid Resuscitation**

1. We suggest that initial resuscitation be applied to children as they are to adults.

Due to low functional residual capacity, young infants and neonates with severe sepsis may require early intubation (300). Drugs used for intubation have important side effects in these patients; for example, concerns have been raised about the safety of using etomidate in children with meningococcal sepsis because of adrenal suppression effect (301). The principles of lung-protective strategies are applied to children as they are to adults.
urine output, capillary refill, and level of consciousness (grade 2C).

Intravenous access for fluid resuscitation and inotrope/vasopressor infusion is more difficult to attain in children than in adults. The American Heart Association and the American Academy of Pediatrics have developed pediatric advanced life support guidelines for emergency establishment of intravascular support encouraging early intravascular access (302). On the basis of a number of studies, it is accepted that aggressive fluid resuscitation with crystalloids or colloids is of fundamental importance to survival of septic shock in children (303–308). Three randomized controlled trials compared the use of colloid to crystalloid resuscitation in children with dengue shock (303, 307, 308). No difference in mortality between colloid or crystalloid resuscitation was shown.

Children normally have a lower blood pressure than adults, and fall in blood pressure can be prevented by vasoconstriction and increasing heart rate. Therefore, blood pressure by itself is not a reliable end point for assessing the adequacy of resuscitation. However, once hypotension occurs, cardiovascular collapse may soon follow. Hepatomegaly occurs in children who are fluid overloaded and can be a helpful sign of adequacy of fluid resuscitation. Large fluid deficits typically exist, and initial volume resuscitation usually requires 40–60 mL/kg but can be much higher (304–308). However, the rate of fluid administration should be reduced substantially when there are (clinical) signs of adequate cardiac filling without hemodynamic improvement.

D. Vasopressors/Inotropes (Should Be Used in Volume-Loaded Patients With Fluid Refractory Shock)

1. We suggest dopamine as the first choice of support for the pediatric patient with hypotension refractory to fluid resuscitation (grade 2C).

In the initial resuscitation phase, vasopressor therapy may be required to sustain perfusion pressure, even when hypovolemia has not yet been resolved. Children with severe sepsis can present with low cardiac output and high systemic vascular resistance, high cardiac output and low systemic vascular resistance, or low cardiac output and low systemic vascular resistance shock. At various stages of sepsis or the treatment thereof, a child may move from one hemodynamic state to another. Vasopressor or inotrope therapy should be used according to the clinical state of the child.

Dopamine-refractory shock may reverse with epinephrine or norepinephrine infusion (309).

2. We suggest that patients with low cardiac output and elevated systemic vascular resistance states (cool extremities, prolonged capillary refill, decreased urine output but normal blood pressure following fluid resuscitation) be given dobutamine (grade 2C).

The choice of vasoactive agent is determined by the clinical examination. For the child with a persistent low cardiac output state with high systemic vascular resistance despite fluid resuscitation and inotropic support, vasodilator therapy may reverse shock (310). When pediatric patients remain in a normotensive low cardiac output and high vascular resistance state despite epinephrine and vasodilator therapy, the use of a phosphodiesterase inhibitor may be considered (311–313). In the case of extremely low systemic vascular resistance despite the use of norepinephrine, vasopressin use has been described in a number of case reports. There is no clear evidence for the use of vasopressin in pediatric sepsis (314, 315).

E. Therapeutic End Points

1. We suggest that the therapeutic end points of resuscitation of septic shock be normalization of the heart rate, capillary refill of <2 sec, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output >1 mL·kg⁻¹·hr⁻¹, and normal mental status (290) (grade 2C).

Capillary refill may be less reliable in a cold environment. Other end points that have been widely used in adults and may logically apply to children include decreased lactate and improved base deficit, S\textsubscript{v}CO\textsubscript{2} ≥70% or S\textsubscript{v}VO\textsubscript{2} ≥65%, central venous pressure of 8–12 mm Hg, or other methods to analyze cardiac filling. Optimizing preload optimizes cardiac index. In terms of identifying acceptable cardiac output in children with systemic arterial hypoxemia, such as cyanotic congenital heart disease or severe pulmonary disease, arterial-venous oxygen content difference is a better marker than mixed venous hemoglobin saturation with oxygen. As noted previously, blood pressure by itself is not a reliable end point for resuscitation. If a thermolulation catheter is used, therapeutic end points are cardiac index >3.3 and <6.0 L·min⁻¹·m⁻² with normal coronary perfusion pressure (mean arterial pressure minus central venous pressure) for age (290). Using clinical end points, such as reversal of hypotension and restoration of capillary refill, for initial resuscitation at the community hospital level before transfer to a tertiary center was associated with significantly improved survival rates in children with septic shock (305). Development of a transport system including publicizing to local hospitals and transport with mobile intensive care services significantly decreased the case fatality rate from meningococcal disease in the United Kingdom (316).

F. Approach to Pediatric Septic Shock

Figure 1 shows a flow diagram summarizing an approach to pediatric septic shock (317).

G. Steroids

1. We suggest that hydrocortisone therapy be reserved for use in children with catecholamine resistance and suspected or proven adrenal insufficiency (grade 2C).

Patients at risk for adrenal insufficiency include children with severe septic shock and purpura (318, 319), children who have previously received steroid therapies for chronic illness, and children with pituitary or adrenal abnormalities. Children who have clear risk factors for adrenal insufficiency should be treated with stress-dose steroids (hydrocortisone 50 mg/m²/24 hrs).

Adrenal insufficiency in pediatric severe sepsis is associated with a poor prognosis (320). No strict definitions exist, but absolute adrenal insufficiency in the case of catecholamine-resistant septic shock is assumed at a random total cortisol concentration <18 μg/dL (496 nmol/L). A post 30- or 60-min ACTH stimulation test increase in cortisol of ≤9 μg/dL (248 nmol/L) has been used to define relative adrenal insufficiency. The treatment of relative adrenal insufficiency in children with septic shock is controversial. A retrospective study from a large administrative database recently
reported that the use of any corticosteroids in children with severe sepsis was associated with increased mortality (odds ratio 1.9, 95% confidence interval 1.7–2.2) (321). While steroids may have been given preferentially to more severely ill children, the use of steroids was an independent predictor of mortality in multivariable analysis (321). Given the lack of data in children and potential risk, steroids should not be used in children who do not meet minimal criteria for adrenal insufficiency. A randomized, controlled trial in children with septic shock is very much needed.

**H. Protein C and Activated Protein C**

1. We recommend against the use rhAPC in children (grade 1B).

Protein C concentrations in children reach adult values at the age of 3 yrs. This might indicate that the importance of protein C supplementation either as protein C concentrate or as rhAPC is even greater in young children than in adults (322). There has been one dose-finding, randomized, placebo-controlled study performed using protein C concentrate. This study was not powered to show an effect on mortality rate but did show a positive effect on sepsis-induced coagulation disturbances (323). An RCT of rhAPC in pediatric severe sepsis patients was stopped by recommendation of the Data Monitoring Committee for futility after enrollment of 399 patients: 28-day all cause mortality was 18% placebo group vs. 17% APC group. Major amputations occurred in 3% of the placebo group vs. 2% in the APC group (324). Due to the increased risk of bleeding (7% vs. 6% in the pediatric trial) and lack of proof of efficacy, rhAPC is not recommended for use in children.

**I. DVT Prophylaxis**

1. We suggest the use of DVT prophylaxis in postpubertal children with severe sepsis (grade 2C).

Most DVTs in young children are associated with central venous catheters. Femoral venous catheters are commonly used in children, and central venous catheter-associated DVTs occur in approximately 25% of children with a femoral central venous catheter. Heparin-bonded catheters may decrease the risk of catheter-associated DVT and should be considered for use in children with severe sepsis (325, 326). No data on the efficacy of UFH or LMWH prophylaxis to prevent catheter-related DVT in children in the ICU exist.

**J. Stress Ulcer Prophylaxis**

No graded recommendations. Studies have shown that the rate of clinically important gastrointestinal bleeding in children occurs at rates similar to adults (327, 328). As in adults, coagulopathy and mechanical ventilation are risk factors for clinically important gastrointestinal bleeding. Stress ulcer prophylaxis strategy is commonly used in mechanically ventilated children, usually with H2 blockers. Its effect is not known.

**K. Renal Replacement Therapy**

No graded recommendations.

Continuous veno-venous hemofiltration (CVVH) may be clinically useful in children with anuria/severe oliguria and fluid overload, but no large RCTs have been performed comparing CVVH with intermittent dialysis. A retrospective study of 113 critically ill children reported that children with less fluid overload before CVVH had better survival, especially in those children

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**Figure 1. Approach to pediatric shock.** *Normalization of blood pressure and tissue perfusion; **hypotension, abnormal capillary refill or extremity coolness. PALS, Pediatric Advanced Life Support; PICU, pediatric intensive care unit; CI, cardiac index; ECMO, extracorporeal membrane oxygenation.*

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with dysfunction of three or more organs (329). CVVH or other renal replacement therapy should be instituted in children with anuria/severe oliguria before significant fluid overload occurs.

L. Glycemic Control

No graded recommendations.

In general, infants are at risk for developing hypoglycemia when they depend on intravenous fluids. This means that a glucose intake of 4–6 mg·kg⁻¹·min⁻¹ or maintenance fluid intake with glucose 10%/NaCl-containing solution is advised. Associations have been reported between hyperglycemia and an increased risk of death and longer length of stay (330). A recent retrospective pediatric ICU study reported associations of hyperglycemia, hypoglycemia, and glucose variability with length of stay and mortality rates (331). No studies in pediatric patients (without diabetes mellitus) analyzing the effect of strict glycemic control using insulin exist. In adults, the recommendation is to maintain serum glucose <150 mg/dL. Insulin therapy to avoid long periods of hyperglycemia seems sensible in children as well, but the optimal goal glucose is not known. However, continuous insulin therapy should only be conducted with frequent glucose monitoring in view of the risks for hypoglycemia.

M. Sedation/Analgesia

1. We recommend sedation protocols with a sedation goal when sedation of critically ill mechanically ventilated patients with sepsis is required (grade 1D).

Appropriate sedation and analgesia are the standard of care for children who are mechanically ventilated. Although there are no data supporting any particular drugs or regimens, it should be noted that propofol should not be used for long-term sedation in children because of the reported association with fatal metabolic acidosis (332, 333).

N. Blood Products

No graded recommendations.

The optimal hemoglobin for a critically ill child with severe sepsis is not known. A recent multicenter trial reported similar outcomes in stable critically ill children managed with a transfusion threshold of 7 g/dL compared with those managed with a transfusion threshold of 9.5 g/dL (334). Whether a lower transfusion trigger is safe or appropriate in the initial resuscitation of septic shock has not been determined.

O. Intravenous Immunoglobulin

1. We suggest that immunoglobulin be considered in children with severe sepsis (grade 2C).

Administration of polyclonal intravenous immunoglobulin has been reported to reduce mortality rate and is a promising adjuvant in the treatment of sepsis and septic shock in neonates. A recent randomized controlled study of polyclonal immunoglobulin in pediatric sepsis syndrome patients (n = 100) showed a significant reduction in mortality and LOS and less progress to complications, especially disseminated intravascular coagulation (335).

P. Extracorporeal Membrane Oxygenation (ECMO)

1. We suggest that use of ECMO be limited to refractory pediatric septic shock and/or respiratory failure that cannot be supported by conventional therapies (grade 2C).

ECMO has been used in septic shock in children, but its impact is not clear. Survival from refractory shock or respiratory failure associated with sepsis is 80% in neonates and 50% in children. In one study analyzing 12 patients with meningococcal sepsis in ECMO, eight of the 12 patients survived, with six leading functionally normal lives at a median of 1 yr (range, 4 months to 4 yrs) of follow-up. Children with sepsis on ECMO do not perform worse than children without sepsis at long-term follow-up (336, 337).

Although the pediatric considerations section of this article offers important information to the practicing pediatric clinician for the management of critically ill children with sepsis, the reader is referred to the reference list for more in-depth descriptions of appropriate management of pediatric septic patients.

SUMMARY AND FUTURE DIRECTIONS

Although this document is static, the optimum treatment of severe sepsis and septic shock is a dynamic and evolving process. New interventions will be proven and, as stated in the current recommendations, established interventions may need modification. This publication represents an ongoing process. The Surviving Sepsis Campaign and the consensus committee members are committed to updating the guidelines regularly as new interventions are tested and published.

Although evidence-based recommendations have been published frequently in the medical literature, documentation of impact on patient outcome is limited (338). However, there is growing evidence that protocol implementation associated with education and performance feedback does change clinician behavior and may improve outcomes and reduce costs in severe sepsis (20, 24, 25). Phase III of the Surviving Sepsis Campaign targets the implementation of a core set of the previous recommendations in hospital environments where change in behavior and clinical impact are being measured. The sepsis bundles were developed in collaboration with the Institute of Healthcare Improvement (339). Concurrent or retrospective chart review will identify and track changes in practice and clinical outcome. Software and software support are available at no cost in seven languages, allowing bedside data entry and allowing creation of regular reports for performance feedback. The SSC also offers significant program support and educational materials at no cost to the user (www.survivingsepsis.org).

Engendering evidence-based change in clinical practice through multifaceted strategies while auditing practice and providing feedback to healthcare practitioners is the key to improving outcomes in severe sepsis. Nowhere is this more evident than in the worldwide enthusiasm for phase III of the SSC, a performance improvement program using SSC guideline-based sepsis bundles. Using the guidelines as the basis, the bundles have established a global best practice for the management of critically ill patients with severe sepsis. As of November 2007, nearly 12,000 patients had been entered into the SSC central database, representing efforts of 239 hospitals in 17 countries. Changes in practice and potential effects on survival are being measured.

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REFERENCES

69. Levy B, Bollaeert PE, Charpentier C, et al: Comparison of norepinephrine and dobut- amine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: A prospective, ran-

141. Tobin MJ: Culmination of an era in research
with T-tube or pressure support ventilation. Am J Respir Crit Care Med 1997; 156: 459–463.


severe sepsis and septic shock is associated with an increased rate of hypoglycemia—
Results from a randomized multicenter study (VISEP). Absbr. Infection 2005; 33:
19–20

213. Preiser JC: Intensive glycemic control in med-
surg patients (European Glucotrol trial). Program and abstracts of the Society of Crit-
ical Care Medicine 36th Critical Care Con-
gress, February 17–21, 2007, Orlando, FL

214. Current Controlled Trials: A multi-center, open
label, randomised controlled trial of two target
ranges for glycaemic control in intensive care
unit (ICU) patients. http://controlled-trials.com/
isrctn/trial/ISRCTN04968275/0/04968275.

215. Nichols JH: Bedside testing, glucose moni-
toring, and diabetes management. In: Prin-
ciples of Point of Care Testing. Kost GJ
(Ed). Philadelphia, Lippincott Williams &
Wilkins, 2002

of point-of-care testing for glucose mea-
surement in critically ill adults. Crit Care
Med 2005; 33:2778–2785

Continuous versus intermittent renal re-
placement therapy: A meta-analysis. Inten-
sive Care Med 2002; 28:29–37

Continuous venovenous haemodiafiltration
versus intermittent haemodialysis for acute
renal failure in patients with multiple-
organ dysfunction syndrome: A multicentre
randomised trial. Lancet 2006; 368:379–85

of different doses in continuous venous
hemofiltration on outcomes of acute renal
failure. Nephrol Dial Transplant 2005; 20:
1630–1637

of pulmonary emboli in a respiratory intensive

of deep vein thrombosis in medical patients
26:115–117

222. Gardlund B: Randomized, controlled trial of
low-dose heparin for prevention of fatal pul-
monary embolism in patients with infec-
tious diseases: The Heparin Prophylaxis

223. Kupfer Y, Anwar J, Seneviratne C, et al: Pre-
vention of deep vein thrombosis in elderly
medical in-patients by a low molecular
weight heparin: A randomized double-blind
trial. Haemostasis 1986; 16:159–164

Continuous arteriovenous haemofiltration:
Improved survival in surgical acute renal
failure. Surgery 1986; 100:400–408

225. Kruzzinski K, Irvine-Bird K, Toffelmire EB,
et al: A comparison of continuous arterio-
venous haemofiltration and intermittent he-
modialysis in acute renal failure patients in
intensive care unit. Am Soc Artif Intern Organs
1992; 38:M654–M657

226. Bouman CS, Oudemans-Van Straaten HM,
Tijssen JG, et al: Effects of early high-
volume continuous venovenous hemofiltration
on survival and recovery of renal func-
tion in intensive care patients with acute
renal failure: A prospective, randomized

227. Vinsonneau C, Lang SM, Fischer R: Daily hemo-
dialysis and the outcome of acute renal

of different doses in continuous venous
hemofiltration on outcomes of acute renal
failure: A prospective random-

namics in critically ill patients who have lactic
acidosis: A prospective, controlled clinical

230. Kellum JA, Angus DC, Johnson JP, et al: Con-
tinuous versus intermittent renal re-
placement therapy: A meta-analysis. Inten-
sive Care Med 2002; 28:29–37

Comparison of continuous and intermittent
renal replacement therapy for acute renal

Continuous arteriovenous haemofiltration:
Improved survival in surgical acute renal
failure. Surgery 1986; 100:400–408

randomised clinical trial. Nephrol Dial
Transplant 2001; 16:320–327

of different doses in continuous venous
hemofiltration on outcomes of acute renal
failure: A prospective random-

235. Bouman CS, Oudemans-Van Straaten HM,
Tijssen JG, et al: Effects of early high-
volume continuous venovenous hemofiltration
on survival and recovery of renal func-
tion in intensive care patients with acute
renal failure: A prospective, randomized

236. Van Bommel EH, Bouvy ND, Sob KL, et al:
Acute dialytic support for the critically ill:
Intermittent hemodialysis versus contin-
uous arteriovenous hemodialfiltration. Am J

tent versus continuous renal replacement
therapy for acute renal failure in intensive
care units: Results from a multicenter pro-
spective epidemiological survey. Intensive
Care Med 2002; 28:1411–1417

renal failure in the intensive care unit: A systematic review of the impact of
diabetic modality on mortality and renal re-

239. Mehta RL, McDonald B, Gabbai FB, et al: A
randomized clinical trial of continuous versus
intermittent dialysis for acute renal fail-

namics in critically ill patients who have lactic
acidosis: A prospective, controlled clinical

fects of bicarbonate therapy on hemody-
namics and tissue oxygenation in patients
with lactic acidosis: A prospective, con-
19:1352–1356

duction in mortality in general medical in-
patients by low-dose heparin prophylaxis.

Prevention of pulmonary emboli in a respira-
tory intensive care unit. Chest 1981;
79:647–650

244. Bellch JJ, Lowe DO, Ward AG, et al: Preven-
tion of deep vein thrombosis in medical pa-

tients by low-dose heparin. Scott Med J
1981; 26:115–117

245. Kruzzinski K, Irvine-Bird K, Toffelmire EB,
et al: A comparison of continuous arterio-
venous haemofiltration and intermittent he-
modialysis in acute renal failure patients in
intensive care unit. Am Soc Artif Intern Organs
1993; 38:M778–M781

246. Van Bommel EH, Bouvy ND, Sob KL, et al:
Acute dialytic support for the critically ill:
Intermittent hemodialysis versus contin-
uous arteriovenous hemodialfiltration. Am J

247. Kruzzinski K, Irvine-Bird K, Toffelmire EB,
et al: A comparison of continuous arterio-
venous haemofiltration and intermittent he-
modialysis in acute renal failure patients in
intensive care unit. Am Soc Artif Intern Organs
1993; 38:M778–M781

248. Van Bommel EH, Bouvy ND, Sob KL, et al:
Acute dialytic support for the critically ill:
Intermittent hemodialysis versus contin-
uous arteriovenous hemodialfiltration. Am J

249. Fraisse F, Holzapfel L, Coulard JM, et al: Na-
droparin in the prevention of deep vein
thrombosis in acute decompensated COPD:
The Association of Non-University Affiliated
Intensive Care Specialist Physicians of
France. Am J Respir Crit Care Med 2000;
161:1109–1114

250. Kupfer Y, Anwar J, Seneviratne C, et al: Pro-
phylaxis with subcutaneous heparin sig-
ificantly reduces the incidence of deep ve-
thromboembolitis in the critically ill. Abstr.
Am J Crit Care Med 1999; 159(Sup-
p19

thromboembolism and its prevention in

thrombosis and its prevention in critically ill
adults. Arch Intern Med 2001; 161:
1268–1279


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vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: A metaanalysis. *Chest* 2007; 131:507–516


**APPENDIX A**

**Source Control**

<table>
<thead>
<tr>
<th>Source Control Technique</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drainage</td>
<td>Intra-abdominal abscess Thoracic empyema Septic arthritis</td>
</tr>
<tr>
<td>Debridement</td>
<td>Pyelonephritis, cholangitis Infected pancreatic necrosis Intestinal infarction Mediastinitis</td>
</tr>
<tr>
<td>Device removal</td>
<td>Infected vascular catheter Urinary catheter Infected intrauterine contraceptive device</td>
</tr>
<tr>
<td>Definitive control</td>
<td>Sigmoid resection for diverticulitis Cholecystectomy for gangrenous cholecystitis Amputation for clostridial myonecrosis</td>
</tr>
</tbody>
</table>

**APPENDIX B**

**Steroids**

Considerable difference of opinion existed among committee members as to the best option for the style of the recommendations for steroid use in septic shock. Some committee members argued for two recommendations and pointed to the two distinct patient populations of the French Trial (enrollment early in septic shock and blood pressure unresponsive to vasopressors) and the CORTICUS trial (enrollment allowed up to 72 hrs and did not target patients with blood pressure unresponsive to vasopressin), leading to two distinct results. Furthermore, a single recommendation suggested to some that this approach might lead to excessive use of steroids and increased incidence of superinfections, citing the sepsis and septic shock adverse events in the steroid-treated patients in the CORTICUS trial. Those who argued for one recommendation pointed to problems with two different recommendations that would require the bedside clinician to choose a time point for classification of one or the other as well as a distinct blood pressure cutoff with the potential for the blood pressure to vary over time. In addition, there are inadequate data to provide standardization of how much fluids and vasopressors should be in place to call the blood pressure unresponsive or poorly responsive. These members also pointed to the fact that the increased superinfection/sepsis/septic shock adverse events in CORTICUS are contrary to the results of other stress-dose steroid trials, such as early ARDS (lower incidence of infections) (341), late ARDS (decreased development of septic shock), and community-acquired pneumonia (decreased development of septic shock) (114). Based on GRADE adjudication guidelines, a secret ballot vote was conducted to resolve the issue.

The two options put to vote were:

**Two-Recommendation Option**

1. We suggest that intravenous hydrocortisone be given to adult septic shock patients if blood pressure is inadequate with appropriate fluid resuscitation and vasopressor therapy (grade 2B).

2. We suggest intravenous hydrocortisone not be given to adult septic shock patients if blood pressure is adequate with appropriate fluid resuscitation and vasopressor therapy (grade 2B).

**One-Recommendation Option**

1. We suggest that intravenous hydrocortisone be given only to adult septic shock patients if blood pressure is adequate with appropriate fluid resuscitation and is contraindicated in patients with recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma. Trauma with an increased risk of life-threatening bleeding. Presence of an epidural catheter. Intracranial neoplasm or mass lesion or evidence of cerebral herniation. Known hypersensitivity to rhAPC or any component of the product.


**APPENDIX C**

**Contraindications to Use of Recombinant Human Activated Protein C (rhAPC)**

rhAPC increases the risk of bleeding and is contraindicated in patients with the following clinical situations in which bleeding could be associated with a high risk of death or significant morbidity:

- Active internal bleeding
- Recent (within 3 months) hemorrhagic stroke
- Recent (within 2 months) intracranial or intraspinal surgery, or severe head trauma
- Trauma with an increased risk of life-threatening bleeding
- Presence of an epidural catheter
- Intracranial neoplasm or mass lesion or evidence of cerebral herniation
- Known hypersensitivity to rhAPC or any component of the product.


**APPENDIX D**

**Recombinant Activated Protein C Nominal Group Vote**

- Strong for use, 6
- Weak for use, 15
- Neutral, 1
- Weak for not using, 0
- Strong for not using, 0

**APPENDIX E**

**ARDSNet Ventilator Management**

Assist control mode—volume ventilation (96)
Reduce tidal volume to 6 mL/kg lean body weight
Keep inspiratory plateau pressure (Pplat) ≤30 cm H2O
Reduce tidal volume as low as 4 mL/kg predicted body weight to limit Pplat
Maintain arterial oxygen saturation/pulse oximetry oxyhemoglobin saturation (SpO2) 88% to 95%
Anticipated PEEP settings at various FIO2 requirements
FIO2 0.3, 0.4, 0.4, 0.5, 0.6, 0.7, 0.7, 0.8, 0.9, 0.9, 0.9, 1.0
PEEP 5, 5, 8, 8, 10, 10, 10, 12, 14, 14, 14, 16, 18, 20–24

Predicted Body Weight Calculation
Male—50 + 2.3 (height [inches] – 60) or 50 + 0.91 (height [cm] – 152.4)
Female—45.5 + 2.3 (height [inches] – 60) or 45.5 + 0.91 (height [cm] – 152.4)

APPENDIX G

Glycemic Control Committee Vote
Glycemic control—90%
Total votes = 51
Agree—34
Too conservative, but accept—4
Too liberal, but accept—8
Disapprove, too conservative—0
Disapprove, too liberal—5
Disapprove, other—0

APPENDIX F

Use of spontaneous breathing trial in weaning ARDS patients

Original illness resolving; no new illness
Off vasopressors and continuous sedatives
Cough during suctioning
\( \text{PaO}_2/\text{FIO}_2 > 200 \)
\( \text{PEEP} \leq 5 \text{ cm H}_2\text{O} \)
Minute ventilation < 15 L min
Frequency/tidal volume (F/TV) ratio \( \leq 105 \) during two-minute spontaneous breathing trial

Spontaneous Breathing Trial * (30 to 120 minutes)

- Respiratory rate > 35
- Oxygen saturation < 90
- Pulse > 140/min or change \( \geq 20\% \)
- SBP > 180 mm Hg or < 90 mm Hg
- Agitation, diaphoresis, or anxiety
- F/TV ratio > 105

Note: Achieving any of these criteria for a sustained period at any time during the trial represents a weaning failure and the need to return to maintenance MV.

PEEP, positive end-expiratory pressure; F/TV, frequency/tidal volume; SBP, systolic blood pressure; MV, mechanical ventilation

*Options include T-Piece, continuous positive airway pressure 5 cm H_2O or low level (5-10 cm H_2O typically based on ET tube size) pressure support ventilation (167-170)
Appendix H. Selective Digestive Decontamination Nominal Group Vote

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Strong for Use</th>
<th>Weak for Use</th>
<th>Neutral</th>
<th>Weak for Not Using</th>
<th>Strong for Not Using</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic and oral alone</td>
<td>—</td>
<td>9</td>
<td>4</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Systemic alone</td>
<td>—</td>
<td>2</td>
<td>7</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

APPENDIX 1

2008 SSC Guidelines Committee


a American Association of Critical-Care Nurses; b Japanese Association for Acute Medicine; c European Society of Intensive Care Medicine; d Surgical Infection Society; e Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Group; f Japanese Society of Intensive Care Medicine; g Society of Critical Care Medicine; h American College of Emergency Physicians; i Canadian Critical Care Society; j European Society of Clinical Microbiology and Infectious Diseases; k German Sepsis Society; l Latin American Sepsis Institute; m American College of Chest Physicians; n International Sepsis Forum; o European Respiratory Society.

APPENDIX J

Author Disclosure Information 2006–2007

Dr. Dellinger has consulted for AstraZeneca, Talecris, and B Braun. He has received honoraria from Eli Lilly (2), Brahms (2), INO Therapeutics (1), Pulsion (1), and bioMerieux (1). He has also received grant support from AstraZeneca and Artisan.

Dr. Levy has received honoraria from Eli Lilly and Edwards Lifesciences. He has also received grant support from Philips Medical Systems, Edwards Life-sciences, Philips Medical Systems, Novartis, Biosite, and Eisai.

Dr. Carlet has consulted for Forrest, SmithKline, Roche Diagnostics, Takeda, Pfizer, Spectral Diagnostics, Eisai, and Leo-Pharma. He has also received honoraria from Spectral Diagnostics.

Dr. Ranieri has served on the advisory board for Maquet and received support for a sponsored trial from Eli Lilly. He has also received grant support from Tyco, Draeger, and Hamilton.

Dr. Ramsay has consulted for Edwards Lifesciences and Respiromics.

Dr. Sevransky has not disclosed any potential conflicts of interest.

Dr. Thompson has consulted for Eli Lilly, Abbott, and AstraZeneca. He has also received grant support from the NIH for a study on computerized glucose control.

Dr. Townsend has not disclosed any potential conflicts of interest.

Dr. Vender has consulted and received honoraria from Eli Lilly.

Dr. Zimmerman has not disclosed any potential conflicts of interest.

Dr. Vincent has consulted for AstraZeneca, Biosite, bioMerieux, Edwards Lifesciences, Eli Lilly, Eisai, Ferring, GlaxoSmithKline, Intercell, Merck, Novartis, NovoNordisk, Organon, Pfizer, Philips Medical Systems, Roche Diagnostics, Spectral Diagnostics, Takeda, and Wyeth-Lederle. He has also received honoraria from Eli Lilly, Edwards Lifesciences, Eisai, GlaxoSmithKline, Novartis, NovoNordisk, and Pfizer.
A better understanding of the inflammatory, procoagulant, and immunosuppressive aspects of sepsis has contributed to rational therapeutic plans from which several important themes emerge. First, rapid diagnosis (within the first 6 hours) and expeditious treatment are critical, since early, goal-directed therapy can be very effective. Second, multiple approaches are necessary in the treatment of sepsis. Third, it is important to select patients for each given therapy with great care, because the efficacy of treatment — as well as the likelihood and type of adverse results — will vary, depending on the patient.

**The Spectrum of Sepsis**

Nomenclature is important when it helps us understand the pathophysiology of a disease. This is true for sepsis, since nomenclature has informed the design of randomized, controlled trials and, ultimately, the prognosis of sepsis. Sepsis is defined as suspected or proven infection plus a systemic inflammatory response syndrome (e.g., fever, tachycardia, tachypnea, and leukocytosis). Severe sepsis is defined as sepsis with organ dysfunction (hypotension, hypoxemia, oliguria, metabolic acidosis, thrombocytopenia, or obtundation). Septic shock is defined as severe sepsis with hypotension, despite adequate fluid resuscitation. Septic shock and multiorgan dysfunction are the most common causes of death in patients with sepsis. The mortality rates associated with severe sepsis and septic shock are 25 to 30% and 40 to 70%, respectively.

There are approximately 750,000 cases of sepsis a year in the United States, and the frequency is increasing, given an aging population with increasing numbers of patients infected with treatment-resistant organisms, patients with compromised immune systems, and patients who undergo prolonged, high-risk surgery.

**Pathophysiology**

Sepsis is the culmination of complex interactions between the infecting microorganism and the host immune, inflammatory, and coagulation responses. The rationale for the use of therapeutic targets in sepsis has arisen from concepts of pathogenesis (Table 1).

Both the host responses and the characteristics of the infecting organism influence the outcome of sepsis. Sepsis with organ dysfunction occurs primarily when host responses to infection are inadequate. In addition, sepsis often progresses when the host cannot contain the primary infection, a problem most often related to characteristics of the microorganism, such as a high burden of infection and the presence of superantigens and other virulence factors, resistance to opsonization and phagocytosis, and antibiotic resistance.
INNATE IMMUNITY AND INFLAMMATION IN EARLY SEPSIS

Host defenses can be categorized according to innate and adaptive immune system responses. The innate immune system responds rapidly by means of pattern-recognition receptors (e.g., toll-like receptors [TLRs]) that interact with highly conserved molecules present in microorganisms. For example, TLR-2 recognizes a peptidoglycan of gram-positive bacteria, whereas TLR-4 recognizes a lipopolysaccharide of gram-negative bacteria. Binding of TLRs to epitopes on microorganisms stimulates intracellular signaling, increasing transcription of proinflammatory molecules such as tumor necrosis factor α (TNF-α) and interleukin-1β, as well as antiinflammatory cytokines such as interleukin-10.

Microorganisms stimulate specific humoral and cell-mediated adaptive immune responses that amplify innate immunity. B cells release immunoglobulins that bind to microorganisms, facilitating their delivery by antigen-presenting cells to natural killer cells and neutrophils that can kill the microorganisms. T-cell subgroups are modified in sepsis. Helper (CD4+) T cells can be categorized as type 1 helper (Th1) or type 2 helper (Th2) cells. Th1 cells generally secrete proinflammatory cytokines such as TNF-α and interleukin-1β, and Th2 cells secrete antiinflammatory cytokines such as interleukin-4 and interleukin-10, depending on the infecting organism, the burden of infection, and other factors.

DISTURBANCE OF PROCOAGULANT–ANTICOAGULANT BALANCE

Another important aspect of sepsis is the alteration of the procoagulant–anticoagulant balance, with an increase in procoagulant factors and a decrease in anticoagulant factors. Lipopolysaccharide stimulates endothelial cells to up-regulate tiss-

---

**Table 1. Pathways and Mediators of Sepsis, Potential Treatments, and Results of Randomized, Controlled Trials (RCTs).**

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Mediators</th>
<th>Treatment</th>
<th>Results of RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innate immunity</td>
<td>Lipopolysaccharide (endotoxin)</td>
<td>Antilipopolysaccharide</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>TLR-2, TLR-4</td>
<td>TLR agonists and antagonists</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Monocytes, macrophages</td>
<td>GM-CSF, interferon gamma</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td>G-CSF</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Adaptive immunity</td>
<td>B cells (plasma cells and immunoglobulins)</td>
<td>IgG</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>CD4+ T cells (Th1, Th2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proinflammatory pathway</td>
<td>TNF-α</td>
<td>Anti–TNF-α</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Interleukin-1β</td>
<td>Interleukin-1–receptor antagonist</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Interleukin-6</td>
<td>Interleukin-6 antagonist</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Prostaglandins, leukotrienes</td>
<td>Ibuprofen, high-dose corticosteroids</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Bradykinin</td>
<td>Bradykinin antagonist</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Platelet-activating factor</td>
<td>Platelet-activating factor acetyl hydrolase</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Proteases (e.g., elastase)</td>
<td>Elastase inhibitor</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Oxidants</td>
<td>Antioxidants (e.g., N-acetylcysteine)</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Nitric oxide</td>
<td>Nitric oxide synthase inhibitor</td>
<td>Negative</td>
</tr>
</tbody>
</table>
Drug therapy

Table 1. (Continued.)

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Mediators</th>
<th>Treatment</th>
<th>Results of RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procoagulant pathway</td>
<td>Decreased protein C</td>
<td>Activated protein C&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Decreased protein S</td>
<td>Protein S&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Decreased antithrombin III</td>
<td>Antithrombin III&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Decreased tissue factor–pathway inhibitor</td>
<td>Tissue factor–pathway inhibitor&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Increased tissue factor</td>
<td>Tissue factor antagonist&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Increased plasminogen-activator inhibitor 1</td>
<td>Tissue plasminogen activator 1</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Antiinflammatory</td>
<td>Interleukin-10</td>
<td>Interleukin-10&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>TNF-α receptors</td>
<td>TNF-α receptors&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Negative</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Hypoxia-inducing factor 1, vascular endothelial growth factor</td>
<td>Early, goal-directed therapy&lt;sup&gt;2&lt;/sup&gt;, Supernormal oxygen delivery, Erythropoietin&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Positive, Negative, Not evaluated</td>
</tr>
<tr>
<td>Immunosuppression or apoptosis</td>
<td>Lymphocyte apoptosis</td>
<td>Anticaspases&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Apoptosis of intestinal epithelial cells</td>
<td>Anticaspases&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Not evaluated</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Adrenal insufficiency</td>
<td>Corticosteroids&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Mixed results&lt;sup&gt;¶&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Vasopressin deficiency</td>
<td>Vasopressin&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Not evaluated</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
<td>Intensive insulin therapy&lt;sup&gt;30,31&lt;/sup&gt;</td>
<td>Not evaluated&lt;sup&gt;∥&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* TSST denotes staphylococcal toxic shock syndrome toxin 1, GM-CSF granulocyte–macrophage colony-stimulating factor, G-CSF granulocyte colony-stimulating factor, TH1 type 1 helper T cells, and TH2 type 2 helper T cells. Organism features means components of bacteria that are toxic to the host and that are potential therapeutic targets in sepsis.
† G-CSF is effective in patients with sepsis who have profound neutropenia.<sup>12</sup>
‡ Elastase inhibitor was ineffective in a phase 2 trial involving patients with acute lung injury.
§ Interleukin-10 was ineffective in a phase 2 trial involving patients with acute lung injury.
¶ Corticosteroids had no effect on overall 28-day mortality but decreased mortality in a subgroup of patients with no response to corticotropin (see text for details). Additional trials of corticosteroids in patients with septic shock are in progress.
∥ Intensive insulin therapy decreased the mortality rate among critically ill surgical patients but has not yet been evaluated in patients with sepsis.

Sepsis lowers levels of protein C, protein S, antithrombin III, and tissue factor–pathway inhibitor. Lipopolysaccharide and TNF-α decrease the synthesis of thrombomodulin and endothelial protein C receptor, impairing the activation of protein C, and increase the synthesis of plasminogen-activator inhibitor 1, thus impairing fibrinolysis.

Key to an understanding of sepsis is the recognition that the proinflammatory and procoagulant responses can be amplified by secondary ischemia (shock) and hypoxia (lung injury) through the release of tissue factor and plasminogen-activator inhibitor 1.<sup>43</sup>

**IMMUNOSUPPRESSION AND APOPTOSIS IN LATE SEPSIS**

Host immunosuppression has long been considered a factor in late death in patients with sepsis,<sup>44</sup> since the sequelae of anergy, lymphopenia,<sup>45</sup> hypothermia, and nosocomial infection all appear to be involved.<sup>46</sup> When stimulated with lipopolysaccharide ex vivo, monocytes from patients with sepsis express lower amounts of proinflammatory cytokines than do monocytes from healthy subjects, possibly indicating relative immunosuppression.<sup>47</sup>
Multiorgan dysfunction in sepsis may be caused, in part, by a shift to an antiinflammatory phenotype and by apoptosis of key immune, epithelial, and endothelial cells. In sepsis, activated helper T cells evolve from a Th1 phenotype, producing proinflammatory cytokines, to a Th2 phenotype, producing antiinflammatory cytokines. In addition, apoptosis of circulating and tissue lymphocytes (B cells and CD4+ T cells) contributes to immunosuppression. Apoptosis is initiated by proinflammatory cytokines, activated B and T cells, and circulating glucocorticoid levels, all of which are increased in sepsis. Increased levels of TNF-α and lipopolysaccharide during sepsis may also induce apoptosis of lung and intestinal epithelial cells.

**SEPSIS AND WIDESPREAD ORGAN DYSFUNCTION**

The altered signaling pathways in sepsis ultimately lead to tissue injury and multiorgan dysfunction. For example, cardiovascular dysfunction is characterized by circulatory shock and the redistribution of blood flow, with decreased vascular resistance, hypovolemia, and decreased myocardial contractility associated with increased levels of nitric oxide, TNF-α, interleukin-6, and other media-
Tors. Respiratory dysfunction is characterized by increased microvascular permeability, leading to acute lung injury. Renal dysfunction in sepsis, as discussed recently by Schrier and Wang, may be profound, contributing to morbidity and mortality.

TREATMENT ACCORDING TO THE EARLY AND LATER STAGES OF SEPSIS

Consensus guidelines for the management of sepsis have recently been published. The following therapeutic plan, informed by such guidelines, considers emergency care for the early stage of sepsis (0 to 6 hours) and treatment for patients in later stages who require critical care.

Figure 2. Procoagulant Response in Sepsis.

Sepsis initiates coagulation by activating endothelium to increase the expression of tissue factor. Activation of the coagulation cascade, and especially factors Va and VIIIa, leads to the formation of thrombin-α, which converts fibrinogen to fibrin. Fibrin binds to platelets, which in turn adhere to endothelial cells, forming microvascular thrombi. Microvascular thrombi amplify injury through the release of mediators and by microvascular obstruction, which causes distal ischemia and tissue hypoxia. Normally, natural anticoagulants (protein C and protein S), antithrombin III, and tissue factor–pathway inhibitor (TFPI) dampen coagulation, enhance fibrinolysis, and remove microthrombi. Thrombin-α binds to thrombomodulin on endothelial cells, which dramatically increases activation of protein C to activated protein C. Protein C forms a complex with its cofactor protein S. Activated protein C proteolytically inactivates factors Va and VIIIa and decreases the synthesis of plasminogen-activator inhibitor 1 (PAI-1). In contrast, sepsis increases the synthesis of PAI-1. Sepsis also decreases the levels of protein C, protein S, antithrombin III, and TFPI. Lipopolysaccharide and tumor necrosis factor α (TNF-α) decrease the synthesis of thrombomodulin and endothelial protein C receptor (EPCR), thus decreasing the activation of protein C. Sepsis further disrupts the protein C pathway because sepsis also decreases the expression of EPCR, which amplifies the deleterious effects of the sepsis-induced decrease in levels of protein C. Lipopolysaccharide and TNF-α also increase PAI-1 levels so that fibrinolysis is inhibited. The clinical consequences of the changes in coagulation caused by sepsis are increased levels of markers of disseminated intravascular coagulation and widespread organ dysfunction. t-PA denotes tissue plasminogen activator.

EARLY, GOAL-DIRECTED THERAPY

The cornerstone of emergency management of sepsis is early, goal-directed therapy, plus lung-protective ventilation, broad-spectrum antibiotics, and possibly activated protein C (Fig. 3 and Table 2). Rivers and colleagues conducted a randomized, controlled trial in which patients with severe sepsis and septic shock received early, goal-directed, protocol-guided therapy during the first 6 hours after enrollment or the usual therapy. In the group receiving early, goal-directed therapy, central venous oxygen saturation was monitored continuously with the use of a central venous catheter. The level of central venous oxygen saturation served to trigger further interventions recommended in the...
**Clinical Evaluation**

- Assess airway
- Assess breathing
- Respiratory rate
- Signs of respiratory distress
- Pulse oximetry
- Circulation
- Heart rate, blood pressure
- Skin
- Jugular venous pressure

**Laboratory Evaluation**

- Measure
  - Arterial blood gas values
  - Arterial lactate

- Identify SIRS
  - Complete blood count
  - White-cell differential

**Management**

- Assess airway intubation for high-risk patients
- Assess breathing
- Administer oxygen
- Maintain tidal volume of 6 ml/kg of IBW if mechanical ventilation needed
- Assess circulation (follow protocol of Rivers et al.)
- Fluids, vasopressors, inotropes, transfusion
- MAP >65 mm Hg
- CVP 8–12 mm Hg
- Hematocrit >30%
- ScvO2 >70%

- Identify source of infection
  - Respiratory (pneumonia, empyema)
  - Abdominal (peritonitis, abscess, cholangitis)
  - Skin (cellulitis, fasciitis)
  - Pyelonephritis
  - CNS (meningitis, brain abscess)

- Identify source of infection
  - Culture and sensitivity, Gram’s staining of blood, sputum, urine; perhaps other fluids and CSF
  - Chest radiography
  - Ultrasonography, CT

- Assess organ function
  - CNS
  - LOC, focal signs
  - Renal function
  - Urinary output

- Assess organ function
  - Renal function
  - Electrolytes, BUN, creatinine
  - Hepatic function
  - Bilirubin, AST, alkaline phosphatase
  - Coagulation
  - INR, PTT, platelets

- Control the source of sepsis
  - Abscess, empyema
  - Cholecystitis, cholangitis
  - Urinary obstruction
  - Peritonitis, bowel infarct
  - Necrotizing fasciitis
  - Gas gangrene

**Figure 3. Therapeutic Plan Based on the Early and Later Stages of Sepsis.**

In the author’s approach, emergency management should focus on simultaneous evaluation and resuscitation. Early diagnosis is critical because of the efficacy of early, goal-directed therapy in the first 6 hours. Critical care management requires frequent, thorough reassessment and supportive measures for organ dysfunction. Assessment focuses on refinement of the antibiotic regimen, control of the source of sepsis, and evaluation for resolution of the signs of the systemic inflammatory response syndrome (SIRS). Supportive measures for organ dysfunction include ongoing cardiovascular support, continued use of lung-protective mechanical ventilation with a tidal volume of 6 ml per kilogram of ideal body weight (IBW), and activated protein C (APC) in appropriate patients for 96 hours. The use of vasopressin, intensive insulin, and corticosteroids is controversial. Critical care management of sepsis also requires attention to new problems such as immunosuppression, nosocomial infection, and persistent ARDS. PaCO2 denotes partial pressure of arterial carbon dioxide, CNS central nervous system, LOC level of consciousness, CSF cerebrospinal fluid, CT computed tomography, BUN blood urea nitrogen, AST serum aspartate aminotransferase, INR international normalized ratio, PTT partial-thromboplastin time, MAP mean arterial pressure, CVP central venous pressure, and ScvO2 central venous oxygen saturation.
Table 2. Results of Positive Randomized, Controlled Trials.*  

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Patients</th>
<th>Intervention Group</th>
<th>Control Group</th>
<th>Mortality Rate†</th>
<th>NNT‡</th>
<th>Level of Evidence</th>
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<tr>
<td>%</td>
<td></td>
<td></td>
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<td>28-day</td>
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<td></td>
<td></td>
<td></td>
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<td>Patients with acute lung injury and ARDS§</td>
<td>861</td>
<td>Low tidal volume (6 ml/kg of ideal body weight)</td>
<td>High tidal volume (12 ml/kg of ideal body weight)</td>
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<td>31</td>
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<tr>
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<td>817</td>
<td>Activated protein C</td>
<td>Placebo</td>
<td>31</td>
<td>44</td>
<td>I</td>
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<td>Patients in septic shock**</td>
<td>299</td>
<td>Hydrocortisone + fludrocortisone</td>
<td>Placebo</td>
<td>55</td>
<td>61</td>
<td>I–II∥</td>
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<tr>
<td>Patients in septic shock††</td>
<td>229</td>
<td>Hydrocortisone + fludrocortisone</td>
<td>Placebo</td>
<td>53</td>
<td>63</td>
<td>I–II∥</td>
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<td>Patients with acute respiratory distress syndrome†</td>
<td>1548</td>
<td>Intensive insulin (to maintain glucose level of 4.4–6.1 mmol/liter)</td>
<td>Usual insulin (to maintain glucose level of 10–11.1 mmol/liter)</td>
<td>4.6</td>
<td>8</td>
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<tr>
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<td>817</td>
<td>Activated protein C</td>
<td>Placebo</td>
<td>31</td>
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<td>4.6</td>
<td>8</td>
<td>I</td>
</tr>
</tbody>
</table>

* The inclusion criteria were as follows: for the ARDS Clinical Trials Network, a ratio of the partial pressure of arterial oxygen to the forced inspiratory volume in 1 second of less than 300, pulmonary infiltrates, mechanical ventilation, and no congestive heart failure; for Rivers et al., sepsis plus either increased lactate levels (severe sepsis) or hypotension (septic shock); for Bernard et al., severe sepsis; for Annane et al., vasopressor-dependent septic shock, mechanical ventilation, oliguria, and increased lactate levels. One study by Van den Berghe et al. involved patients in the surgical ICU.  
† The 28-day mortality rate is shown for all groups except those studied by Van den Berghe, for which the intensive care unit (ICU) or in-hospital mortality rate is shown.  
‡ Values are the number needed to treat (NNT) to save one life.  
§ Many of the patients had sepsis.  
¶ An increased risk of death was defined by an Acute Physiology and Chronic Health Evaluation (APACHE) II score of at least 25.  
** The patients had no response to a corticotropin stimulation test.  
†† This trial is included in the table because its results contrast with those of a similar positive trial involving patients in the surgical ICU.  
∥ The 28-day mortality rate is shown for all groups except those studied by Van den Berghe, for which the ICU or in-hospital mortality rate is shown.  
‡‡ The level of evidence for the overall trial is I, but only for the subgroup of patients with no response to corticotropin stimulation is II.  
§§ The level of evidence for the overall trial is I, but only for the subgroup of patients with no response to corticotropin stimulation is II.  
** The level of evidence for the overall trial is I, but only for the subgroup of patients with no response to corticotropin stimulation is II.  
∥∥ The level of evidence for the overall trial is I, but only for the subgroup of patients with no response to corticotropin stimulation is II.  
‡‡‡ The level of evidence for the overall trial is I, but only for the subgroup of patients with no response to corticotropin stimulation is II.  
††† The level of evidence for the overall trial is I, but only for the subgroup of patients with no response to corticotropin stimulation is II.
protocol. Crystalloids were administered to maintain central venous pressure at 8 to 12 mm Hg. Vasopressors were added if the mean arterial pressure was less than 65 mm Hg; if central venous oxygen saturation was less than 70%, erythrocytes were transfused to maintain a hematocrit of more than 30%. Dobutamine was added if the central venous pressure, mean arterial pressure, and hematocrit were optimized yet venous oxygen saturation remained below 70%. Early, goal-directed therapy in that study decreased mortality at 28 and 60 days as well as the duration of hospitalization. Patients in the early, goal-directed therapy group received more fluids, transfusions, and dobutamine in the first 6 hours, whereas control subjects received more fluids and more control subjects received vasopressors, transfusion, and mechanical ventilation for a period of 7 to 72 hours. The mechanisms of the benefit of early, goal-directed therapy are unknown but may include reversal of tissue hypoxia and a decrease in inflammation and coagulation defects.59

VENTILATION
Once early, goal-directed therapy has been initiated, lung-protective ventilation should be considered. Acute lung injury often complicates sepsis, and lung-protective ventilation — meaning the use of relatively low tidal volumes — is thus another important aspect of management. Furthermore, lung-protective ventilation decreases mortality4 and is beneficial in septic acute lung injury.60 Excessive tidal volume and repeated opening and closing of alveoli during mechanical ventilation cause lung injury. Lung-protective mechanical ventilation, with the use of a tidal volume of 6 ml per kilogram of ideal body weight (or as low as 4 ml per kilogram if the plateau pressure exceeds 30 cm H₂O) as compared with 12 ml per kilogram of ideal body weight (calculated in men as 50 + 0.91 [height in centimeters – 152.4] and in women as 45.5 + 0.91 [height in centimeters – 152.4]) has been shown to decrease the mortality rate (from 40 to 31%), to lessen organ dysfunction, and to lower levels of cytokines.61 Positive end-expiratory pressure (PEEP) decreases oxygen requirements; however, there is no significant difference in mortality between patients treated with the usual PEEP regimen of the Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network2 and those treated with higher PEEP levels.62 Patients receiving ventilation require appropriate but not excessive sedation, given the risks of prolonged ventilation and nosocomial pneumonia.63 Titrating sedation64 and interrupting sedation daily until patients are awake65 decrease the risks associated with sedation. Neuromuscular blocking agents should be avoided to reduce the risk of prolonged neuromuscular dysfunction.65

BROAD-SPECTRUM ANTIBIOTICS
Because the site of infection and responsible microorganisms are usually not known initially in a patient with sepsis, cultures should be obtained and intravenous broad-spectrum antibiotics administered expeditiously while the host immune status is ascertained. The rising prevalence of fungi, gram-positive bacteria, highly resistant gram-negative bacilli, methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococcus, and penicillin-resistant pneumococcus,66 as well as local patterns of antibiotic susceptibility, should be considered in the choice of antibiotics. Observational studies indicate that outcomes of sepsis67 and septic shock68 are worse if the causative microorganisms are not sensitive to the initial antibiotic regimen.

ACTIVATED PROTEIN C
Once goal-directed therapy, lung-protective ventilation, and antibiotic therapy have been initiated, the use of activated protein C should be considered. Therapy with activated protein C (24 μg per kilogram per hour for 96 hours) has been reported to decrease mortality5 and to ameliorate organ dysfunction69 in patients with severe sepsis. Activated protein C is approved for administration to patients with severe sepsis and an increased risk of death (as indicated by an Acute Physiology and Chronic Health Evaluation [APACHE] II score greater than or equal to 25 or dysfunction of two or more organs); such patients have had the greatest benefit — an absolute decrease in the mortality rate of 13% — from this therapy.69 However, a subsequent trial of activated protein C in patients with a low risk of death (the Administration of Drotocogin Alfa [Activated] in Early Stage Severe Sepsis [ADDRESS] trial) was halted after an interim analysis for lack of effectiveness.70 This outcome suggests that activated protein C is not beneficial in low-risk patients. The effectiveness of activated protein C does not appear to depend on the site
of infection or the infecting microorganism, possibly because all bacteria and fungi decrease protein C levels.71

Recent trauma or surgery (within 12 hours), active hemorrhage, concurrent therapeutic anticoagulation, thrombocytopenia (defined as a platelet count of less than 30,000 per cubic millimeter), and recent stroke were exclusion criteria for safety reasons in the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial of activated protein C.5 In that trial, there was a trend toward a higher rate of serious bleeding (defined as bleeding requiring the transfusion of 3 U of packed red cells over a period of 2 days or intracranial hemorrhage) among patients receiving activated protein C than among patients in the placebo group (3.5% vs. 2%, \( P=0.06 \), especially during infusion of the activated protein C (2.4% vs. 1%).5 Intracranial hemorrhage occurred in two patients who received activated protein C and in one who received placebo.5 In the Extended Evaluation of Recombinant Human Activated Protein C United States (ENHANCE U.S.) trial, intracranial hemorrhage occurred in 0.6% of patients given activated protein C.72 Meningitis and severe thrombocytopenia may be risk factors for intracranial hemorrhage.69

When the data are examined together, activated protein C would appear to be cost-effective for patients with severe sepsis and a high risk of death, with the cost per quality-adjusted year of life gained ranging from $24,48473 to $27,400,74 which is similar to the costs of therapies such as organ transplantation75 and drug-eluting stents.76

The mechanism of action by which activated protein C improves the clinical outcome is unknown. Activated protein C was shown to increase protein C and decrease markers of thrombin generation (e.g., D-dimer, a marker of disseminated intravascular coagulation) in one study.77 Although activated protein C prevents hypotension, it has little effect on coagulation in a human intravenous endotoxin model of sepsis,78 suggesting that modulation of coagulation may not be the primary mechanism underlying the cardiovascular benefit. Other anticoagulant therapies have included antithrombin III73 and tissue factor–pathway inhibitor,24 yet only activated protein C was effective, perhaps because of its complex antinflammatory,79 antiapoptotic, and anticoagulant35 actions.

### Treatment of Anemia in Sepsis

Anemia is common in sepsis80 in part because mediators of sepsis (TNF-α and interleukin-1β) decrease the expression of the erythropoietin gene and protein.81 Although treatment with recombinant human erythropoietin decreases transfusion requirements,56 its use in randomized, controlled trials failed to increase survival. Erythropoietin takes days to weeks to induce red-cell production and thus may not be effective.

Two trials used different transfusion strategies in different stages of sepsis.2,80 Rivers et al.2 used a hematocrit of 30% as a threshold for transfusion in early sepsis as part of a 6-hour protocol. Transfusion was associated with an improved outcome. Hebert et al. compared hemoglobin values of 70 and 100 g per liter as a threshold for transfusion later in the course of critical care.80 Patients were expected to stay in the intensive care unit (ICU) for more than 3 days, and two transfusion strategies were compared during their entire ICU stay. There was no significant difference in mortality between patients who received transfusion on the basis of higher hemoglobin levels (100 to 120 g per liter) and those who did so on the basis of lower levels (70 to 90 g per liter).80

Transfusion is worthwhile if needed during the emergency stage of sepsis; Rivers et al. observed a marked decrease in mortality when transfusion was provided early.2 Hebert et al. suggest maintaining hemoglobin levels at 70 to 90 g per liter after the first 6 hours to decrease transfusion requirements.80 (Because the protocol of Rivers et al. did not extend beyond 6 hours, it is not known whether a higher transfusion threshold would be useful after 6 hours.)

### Corticosteroids in Patients Who Require Critical Care

Although corticosteroids have been considered for the management of sepsis for decades, randomized, controlled trials suggest that an early, short course (48 hours) of high-dose corticosteroids does not improve survival in severe sepsis.82,83 Because adrenal insufficiency is being reconsidered as part of septic shock, there has been renewed interest in therapy with corticosteroids, with a focus on timing, dose, and duration. Several controversies over their use persist, however. First, the concept of adrenal insufficiency in sepsis is controversial.
Second, only two (of five) small randomized, controlled trials have shown that corticosteroid therapy (low-dose hydrocortisone) decreases the need for vasopressor support in patients with sepsis. Third, only one adequately powered trial reported a survival benefit of such treatment in patients who had no response to a corticotropin-stimulation test.

Annane and colleagues evaluated oliguric patients with vasopressor-dependent septic shock who required ventilation. Patients underwent a 250-μg corticotrophin-stimulation test and were classified as having adrenal insufficiency (no response) when the serum total cortisol level rose by less than 10 μg per deciliter. Patients were then randomly assigned to receive placebo or hydrocortisone plus fludrocortisone for 7 days. Corticosteroids significantly improved survival both in the overall cohort and in the prospectively defined subgroup of patients who had no response to corticotropin; however, over a 28-day period, the difference in mortality was not significant (P=0.09). Patients without a response to corticotropin who received corticosteroids had significantly lower mortality than patients who received placebo. Subgroup analyses provide inadequate evidence for a change in therapy, however, given the many examples of therapies that were purportedly successful according to subgroup analysis but were subsequently shown not to be useful in adequately powered, randomized, controlled trials.

Observational studies offer no data that indicate how patients respond to corticosteroids and thus provide limited guidance as compared with randomized, controlled trials. Marik and Zaloga reported that 95% of patients in septic shock had serum cortisol levels of less than 15 μg per deciliter; another group have stated that during septic shock, cortisol levels of less than 15 μg per deciliter should be used as an indicator of relative adrenal insufficiency.

A recent study of serum free cortisol has added further complexity to the diagnosis of adrenal insufficiency in the critically ill. Serum total cortisol reflects both cortisol bound to protein (cortisol-binding globulin and albumin) and free cortisol (the physiologically active form). Patients with sepsis who have low serum albumin levels may have low serum total cortisol levels (falsely suggesting adrenal insufficiency), despite normal or even increased serum free cortisol levels (indicating truly normal cortisol levels) — a relevant point because hypoalbuminemia is common in sepsis. Indeed, Hamrahian and colleagues reported that critically ill patients with hypoalbuminemia had corticotropin-stimulated serum total cortisol levels that were subnormal but corticotropin-stimulated serum free cortisol levels that were higher than normal. When survivors were reassessed 6 to 10 weeks after hospital discharge, their corticotropin-stimulated serum free cortisol levels had declined to the normal range. Therefore, random and corticotropin-stimulated serum total cortisol levels must be interpreted cautiously in patients with sepsis and hypoalbuminemia. Annane and colleagues measured serum total cortisol to identify patients who would have a response to corticotropin. Further studies of corticotropin-induced changes in serum free cortisol levels during septic shock are needed.

Corticosteroids have also been considered for the treatment of persistent ARDS. Although mortality was lower among patients treated with methylprednisolone than among those given placebo in one small trial, patients in the placebo group crossed over to the methylprednisolone group. A randomized, placebo-controlled trial of methylprednisolone for persistent ARDS, conducted by the ARDS Network, showed no difference between groups in 60-day mortality.

Corticosteroids can have important adverse effects in patients with sepsis, including neuro-myopathy and hyperglycemia, as well as decreased numbers of lymphocytes, immunosuppression, and loss of intestinal epithelial cells through apoptosis. The immunosuppression that accompanies corticosteroid use in sepsis may lead to nosocomial infection and impaired wound healing.

Thus, the use of corticosteroids, as well as the diagnosis of adrenal insufficiency, in patients with sepsis is complex. Randomized, controlled trials indicate that early use of short-course, high-dose corticosteroids does not improve survival in severe sepsis.

EVALUATION AND CONTROL OF THE SOURCE OF SEPSIS

Successful management of the critical care stage of sepsis requires support of affected organs (Fig. 3). If a causative organism is identified (20% of patients with sepsis have negative cultures), then the antibiotic regimen should be narrowed to decrease the likelihood of the emergence of resis-
tant organisms. A thorough search for the source of sepsis may require imaging (e.g., ultrasonography or computed tomography) and drainage (e.g., thoracentesis).

**VASOPRESSIN**

Vasopressin deficiency and down-regulation of vasopressin receptors are common in septic shock. Vasopressin dilates renal, pulmonary, cerebral, and coronary arteries. Intravenous infusion of low-dose vasopressin (0.03 to 0.04 U per minute) has been reported to increase blood pressure, urinary output, and creatinine clearance, permitting a dramatic decrease in vasopressor therapy. However, vasopressin therapy may cause intestinal ischemia, decreased cardiac output, skin necrosis, and even cardiac arrest, especially at doses greater than 0.04 U per minute. Virtually all studies of vasopressin in patients with sepsis have been small and have involved acute infusion (an infusion provided in 1 to a few hours as compared with 1 or more days). Inhibition of nitric oxide synthase with NG-methyl-L-arginine hydrochloride also decreased vasopressor use but significantly increased mortality from septic shock, suggesting that apparent short-term improvement in surrogate markers such as hemodynamics can be associated with an increased risk of death.

**HYPERGLYCEMIA AND INTENSIVE INSULIN THERAPY**

Hyperglycemia and insulin resistance are virtually universal in sepsis. Hyperglycemia is potentially harmful because it acts as a procoagulant, induces apoptosis, impairs neutrophil function, increases the risk of infection, impairs wound healing, and is associated with an increased risk of death. Conversely, insulin can control hyperglycemia and improve lipid levels; insulin has anti-inflammatory, anticoagulant, and antiapoptotic actions.

The appropriate target glucose range and insulin dose in patients with sepsis are unknown, because no randomized, controlled trial has been conducted to specifically study patients with sepsis. The results of a randomized, controlled trial of insulin in surgical patients suggested that intensive insulin therapy might be of benefit in sepsis. Van den Berghe and colleagues randomly assigned critically ill surgical patients to receive insulin infusion to maintain blood glucose levels at 4.4 to 6.1 mmol per liter (intensive insulin dose) or 10.0 to 11.1 mmol per liter (conventional insulin dose). The study involved intubated surgical patients (primarily those undergoing cardiac surgery), not patients with sepsis. Intensive insulin therapy decreased the rate of death in the ICU, especially among patients who remained in the ICU for at least 5 days. Intensive insulin therapy also significantly decreased the prevalence of prolonged ventilatory support, renal-replacement therapy, peripheral neuromuscular dysfunction, and bacteremia. A recent trial by the same group in medical ICU patients showed no significant difference in mortality with the use of intensive or conventional insulin therapy; intensive insulin therapy decreased the rate of death among patients who remained in the ICU for 3 or more days but increased the rate of death among patients whose stay lasted fewer than 3 days.

The mechanisms by which intensive insulin therapy benefits surgical patients are not known, but they could include the induction of euglycemia, the benefits related to increased insulin levels, or both. Intensive insulin therapy is antiinflammatory and protects endothelial and mitochondrial function.

Although intensive insulin therapy appears to be beneficial in surgical patients, the lack of efficacy in medical patients, combined with the risks involved for patients who have a short stay in the ICU, indicates clinical equipoise and the need for a randomized, controlled trial in patients with sepsis.

**RENAL DYSFUNCTION AND DIALYSIS**

Acute renal failure is associated with increased morbidity, mortality, and resource use in patients with sepsis. Continuous renal-replacement therapy decreases the incidence of adverse biomarkers, but there is little evidence that it changes outcomes. Low-dose dopamine (2 to 4 μg per kilogram per minute) neither decreases the need for renal support nor improves survival and, consequently, is not recommended. Lactic acidosis is a common complication of septic shock; however, sodium bicarbonate improves neither hemodynamics nor the response to vasopressor medications.

**SUPPORT AND GENERAL CARE**

The goal of cardiovascular support should be adequate perfusion, though whether it is beneficial to try to maintain central venous oxygen saturation...
above 70% after the first 6 hours is unknown. Respiratory support requires continued application of a tidal volume of 6 ml per kilogram and a well-defined weaning protocol (e.g., that of the ARDS Clinical Trials Network). Because sepsis increases the risk of deep venous thrombosis, prophylactic heparin — which can be added to activated protein C — is recommended for patients who do not have active bleeding or coagulopathy.

Enteral nutrition is important because it is generally safer and more effective than total parenteral nutrition. However, total parenteral nutrition may be required in patients who have had abdominal sepsis, surgery, or trauma. For patients with sepsis who are receiving mechanical ventilation, stress ulcer prophylaxis with the use of histamine H2-receptor antagonists may decrease the risk of gastrointestinal hemorrhage. Proton-pump inhibitors may be effective but have not been fully evaluated for stress ulcer prophylaxis.

Use of sedation, neuromuscular-blocking agents, and corticosteroids should be minimized because they can exacerbate the septic encephalopathy, polyneuropathy, and myopathy of sepsis. The use of immune support benefits specific subgroups of patients with sepsis (e.g., patients with neutropenia benefit from treatment with granulocyte colony-stimulating factor). The risk of nosocomial infection in patients with sepsis may be decreased by using narrow-spectrum antibiotics, weaning patients from ventilation, avoiding immunosuppression, and removing catheters.

**INEFFECTIVE THERAPIES**

Several types of therapy have proven ineffective. Antilipopolysaccharide therapy was ineffective, perhaps because it was applied late (after the lipopolysaccharide peak in sepsis) or because the antibodies used lacked the ability to neutralize lipopolysaccharide. Numerous therapies that block proinflammatory cytokines have failed, perhaps because the approach was narrowly focused, pathways are redundant, or cytokines are critical to host defense and their blockade is excessively immunosuppressive. Ibuprofen, platelet-activating factor acetylhydrolase, bradykinin antagonists, and other therapies have not improved survival among patients with sepsis.

**POTENTIAL NEW THERAPIES**

Superantigens and mannose are bacterial products that may be potential therapeutic targets. Inhibition of tissue factor, a proximal target, might mitigate excessive procoagulant activity. Strategies to boost immunity could improve the outcome of sepsis when applied early in sepsis if measures of immune competence indicate impaired immunity or when applied late in sepsis. Interferon gamma improved macrophage function and increased survival in one study of sepsis. Inhibition of apoptosis (e.g., with anticaspases) improved survival in an animal model of sepsis. Lipid emulsion (which binds and neutralizes lipopolysaccharide) is being evaluated in a phase 3 trial; lipids may modulate innate immunity by inhibiting lipopolysaccharide.

**SUMMARY**

Optimal management of sepsis requires early, goal-directed therapy; lung-protective ventilation; antibiotics; and possibly activated protein C. The use of corticosteroids, vasopressin, and intensive insulin therapy requires further study. Later in the course of sepsis, appropriate management necessitates organ support and prevention of nosocomial infection. Studies focused on novel targets, mechanisms of action, and combination therapy may improve current treatment.

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**REFERENCES**

6. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B. Current epidemiology of...
42. Liaw PC, Esmon CT, Kahanmouki K, et al. Patients with severe sepsis vary markedly in their ability to generate activated protein C. Nat Med 2001;7:1098-64.


71. Mani I, Mehta S, Stansbury UE, et al. Therapeutic effects of drotrecogin alfa (activated) were analyzed by causative microorganism and treatment across clinically important subgroups of patients with severe sepsis. Crit Care Med 2003;31:12-9.


A DISORDER DUE TO UNCONTROLLED INFLAMMATION?

The prevailing theory has been that sepsis represents an uncontrolled inflammatory response. Lewis Thomas popularized this notion when he wrote that “the microorganisms that seem to have it in for us... turn out... to be rather more like bystanders.... It is our response to their presence that makes the disease. Our arsenals for fighting off bacteria are so powerful... that we are more in danger from them than the invaders.”

A consensus conference defined sepsis as “the systemic inflammatory response syndrome that occurs during infection.” Numerous trials were conducted of agents that block the inflammatory cascade — corticosteroids, antienzyme antibodies, tumor necrosis factor (TNF) antagonists, interleukin-1–receptor antagonists, and other agents. The failure of antiinflammatory agents led investigators to question whether death in patients with sepsis results from uncontrolled inflammation.

Clinical trials of treatments for sepsis are difficult because of the heterogeneity of patients and the high rates of culture-negative sepsis. Interpretation is complicated, because the analysis of outcomes generates post hoc stratifications that have not been prospectively defined.

The theory that death from sepsis was attributable to an overstimulated immune system was based on studies in animals that do not seem to reflect the clinical picture in humans. These studies used large doses of endotoxin or bacteria; consequently, levels of circulating cytokines such as tumor necrosis factor (TNF-α) were exponentially higher in animals than they are in patients with sepsis. In these studies, the animals died from “cytokine storm,” and compounds and macromolecules that block these mediators improved survival.

In certain forms of sepsis — for example, meningococcemia — circulating TNF-α levels are high and correlate with mortality. Of 55 children with severe infectious purpura (32 of them with N. meningitidis infection), 91 percent had elevated levels of circulating TNF-α. Nevertheless, studies have shown that the frequency of an exaggerated systemic inflammatory response is lower than it was originally thought to be.

Debets et al. reported that only 11 of 43 patients with sepsis had detectable circulating TNF (limit of detection, 5 to 10 pg per milliliter). In another study of 87 pa-
Patients with sepsis, fewer than 10 percent had measurable TNF-α or interleukin-1β. Although cytokines are considered to be culprits, they also have beneficial effects in sepsis. Studies in an animal model of peritonitis demonstrated that blocking TNF-α worsens survival. Combination immunotherapy against TNF-α and interleukin-1 receptors was fatal in a neutropenic model of sepsis. In clinical trials, a TNF antagonist increased mortality. The role of TNF-α in combating infection has recently been underscored by the finding that sepsis and other infectious complications developed in patients with rheumatoid arthritis who were treated with TNF antagonists.

The debate about the merits of inhibiting cytokines in patients with sepsis has been rekindled by a recent trial that indicated that a subgroup of patients with sepsis who had therapy directed against TNF-α had improved survival. Also, a meta-analysis of clinical trials of antiinflammatory agents in patients with sepsis showed that although high doses of antiinflammatory agents were generally harmful in such patients, a subgroup of patients (approximately 10 percent) benefited.

Advances in our understanding of cell-signaling pathways that mediate the response to microbes have demonstrated that the concept of blocking endotoxin in order to prevent septic complications may be simplistic. Cells of the innate immune system recognize microorganisms and initiate responses through pattern-recognition receptors called toll-like receptors (TLRs). Insight into the role of TLRs in combating infection has been provided by studies in C3H/HeJ mice, which are resistant to endotoxin because of a mutation in the toll-like receptor 4 gene (TLR4). Despite their resistance to endotoxin, these mice have increased mortality with authentic sepsis. TLR4 mutations have been identified in humans and may make persons more susceptible to infection. Therefore, although endotoxin has deleterious effects, total blockade of endotoxin may be detrimental. Reasons for the failure of monoclonal antiendotoxin antibodies to improve outcomes in trials involving patients with sepsis are complex.

MECHANISMS OF IMMUNE SUPPRESSION IN SEPSIS

A SHIFT TO ANTIINFLAMMATORY CYTOKINES

Activated CD4 T cells are programmed to secrete cytokines with either of two distinct and antagonistic profiles. They secrete either cytokines with inflammatory (type 1 helper T-cell [Th1]) properties, including TNF-α, interferon-γ, and interleukin-2, or cytokines with antiinflammatory (type 2 helper T-cell [Th2]) properties — for example, interleukin-4 and interleukin-10 (Fig. 1). The factors that determine whether CD4 T cells have Th1 or Th2 responses are unknown but may be influenced by the type of pathogen, the size of the bacterial inoculum, and the site of infection. Mononuclear cells from patients with burns or trauma have reduced levels of Th1 cytokines but increased levels of the Th2 cytokines interleukin-4 and interleukin-10, and reversal of the Th2 response improves survival among patients with sepsis. Other studies have demonstrated that the level of interleukin-10 is increased in patients with sepsis and that this level predicts mortality.

ANERGY

Anergy is a state of nonresponsiveness to antigen. T cells are anergic when they fail to proliferate or secrete cytokines in response to their specific antigens. Heidecke et al. examined T-cell function in patients with peritonitis and found that they had decreased Th1 function without increased Th2 cytokine production, which is consistent with anergy. Defective T-cell proliferation and cytokine secretion...
Figure 1. The Response to Pathogens, Involving “Cross-Talk” among Many Immune Cells, Including Macrophages, Dendritic Cells, and CD4 T Cells.

Macrophages and dendritic cells are activated by the ingestion of bacteria and by stimulation through cytokines (e.g., interferon-γ) secreted by CD4 T cells. Alternatively, CD4 T cells that have an antiinflammatory profile (type 2 helper T cells [Th2]) secrete interleukin-10, which suppresses macrophage activation. CD4 T cells become activated by stimulation through macrophages or dendritic cells. For example, macrophages and dendritic cells secrete interleukin-12, which activates CD4 T cells to secrete inflammatory (type 1 helper T-cell [Th1]) cytokines. Depending on numerous factors (e.g., the type of organism and the site of infection), macrophages and dendritic cells will respond by inducing either inflammatory or antiinflammatory cytokines or causing a global reduction in cytokine production (anergy). Macrophages or dendritic cells that have previously ingested necrotic cells will induce an inflammatory cytokine profile (Th1). Ingestion of apoptotic cells can induce either an antiinflammatory cytokine profile or anergy. A plus sign indicates up-regulation, and a minus sign indicates down-regulation; in cases where both a plus sign and a minus sign appear, either up-regulation or down-regulation may occur, depending on a variety of factors.
Patients with trauma or burns have reduced levels of circulating T cells, and their surviving T cells are anergic.\textsuperscript{47}

Apoptotic cell death may trigger sepsis-induced anergy. Although the conventional belief was that cells die by necrosis, recent work has shown that cells can die by apoptosis — genetically programmed cell death. In apoptosis, cells “commit suicide” by the activation of proteases that disassemble the cell.\textsuperscript{48,49} Large numbers of lymphocytes and gastrointestinal epithelial cells die by apoptosis during sepsis.\textsuperscript{50-52} A potential mechanism of lymphocyte apoptosis may be stress-induced endogenous release of glucocorticoids.\textsuperscript{53,54} The type of cell death determines the immunologic function of surviving immune cells (Fig. 1).\textsuperscript{55-57} Apoptotic cells induce anergy or antiinflammatory cytokines that impair the response to pathogens, whereas necrotic cells cause immune stimulation and enhance antimicrobial defenses (Fig. 1).\textsuperscript{55-57}

Autopsy studies in persons who had died of sepsis disclosed a profound, progressive, apoptosis-induced loss of cells of the adaptive immune system.\textsuperscript{50-52} Although no loss of CD8 T cells, natural killer cells, or macrophages occurred, sepsis markedly decreased the levels of B cells (Fig. 2), CD4 T cells (Fig. 3), and follicular dendritic cells (Fig. 3). The loss of lymphocytes and dendritic cells was especially important, because it occurred during life-threatening infection, when clonal expansion of lymphocytes might have been expected.

The magnitude of the apoptosis-induced loss in lymphocytes during sepsis was apparent in examinations of the circulating lymphocyte count in patients.\textsuperscript{50} In one study, 15 of 19 patients with sepsis had absolute lymphocyte counts below the lower limit of normal (a mean $\pm$ SD of 500$\pm$270 per cubic millimeter vs. the lower limit of 1200 per cubic millimeter). Losses of B cells, CD4 T cells, and dendr-

**Figure 2.** Unmagnified View of Six Microscope Slides of Spleens from Patients with Trauma (Panels A, C, and E) and Patients Who Died of Sepsis (Panels B, D, and F), with Staining for B Cells (CD20). The dark stained regions are concentrations of B cells in lymphoid follicles that are visible to the naked eye. The patients with sepsis have dramatically smaller and fewer lymphoid follicles than the patients with trauma.
ic cells decrease antibody production, macrophage activation, and antigen presentation, respectively. The potential importance of the depletion of lymphocytes is illustrated by studies in animals showing that prevention of lymphocyte apoptosis improves the likelihood of survival. Immune defects identified in patients with sepsis, including monocyte dysfunction, are listed in Table 1.

Investigators are challenging Lewis Thomas’s theory that the body’s primary response to infection and injury is uncontrolled hyperinflammation. Munford and Pugin maintain that the body’s normal stress response is activation of anti-inflammatory mechanisms and that, outside of affected tissues, the body’s systemic antiinflammatory responses predominate. They postulate that immune cells and cytokines have both pathogenic and protective roles and that blocking these mediators may worsen the outcome. Heidecke et al. examined T-cell function in patients with sepsis and reported that immunosuppression was evident at the onset of sepsis, suggesting a primary hypoimmune response.

Weighardt and associates examined lipopoly-

Figure 3. Immunohistochemical Staining for Follicular Dendritic Cells (CD21) (Top Panels, x600) and CD4 T Cells (Bottom Panels, x600) in Spleens from Patients with Trauma (Panels A and C) or Patients Who Died of Sepsis (Panels B and D). The patients with sepsis have dramatically fewer follicular dendritic cells and CD4 T cells (located in the T-cell–rich periarteriolar zone) than patients with trauma.
Table 1. Potential Mechanisms of Immune Suppression in Patients with Sepsis.*

<table>
<thead>
<tr>
<th>Potential Mechanism</th>
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<tr>
<td>Shift from an inflammatory (Th1) to an anti-inflammatory (Th2) response</td>
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<tr>
<td>Anergy</td>
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<tr>
<td>Apoptosis-induced loss of CD4 T cells, B cells, and dendritic cells</td>
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<tr>
<td>Loss of macrophage expression of major-histocompatibility-complex class II and costimulatory molecules</td>
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<tr>
<td>Immunosuppressive effect of apoptotic cells</td>
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* Th1 denotes type 1 helper T cell, and Th2 type 2 helper T cell.

Neutrophils have been regarded as double-edged swords in sepsis. Although neutrophils were thought to be essential for the eradication of pathogens, excessive release of oxidants and proteases by neutrophils was also believed to be responsible for injury to organs. Because of the intrapulmonary sequestration of neutrophils and the frequent complication of the acute respiratory distress syndrome in patients with sepsis, this link between overly exuberant neutrophil activation and organ injury was thought to affect the lungs in particular.70 Although findings from studies in animals implicated neutrophil-mediated injury, other studies in which granulocyte colony-stimulating factor (G-CSF) was used — to increase the number of neutrophils and enhance their function — demonstrated improved survival among patients with sepsis.

Two randomized trials of G-CSF were conducted in patients with community-acquired and hospital-acquired pneumonia.71,72 Despite an increase in the white-cell count to 70,000 per cubic millimeter, there was no evidence of adverse effects on lung function in patients with community-acquired pneumonia.71 Although a subgroup of patients with multilobar pneumonia had fewer complications and shorter stays in the intensive care unit with G-CSF, there was no improvement in survival. Similarly, hospitalized patients with community-acquired or nosocomial pneumonia who were treated with G-CSF had no survival benefit, no decrease in organ dysfunction, and no decrease in the number of days in intensive care.72

Although marked leukocytosis resulting from G-CSF was not injurious, it is not necessarily possible to extrapolate from such data whether marked leukocytosis would be harmful in patients with severe sepsis. However, these two clinical studies imply that blocking neutrophil function to prevent complications of sepsis would be unlikely to be beneficial. Furthermore, therapies aimed at enhancing the number or function of neutrophils in patients with sepsis are also unlikely to be efficacious.

HOST GENETIC FACTORS

On the basis of studies in identical twins and adoptees, genetic factors are known to be major determinants of susceptibility to death from infectious disease.68 Some persons have single base-pair alterations (single-nucleotide polymorphisms) in genes controlling the host response to microbes.67,69 Identified alterations include polymorphisms in TNF receptors, interleukin-1 receptors, Fcy receptors, and TLRs.67–69 Polymorphisms in cytokine genes may determine the concentrations of inflammatory and anti-inflammatory cytokines produced and may influence whether persons have marked hyperinflammatory or hypoinflammatory responses to infection. The risk of death among patients with sepsis has been linked to genetic polymorphisms for TNF-α and TNF-β.69 Trials examining the effect of polymorphisms in patients with pneumonia and sepsis are under way; such polymorphisms may ultimately be used to identify patients at high risk for the development of sepsis and organ dysfunction during infection. Thus, physicians may, in the future, be able to use genetic information to dictate immune-based therapy to modulate the response in a given patient.
LESSONS FROM AUTOPSY STUDIES

Autopsy studies in persons who died in the intensive care unit show that the failure to diagnose and appropriately treat infections with antibiotics or surgical drainage is the most common avoidable error.73,74 Our laboratory conducted an autopsy study of 20 patients who died in intensive care units;50 consent was obtained immediately after each patient’s death, so that tissues were usually acquired within 30 to 90 minutes after death, thereby permitting tissue morphology to be assessed before autolytic changes occurred. Autopsies were also performed in a control group consisting of patients who had died while critically ill but who did not have clinical sepsis. Immunohistochemical analysis showed that in the majority of patients with sepsis, only two types of cells — lymphocytes and gastrointestinal epithelial cells — were dying; this finding parallels those of studies in animals.39,54,75

As had been noted previously, there was a profound loss of cells of the adaptive immune system. Lymphocytes and gastrointestinal epithelial cells normally undergo rapid turnover through apoptosis, and sepsis most likely accelerates these physiologic processes. Focal necrosis occurred in hepatocytes in the region of the central vein (presumably because this region is vulnerable to hypoxia) in 7 of 20 patients, as well as in the brain and heart in 3 patients who had evidence of infarction before death.

CELLULAR HIBERNATION AS A MECHANISM OF ORGAN DYSFUNCTION

Another intriguing finding from the autopsy study was a discordance between histologic findings and the degree of organ dysfunction seen in patients who died of sepsis.50 Cell death in the heart, kidney, liver, and lung was relatively minor and did not reflect the clinical evidence of more profound organ dysfunction. There was no evidence of injury to cardiac myocytes in patients with sepsis who had myocardial depression. (No patient had meningococcemia, which causes myocarditis with infiltration of organisms and granulocytes.) Histologic findings in patients with sepsis and acute renal failure showed only focal injury with preservation of normal glomeruli and renal tubules.50 These results are similar to those of studies in patients with acute renal failure in which microscopy showed a dissociation between the degree of tubular necrosis and the level of renal dysfunction.76,77 Most patients who survive sepsis and acute renal failure recover base-line renal function, suggesting that renal-cell death is not overwhelming during sepsis.78

We speculate that much organ dysfunction in patients with sepsis can be explained by “cell hibernation” or “cell stunning,” as occurs during myocardial ischemia.79 Presumably, sepsis activates defense mechanisms that cause cellular processes to be reduced to basic “housekeeping” roles. A possible molecular basis for cellular stunning was suggested by work from the laboratory of Fink et al.,80 who showed that immunostimulated enterocytes have diminished oxygen consumption as a result of depletion of nicotinamide adenine dinucleotide secondary to activation of the nuclear enzyme poly–adenosine diphosphate (ADP)–ribose polymerase by peroxinitrite or other oxidants.

DEATH OF PATIENTS WITH SEPSIS

No autopsy studies have revealed why patients with sepsis die. Occasionally, a patient with sepsis may die of refractory shock, but this is exceptional. Although patients with sepsis have profound myocardial depression, cardiac output is usually maintained because of cardiac dilatation and tachycardia.81 Although the acute respiratory distress syndrome frequently develops in patients with sepsis, such patients rarely die of hypoxemia or hypercarbia.82 Renal failure is common, but that alone is not fatal, because dialysis may be used. Liver dysfunction rarely progresses to hepatic encephalopathy. Thus, the exact cause of death in patients with sepsis remains elusive. Many patients die when care is withdrawn or not escalated when families, in consultation with physicians, decide that continued therapy is futile.

NEW CONCEPTS IN THE TREATMENT OF SEPSIS

Physicians caring for patients in intensive care units need a thorough knowledge of common infectious and noninfectious causes of fever in this population of patients (Table 2). Many patients in whom sepsis develops — for example, elderly patients or patients with uremia — do not become febrile.83 The lack of an apparent acute-phase response in patients with sepsis is associated with high mortality and may reflect the immunosuppressive phase of sepsis. Early manifestations of sepsis include sub-
Anticoagulant agents work at different sites in the coagulation cascade. Also, activated protein C has antiapoptotic actions that may contribute to its efficacy.

The debate regarding the appropriate use of activated protein C, as well as its potential adverse effects, particularly bleeding, has been discussed in recent articles. A major risk associated with activated protein C is hemorrhage; in a study of activated protein C, 3.5 percent of patients had serious bleeding (intracranial hemorrhage, a life-threatening bleeding episode, or a requirement for 3 or more units of blood), as compared with 2 percent of patients who received placebo (P < 0.06). With open-label use of activated protein C after the trial, 13 of 520 patients (2.5 percent) had intracranial hemorrhage. Caution is advised in the use of activated protein C in patients with an international normalized ratio greater than 3.0 or a platelet count of less than 30,000 per cubic millimeter. Currently, activated protein C is approved only for use in patients with sepsis who have the most severe organ compromise and the highest likelihood of death. Use of activated protein C is restricted in many hospitals to the more seriously ill patients who meet the criteria for sepsis specified by the Acute Physiology and Chronic Health Evaluation (APACHE II) scoring system.

**ACTIVATED PROTEIN C**

Recombinant human activated protein C, an anticoagulant, is the first antiinflammatory agent that has proved effective in the treatment of sepsis. In patients with sepsis, the administration of activated protein C resulted in a 19.4 percent reduction in the relative risk of death and an absolute risk reduction of 6.1 percent. Activated protein C inactivates factors Va and VIIIa, thereby preventing the generation of thrombin. The efficacy of an anticoagulant agent in patients with sepsis has been attributed to feedback between the coagulation system and the inflammatory cascade. Inhibition of thrombin generation by activated protein C decreases inflammation by inhibiting platelet activation, neutrophil recruitment, and mast-cell degranulation. Activated protein C has direct antiinflammatory properties, including blocking of the production of cytokines by monocytes and blocking cell adhesion.

A puzzling issue is why activated protein C was successful whereas two other anticoagulants — antithrombin III and tissue factor–pathway inhibitor — failed as treatments of sepsis. A possible explanation for the failure of these two anticoagulant agents is that they work at different sites in the coagulation cascade. Also, activated protein C has antiapoptotic actions that may contribute to its efficacy.

**INTENSIVE INSULIN THERAPY FOR HYPERGLYCEMIA**

Van den Berghe et al. demonstrated that intensive insulin therapy that maintained the blood glucose level at 80 to 110 mg per deciliter (4.4 to 6.1 mmol per liter) resulted in lower morbidity and mortality among critically ill patients than did conventional therapy that maintained the blood glucose level at 180 to 200 mg per deciliter (10.0 to 11.1 mmol per liter). Intensive insulin therapy reduced the frequency of episodes of sepsis by 46 percent. Patients with bacteremia who were treated with intensive insulin therapy had lower mortality than those who received conventional therapy (12.5 percent vs. 29.5 percent). Insulin therapy reduced the rate of death from multiple-organ failure among patients with sepsis, regardless of whether they had a history of diabetes.

The protective mechanism of insulin in sepsis is unknown. The phagocytic function of neutrophils is impaired in patients with hyperglycemia, and correcting hyperglycemia may improve bacterial phagocytosis. Another potential mechanism involves the antiapoptotic effect of insulin. Insulin prevents apoptotic cell death from numerous stimu-
li by activating the phosphatidylinositol 3-kinase–Akt pathway.®Regardless of mechanism, it seems reasonable to control blood glucose more tightly in critically ill patients. Clinicians must avert hypoglycemic brain injury in attempting to maintain the blood glucose level at 80 to 110 mg per deciliter. Frequent monitoring of blood glucose is imperative, and studies are needed to determine whether less tight control of blood glucose — for example, a blood glucose level of 120 to 160 mg per deciliter (6.7 to 8.9 mmol per liter) — provides similar benefits.

**VOLUME RESUSCITATION**

Another recent study by Rivers et al. showed that early aggressive therapy that optimized cardiac preload, afterload, and contractility in patients with severe sepsis and septic shock improved the likelihood of survival.® Rivers et al. used infusions of colloid or crystalloid, vasoactive agents, and transfusions of red cells to increase oxygen delivery. Resuscitation end points chosen for assessment of the adequacy of oxygen delivery were the normalization of values for mixed venous oxygen saturation, lactate concentration, base deficit, and pH. Patients in the group that received early goal-directed therapy received more fluid, inotropic support, and blood transfusions during the first six hours than did control patients, who received standard resuscitation therapy. During the interval from 7 to 72 hours, patients in the group receiving early goal-directed treatment had a higher mean central venous oxygen concentration, a lower mean lactate concentration, a lower mean base deficit, and a higher mean pH than the control group. Mortality was 30.5 percent in the group receiving early goal-directed treatment, as compared with 46.5 percent in the control group (P=0.009). Thus, early therapeutic intervention to restore balance between oxygen delivery and oxygen demand improved survival among patients presenting with severe sepsis. The use of objective measures, including lactate concentration, base deficit, pH, and possibly central venous oxygen saturation, in the follow-up of patients who are receiving resuscitation therapy is advisable.

**CORTICOSTEROIDS**

Administration of high doses of corticosteroids (e.g., 30 mg of methylprednisolone per kilogram of body weight) does not improve survival among patients with sepsis and may worsen outcomes by increasing the frequency of secondary infections.® Despite the negative effects of high-dose corticosteroids, a 2001 study by Annane indicated that patients with sepsis who are extremely ill and have persistent shock requiring vasopressors and prolonged mechanical ventilation may benefit from “physiologic” doses of corticosteroids.® It is postulated that such patients may have “relative” adrenal insufficiency despite elevated levels of circulating cortisol.®

The proposed explanation for the physiological response to corticosteroids (despite normal or elevated plasma cortisol levels) is desensitization of corticosteroid responsiveness with down-regulation of adrenergic receptors.® Catecholamines increase arterial pressure through effects on adrenergic receptors of the vasculature; corticosteroids increase the expression of adrenergic receptors. Testing involving stimulation by adrenocorticotropic hormones may not be useful in identifying patients with relative adrenal insufficiency. Such patients may have markedly elevated base-line plasma cortisol levels and a blunted response to stimulation by adrenocorticotropic hormones. A random plasma cortisol concentration of less than 20 µg per deciliter suggests an inadequate adrenal response to stress.®

A recent study, also by Annane and colleagues, in which hydrocortisone (a 50-mg intravenous bolus four times per day) and fludrocortisone (50 µg per day) were administered for seven days to patients in septic shock showed improved survival in comparison with controls.® Combination therapy was beneficial even in patients with elevated base-line plasma cortisol levels if their serum cortisol level did not increase by more than 9 µg per deciliter when stimulated by adrenocorticotropic hormone. Somewhat worrisome was the fact that patients who did not have adrenal insufficiency and who received corticosteroids had a slight, albeit not statistically significant, trend toward increased mortality.® A second issue that has been raised is the high mortality rate in the population of patients — 63 percent in the placebo group. In summary, clinicians should not use high-dose corticosteroids in patients with sepsis. Low-dose hydrocortisone was effective in one study in patients with septic shock, but that finding has not been confirmed by other groups.
AN EMERGING CONCEPT OF THE NATURE OF THE IMMUNE RESPONSE IN SEPSIS

Our current hypothesis regarding the activity of the immune system during sepsis is illustrated in Figure 4, which depicts the responses of three hypothetical patients. The type of response is determined by many factors, including the virulence of the organism, the size of the inoculum, and the patient’s coexisting conditions, nutritional status, age, and polymorphisms in cytokine genes or other immune-effector molecules or their receptors.

Our evaluation of spleens removed after the death of patients with sepsis demonstrated that the more prolonged the sepsis, the more profound was the loss of B cells and CD4 T cells. Most deaths occurred during the prolonged hypoimmune state, and reversal or prevention of this immune deficiency should be a major focus of research. Antiinflammatory strategies applied early in patients with a hyperinflammatory immune response may be lifesaving. In addition to TNF-α and interleukin-1β, other inflammatory mediators may have critical roles in mediating cell injury in sepsis. Recently, high-mobility group 1 protein was identified as a late mediator of the lethality of endotoxin in mice and has correlated with outcome in patients with sepsis.

Measurement of circulating concentrations of inflammatory mediators may prove to be useful in evaluating the stage of sepsis and in tailoring the administration of antiinflammatory agents. Alternatively, antiinflammatory agents used during the hypoimmune phase may worsen outcome.

When patients are determined to be in a hypoimmune state, inflammatory strategies that enhance the function of the innate or adaptive immune system may be found to be efficacious. The ability of interferon-γ, a potent macrophage activator, to improve survival in a subgroup of patients with sepsis may be the first example of immune-enhancing therapy for sepsis. Interferon-γ was found to restore macrophage HLA-DR expression and TNF-α production in patients with sepsis.

POTENTIAL THERAPIES FOR SEPSIS

Diverse new agents have shown efficacy in clinically relevant animal models and offer hope as well as new insight into sepsis. O’Suilleabhain et al. noted that interleukin-12, a potent immune stimulant and Th1 inducer, reduced mortality from subsequent sepsis when administered after burn injury. Administration of antibodies against complement-activation product C5a decreased the frequency of bacteremia, prevented apoptosis, and improved survival. Calandra and associates reported that high concentrations of macrophage inhibitory factor were present in patients with sepsis and that the administration of antibodies against macrophage migration inhibitory factor protected mice from peritonitis. Strategies that block apoptosis of lymphocytes or gastrointestinal epithelial cells have improved survival in experimental models of

Figure 4. Immunologic Response of Three Hypothetical Patients with Sepsis.

The individual response is determined by many factors, including the virulence of the organism, the size of the inoculum, and the patient’s coexisting conditions, age, and polymorphisms in genes for cytokines. The initial immune response is hyperinflammatory, but the response rapidly progresses to hypoinflammatory. A secondary bump in the hyperimmune state can occur during the hospital course with secondary infections. In the hypothetical healthy person who has contracted a serious meningococcal infection, there is an initial robust hyperinflammatory response. This patient would have extremely high plasma concentrations of TNF-α and other inflammatory cytokines. Death may occur due to a hyperinflammatory state, and antiinflammatory treatments may improve the likelihood of survival. If infection resolves rapidly, there is only a minimal hypoinflammatory state. In the hypothetical elderly person with diverticulitis, the initial response is limited, and, if infection persists, a prolonged hypoinflammatory response develops, followed by either recovery or death. In the hypothetical patient with diabetes, chronic renal failure, and pneumonia, the initial response is blunted, and there is prolonged depression of immune function, culminating in death.
Mice with sepsis that are deficient in poly-ADP-ribose polymerase 1 (PARP) have improved survival, and administration of a PARP inhibitor was beneficial in pig models. The central nervous system is an important modulator of inflammation; electrical stimulation of the vagus nerve protects against endotoxic shock. Thus, a variety of agents hold promise as effective new therapies for sepsis.

**CONCLUSIONS**

A major shift has occurred in the way investigators view the problem of sepsis. Sepsis may not be attributable solely to an “immune system gone haywire” but may indicate an immune system that is severely compromised and unable to eradicate pathogens. Mechanisms of organ failure and death in patients with sepsis remain unknown, and autopsy studies do not reveal widespread necrosis. Current clinical advances in the treatment of sepsis include therapy with activated protein C, tight control of blood glucose, and early goal-directed therapy to treat the cellular oxygen deficit. Future therapy may be directed at enhancing or inhibiting the patient’s immune response, depending on genetic polymorphisms, the duration of disease, and the characteristics of the particular pathogen.

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**REFERENCES**


64. Munford RS, Pugin J. Normal responses to injury prevent systemic inflammation and can be immunosuppressive. Am J Respir Crit Care Med 2001;163:316-21.
75. Hotchkiss RS, Swanson PE, Cobb JP, Jacobson A, Buchman TG, Karl IE. Apoptosis in lymphoid and parenchymal cells during sepsis: findings in normal and T-
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MECHANISMS OF DISEASE
FRANKLIN H. EPSTEIN, M.D., Editor

PATHOGENETIC MECHANISMS OF SEPTIC SHOCK
JOSEPH E. PARRILLO, M.D.

ONE of the most frequent and serious problems confronting clinicians is the management of a serious infection and the systemic response to infection, a syndrome termed sepsis. When this syndrome results in hypotension and organ dysfunction, it is called septic shock. Septic shock is the most common cause of death in intensive care units, and it is the 13th most common cause of death in the United States. The incidence of the two disorders continues to rise: 400,000 cases of sepsis and 200,000 episodes of septic shock are estimated to occur annually, resulting in more than 100,000 deaths.

The mortality rate in patients with septic shock ranges from 20 to 80 percent. This wide range reflects differing definitions of the syndrome and the heterogeneity of the patients studied. Mortality is related to the severity of both the sepsis and the underlying disorder that is nearly always present. The manifestations of sepsis include those related to the systemic response to infection (tachycardia, tachypnea, alterations in temperature, and leukocytosis) and those related to organ-system dysfunction (cardiovascular, respiratory, renal, hepatic, and hematologic abnormalities). More recently, emphasis has been placed on the fact that sepsis is one example of a systemic inflammatory response that can be triggered not only by infections but also by noninfectious disorders, such as trauma and pancreatitis. Sepsis is said to be severe when it is associated with organ dysfunction, hypoperfusion (lactic acidosis, oliguria, or altered mental status), or hypotension (septic shock). These associations confer a poorer prognosis but are not precise enough to predict the outcome in an individual patient. If these findings are used in conjunction with other scoring systems assessing the severity of illness, we may be better able to predict the outcome.

Pathogenetic Sequence in Sepsis

Figure 1 shows a diagram of the pathogenesis of septic shock. Gram-positive organisms and fungi, as well as endotoxin-containing gram-negative organisms, can initiate this pathogenetic cascade. The process begins with the proliferation of microorganisms at a nidus of infection. The organisms may invade the bloodstream directly (leading to positive blood cultures) or may proliferate locally and release various substances into the bloodstream. These substances include both structural components of the microorganisms (teichoic acid antigen, endotoxin, and others) and exotoxins synthesized by them, which in turn stimulate the release from plasma precursors or cells (monocytes or macrophages, endothelial cells, neutrophils, and others) of endogenous mediators of sepsis (Fig. 1).

These mediators have profound physiologic effects on the heart and other organs and the vasculature. Approximately 50 percent of patients with hypotension due to sepsis who are admitted to an intensive care unit survive; the other 50 percent die of refractory hypotension or progressive failure of multiple organ systems. Even late in the illness, unresponsive hypotension is usually associated with a very low systemic vascular resistance, but in 10 to 20 percent of patients it is associated with low cardiac output caused by decreased myocardial function. The organ systems affected commonly include the heart, kidneys, lungs, liver, central nervous system, and coagulation system. The consequences are myocardial dysfunction, acute renal failure, adult respiratory distress syndrome, hepatic failure, and disseminated intravascular coagulation. Death usually ensues if one or more organ systems fail completely.

Cardiovascular Dysfunction

Shock is classically defined as inadequate perfusion of tissues resulting in cell dysfunction and (if prolonged) cell death. This definition adequately describes shock due to cardiogenic, vascular obstructive, and hypovolemic mechanisms that result in poor tissue perfusion. In these forms of shock, systemic vascular resistance is elevated, as a compensatory mechanism to maintain blood pressure, and pulmonary-artery oxygenation is decreased, reflecting enhanced systemic extraction of oxygen from red cells by hypoperfused tissues. However, sepsis results in a much more complex form of shock. The onset of sepsis is frequently accompanied by hypovolemia due to both arterial and venous dilatation and the leakage of plasma into the extravascular space. If this hypovolemia is corrected by aggressive intravenous administration of fluids, it will lead to low systemic vascular resistance, normal or increased cardiac output, tachycardia, and elevated oxygen concentrations in pulmonary-artery blood — a hyperdynamic shock syndrome — in more than 90 percent of patients. This constellation of hemodynamic abnormalities has been categorized as distributive shock to emphasize the presumed maldistribution of blood flow to various tissues.

Despite the fact that cardiac output is normal or increased in septic shock, ventricular function is abnormal. Stroke work, the product of stroke volume and mean arterial pressure, is usually reduced as a result of the hypotension. However, stroke work is not
a good measure of cardiac performance because it is so dependent on blood pressure (afterload) and preload. The ejection fraction — the fraction or percentage of the end-diastolic volume ejected with each beat — has proved to be an extremely useful measure of ventricular performance during sepsis and septic shock. With the use of radionuclide gated blood-pool scanning and simultaneous thermodilution hemodynamic measurements, the characteristic pattern of cardiac performance during septic shock has been proved to be one of reduced left and right ventricular ejection fractions, increased end-diastolic and end-systolic volumes of both ventricles, and normal stroke volume;7, heart rate and cardiac output are elevated, and systemic vascular resistance is reduced (Fig. 2). The reduction in the ejection fraction and the biventricular dilatation occur 24 to 48 hours after the onset of sepsis; they are reversible in patients who survive 5 to 10 days after their onset. This reversible myocardial depression has been confirmed with the use of other measures of ventricular performance — for example, Starling—ventricular-function curves,8 load-independent pressure—volume relations,9 and echocardiography.

Certain hemodynamic patterns have prognostic implications. At the onset of disease, a lower heart rate is predictive of survival, probably reflecting less severe disease.5 Interestingly, a low ejection fraction and ventricular dilatation are also associated with survival, perhaps reflecting greater ventricular compensation (by means of the Frank—Starling mechanism) for sepsis-induced myocardial depression. Conversely, a lack of ventricular dilatation may contribute to death.10 Serial hemodynamic studies in patients with septic shock reveal that rapid (within 24 hours) normalization of either tachycardia or elevated cardiac index is also associated with survival, whereas persistence of the hyperdynamic state increases the likelihood of death.

**MEDIATORS AND MYOCARDIAL DYSFUNCTION**

Endotoxin, the lipopolysaccharide associated with cell membranes of gram-negative microorganisms, causes a shock-like state with hypotension and organ dysfunction when injected into animals. In patients with septic shock, detectable levels of circulating endotoxins are correlated with positive blood cultures, lactic acidemia, low systemic vascular resistance, and a depressed ventricular ejection fraction.11 In patients with septic shock and positive blood cultures, endotoxemia has been associated with increased mortality (39 percent, as compared with 7 percent for patients without endotoxemia; P<0.05).11

The relation between endotoxin and the typical cardiovascular manifestations of sepsis has been studied in normal subjects with the use of a very small intravenous dose of highly purified endotoxin. This small dose activates several aspects of the inflammatory response; most subjects have fever and mild constitu-
tional symptoms that last two to three hours and subside completely within four to six hours. Hemodynamically, the administration of endotoxin induces tachycardia, increases the cardiac index, and reduces blood pressure and systemic vascular resistance; the stroke volume does not change. These changes are mild and not clinically apparent, but they can be detected by careful cardiovascular monitoring. After the administration of endotoxin and infusion of fluid (to simulate the management of sepsis), the left ventricular ejection fraction decreases and ventricular volumes increase. The ratio of peak systolic pressure to end-systolic volume, an index independent of load, is reduced. Thus, the administration of endotoxin produces changes in cardiovascular function very similar to those effected by spontaneous sepsis (Fig. 2), with a hyperdynamic response accompanied by reversible myocardial depression and ventricular dilatation.

Studies of septic shock in dogs have confirmed and extended our understanding of sepsis-induced cardiovascular dysfunction. Myocardial depression is dependent on the dose of microorganisms, and gram-positive bacteria (not containing or releasing endotoxin) produce the same pattern of cardiac abnormalities as gram-negative bacteria or endotoxin.

Tumor necrosis factor is a 17-kd polypeptide produced by monocytes, macrophages, and other cells exposed to endotoxin or microorganisms. Pretreatment with antibodies against tumor necrosis factor can prevent death both in mice given endotoxin or microorganisms and in nonhuman primates. The administration of tumor necrosis factor to dogs depresses cardiovascular function in a manner that is temporally and qualitatively similar to that produced by the administration of live microorganisms. These results suggest that tumor necrosis factor is an important mediator of the cardiovascular abnormalities characteristic of sepsis.

Mechanisms of Myocardial Dysfunction in Sepsis

One hypothesis, based largely on studies of animals with endotoxemia, is that myocardial depression in sepsis results from global myocardial ischemia caused by reduced coronary blood flow. This hypothesis has been evaluated in humans by measuring coronary blood flow during septic shock. As compared with normal subjects, patients with septic shock have normal or increased coronary blood flow. The myocardium of the patients also extracts lactate from the coronary circulation, but there is no difference in the level of lactate extraction between patients with septic shock who have myocardial depression and those who do not have such depression. These results argue against the hypothesis that global myocardial ischemia accounts for myocardial depression in septic shock.

A second hypothesis is that myocardial depression results from the direct or indirect effects of one or more circulating myocardial depressant substances. The existence of such substances was postulated more than 20 years ago to explain the reduction in cardiac function during hemorrhagic and endotoxin shock in
animals, but evidence in support of this hypothesis was sparse until recently. When serum obtained from patients during the acute phase of septic shock is incubated with myocardial cells from newborn rats, the extent and velocity of myocyte shortening are reduced (Fig. 3), as compared with those produced by serum from normal subjects, patients with structural heart disease, or critically ill patients without sepsis. The depressant activity is not present in patients who are recovering from septic shock. The extent of the in vitro depression correlates with the decrease in the ejection fraction in vivo. These findings provide strong evidence that a circulating substance has a pathophysiological role in the myocardial depression of septic shock. Subsequent studies have documented that patients with septic shock whose serum contains this myocardial depressant activity have lower ejection fractions, larger end-diastolic volumes, higher pulmonary-artery wedge pressures, and higher peak blood lactate concentrations than those without such activity; their mortality rate is also higher (36 percent vs. 10 percent). Thus, high levels of myocardial depressant activity are associated with myocardial dysfunction and perfusion abnormalities and portend a poor prognosis.

This circulating myocardial depressant substance has not been isolated. Early studies suggested it was a lipid-soluble compound with a low molecular weight (<500), possibly a leukotriene, but more recent studies suggest that it is water-soluble and has a molecular weight of 10,000 to 30,000. Since a number of cytokines have the latter characteristics, the effect of cytokines on myocardial-cell function has been studied. Tumor necrosis factor produces a concentration-dependent depression of myocardial-cell shortening that begins 10 minutes after its addition to the myocytes; its action may be calcium-dependent.

**Vascular and Multiorgan Dysfunction**

Among the most prominent clinical and hemodynamic features of septic shock are low systemic vascular resistance and decreased peripheral use of oxygen and other nutrients. The decreased arteriovenous oxygen difference suggests that oxygen is not reaching or being used by cells. The exact nature of this abnormality is poorly understood. One possibility is that vascular abnormalities (see below) result in decreased tissue perfusion, similar to the decreased perfusion caused by severely decreased cardiac output in patients with cardiogenic or hypovolemic shock. Another is that tissue perfusion is adequate but cellular metabolism is reduced.

A large number of vascular abnormalities have been described in patients with septic shock. Many vascular beds are dilated, but some are constricted, resulting in the maldistribution of blood flow. The aggregation of neutrophils and platelets may reduce blood flow; neutrophil margination occurs along the vascular endothelium, resulting in the release of many mediators and the migration of neutrophils into tissues. Neutrophils can release active oxygen species, such as superoxide radicals, that can directly damage cells. Many of these neutrophil and endothelial-cell interactions are mediated by selectins and their receptors on endothelial surfaces. Components of the complement system such as C5a are activated; they can attract neutrophils and result in the release of locally active agents such as leukotrienes.

Inflammatory mediators derived from arachidonic acid — prostaglandins and leukotrienes — are released from multiple types of cells and can cause local vasoconstriction or vasodilatation and the accumulation of inflammatory cells. Another important local mechanism of vascular control is endothelium-derived relaxing factor, or nitric oxide, a potent endogenous vasodilator in the microcirculation. Cytokines also have effects on the microvasculature. Tumor necrosis factor dilates vascular smooth muscle, an action that is not affected by the inhibition of cyclooxygenase but is reduced by the removal of endothelial cells, suggesting that tumor necrosis factor–induced vasodilatation is partially dependent on the formation of nitric oxide by the endothelium. Thus, a large number of mediators and inflammatory cells interact with endothelial and vascular smooth-muscle cells to interfere with blood flow and ultimately lead to microvascular failure. A central question in the pathogenesis of sepsis is whether decreased perfusion due to microvascular dysregulation is a primary cause or only an associated event in sepsis-induced organ failure.

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**Figure 3. Effect of Serum from Normal Subjects and Four Groups of Patients on the Shortening of Spontaneously Beating Myocardial Cells of Newborn Rats in Vitro.**

Open circles indicate survivors, solid circles nonsurvivors, and horizontal lines the means for the groups. The extent of myocardial-cell shortening is reduced in patients in the acute phase of septic shock, as compared with the other groups (P <0.001). Reprinted from Parrillo et al. with the permission of the publisher.
The hypothesis that cellular metabolism is abnormal in patients with septic shock is supported by the findings of increased blood lactate concentrations, metabolic acidosis, increased glycolysis, decreased fractional extraction of oxygen, and abnormal delivery-dependent oxygen consumption, in which oxygen consumption continues to rise as oxygen delivery is increased.36-37 This last observation is controversial.38,39 Much of the research regarding this hypothesis has emphasized the relation between the accumulation of lactate and cellular hypoxia. If a tissue is inadequately perfused, as in hypovolemic or cardiogenic shock, the decrease in oxygen delivery causes a shift from aerobic to anaerobic metabolism, resulting in the accumulation of lactate, the product of anaerobic glycolysis. Hypoperfusion also decreases the intracellular stores of high-energy phosphates. Whether cellular hypoxia occurs in septic shock is uncertain. Although many patients with septic shock have elevated blood lactate concentrations, a substantial number (perhaps one third) do not.30 Lactate production increases not only during cellular hypoxia but also as a result of a primary abnormality in glycolysis.31,32 Studies using phosphorus-31 nuclear-magnetic-resonance spectroscopy to evaluate cellular bioenergetics in rats with sepsis have revealed adequate levels of ATP and phosphocreatine in skeletal muscle, brain, and myocardium.32 In dogs with experimentally induced gram-negative bacteremia and myocardial depression, intracellular levels of high-energy phosphates estimated by nuclear magnetic resonance spectroscopy are adequate even during catecholamine-induced increases in myocardial work.33 These studies suggest that cellular hypoxia and the associated reduction in the stores of high-energy phosphates are not adequate explanations for the pathogenetic abnormalities in septic shock.

The relation between oxygen delivery and consumption may be abnormal in patients with septic shock, especially when the disorder is associated with the adult respiratory distress syndrome,34 in that oxygen consumption continues to increase (rather than plateau, as in normal subjects) as oxygen delivery increases. Some studies have found this discrepancy in patients with hyperlactatemia, supporting the hypothesis that cellular hypoxia is being reversed,35 but others have failed to document this delivery-dependent consumption.36 Clinical trials in surgical30 and medical37 patients have reported improved outcomes when oxygen delivery was increased, but flaws in the selection and randomization of patients in these trials make the results difficult to interpret.

Insights into the pathogenesis of multiorgan dysfunction have been obtained from studies of respiration and blood coagulation in humans given endotoxin. Mixed venous oxygen saturation increases, and the arteriovenous oxygen content narrows. The alveolar–arterial oxygen gradient widens, and the partial pressure of arterial oxygen decreases.38 The rate of clearance of inhaled technetium-99-labeled diethylimino-pentaacetic acid, a measure of alveolar permeability, increases, but the neutrophil content of bronchoalveolar-lavage fluid does not increase. The administration of endotoxin also causes an increase in the levels of tissue plasminogen activator in plasma, which is rapidly counterbalanced by the release of plasminogen-activator inhibitor.39 All these changes occur in patients with septic shock, suggesting that endotoxin is a major cause of the clinical manifestations of sepsis.

**Principles of Management**

There are three points in the sequence of the pathogenesis of septic shock at which therapy can be instituted effectively (Table 1).40 First, the nidus of infection can be eradicated with appropriate antimicrobial therapy, surgical drainage, or both. Second, the sep-

<table>
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<th>Table 1. Guidelines for the Care of Patients with Septic Shock.</th>
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<td><strong>ABNORMALITY</strong></td>
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<tr>
<td>Organ-system dysfunction</td>
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*ICU denotes intensive care unit.
†This therapy is still in the experimental phase.
sis-associated cardiovascular, metabolic, and multigorgan system disturbances can be treated in an intensive care unit. Third, inhibitors of toxic mediators can be administered.

Since sepsis begins with the proliferation of microorganisms at a nidus of infection, antimicrobial therapy is mandatory. In large retrospective studies, the early institution of an appropriate antibiotic regimen was associated with improved survival.14 These results emphasize the importance of identifying the infecting microorganisms and initiating early antimicrobial therapy.

Before intensive care units came into general use, more than 90 percent of patients with septic shock caused by gram-negative bacteria died. Now, about 50 percent of such patients survive, largely because they are treated in intensive care units, where cardiac rhythm, blood pressure, cardiac performance, and oxygen delivery can be monitored constantly. On the basis of the information supplied by monitoring, cardiovascular support is given in the form of volume expansion with whole blood, colloid, or crystalloid; vasoppressor therapy for hypotension; and inotropic drugs to improve cardiac performance. Ensuring adequate oxygenation and reversing metabolic derangements are critical goals of management. As discussed above, whether oxygen delivery should be increased to normal or supranormal levels is controversial.36 Although no controlled trial has evaluated outcomes with and without intensive-care-unit support, two retrospective studies49,50 reported a significant reduction in mortality in patients with septic shock who were treated with aggressive hemodynamic support. A controlled, prospective trial of intensive-care-unit support has been conducted in dogs with gram-negative sepsis; survival was increased only in the animals that received both cardiovascular support and antibiotic therapy — an indication that these two therapies work synergistically.44

Treatments that inhibit the formation or action of mediators are being developed. Although corticosteroids reduce mortality in animals with experimentally induced septic shock, three prospective, controlled clinical trials have convincingly demonstrated that corticosteroids do not improve survival in humans.45 In animals, antibodies against the lipid A (the biologically toxic) portion of the endotoxin molecule confer protection against gram-negative infection. In multicenter clinical trials of polyvalent46 or monoclonal47,48 antibodies against endotoxin in patients with sepsis, the mortality rate and the incidence of organ failure were decreased in some subgroups of patients. These results provide evidence that endotoxin is important in the pathogenesis of shock and organ failure.11 However, the patients in whom the treatment is likely to be effective (e.g., patients with blood cultures positive for gram-negative organisms) cannot be identified early in the course of infection, when therapy must be initiated, and the other characteristics of the patients who benefited from the treatment varied in the different trials. For these reasons, none of these preparations of anti-endotoxin monoclonal antibodies have been approved in the United States.

Other inhibitors of mediators that have considerable promise are also being developed. Pharmacologic inhibitors of the actions of endotoxin reverse many endotoxin-mediated processes49 and may provide inexpensive, effective therapies to treat patients with gram-negative infections in the future. Monoclonal antibodies to tumor necrosis factor have the theoretical advantage of efficacy against gram-positive as well as gram-negative infections. Other innovative therapies under development involve the use of interleukin-1-receptor antagonists50 and soluble (inactivating) receptors for tumor necrosis factor.

A word of caution is warranted regarding the use of inhibitors of the mediators of septic shock. The pathogenetic mechanisms of septic shock are complex and interdependent, and many of them represent the body’s compensatory response to sepsis and therefore have salutary effects. For example, in dogs with gram-negative bacteremia, plasma exchange is associated with an increase in mortality, suggesting that the removal of all circulating mediators may result in more harm than benefit.51 Some investigators have reported an increase in blood pressure in patients with septic shock after the administration of an inhibitor of nitric oxide synthesis,52 but studies in animals suggest that such inhibition may increase mortality.53

Further improvements in the care of patients with septic shock will require a better understanding of the complex pathogenetic mechanisms leading to morbidity and mortality in this syndrome. The interruption of the pathogenetic sequence at multiple points is our best hope of reducing the continuing high mortality from this serious disorder.

REFERENCES

Pharmacokinetics/Pharmacodynamics for Critical Care Clinicians

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Since the advent of antimicrobial therapy, considerable controversy has existed as to the most appropriate method to administer antibiotics to maximize the killing of microorganisms, while minimizing toxicity to the patient, the emergence of bacterial resistance, and costs. Over the past decade, data gained from animal models of infection, in vitro pharmacokinetic (PK) and pharmacodynamic (PD) studies, volunteer studies, and clinical trials have enabled clinicians to establish the best mode of drug administration to achieve these goals. This article addresses these issues with particular attention to PK-PD concepts.

Pharmacokinetic and pharmacodynamic considerations

The study of the movement of a drug from its administration site to the place of its pharmacologic activity and its elimination from the body is called “pharmacokinetics.” Factors affecting the movement (kinetics) and fate of a drug in the body are (1) release from the dosage form; (2) absorption from the site of administration into the bloodstream; (3) distribution to various parts of the body, including the site of action; and (4) rate of elimination from the body by metabolism or excretion of unchanged drug. These processes are often referred to by using the acronym ADME: Absorption, Distribution, Metabolism, and Excretion. The ADME parameters of a drug are described by various terms, such as \( C_{\text{max}} \) (maximum concentration of the drug in serum); \( T_{\text{max}} \) (time to maximum concentration of the
drug in serum after a dose); $T/2$ (half-life of a drug in serum); $AUC_{0–24hr}$ or $AUC_{0}$ (area under the curve over 24 hours from the time of administration to infinity, representing the concentration of the drug in serum over time); and $CL$ (clearance of the drug from the serum), which may include renal and nonrenal clearance.

Drug concentrations in interstitial fluid drive the antibiotic into the bacterium and, ultimately, to its binding site within the organism. Because interstitial fluid drug concentrations are proportional to and in rapid equilibrium with blood, antibiotic concentrations in serum are correlated with bacterial eradication. Although one cannot yet measure the drug’s concentration directly at the site of attachment to the bacterium on the outside membrane of the organism, serum levels still allow one to determine the concentrations of the antibiotic that are necessary to inhibit (minimum inhibitory concentration [MIC]) or to be bactericidal (minimum bactericidal concentration [MBC]) to microorganisms. As a result, drug concentrations in the blood (plasma, serum) have been correlated with in vivo bacterial eradication.

Pharmacodynamics correlates the concentration of the drug with its pharmacologic or clinical effects. For an antibiotic, this correlation refers to the ability of the drug to kill or inhibit the growth of microorganisms. Antibiotics elicit their activity against bacteria by binding to a specific protein or structure in the organism.

For an antibiotic to eradicate an organism, three major factors must occur. First, the antibiotic must bind to its target sites in the bacterium. To reach the binding site is no easy matter. It must penetrate the outer membrane of the organism (penetration resistance); avoid being pumped out of the membrane (efflux pump resistance); and remain intact as a molecule (e.g., avoid hydrolysis by $\beta$-lactamases). Once reaching its target, the antibiotic can still be frustrated if the binding site has changed its molecular configuration and now no longer allows the drug to attach. Until the antibiotic overcomes all these obstacles, there is no detrimental effect on the organism.

A range of different binding sites has been identified including ribosomes, penicillin-binding proteins, DNA topoisomerase-gyrase, and the cell membrane itself. The crucial binding site varies with the antibiotic class. These binding sites can be defined as points of biochemical reaction within the bacterium, which must be properly executed to continue the cell’s life cycle. By binding to them, the antibiotic interferes with a crucial chemical reaction resulting in the death of the bacterium.

The second factor relates to concentration. The drug must not only attach to its binding target but also must occupy an adequate number of binding sites, which is related to its concentration within the microorganism. The third factor necessary for an antibiotic to work effectively is that it should remain at the binding site for a sufficient period of time for the metabolic processes of the bacterium to be sufficiently inhibited.

The two major determinants of bacteria killing include the concentration and the time that the antibiotic remains on its target binding sites. The
integration of how high (concentration [C]) and how long (time [T]) an antibiotic’s level remains above a zero concentration over a dosing interval is referred to as the “area under the plasma concentration curve” (AUC). In essence, the AUC measures the concentration of the drug over a given time period and reflects the amount of exposure of the organism to the antibiotic over a dosing interval.

For certain classes of antibiotics, the major killing effect against an organism is produced by either the time or the concentration of the drug at the binding site. Of these two factors of bacterial killing, one may be so minimal in the killing process that it can be ignored in the prediction of a clinical response. For instance, certain antibiotics, like β-lactams (penicillins, cephalosporins, carbapenems, monobactams, and β-lactamase inhibitors), clindamycin, macrolides (erythromycin, clarithromycin), oxazolidinones (linezolid), and vancomycin, use mainly time at the binding site to eradicate organisms. Apparently, once the concentration exceeds a critical value, which seems to be about two to four times above the MIC for an organism, bacterial killing proceeds at a zero order rate, and increasing the drug concentration does not increase the microbial death rate.

As a result, these antibiotics are referred to as “concentration-independent” or “time-dependent” antibiotics (Box 1). For these drugs, the duration that the antibiotic’s concentration remains above their MBC or MIC (T > MIC or MBC) in any one dosing interval becomes the best predictor of clinical outcomes. For β-lactam antibiotics, the time above the MIC or MBC for the drug in serum is generally proportional to that in the fluid bathing the organism (ie, the interstitial fluid or wound fluid in tissues) because the antibiotic distributes to extracellular water, which is in dynamic equilibrium with serum.

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**Box 1. Mode of bacterial killing by anti-infective agents**

*Time-dependent*

- β-Lactams (eg, penicillins, cephalosporins, carbapenems, β-lactamase inhibitors, monobactams)
- Clindamycin
- Erythromycin
- Clarithromycin
- Linezolid
- Vancomycin

*Concentration-dependent*

- Fluoroquinolones
- Aminoglycosides
- Metronidazole
- Amphotericin
- Daptomycin
Certain classes of antibiotics, however, like aminoglycosides and quinolones, use mainly concentration at the binding site to eradicate organisms. Unlike concentration-independent killing antibiotics, the aminoglycosides and fluoroquinolones eliminate bacteria most rapidly when their concentrations are appreciably above their MICs for organisms and, hence, their type of killing is referred to as “concentration-dependent” or “dose-dependent” (see Box 1). For these drugs, the rate of bacterial eradication rises with increasing concentration up to a specific amount. After this specific concentration is achieved, increasing the concentration further does not increase the magnitude of bacterial killing (interestingly, even concentration-dependent antibiotics eventually behave like concentration-independent agents). If the concentration is high enough, most bacteria die within a short time. In these conditions, the effect of the duration of drug exposure is minimal. For concentration-dependent agents, the PD parameter of AUC/MIC or C \times T/MIC can be simplified to peak or C_{\text{max}}/\text{MIC} (Fig. 1).

These concepts have been even further refined. How long the concentration of a time-dependent antibiotic in serum should remain above its MIC or MBC for pathogens in any one dosing interval remains controversial. It is likely that this time may vary with different pathogens, the site of infection, and immunocompetence of the patients. Nevertheless, it seems from animal models of infection, in vitro PD models, volunteer studies, and clinical trials that β-lactam antibiotics levels should remain above their MIC or MBC for the target pathogen for at least 50% of the dosing interval to ensure the highest degree of bacterial eradication [1].

For agents with concentration-dependent killing, like aminoglycosides or fluoroquinolones, the best responses occur when the concentrations are greater than or equal to 10 times above the MIC for their target organisms at the site of infection [2]. For agents with concentration-dependent killing, it has also been shown that clinical responses can be predicted and the peak/MIC ratio by measuring the antibiotic’s AUC over the dosing interval and dividing that value by its MIC against the target organism [3]. In essence,

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![Fig. 1. Pharmacokinetic and pharmacodynamic parameters affecting antibiotic potency. AUC, area under the curve; MIC, minimum inhibitory concentration.](image-url)
the AUC/MIC ratio becomes a default PD concept for the peak/MIC ratio for antibiotics with concentration-dependent killing.

Clinical application of concentration-dependent or dose-dependent killing antibiotics

Being a concentration-dependent drug, aminoglycosides eradicate organisms best when they achieve concentrations that are greater than or equal to 10 times above their MIC. In animal models of infection (including neutropenic animals), many more animals survive a potentially lethal challenge of bacteria if the aminoglycoside is given as a single daily dose than when given in divided doses on an every 8-hour basis [4]. To obtain this favorable ratio (the typical MIC of gentamicin and tobramycin against *Pseudomonas aeruginosa* is 2 mg/mL), the aminoglycoside should be given at a dose of 7 mg/kg once daily but may be given even less frequently in patients with renal dysfunction based on a nomogram [5]. This 7 mg/kg dose usually achieves a peak serum concentration of 20 mg/mL, thereby achieving the target of 10 times above the MIC for these aminoglycosides. In a meta-analysis comparing once-daily aminoglycoside with intermittent dosing in immunocompetent adults, once-daily dosing was equivalent with regard to bacteriologic cure, but showed a trend toward reduced mortality rates and reduced toxicity [6]. Compared with intermittent dosing, once-daily dosing of aminoglycosides has shown less rather than more damage of tissue, like the organ of Corti or the renal tubular cells, on pathologic examination [7,8]. The ototoxicity or nephrotoxicity of aminoglycosides correlates with tissue accumulation and not peak concentration in serum [4]. Further advantages of once-daily aminoglycoside dosing include reduction in supply and labor costs and the emergence of bacterial resistance [9]. This new once-daily dosing method for aminoglycosides based on the PD concepts mentioned previously has emerged as the preferred dosing method, except for patients with enterococcal endocarditis; pregnancy; ascites; renal dialysis; and burns (>20%).

Although fluoroquinolones also exhibit concentration-dependent killing of bacteria, excessively high serum concentrations of these agents can, unfortunately, be associated with seizures and other potentially serious central nervous system adverse reactions. This has been the major reason why quinolones cannot be dosed at very high concentrations. When peak/MIC ratios of greater than or equal to 10 cannot be reached without excessive toxicity, then time of exposure of the organism to the drug cannot be ignored, and bacterial eradication again becomes a function of concentration and time of exposure (ie, AUC/MIC).

Most of the currently available fluoroquinolones given at their usual dose, even orally, achieve urinary concentrations far above 10 times their MIC for even difficult organisms like *P aeruginosa*. Despite ciprofloxacin’s slightly lower MIC against this bacterium compared with levofloxacin and...
gatifloxacin, the patient outcomes are the same with all these fluoroquinolones because they all attain urine concentrations greater than or equal to 10 times their MICs against this bacterium. Interestingly, the only fluoroquinolone that was contraindicated for the treatment of \textit{P. aeruginosa} urinary tract infection was trovafloxacin, because of its very low urine concentrations (approximately 6 \(\mu g/mL\)) and its relatively high MIC (approximately 4 \(\mu g/mL\)) for this organism. Moxifloxacin is also an unwise choice because only 25% of active drug is eliminated in the urine. This is the reason why microbiology laboratories do not report the susceptibility of any urinary pathogens. The percentages of a dose of ciprofloxacin, levofloxacin, and gatifloxacin eliminated in the urine are 50%, 90%, and 90%, respectively. For evaluating the efficacy of fluoroquinolones, the PK-PD concept used for predicting outcomes in urinary tract infection is the concentration in urine/MIC greater than or equal to 10, whereas in systemic infection it is the AUC/MIC.

An indexing of the AUC with the MIC to predict clinical response has been used mainly with the respiratory quinolones. For instance, certain organisms require modest AUC/MIC ratio for their prompt eradication. \textit{Streptococcus pneumoniae} are typically rapidly killed by quinolones at an AUC/MIC\textsubscript{24hr} ratio of 30 to 35, whereas others, like \textit{P. aeruginosa} and most other aerobic gram-negative bacteria, require much greater exposure to quinolones (AUC/MIC\textsubscript{24hr} ratios \(\geq 100–125\)) to be eradicated. The term “target attainment” is often used to determine the likelihood of an antibiotic to attain these ratios. The necessary dose and dosing interval of an antibiotic can be calculated to achieve these ratios that have been correlated with favorable outcomes. Unfortunately, for some antibiotics, particularly those with high MICs against a bacterium, these target rations either cannot be achieved or only in a small percent of the time. These ratios should be reported as 24-hour unbound or free drug AUC/MIC and not as total drug because only the unbound drug is in equilibrium with its targets binding sites in the organism [10]. It should also be emphasized that it is only the unbound or free concentrations of an antibiotic that can cross biologic membranes (human and bacterial) and interact with target sites leading to a biologic effect (efficacy or toxicity). For an antibiotic to reach its target site in an organism it must first penetrate through the organism’s outer membrane. Because typically only molecules of less than 1000 d can pass through the channels (porins) in the outer membrane, and because albumin has a molecular weight of about 40,000 d, an antibiotic bound to albumin has no chance of reaching its binding site.

\textbf{Clinical application of concentration-independent or time-dependent killing antibiotics}

For antibiotics with time-dependent or concentration-independent killing, like \(\beta\)-lactams, the often mentioned advice in package inserts is that
the drug should be given in larger and more frequent doses for infections considered to be “severe” as compared with those that are deemed “mild” or “moderate.” This dosing concept makes little, if any, PD or pharmacoeconomic sense, except possibly for infections located in body areas (eg, cerebrospinal fluid, vitreous humor of the eye) where the higher serum concentrations may improve drug penetration. It should be remembered the high serum levels of β-lactam antibiotics do not drive more drug intracellularly or into “tissue” because these agents exhibit insignificant intracellular penetration. The higher serum levels merely result in similar levels in the interstitial fluid that surround the cells and the same PK-PD concepts that apply to serum levels also apply to interstitial concentrations. Although there typically exists a slight lag period before interstitial and serum levels attain equilibrium, there is a close parallel with β-lactam antibiotics between their concentrations in serum and interstitial fluid compartments. The poor intracellular penetration of β-lactam antibiotics is the explanation why these agents do not eradicate intracellular pathogens like Chlamydia sp, Mycoplasma sp, and Legionella sp.

There are five major ways to prolong the duration of a β-lactam concentration above its MIC for bacteria in any dosing interval: (1) use another drug (eg, probenecid) that interferes with its elimination; (2) dose frequently; (3) increase the dose of the antibiotic; (4) replace with another therapeutically equivalent antibiotic with a longer serum half-life; and (5) administer by constant infusion.

Although probenecid blocks the renal tubular secretion of most β-lactam antibiotics, it may do the same for other drugs, resulting in unexpected adverse reactions. Moreover, if a patient develops a hypersensitivity reaction it is difficult, if not impossible, to determine whether the reaction was caused by probenecid or the antibiotic.

Dosing frequently or increasing the dose is usually unacceptable in today’s medical era of fiscal restraints because of excessive cost from high drug acquisition costs and ancillary service time. Moreover, doubling the dose of a β-lactam antibiotic is generally inefficient, yielding an increase in T greater than MIC of only one half-life.

Using an antibiotic with a longer half-life is sensible as long as the one with the longer half-life is therapeutically equivalent and is not appreciably more expensive. Examples of this type of interchange include replacing cephalothin with cefazolin, cefoxitin with cefotetan, and cefotaxime with ceftriaxone.

There has been a renewed interest in administering β-lactam antibiotics by a 24-hour constant infusion because this represents an easy way using the least amount of drug, supply, and labor costs to maintain drug concentrations above the antibiotic’s MIC for the entire day or 100% of the dosing interval.

For the antipseudomonas β-lactams, constant infusion dosing methods are an alternative dosing approach because most of these agents have
a relatively short half-life. For instance, the recommended dose in the package insert of piperacillin-tazobactam to treat nosocomial pneumonia is 4.5 g every 4 to 6 hours. To optimize clinical outcomes, minimize toxicity, and reduce costs in view of the PK-PD considerations mentioned previously, piperacillin-tazobactam could be administered by constant infusion once daily. In the constant infusion program at Hartford Hospital, 12 g a day is used for a patient with suspected or proved pseudomonas infection; 9 g a day in patients not suspected to have pseudomonas infection; and an even lower infusion dose (based on a nomogram) if the patient has renal impairment [11]. Moreover, in a study [12] comparing intermittent with constant infusion ceftazidime with nosocomial pneumonia, similarities were noted in clinical outcomes but a major reduction in costs associated with constant infusion.

Further clinical outcomes studies are needed to confirm whether this constant infusion dosing method will become the preferred dosing approach for those β-lactam antibiotics that have relatively short half-lives and require high daily dose (eg, oxacillin, nafcillin, ceftazidime, piperacillin-tazobactam, ticarcillin–clavulaniic acid).

Volume of distribution

One of the simplest models in PK describes the body as a single homogenous compartment into which the drug seems to dissolve. The volume of this compartment measured in liters per kilogram, called the apparent volume of distribution, rarely relates to physiologic volumes but serves as a proportionality constant between the dose of drug administered and the observed plasma or serum concentration just after the intravenous administration of a bolus dose.

This concept can be more easily understood using a hydrodynamic or “bathtub” model. In the bathtub model, one adds a known amount of dye to a bathtub of known volume. Clearly, a large bathtub yields a smaller concentration than a small bathtub if the same quantity of dye is placed in each one. Drugs that distribute widely through the body tend to have large volumes of distribution and low serum concentrations; drugs that remain only in the blood volume typically have small volumes of distribution and high serum concentrations. In general, drugs with a high level of serum protein binding penetrate to a lesser extent into the interstitial spaces, produce higher peak serum concentrations, and exhibit a slower rate of elimination from the body, especially if the major elimination mode is by glomerulofiltration. An inverse relationship exists between protein binding and volume of distribution. There is no relationship between renal tubular secretion and protein binding.

The value of volume of distribution for the clinician is that this term roughly describes whether or not the antibiotic will be widely distributed
Drugs that have poor tissue penetration (e.g., β-lactam antibiotics) typically have low (<20 L) volumes of distribution at steady state, whereas agents with widespread tissue distribution (e.g., fluoroquinolones) have high (>100 L/kg) volumes of distribution at steady state. Drugs with low volume of distribution indicate their distribution is limited, mainly to extracellular fluids and not into tissue.

Clearance

Drug concentrations decline in the body as a result of elimination, usually from the kidneys or liver, or both. The term “clearance” is used to describe the intrinsic ability of the body to remove drug. Clearance represents a theoretical volume of blood or plasma that is cleared or completely removed of drug within a period of time. It is expressed as units of volume per time. The clearance volume for a drug is generally constant during a dosing interval. The amount of drug removed per unit of time can be determined if one recalls that concentration and volume are related. Because the clearance of a drug remains constant after distribution is complete, but the serum concentrations decline as drug is removed from the body, the amount of drug removed per unit of time is highest when the serum concentration is highest (i.e., just after administration of a dose).

Half-life and steady-state

In the one-compartment PK model, which most antibiotics follow, drug distribution is assumed to be instantaneous, and elimination from the body follows first-order (log linear) decline. A semilogarithmic plot of drug concentration versus time yields a linear graft. This type of plot can be used to determine the half-life of a drug, which refers to the amount of time required for the drug concentration to decrease by 50%. A simple rule for drugs that follow a one-compartment model is to multiply the half-life by 5, and that predicts the time the serum concentrations decline to their lowest or trough concentration. Antibiotics with very short half-lives (e.g., penicillin, nafcillin, oxacillin, cephalothin) require very frequent dosing, such as every 4 hours, because their half-lives are only 30 minutes. Now there are many antibiotics with long half-lives, like the respiratory quinolones (e.g., levofloxacin, gatifloxacin, and moxifloxacin), ceftriaxone, and azithromycin, legitimizing once-daily dosing.

If the half-life of a drug is known, one can predict the time required to reach steady-state when all the peak and trough concentrations are the same after the dose. Fifty percent of the final steady-state concentration accumulates during each half-life, so that after five half-lives, approximately 97% of the final steady-state concentration has been achieved. For example, an antibiotic with a half-life of 2 hours (e.g., ceftazidime) takes about 10 hours...
to attain steady-state, whereas an agent with an 8-hour half-life (e.g., ceftriaxone) reaches steady-state in about 40 hours.

The longer the half-life of a drug, the longer it takes to achieve a steady-state concentration. This can be particularly important for patients receiving drugs that have long half-lives and narrow therapeutic ranges of serum concentrations. In these patients often a loading dose is used to achieve rapidly therapeutic drug concentrations.

**Postantibiotic effect**

The postantibiotic effect (PAE) describes the persistent suppression of bacterial growth after exposure of a microorganism to an antibiotic. The term should not be confused with the effects of bacterial suppression caused by antibiotic subinhibitory concentrations. Antibiotics that kill bacteria by interfering with protein synthesis (e.g., aminoglycosides, chloramphenicol, macrolides, tetracyclines) or DNA replication (e.g., quinolones) usually demonstrate prolonged PAEs (e.g., 1–5 hours) against gram-negative bacteria, whereas agents that kill bacteria by interfering with cell wall synthesis (e.g., β-lactam antibiotics, glycopeptides) have little, if any, PAE against these types of organisms. The one major exception is the carbapenems (e.g., imipenem, meropenem) that exhibit fairly long PAEs against *P. aeruginosa*. Against gram-positive bacteria, both types of antibiotics typically exhibit short PAEs of about 1 hour. The clinical relevance of the PAE is related to its use in establishing dosage regimens that are directed against a specific pathogen. The PAE has been one of many explanations for the success of intermittent dosing with drugs that exhibit short half-lives.

**Bioavailability**

The degree of absorption or bioavailability of an antibiotic has become an extremely important PK and pharmacoeconomic property of an antibiotic because it often allows for inexpensive and the effective treatment of an infection without the use of injectable agents or hospitalization. Moreover, there are many other advantages to replacing an intravenous antibiotic rapidly with an oral formulation. Probably the greatest advantage is the avoidance of so-called “intravenous line sepsis,” the major source for hospital-acquired bacteremias and fungemia. Proactive programs converting patients rapidly from intravenous to oral therapy is often designated as sequential, transitional, or switch therapy. To replace an intravenous antibiotic with an oral formulation, the oral drug should have a high degree of bioavailability, preferably over 90%. In this situation, the concentrations of the oral antibiotic in tissue or serum can rival the levels that are obtained if the patient is kept on the intravenous formulation. Box 2 records the oral antibiotics that exhibit greater than or equal to 90% bioavailability.
Replacing intravenous antibiotic with an oral drug is probably unwise for those oral agents with less than 50% bioavailability.

Common mistakes in the interpretation of pharmacokinetic and pharmacodynamic concepts

For decades, it has been traditional to view an antibiotic with bactericidal activity against a pathogen as a preferable choice over one that exhibits bacteriostatic activity. It is now well recognized that antibiotics cannot be categorized in such a simplistic manner, because their type of activity varies against different pathogens and under different conditions. Antibiotics with bacteriostatic activity may be as efficacious as ones with bactericidal activity against an organism even in difficult infections (eg, meningitis, endocarditis, osteomyelitis, the febrile neutropenic patient) where it has been customary to recommend a drug that exhibits bactericidal action against the target pathogen. It now probably makes sense for clinicians to avoid using this concept in selecting one antibiotic over another.

It must be emphasized that once target AUC/MIC ratios, peak concentration/MIC ratio and \( t > \text{MIC} \) are achieved, there is no evidence that higher values result in more rapid bacterial killing or less emergence of bacterial resistance. Even concentration-dependent antibiotics eventually behave like a concentration-independent agent. For instance, if one compares the AUC/MIC rations of the three respiratory quinolones (levofloxacin, gatifloxacin, moxifloxacin, gemifloxacin) against \( S \) pneumoniae, all attain the target ratio of 30 to 35. Compared with moxifloxacin, gemifloxacin, and gatifloxacin, levofloxacin achieves somewhat lower ratios against this bacterium, yet, as predicted, has identical efficacy in infections, like community-acquired pneumonia, caused by this bacterium.

Excessive AUC/MIC ratios may produce unwanted adverse reactions by disrupting the normal gastrointestinal flora (collateral damage) and

<table>
<thead>
<tr>
<th>Box 2. Oral anti-infectives with greater than or equal to 90% bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin (Levaquin)(^a), gatifloxacin (Tequin), moxifloxacin (Avelox)</td>
</tr>
<tr>
<td>Metronidazole (Flagyl), clindamycin, TMP-SMX (Bactrim), rifampin(^a)</td>
</tr>
<tr>
<td>Minocycline(^a), doxycycline, fluconazole (Diflucan)(^a), voriconazole (Vfend), linezolid (Zyvok)(^a)</td>
</tr>
<tr>
<td>Cephalexin, cefadroxil, cefprozil</td>
</tr>
</tbody>
</table>

\(^a\) 100% bioavailable.
producing organ dysfunction. For instance, it has recently been shown that AUC/MIC ratios greater than or equal to 60 with gatifloxacin have an association with hyperglycemia [13] and the high fecal concentration with moxifloxacin has been associated with an increase in gastrointestinal colonization with *Clostridium difficile*, vancomycin-resistant enterococci, and *Candida albicans* [14].

Another common mistake is to equate an antibiotic’s potency against an organism solely by its MIC, assuming that the antibiotic with the lowest value has the greatest activity. It must be underscored that the MIC or MBC of an antibiotic against a pathogen is only one of many factors that determines the best or preferred drug to cure an infection. When determining the potency of an antibiotic against a bacterium, one must include other items, such as protein binding, PK, distribution into the site of infection, the adequacy of the patient’s host defenses, and the amount of exposure an organism requires to an antibiotic for its eradication. Paradoxically, microbiologic reports that provide both MIC data along with susceptibility data may actually encourage a clinician to select the wrong antibiotic because of the tendency of clinicians to view potency only in terms of the MICs. Reporting systems that merely report the data in terms of sensitive, intermediate, or resistant are actually better for most clinicians because these values are determined by an integration of the microbiologic and PK properties of the antibiotic.

A common example of this type of mistake is the popular view by clinicians that ciprofloxacin has more activity or potency compared with levofloxacin against *P. aeruginosa* based solely on its slightly lower MIC against this bacterium (ciprofloxacin, approximately 0.5 μg/mL; levofloxacin, approximately 1 μg/mL). This slightly lower MIC of ciprofloxacin is cancelled out by its lower serum concentration compared with levofloxacin resulting in no difference in potency of these two agents against this organism. At equivalent dosages for nosocomial pneumonia, levofloxacin, 750 mg intravenously every 24 hours, has a threefold higher peak serum level and AUC_{24h} than ciprofloxacin, 400 mg intravenously every 8 hours. As expected, national surveillance studies [15,16] performed over the last 7 years comparing the susceptibility of *P. aeruginosa* to ciprofloxacin and levofloxacin have shown no difference. In a PD study [12] comparing the likelihood of either ciprofloxacin, 400 mg every 8 hours, or levofloxacin, 750 mg every 24 hours, achieving a target AUC/MIC in serum of greater than or equal to 125 against *P. aeruginosa*, there was no significant difference (ciprofloxacin 61.8%; levofloxacin 61.2%). These low attainment values suggest that neither ciprofloxacin nor levofloxacin should be given alone to treat serious systemic *P. aeruginosa* infection and that addition of another antipseudomonas agent is required. In a large multicenter, randomized, double-blind trial in the treatment of severe pneumonia that compared intravenous ciprofloxacin with imipenem-cilastatin, the incidence of failure to eradicate *P. aeruginosa* and the development of bacterial resistance in this bacterium in
patients treated with monotherapy with ciprofloxacin was 67% and 38%, respectively [17].

Summary

The ultimate goal of antimicrobial therapy is to eradicate microbial pathogens at the specific site of infection. To accomplish this goal, the clinician must become familiar with PK and PD concepts because an understanding of this information establishes the basis for appropriate dosing strategies to optimize clinical efficacy and minimize toxicity, costs, and the emergence of bacterial resistance. Appreciation of these concepts results in dosing of antibiotics in a scientifically and economically sound fashion.

References


Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project

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Abstract

In January 2003, leadership of the Medicare National Surgical Infection Prevention Project hosted the Surgical Infection Prevention Guideline Writers Workgroup meeting. The objectives were to review areas of agreement among the published guidelines for surgical antimicrobial prophylaxis, to address inconsistencies, and to discuss issues not currently addressed. The participants included authors from most of the published North American guidelines for antimicrobial prophylaxis and several specialty colleges. The workgroup reviewed currently published guidelines for antimicrobial prophylaxis. Nominal group process was used to draft a consensus paper that was widely circulated for comment. The consensus positions of the workgroup include that infusion of the first antimicrobial dose should begin within 60 minutes before surgical incision and that prophylactic antimicrobial agents should be discontinued within 24 hours of the end of surgery. This advisory statement provides an overview of other issues related to antimicrobial prophylaxis including specific suggestions regarding antimicrobial selection.

Keywords: Antibiotics; Postoperative complications; Practice guidelines; Surgical site infection

Surgical site infections (SSIs) are the second most common cause of nosocomial infections [1,2]. Up to 2% to 5% of patients undergoing clean extra-abdominal operations and up to 20% undergoing intra-abdominal operations will develop an SSI [3, Available at: http://www.ahrq.gov/clinic/ptsafety/pdf/ptsafety.pdf. Accessed: December 8, 2003]. The Centers for Disease Control and Prevention (CDC) estimates that approximately 500,000 SSIs occur annually in the United States [4]. Patients who develop SSIs are up to 60% more likely to spend time in an intensive care unit, five times more likely to be readmitted to the hospital, and to have twice the mortality rate compared with patients without an SSI [5]. Health care costs are substantially increased in patients who develop SSIs [1,5–8].

In August 2002, the Centers for Medicare and Medicaid Services (CMS) and the CDC implemented the National Surgical Infection Prevention (SIP) Project [9]. The goal of the project is to decrease the morbidity and mortality associated with postoperative SSIs by promoting appropriate selection and timing of administration of prophylactic antimicrobial agents. A panel of experts in surgical infection prevention, hospital infection control, and epidemiology developed 3 performance measures for national surveillance and quality improvement [9]. These measures are as follows: (1) the proportion of patients who have parenteral antimicrobial prophylaxis initiated within 1 hour before the incision; (2) the proportion of patients who are given a prophylactic antimicrobial agent that is consistent with currently published guidelines; and (3) the proportion of patients whose prophylactic antimicrobial is discontinued within 24 hours of the end of surgery. For the purposes of national surveillance, the project focuses on operations commonly performed on Medicare patients and for whom there is no controversy about the need for antimicrobial prophylaxis. These include coronary artery bypass grafting; other open-chest cardiac surgery (excluding transplant surgery); vascular surgery including aneurysm repair, thromboendarterectomy, and vein bypass; general abdominal colorectal surgery; hip and knee arthroplasty (excluding revisions); and abdominal and vaginal hysterectomy [9].

Several guidelines for antimicrobial prophylaxis in sur-

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gery have been published [10–16]. Although there is considerable agreement in recommendations for antimicrobial selection and timing (Table 1), inconsistencies exist, and several important issues are not addressed. In January 2003, leadership of the National SIP Project hosted a meeting of the Surgical Infection Prevention Guideline Writers Workgroup (Appendix). Authors from most of the North American guidelines and representatives of several additional specialty societies interested in surgical infection prevention attended. The objectives of the meeting were to review areas of agreement, to address issues of inconsistency, and to discuss issues not currently addressed in published guidelines.

This advisory statement summarizes the workgroup’s meeting and subsequent discussions, provides an overview of current guidelines on antimicrobial prophylaxis, and provides expert consensus on issues that are inconsistent or not addressed in the guidelines. Specific recommendations regarding the national performance measures and antimicrobial prophylaxis for operations targeted in the National SIP

<table>
<thead>
<tr>
<th>Operations</th>
<th>Prophylactic antibiotic recommendation*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiothoracic surgery</td>
<td>Cefazolin†, ‡, §, ¶, #</td>
<td>Most of the guidelines agree that duration of prophylaxis for cardiac surgery should not exceed 24 hours. The ASHP recommends continuation of prophylaxis for cardiothoracic surgery for up to 72 hours; however, the authors suggest that prophylaxis for up to 24 hours may be appropriate.§,**</td>
</tr>
<tr>
<td></td>
<td>Cefuroxime§, ¶, ¶</td>
<td>Cefamandole is not available in the United States.</td>
</tr>
<tr>
<td></td>
<td>If β-lactam allergy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vancomycin†, ‡, §, ¶, ¶</td>
<td></td>
</tr>
<tr>
<td></td>
<td>clindamycin#</td>
<td></td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>Cefazolin†, ‡, §, ¶</td>
<td>Currently, none of the guidelines address antimicrobial prophylaxis for patients with documented β-lactam allergy.</td>
</tr>
<tr>
<td></td>
<td>Cefuroxime¶</td>
<td>Cefmetazole is not available in the United States:†,§</td>
</tr>
<tr>
<td></td>
<td>If β-lactam allergy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin†, ‡, §, ¶, ¶</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin with or without gentamicin§</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clindamycin#</td>
<td></td>
</tr>
<tr>
<td>Colon surgery</td>
<td>Oral:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neomycin plus erythromycin base†, ‡, §, ¶</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neomycin plus metronidazole¶</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parenteral:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefoxitin or cefotetan†, ‡, §, ¶, ¶</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefazolin plus metronidazole¶</td>
<td></td>
</tr>
<tr>
<td>Hip or knee arthroplasty</td>
<td>Cefazolin†, ‡, §, ¶</td>
<td>Although not addressed in any of the published guidelines, the workgroup recommends that the prophylactic antibiotic be completely infused before inflation of a tourniquet.</td>
</tr>
<tr>
<td></td>
<td>Cefuroxime¶</td>
<td>Cefuroxime is recommended for patients undergoing total hip arthroplasty.</td>
</tr>
<tr>
<td></td>
<td>If β-lactam allergy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vancomycin†, ‡, §, ¶, ¶</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clindamycin#</td>
<td></td>
</tr>
<tr>
<td>Vaginal or abdominal</td>
<td>Cefazolin†, ‡, §, ¶, † †</td>
<td>Metronidazole monotherapy is recommended in the ACOG Practice Bulletin as an alternative to cephalosporin prophylaxis for patients undergoing hysterectomy††</td>
</tr>
<tr>
<td>hysterectomy</td>
<td>Cefotetan§, ¶, † †</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefoxitin§, ¶, † †</td>
<td>Trovafloxacin, while still available in the United States, is recommended on a limited basis only.‡ † †</td>
</tr>
<tr>
<td></td>
<td>Cefuroxime¶</td>
<td></td>
</tr>
</tbody>
</table>

ACOG = American College of Obstetricians and Gynecologists; ASHP = American Society of Health-System Pharmacists; HICPAC = Hospital Infection Control Practices Advisory Committee; SIP = Surgical Infection Prevention.

* The antibiotics in this column are currently used to assess quality of care on the national performance measure on the proportion of patients who receive prophylactic antimicrobials consistent with current recommendations in the National SIP Project.

† Surgical Infection Society Antimicrobial Agents Committee [10].
‡ Infectious Diseases Society of America Quality Standards Subcommittee of the Clinical Affairs Committee [11].
§ ASHP Commission on Therapeutics [12].
¶ Medical Letter on Drugs and Therapeutics [14].
†† The Sanford Guide to Antimicrobial Therapy, 2003 [16].
# HICPAC [13] recommends either clindamycin or vancomycin as alternatives for gram-positive bacterial coverage if a patient is unable to receive a cephalosporin because of β-lactam allergy.
** The ASHP recommendation for duration of prophylaxis for cardiothoracic surgery was based on expert opinion, and the authors suggest that prophylaxis for 24 hours may be appropriate [12].
†† ACOG Committee on Practice Bulletins [15].
Project are discussed. This article is not meant to be an exhaustive review of the literature of antimicrobial prophylaxis for surgery because published guidelines provide such reviews, and the workgroup discussions were generally limited to operations being evaluated in the national project.

**General Recommendations**

**Timing of antimicrobial first dose**

The goal of antimicrobial prophylaxis is to achieve serum and tissue drug levels for the duration of the operation that exceed the minimum inhibitory concentration for organisms likely to be encountered during the operation. As early as 1961, Burke [17] demonstrated that experimental incisions contaminated with *Staphylococcus aureus* could not be distinguished from incisions that had not been contaminated when antimicrobial agents were administered before the incision. He found that antimicrobial agents were effective in decreasing lesion size if administered no later than 3 hours after bacterial contamination was introduced. In 1969, Polk and Lopez-Mayor [18] reported a randomized trial of antimicrobial prophylaxis in patients undergoing elective gastrointestinal tract surgery that demonstrated a significant decrease in the frequency of wound and intra-abdominal sepsis among treated patients. In 1976, Stone et al [19] demonstrated the lowest SSI rates in patients undergoing gastrointestinal, biliary, and colon operations when antimicrobial agents were administered within 1 hour before incision. Administration of first antimicrobial dose after surgery resulted in SSI rates almost identical to those in patients who did not receive prophylaxis [19]. Ideally, the antimicrobial agent should be administered as near to the incision time as possible to achieve low SSI rates [17–25]. Based on published evidence, the workgroup endorsed the national performance measure that infusion of the first antimicrobial dose should begin within 60 minutes before incision. However, when a fluoroquinolone or vancomycin is indicated, the infusion should begin within 120 minutes before incision to prevent antibiotic-associated reactions. Although research has demonstrated that administration of the antimicrobial agent at the time of anesthesia induction is safe and results in adequate serum and tissue drug levels at the time of incision, there was no consensus that the infusion must be complete before incision. Whenever a proximal tourniquet is required, however, the entire antimicrobial dose should be administered before the tourniquet is inflated.

**Duration of antimicrobial prophylaxis**

The majority of published evidence demonstrates that antimicrobial prophylaxis after wound closure is unnecessary, and most studies comparing single- with multiple-dose prophylaxis have not shown benefit of additional doses [3,10–14,26–28]. Prolonged use of prophylactic antimicrobial agents is associated with emergence of resistant bacterial strains [29–31]. For the majority of operations being evaluated in the National SIP Project, the guidelines cited in this article recommend that prophylaxis end within 24 hours after the operation. The one exception is the preferred regimen of antimicrobial prophylaxis for cardiothoracic surgery recommended by the American Society of Health-System Pharmacists (ASHP). It includes continuation of prophylaxis for up to 72 hours [12]. This ASHP recommendation was based on expert opinion, and the authors suggest that prophylaxis for ≤24 hours may be appropriate [12]. Based on published evidence, the workgroup endorsed the national performance measure that prophylactic antimicrobial agents should be discontinued within 24 hours of the end of surgery.

**Beta-Lactam Allergy**

**Screening for allergy**

Although many patients have documented drug allergies in their medical records, symptoms or circumstances of these are rarely documented. Several studies have demonstrated that the incidence of true drug “allergy” is lower than that recorded in medical records [32–34]. Because beta-lactam antimicrobial agents often represent agents of choice for prophylaxis, the medical history should be adequate to determine if the patient likely had a true allergy (eg, urticaria, pruritus, angioedema, bronchospasm, hypotension, or arrhythmia) or serious adverse drug reaction (eg, drug-induced hypersensitivity syndrome, drug fever, or toxic epidermal necrolysis) [35]. In operations for which cephalosporins represent appropriate prophylaxis, alternate antimicrobial agents should be given to those with a high likelihood of past serious adverse reaction or allergy based on patient history or diagnostic tests such as skin testing. However, the incidence of adverse reactions to cephalosporins in patients with reported penicillin allergy is rare, and penicillin skin tests do not predict the likelihood of allergic reactions to cephalosporins in patients reporting penicillin allergy. Practical approaches to patients with a history of antibiotic allergy have been previously published [35–37].

**Antimicrobial choice for beta-lactam allergy**

Recommendations for confirmed beta-lactam allergy are provided in the discussion of specific operations that follow. In operations where prophylaxis is directed primarily at gram-positive cocci—such as orthopedic operations with joint replacement; cardiothoracic operations; or general, vascular, and neurosurgical operations with implants—alternatives to cephalosporins for beta-lactam allergy are vancomycin and clindamycin [13]. The decision to use vancomycin or clindamycin should involve examination of local antimicrobial resistance patterns and institutional incidence of hospital-acquired infections [36,37].
of infections caused by organisms such as *Clostridium difficile* and *Staphylococcus epidermidis* [38]. Based on antimicrobial spectrum, vancomycin and clindamycin are appropriate alternatives to beta-lactams, although few data exist to support the use of either for routine prophylaxis.

**Methicillin-Resistant Staphylococcus aureus**

The Hospital Infection Control Practices Advisory Committee guideline suggests that “high” levels of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in an institution should influence the use of vancomycin for prophylaxis [13]. However, there is no consensus about what constitutes high levels of methicillin resistance. In addition, there is no evidence that routine use of vancomycin for prophylaxis in institutions with perceived high rates of MRSA will decrease SSIs more than agents such as cefazolin. In a study of cardiac surgery in an institution with a perceived high rate of MRSA, Finkelstein et al [39] randomized 885 patients to prophylaxis with cefazolin or vancomycin. There was no difference in SSI rates between the 2 groups (9.0% cefazolin vs. 9.5% vancomycin, *P* = .8). However, patients who received cefazolin and later developed an SSI were more likely to be infected with MRSA. Patients who developed an SSI after vancomycin prophylaxis were more likely to be infected with methicillin-sensitive *Staphylococcus aureus*. The choice of antimicrobial changed the flora of infections that occurred but did not alter infection rates. Similarly, Manian et al [40] recently demonstrated that 2 postoperative factors (postoperative antibiotic treatment >1 day and discharge to a long-term care facility) were associated with development of MRSA SSIs. Lack of vancomycin use for prophylaxis was not associated with risk of MRSA SSI [40].

For patients with known MRSA colonization, vancomycin should be considered the appropriate antimicrobial agent for prophylaxis. The Society for Healthcare Epidemiology of America recently recommended routine surveillance cultures at the time of admission for patients at high-risk for carriage of MRSA [41]. Rates of MRSA colonization may be greater in patients who have previously spent ≥5 days in an institutional setting including long-term or acute care [41–44].

**Limitation of Additional Agents**

The goal of antimicrobial prophylaxis is to prevent infection of the wound with the most probable organisms to be encountered for that type of operation. For most operations, a single antimicrobial is sufficient to prevent SSIs. However, there may be cases where an unlikely contaminant is present or suspected (eg, there is coexisting infection) in which additional coverage is necessary. For clean procedures, it is recommended to treat or remove other sources of infection before an elective operation [13]. If it is not possible to postpone the operation, antimicrobial pro-

...
Gynecologic and obstetric surgery

For abdominal or vaginal hysterectomy, cefotetan is preferred, but reasonable alternatives are cefazolin or cefoxitin [10–12,14–16,60]. Metronidazole monotherapy is included in the American College of Obstetricians and Gynecologist’s Practice Bulletin as an alternative for patients undergoing hysterectomy, although it may be less effective as a single agent for prophylaxis [15]. In cases of beta-lactam allergy, the workgroup recommends the use of 1 of the following regimens: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; metronidazole combined with gentamicin or ciprofloxacin; or clindamycin monotherapy. Levofloxacin, 750 mg, given once can be substituted for ciprofloxacin.

Patients undergoing cesarean section can be divided into low- and high-risk groups for postoperative infection [61]. High-risk patients include cesarean deliveries after rupture of the membranes, onset of labor, or both, and patients who undergo emergency operations for which preoperative cleansing may have been inadequate. Although antimicrobial prophylaxis is recommended for both risk groups, the benefits are greatest for high-risk patients. A narrow-spectrum antimicrobial regime similar to that recommended for hysterectomy provides adequate prophylaxis [62,63]. In the United States, the antimicrobial is usually not administered until the umbilical cord is clamped. Although there is no evidence to support the delay in administration, it is standard

Table 2  
Suggested initial dose and time to redosing for antimicrobials commonly used for surgical prophylaxis [88–90]

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Half-life normal renal function (h)</th>
<th>Half-life end-stage renal disease (h)</th>
<th>Recommended infusion time (min)</th>
<th>Standard intravenous dose (g)</th>
<th>Weight-based dose recommendation* (mg)</th>
<th>Recommended redosing interval† (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td>1.5–2</td>
<td>6</td>
<td>3–5‡</td>
<td>1–2</td>
<td>Maximum 2 g (adults)</td>
<td>3–5</td>
</tr>
<tr>
<td>Ciprifloxacin</td>
<td>3.5–5</td>
<td>5–9</td>
<td>60</td>
<td>400 mg</td>
<td>400 mg</td>
<td>4–10</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>1.2–2.5</td>
<td>40–70</td>
<td>3–5‡</td>
<td>1–2</td>
<td>20–30 mg/kg</td>
<td>2–5</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>1–2</td>
<td>15–22</td>
<td>3–5‡</td>
<td>1.5</td>
<td>50 mg/kg</td>
<td>3–4</td>
</tr>
<tr>
<td>Cefamandole</td>
<td>0.5–2.1</td>
<td>12.3–18</td>
<td></td>
<td></td>
<td>3–5‡</td>
<td>15–60§</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>0.5–1.1</td>
<td>6.5–23</td>
<td>3–5‡</td>
<td>1–2</td>
<td>20–40 mg/kg</td>
<td>3–6</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>2.8–4.6</td>
<td>13–25</td>
<td>3–5‡</td>
<td>1–2</td>
<td>20–40 mg/kg</td>
<td>3–6</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>2–5.1</td>
<td>3.5–5.0¶</td>
<td>10–60</td>
<td>600–900 mg</td>
<td>&lt;10 kg: at least 37.5 mg</td>
<td>3–6</td>
</tr>
<tr>
<td>Erythromycin base</td>
<td>0.8–3</td>
<td>5–6</td>
<td>NA</td>
<td>1 g orally 19, 18, 9 h before surgery</td>
<td>9–13 mg/kg</td>
<td>NA</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2–3</td>
<td>50–70</td>
<td>30–60</td>
<td>1.5 mg/kg#</td>
<td>See footnote#</td>
<td>3–6</td>
</tr>
<tr>
<td>Neomycin</td>
<td>2–3 hours (3% absorbed under normal gastrointestinal conditions)</td>
<td>12–≤24</td>
<td>NA</td>
<td>1 gm orally 19, 18, 9 h before surgery</td>
<td>20 mg/kg</td>
<td>NA</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>6–14</td>
<td>7–21 no change</td>
<td>30–60</td>
<td>0.5–1</td>
<td>15 mg/kg (adult) 7.5 mg/kg on subsequent doses</td>
<td>6–8</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>4–6</td>
<td>44.1–406.4 (Clcr &lt;10 mL/min)</td>
<td>1 g ≥60 min (use longer infusion time if dose &lt;1 g)</td>
<td>1.0</td>
<td>10–15 mg/kg (adult)</td>
<td>6–12</td>
</tr>
</tbody>
</table>

DW = dosing weight; IBW = ideal body weight; NA = not applicable.

* Weight-based doses are primarily from published pediatric recommendations.
† For procedures of long duration, antimicrobials should be redosed at intervals of 1 to 2 times the half-life of the drug. The intervals in the table were calculated for patients with normal renal function.
‡ Dose injected directly into vein or running intravenous fluids.
§ Intermittent intravenous infusion.
¶ The half-life of clindamycin is the same or slightly increased in patients with end-stage renal disease compared with patients with normal renal function.
# If the patient’s weight is 30% above their ideal body weight, dosing weight can be determined as follows: DW = IBW + 0.4 (total body weight-IBW).
practice and is preferred by neonatologists because of concern of masking septic manifestations in the neonate [64].

Orthopedic total joint (hip and knee) arthroplasty

The preferred antimicrobial for prophylaxis in patients undergoing hip or knee arthroplasty is either cefazolin or cefuroxime [10–12,14,16]. Vancomycin or clindamycin may be used in patients with serious allergy or adverse reactions to beta-lactam agents. Several studies comparing short- versus long-duration antimicrobial prophylaxis for total joint arthroplasty have shown no advantage to prolonged prophylaxis [3,65–70]. The workgroup recommends that antimicrobial prophylaxis be discontinued within 24 hours after the end of the operation [3,10–12,14,16,65–70]. If a proximal tourniquet is used, the antimicrobial should be completely infused before inflation.

There is no evidence that continuing antimicrobial agents until all catheters and drains are removed will lower infection rates. However, the use of drains has been associated with numerous complications including infection, drain retention, and soft tissue problems [71–73]. The necessity of drains for total joint arthroplasty is controversial [72–80]. With time, there is increased bacterial colonization of the drain tip and migration of skin organisms into the wound [81–83].

Despite the potential benefits of antibiotic-impregnated bone cement for joint arthroplasty, controversies remain regarding its use. There are no established guidelines for use of these agents for prophylaxis. Commercially available, preblended antibiotic bone cements are indicated only for use in the second stage of a 2-stage revision for total joint arthroplasty after elimination of active infection. These products are not currently approved for prophylaxis.

Cardiothoracic and vascular surgery

The recommended antimicrobial agents for cardiothoracic and vascular operations include cefazolin or cefuroxime [10–12,14,16]. For patients with serious allergy or adverse reaction to beta-lactam agents, vancomycin is appropriate, and clindamycin may be an acceptable alternative [13]. The workgroup acknowledged the concern of some cardiovascular surgeons about discontinuing the antimicrobial before all invasive lines and drains are removed. Although a number of studies have found no advantage of long- over short-duration prophylaxis during cardiothoracic surgery, the consequences of deep sternal infections or infected prostheses are devastating. Longer-duration prophylaxis has been associated with higher rates of resistant organisms when SSI occurs [29]. The consensus of the workgroup is that prophylaxis lasting ≤24 hours is acceptable and that there is no evidence showing that giving antimicrobial agents for longer periods of time will decrease SSI rates. Table 3 Pending a systematic review of the literature by its Committee on Evidence-based Medicine, the Society of Thoracic Surgeons currently recommends that antimicrobial prophylaxis be continued for 24 to 48 hours.

Colorectal surgery

Antimicrobial prophylaxis for colorectal operations can consist of an oral antimicrobial bowel preparation, preoperative parenteral antimicrobial, or a combination of both. Recommended oral prophylaxis consists of neomycin plus erythromycin, or neomycin plus metronidazole, started no more than 18 to 24 hours before surgery along with a mechanical bowel preparation. Cefotetan or cefoxitin are recommended for parenteral prophylaxis [10–12,14,16]. The combination of parenteral cefazolin and metronidazole is also recommended as a cost-effective alternative [84,85]. Although a recent study suggested that the combination of oral prophylaxis with parenteral antimicrobial prophylaxis might result in lower SSI rates, this is not specified in any published guideline [86]. A survey of colorectal surgeons found that combination oral and parenteral prophylaxis is common practice in the United States [87]. For patients with confirmed allergy or adverse reaction to beta-lactam agents, use of one of the following regimens is recommended: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; or metronidazole combined with gentamicin or ciprofloxacin. Levofloxacin, 750 mg, given once can be substituted for ciprofloxacin.

Conclusion

Optimal prophylaxis ensures that adequate concentrations of an appropriate antimicrobial are present in the serum, tissue, and wound during the entire time that the incision is open and at risk for bacterial contamination. The antimicrobial agent should be active against bacteria that are likely to be encountered in the particular type of operation and should be safe for the patient and economical for the hospital. The selection and duration of antimicrobial prophylaxis should have the smallest impact possible on the normal bacterial flora of the patient and the microbiologic ecology of the hospital.

In this advisory statement, the Surgical Infection Prevention Guideline Writers Workgroup attempted, as they did with their own individual guidelines, to address the need for effective, safe, economical prophylaxis that does not promote antimicrobial-resistant bacteria. The advice included in this report will fit most patients at the majority of facilities. However, sound clinical judgment must be exercised to recognize those unusual cases in which an alternative approach is necessary. Many of the studies that have supported the development of antimicrobial prophylaxis guidelines are quite old, and antimicrobial susceptibility patterns change with time. Clinicians must continue to evaluate current literature and carefully examine susceptibility patterns within their own institutions.
Table 3
Summary of the Surgical Infection Prevention Guideline Writers Workgroup consensus positions

<table>
<thead>
<tr>
<th>Principals and antibiotic selection</th>
<th>Consensus position</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General principles</strong></td>
<td>Infusion of the first antimicrobial dose should begin within 60 minutes before the surgical incision is made.*</td>
</tr>
<tr>
<td><strong>Duration of prophylaxis</strong></td>
<td>Prophylactic antimicrobials should be discontinued within 24 hours of the end of surgery.</td>
</tr>
<tr>
<td><strong>Screening for β-lactam allergy</strong></td>
<td>For those operations for which the cephalosporins represent the most appropriate antimicrobials for prophylaxis, the medical history should be adequate to determine if the patient has a history of allergy or serious adverse antibiotic reaction. Alternative testing strategies (eg, skin testing) may be useful in patients with reported allergy [35–37].</td>
</tr>
<tr>
<td><strong>Antimicrobial dosing</strong></td>
<td>The initial antimicrobial dose should be adequate based on the patient’s weight, adjusted dosing weight, or body mass index. An additional dose of antimicrobial should be given intraoperatively if the operation is still continuing two half-lives after the initial dose.†</td>
</tr>
</tbody>
</table>

**Antibiotic selection**

**Abdominal or vaginal hysterectomy**
- Cefotetan is preferred; cefazolin or cefoxitin are alternatives; metronidazole monotherapy.‡
- If β-lactam allergy:
  - Clindamycin combined with gentamicin or ciprofloxacin§ or aztreonam
  - Metronidazole combined with gentamicin or ciprofloxacin§
  - Clindamycin monotherapy

**Hip or knee arthroplasty**
- Cefazolin or cefuroxime
  - If β-lactam allergy:
    - Vancomycin
    - Clindamycin

**Cardiothoracic and vascular surgery**
- Cefazolin or cefuroxime
  - If β-lactam allergy:
    - Vancomycin
    - Clindamycin

**Colon surgery**
- Oral antimicrobial prophylaxis:
  - Neomycin plus erythromycin base
  - Neomycin plus metronidazole
- Parenteral antimicrobial prophylaxis:
  - Cefotetan or cefoxitin
  - Cefazolin plus metronidazole
- If β-lactam allergy:
  - Clindamycin combined with gentamicin or ciprofloxacin§ or aztreonam
  - Metronidazole with gentamicin or ciprofloxacin§

* In those settings where a fluoroquinolone or vancomycin is indicated, the infusion of the first antimicrobial dose should begin within 120 minutes before the incision.
† See Table 2.
‡ Metronidazole monotherapy is included in the American College of Obstetricians and Gynecologist’s Practice Bulletin as an alternative to beta-lactams for patients undergoing hysterectomy although it may be less effective as a single agent for prophylaxis [15].
§ Levofloxacin 750 mg given once may be substituted for ciprofloxacin.

**Required Disclaimer**

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**Appendix**

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Acknowledgments

The following organizations have endorsed this advisory statement: American Academy of Orthopaedic Surgeons; American Association of Nurse Anesthetists; American College of Surgeons; American College of Osteopathic Surgeons; American Geriatrics Society; American Society of Anesthesiologists; American Society of Colon and Rectal Surgeons; ASHP; American Society of PeriAnesthesia Nurses; Ascension Health; Association of periOperative Registered Nurses; Association for Professionals in Infection Control and Epidemiology; Infectious Diseases Society of America; The Medical Letter; Premier, Inc.; Society for Healthcare Epidemiology of America; Society of Thoracic Surgeons; Surgical Infection Society. The following organizations have had the opportunity to review and provide comment on this advisory statement: American College of Obstetricians and Gynecologists; American Hospital Association; CDC; Joint Commission on Accreditation of Healthcare; VHA, Inc.

References


[46] Laupland KB, Conly JM. Treatment of Staphylococcus aureus coloni-

zation and prophylaxis for infection with topical intranasal mup-


SMART Approaches for Reducing Nosocomial Infections in the ICU

Marin Kollef

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The online version of this article, along with updated information and services can be found online on the World Wide Web at: http://www.chestjournal.org/content/134/2/447.full.html
SMART Approaches for Reducing Nosocomial Infections in the ICU*

Marin Kollef, MD, FCCP

Nosocomial infections are problematic in the ICU because of their frequency, morbidity, and mortality. The most common ICU infections are pneumonia, bloodstream infection, and urinary tract infection, most of which are device related. Surgical site infection is common in surgical ICUs, and Clostridium difficile-associated diarrhea is occurring with increasing frequency. Prospective observational studies confirm that use of evidence-based guidelines can reduce the rate of these ICU infections, especially when simple tactics are bundled. To increase the likelihood of success, follow the specific, measurable, achievable, relevant, and time bound (SMART) approach. Choose specific objectives that precisely define and quantify desired outcomes, such as reducing the nosocomial ICU infection rate of an institution by 25%. To measure the objective, monitor staff adherence to tactics and infection rates, and provide feedback to ICU staff. Make objectives achievable and relevant by engaging stakeholders in the selection of specific tactics and steps for implementation. Nurses and other stakeholders can best identify the tactics that are achievable within their busy ICUs. Unburden the bedside provider by taking advantage of new technologies that reduce nosocomial infection rates. Objectives should also be relevant to the institution so that administrators provide adequate staffing and other resources. Appoint a team to champion the intervention and collaborate with administrators and ICU staff. Provide ongoing communication to reinforce educational tactics and fine-tune practices over time. Make objectives time bound; set dates for collecting baseline and periodic data, and a completion date for evaluating the success of the intervention.

(CHEST 2008; 134:447–456)

Key words: catheter-related bloodstream infection; prevention; surgical-site infection; urinary tract infection; ventilator-associated pneumonia

Abbreviations: BSI = bloodstream infection; CI = confidence interval; CVC = central venous catheter; ETT = endotracheal tube; HICPAC = Healthcare Infection Control Practices Advisory Committee; RR = relative risk; SMART = specific, measurable, achievable, relevant, and time bound; SSI = surgical site infection; UTI = urinary tract infection; VAP = ventilator-associated pneumonia

The Centers for Disease Control and Prevention estimates that 1.7 million nosocomial infections occurred in the United States in 2002. ICUs had the highest rates of infection, at 13 per 1,000 patient-days, and mortality, ranging from 11% for surgical site infection (SSI) to 25% for bloodstream infection (BSI). The most common ICU infections are pneumonia, urinary tract infection (UTI), and BSI, and are usually device related. The rate of device-related ICU infections has decreased during the last 25 years (Fig 1).

The US government is providing new incentives for further improvement. The Centers for Medicare and Medicaid Services will stop reimbursing hospitals for care made necessary by eight preventable complications as of October 1, 2008. Two of these are ICU complications: vascular catheter-related BSI and catheter-associated UTI. Other ICU infections are expected to follow, such as ventilator-associated pneumonia (VAP) and methicillin-resistant Staphylococcus aureus infection.

The need for improvement has generated many articles on ICU infections, including the excellent review by Eggimann and Pittet, and evidence-based guidelines. Many of these guidelines will be updated in 2008, so they are summarized only briefly in this review. Observational studies confirm that evidence-based approaches can reduce infection...
rates. For example, a single surveillance tactic involving German ICUs significantly reduced rates of catheter-related BSI rates (relative risk [RR], 0.80), VAP (RR, 0.71), and SSI (RR, 0.72). Analyses of studies showed that bundled interventions were even more effective and reduced rates of catheter-related BSI by a range of 29 to 95% and VAP by 31 to 57%.

Management guru Peter Drucker conceptualized management by objectives > 50 years ago and advocated the use of specific, measurable, achievable, relevant, and time-bound (SMART) objectives. The purpose of this review is to summarize recent studies of preventive interventions in the ICU, with the aim of identifying SMART objectives to further reduce the infection rate. A PubMed search was conducted to identify observational studies of bundled interventions that aimed to prevent nosocomial infections; studies published since the year 2000 were selected whenever possible.

No decision has been made unless carrying it out in specific steps has become someone’s work assignment and responsibility.

Peter F. Drucker, management guru

**INTRAVASCULAR CATHETER-RELATED BSI**

The Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines for preventing intravascular-catheter-related BSI include educating health-care workers, assessing their knowledge of and adherence to guidelines, and using designated, trained personnel to insert and maintain catheters (Table 1). The guidelines also include routine monitoring to determine infection rates in patients with central venous catheters (CVCs), trends in those rates, and lapses in infection-control practices. Surveillance should include a written plan, maintaining intensity and consistency over time, adequate personnel and other resources, and annual evaluation.

Prospective observational studies confirm that bundled interventions can significantly reduce infection rates (Table 2). Success rates, however, are highly variable depending on institution-specific factors, such as the baseline infection rate, preventive tactics chosen for bundles, and adherence to the tactics. Success rates also vary depending on study design, especially duration of observation, as well as many other variables.

My colleagues conducted a series of studies at our 1,200-bed facility beginning in 1998. Specific...

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Table 1—Guidelines for Preventing Intravascular Catheter-Related Infections

<table>
<thead>
<tr>
<th>Effective interventions (category IA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education of health-care workers, with assessment of knowledge of and adherence to guidelines</td>
</tr>
<tr>
<td>Designated, trained personnel to insert and maintain catheters</td>
</tr>
<tr>
<td>Proper hand hygiene with antiseptic-containing soap and water or with waterless alcohol-based gel or foam</td>
</tr>
<tr>
<td>Aseptic technique during catheter insertion and care</td>
</tr>
<tr>
<td>Clean gloves for insertion of peripheral catheters and sterile gloves for arterial and central catheters</td>
</tr>
<tr>
<td>Maximal sterile barrier precautions for CVC insertion</td>
</tr>
<tr>
<td>Care of catheter site</td>
</tr>
<tr>
<td>Skin disinfection with 2% chlorhexidine or 70% alcohol use of sterile gauze or transparent, semipermeable dressing</td>
</tr>
<tr>
<td>Replacement of damp, loose, or soiled CVC dressing</td>
</tr>
<tr>
<td>Selection of catheter, insertion technique, and site with lowest complication risk</td>
</tr>
<tr>
<td>Prompt removal of catheter that is no longer essential</td>
</tr>
<tr>
<td>Replacement of administration sets not more frequently than every 72 h (unless infection is suspected)</td>
</tr>
<tr>
<td>Cleansing of injection port with 70% alcohol or iodophor before access</td>
</tr>
<tr>
<td>Appropriate preparation and quality control of intravenous admixtures</td>
</tr>
<tr>
<td>Surveillance to determine infection rates, trends, and lapses in infection control</td>
</tr>
</tbody>
</table>

**Interventions to be avoided**

| Routine antibiotic prophylaxis including topical, intranasal, and systemic formulations |
| Routine use of antibiotic lock solution |
| Routine use of arterial or venous cut-down for catheter insertion |
| Routine use of in-line filters for infection control |

*From O’Grady et al. Category IA = strongly recommended for implementation and strongly supported by well-designed studies.
risk-reduction tactics focused on methods for the following: (1) hand hygiene and aseptic technique; (2) detecting signs and symptoms of infection; (3) sending catheter-tip culture; (4) catheter-site care; (5) replacing administration sets and fluids; (6) caring for injection ports and dead-end caps; (7) handling parenteral fluids and multidose vials; and (8) drawing blood cultures. This educational intervention was directed at surgical ICU nurses and decreased the rate of CVC-related infections by 66% ($p < 0.0001$). 26 The number of infections fell to none the second month after intervention, but this level of success was not sustainable over the 18-month postintervention period. Random bedside audits revealed multiple adherence deficiencies,27 the most common being failure to date the dressing (nonadherence rate, 89%) and improper hand hygiene (83%). Next, my colleagues27 designed behavioral interventions for nurses and physicians, which generally improved adherence and led to a nonsignificant trend toward a further decrease in infection rate.

In our third study,28 the educational intervention was expanded to include physicians and provide monthly feedback on infection rates to ICU staff. This bundled approach decreased the CVC-related infection rate by 42% ($p = 0.019$). As in the previous study,26 the early zero infection rate was not sustainable throughout the 24-month postintervention period,28 underscoring the need for achievable objectives. For example, Bhutta and colleagues30 aimed to reduce infection rates below the national rate by the year 2000. They formed a multidisciplinary team to implement evidence-based tactics in a stepwise manner. The overall relative RR of 75% ($p < 0.001$) met their predefined objective. 30 Eggimann and colleagues29 reported a sustained reduction for 6 years after implementing a bundled approach. Adherence may have been improved by involving staff members in program design and requiring training for new nurses, residents, and fellows.29

Three studies confirmed success across multiple institutions. In Pennsylvania,31 an advisory committee of regional infection-control experts discussed

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### Table 2—Effect of Bundled Interventions on CVC-Related Infections

<table>
<thead>
<tr>
<th>Intervention</th>
<th>No. of Infections/1,000 Catheter-Days</th>
<th>p Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-institution studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-study module, specific risk-reduction strategies, before and after testing of surgical ICU nurses</td>
<td>10.8</td>
<td>3.7</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>Audit-based behavioral intervention for surgical ICU physicians and nurses with pictures, lectures, and hands-on demonstrations</td>
<td>3.4</td>
<td>2.8</td>
<td>0.40</td>
</tr>
<tr>
<td>Self-study module, specific risk-reduction strategies, before and after testing of medical ICU physicians and nurses</td>
<td>9.4</td>
<td>5.5</td>
<td>0.019</td>
</tr>
<tr>
<td>Bundle with specific guidelines and on-site education for medical ICU physicians and nurses</td>
<td>24.6</td>
<td>3.0–7.9</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Stepwise program: maximal barrier precaution, antibiotic-impregnated catheter, hand hygiene, between-bed barriers, skin disinfection</td>
<td>9.7</td>
<td>3.0</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td><strong>Multiinstitution studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evidence-based practices, educational module, tools for recording adherence, standardized catheter insertion kits, monitoring, and feedback</td>
<td>Median, 2.7</td>
<td>0</td>
<td>$\leq 0.002$</td>
</tr>
<tr>
<td>Education of ICU physicians and nurses about five evidence-based procedures, with team leaders partnered with infection control for implementation and data collection</td>
<td>Mean, 7.7</td>
<td>1.4</td>
<td>$&lt; 0.002$</td>
</tr>
<tr>
<td>Update of written policies, lectures, self-study module, before and after testing of medical ICU physicians and nurses</td>
<td>11.2</td>
<td>8.9</td>
<td>RR, 0.79 (95% CI, 0.67–0.93)</td>
</tr>
</tbody>
</table>
strategies and collaborated with infection-control professionals and medical staff at participating hospitals. This bundle reduced the mean infection rate by 68% over 4 years. In Michigan, each ICU designated physician and nurse team leaders who partnered with local infection-control practitioners to implement interventions and monitor infection rates. The evidence-based procedures were similar to those in the Pennsylvania study and also included hand hygiene. This bundled intervention significantly reduced the infection rate at 3 months and sustained it for 18 months. In a multistate study, significant improvements occurred in the percentage of CVCs inserted into the femoral vein (relative ratio, 0.73; 95% confidence interval [CI], 0.61 to 0.88), proportion of properly dated dressings (relative ratio, 1.29; 95% CI, 1.17 to 1.42), and infection rate (relative ratio, 0.79, 95% CI, 0.67 to 0.93).

Hand hygiene is a seemingly simple practice that merits consideration because of the impact on CVC-associated BSIs and low staff adherence rate of only 40%. Coopersmith was shocked that none of five physicians washed their hands or used alcohol foam before inserting CVCs. Simply disseminating hand hygiene guidelines does not change practice; bundled approaches are more likely to be effective. Bhutta et al first attempted to improve adherence with annual campaigns that included posters, hospital television video, before and after intervention testing, and newsletters. To further facilitate hand washing, his institution quadrupled the number of hand-washing stations per bed and added two alcohol-gel stations per bed. Collectively, these tactics increased adherence to hand hygiene from 47 to 82%. These practices are generally consistent with HICPAC hand-washing guidelines, which address educational and motivational programs, administrative measures, selection of hand-washing agents, and other aspects of hand hygiene. Adequacy of staffing and other resources also merit consideration because of the impact on CVC-related BSI and other nosocomial ICU infections. For example, the patient-to-nurse ratio was an independent risk factor for CVC-related BSI in the surgical ICU, suggesting that staff reductions contributed to an outbreak of BSIs by impeding adequate catheter care during increased use of total parenteral nutrition.

Novel tactics are being evaluated for added benefit to bundles. For example, antiseptic- or antibiotic-impregnated catheters and antiseptic-impregnated dressings may be useful because these tactics mitigate any adherence problems for busy ICU staff, especially when target infection rates cannot be achieved. Minocycline- and rifampin-impregnated catheters were the second step implemented by Bhutta and colleagues. Each step appeared to further reduce the infection rate; however, the incremental benefit of these catheters was not specified. Vancomycin lock solution was beneficial in high-risk patients (risk ratio, 0.34; 95% CI, 0.12 to 0.98; p = 0.04) in a metaanalysis of seven studies; however, studies are needed to assess the impact on resistance. Staphylococcus aureus conjugate vaccine conferred partial immunity against S aureus bacteremia in a double-blind study of patients undergoing hemodialysis (estimate of efficacy, 57%; 95% CI, 10 to 81%; p = 0.02), but the benefit waned after 40 weeks. A sutureless device for securing peripherally inserted CVCs reduced the infection rate in a randomized comparison with sutures (infection rate, 2% vs 12%; p = 0.032), but larger studies are needed to confirm these findings.

The things included in the measurement become relevant; the things omitted are out of sight and out of mind.

Peter F. Drucker

VAP

The American Thoracic Society and HICPAC rate their recommendations on the strength of supporting evidence (Table 3). These guidelines are based on VAP pathogenesis and aim to prevent bacterial colonization of the aerodigestive tract (eg, routine hand hygiene between patient contacts) and aspiration (eg, continuous aspiration of subglottic secretions and semirecumbent positioning of the patient). Nonadherence is common among physicians and nurses, and does not correlate with the level of evidence. Among physicians, the most common reasons for nonadherence are disagreement with interpretation of clinical studies (35%), lack of resources (31%), and costs (17%). Among nurses, the most common reasons are lack of resources (37%), miscellaneous (overwork, lack of time for hand washing; 22%), patient discomfort (8%), disagreement with reported study results (8%), and fear of potential adverse events (6%). In another survey, nurses perceived that the main determinant of semirecumbency was physicians’ orders, whereas intensivists perceived that the main determinant was nursing preference. These heterogeneous factors should be considered in designing educational approaches.

Prospective observational studies confirm that educational interventions can encourage bundled practices, which in turn can significantly reduce infection rates (Table 4). For example, my colleagues conducted a series of studies, first at our adult teaching hospital and subsequently at three additional local hospitals. Specific risk-reduction tac-
tactics included meticulous hand hygiene, semirecumbent positioning (30° to 45°), oral intubation, and regularly draining condensate from ventilator circuits. This intervention decreased VAP rates by 58% at the teaching hospital (p < 0.001) and 46% at all four hospitals (p < 0.001). Decreases were significant at each hospital, except for one community hospital where respiratory therapists had the lowest educational module completion rate (p < 0.001), suggesting the importance of adherence to educational tactics.

### Table 3—Guidelines for Preventing VAP

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Level of Recommendation†</th>
<th>ATS¹⁵</th>
<th>CCCTG¹⁶</th>
<th>HICPAC¹⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection control program (eg, staff education)</td>
<td>I</td>
<td></td>
<td>IA</td>
<td></td>
</tr>
<tr>
<td>Monitor ICU infections</td>
<td>II</td>
<td>IB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral (nonnasal) intubation</td>
<td>II</td>
<td>Yes</td>
<td>IB</td>
<td></td>
</tr>
<tr>
<td>Avoidance of unnecessary reintubation</td>
<td>I</td>
<td>II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scheduled drainage of condensate from ventilator circuits</td>
<td>I</td>
<td>Yes</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>Continuous subglottic suctioning</td>
<td>I</td>
<td></td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>Maintenance of adequate pressure in ETT cuff</td>
<td>II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand hygiene between patient contacts</td>
<td>I</td>
<td></td>
<td>IA</td>
<td></td>
</tr>
<tr>
<td>Semirecumbent positioning (30° to 45°)</td>
<td>I</td>
<td>Yes</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>Enteral (not parenteral) nutrition</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective interventions for selected (not routine) indications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic prophylaxis for patients with head injuries</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective digestive decontamination for MDR outbreaks</td>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral chlorhexidine (eg, coronary bypass graft)</td>
<td>I</td>
<td></td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>Ineffective interventions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine changes of ventilator circuit</td>
<td></td>
<td>No</td>
<td>No (IA)</td>
<td></td>
</tr>
<tr>
<td>Daily changes of heat and moisture exchangers</td>
<td>No</td>
<td>No</td>
<td>Unresolved</td>
<td></td>
</tr>
<tr>
<td>Chest physiotherapy</td>
<td>No</td>
<td>No</td>
<td>(II)</td>
<td></td>
</tr>
<tr>
<td>Routine use of antibiotic prophylaxis, SDD, or oral chlorhexidine</td>
<td>No (I)</td>
<td>No</td>
<td>Unresolved</td>
<td></td>
</tr>
<tr>
<td>Interventions of equivocal or undetermined effectiveness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passive humidifier or heat-moisture exchanger</td>
<td>No (I)</td>
<td>Yes</td>
<td>Unresolved</td>
<td></td>
</tr>
<tr>
<td>Postural changes</td>
<td>No (I)</td>
<td>Consider</td>
<td>Unresolved</td>
<td></td>
</tr>
<tr>
<td>Sulcrafate (vs histamine type-2 antagonist) to prevent stress ulcers</td>
<td>Yes (I)</td>
<td>No</td>
<td>Unresolved</td>
<td></td>
</tr>
</tbody>
</table>

*CCCTG = Joint Planning Group of the Canadian Critical Care Trials Group and Canadian Critical Care Society; ATS = American Thoracic Society; MDR = multidrug resistant; SDD = selective digestive decontamination.
†Recommendations rated by level of evidence, with I and IA representing stronger evidence than II (see text for details).

### Table 4—Effect of Bundled Interventions on VAP

<table>
<thead>
<tr>
<th>Interventions</th>
<th>No. Infections/1,000 Ventilator-Days</th>
<th>Significance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Intervention</td>
<td>After Intervention</td>
<td></td>
</tr>
<tr>
<td>Self-study module, specific risk-reduction strategies, lectures, fact sheets, posters, before and after testing of respiratory care practitioners and ICU nurses at an adult teaching hospital</td>
<td>12.6</td>
<td>5.7</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Self-study module, specific risk-reduction strategies, lectures, fact sheets, posters, before and after testing of respiratory care practitioners and ICU nurses at four hospitals in St. Louis</td>
<td>8.8</td>
<td>4.7</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Implementation of stepwise strategies by ICU nurses and respiratory therapists: (1) elevating head of bed, (2) using sterile water and enteral valves for nasogastric feeding, (3) prolonging interval for changing in-line suction catheters</td>
<td>Surgical ICU, 45.1</td>
<td>27.9</td>
<td>Incidence rate difference, 17.2; 95% CI, 2.9 to 31.6</td>
</tr>
<tr>
<td></td>
<td>Medical ICU, 22.4</td>
<td>11.6</td>
<td>Incidence rate difference, 10.8; 95% CI, 4.7 to 16.9</td>
</tr>
</tbody>
</table>
Lai and colleagues\textsuperscript{53} assembled a team at the University of Massachusetts Medical Center to outline and implement tactics in a stepwise manner. Steps focused on respiratory therapists and ICU nurses who received quarterly feedback on VAP rates. Diagnosing physicians were not aware of the intervention, potentially limiting bias. Each step further reduced VAP rates, for overall reductions of 38% (surgical ICU) and 48% (medical ICU).\textsuperscript{53}

Novel tactics are being evaluated for added benefit to bundles. For example, a silver-coated endotracheal tube (ETT) is promising because it is the first tactic to become user independent after intubation, circumventing the dual problems of adherence and workload. Clinical benefit was demonstrated in a multicenter, randomized, controlled study.\textsuperscript{54} In patients intubated \textgreek{gamma} 24 h, the silver-coated ETT was associated with reduced rates of microbiologically confirmed VAP at any time after intubation (rate for silver vs uncoated, 4.8\% vs 7.5\%; RR reduction, 35.9\%; \(p = 0.03\)) and within 10 days of intubation (rate, 3.5\% vs 6.7\%; RR reduction, 47.6\%; \(p = 0.005\)). The device appeared to confer additional benefit because participating institutions followed local preventive practices and avoided change during the study. There were no between-group differences in frequency and severity of adverse events.\textsuperscript{54} Subglottic secretion drainage reduced the incidence of VAP by nearly half (relative ratio, 0.51; 95\% CI, 0.37 to 0.71) in a metaanalysis.\textsuperscript{55} The benefit occurred in patients expected to require \textgreek{gamma} 72 h of mechanical ventilation and was primarily attributable to reduced incidence of early onset pneumonia. Subglottic secretion drainage is associated with few complications, except for case reports of tracheal mucosal injury,\textsuperscript{56} and anecdotal reports of plugging of the specialized lumen for aspiration of secretions.\textsuperscript{55}

Can we achieve this idea? Or can we only talk about it?\textsuperscript{57} Peter F. Drucker

HICPAC guidelines\textsuperscript{18} for preventing catheter-associated UTI were published in 1981 (Table 5) and are currently under revision. Current category 1 recommendations include educating staff about correct aseptic catheter insertion and care techniques, hand washing before and after catheter manipulation, maintaining a closed system, properly securing catheters, and maintaining unobstructed urine flow. A practice to be avoided in ICUs is routine use of prophylactic antibiotics.\textsuperscript{57}

Prospective observational studies\textsuperscript{58,59} confirm that preventive interventions can significantly reduce catheter-associated UTI rates (Table 6). For example, Goetz and colleagues\textsuperscript{58} reported that simply providing nurses with unit-specific quarterly feedback on infection rates reduced them by 46\% (p = 0.002). Rosenthal and colleagues\textsuperscript{59} implemented a bundle that led to an RR reduction of 0.58 (95\% CI, 0.39 to 0.86; \(p = 0.006\)).\textsuperscript{59}

Novel tactics should be considered for added benefit to bundles. For example, silver alloy-coated urinary catheters have been studied extensively and shown to significantly reduce catheter-associated UTI rates in metaanalyses.\textsuperscript{60,61} Only two studies\textsuperscript{62,63} have focused specifically on the ICU, and trends favoring silver-coated catheters were not significant. Nonetheless, urinary catheters are used widely across the entire inpatient setting (ICU and non-

<table>
<thead>
<tr>
<th>Table 5—Guidelines for Preventing Catheter-Associated UTI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective interventions (category I)</td>
</tr>
<tr>
<td>Education of health-care workers in correct techniques of catheter insertion and maintenance</td>
</tr>
<tr>
<td>Catheterization only when necessary</td>
</tr>
<tr>
<td>Hand hygiene</td>
</tr>
<tr>
<td>Use of aseptic technique and sterile equipment for catheter insertion</td>
</tr>
<tr>
<td>Proper securing of catheter</td>
</tr>
<tr>
<td>Maintenance of closed sterile drainage</td>
</tr>
<tr>
<td>Aseptic methods for obtaining urine samples</td>
</tr>
<tr>
<td>Maintenance of unobstructed urine flow</td>
</tr>
<tr>
<td>Interventions to be avoided</td>
</tr>
<tr>
<td>Regular bacteriologic monitoring</td>
</tr>
<tr>
<td>Routine use of prophylactic antibiotics†</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
*From Wong et al.\textsuperscript{18} Category I = strongly recommended for adoption. †From Leone et al.\textsuperscript{57}

<table>
<thead>
<tr>
<th>Table 6—Effect of Interventions on Catheter-Associated UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Feedback to nursing staff</td>
</tr>
<tr>
<td>Education about hand washing and positioning catheter to avoid compression, feedback on adherence, and infection rates</td>
</tr>
</tbody>
</table>
One of the most ICU-relevant guidelines involves postoperative incision care, specifying sterile dressing for 24 to 48 h after primary closure, and hand washing before and after any surgical-site contact.19 Prospective observational studies66–68 confirm that preventive interventions can significantly reduce SSI rates (Table 8). For example, Geubbels and colleagues67 reported success with a national surveillance network in the Netherlands that enabled hospitals to compare rates and optimize infection-control practices. The adjusted risk of infection was reduced by 31% during the fourth year (95% CI, 11 to 46%) and 57% during the fifth year (95% CI, 24 to 76%).67 Dellinger and colleagues68 reported success with a 1-year collaborative project in which teams of clinical champions (eg, surgeon and infection-control professional) attended sessions on implementing and measuring change. Multiple types of communication facilitated exchange of innovations, barriers, lessons learned, and results. The infection rate was reduced by 27% from the first to the last quarter (p = 0.0005).68

Time is the scarcest resource and unless it is managed, nothing else can be managed.

Peter F. Drucker

**Clostridium difficile-Associated Diarrhea**

*C difficile* is the most common cause of nosocomial diarrhea,20 an increasingly common ICU problem. When the Society of Healthcare Epidemiology of America published its 1995 position paper,20 the only guidelines supported by good evidence were using gloves to handle body substances, using disposable thermometers during outbreaks, and antimicrobial stewardship. Studies conducted since 1995 support additional practices aiming at the following: (1) to prevent ingestion of *C difficile* through environmental control, staff hygiene, and barrier precautions; and (2) to reduce the risk of infection after

---

### Table 7—Summary of Guidelines for Preventing SSI*

<table>
<thead>
<tr>
<th>Effective interventions (category I)</th>
<th>Infection Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative preparation of patient, hand and forearm antisepsis, and management of infected or colonized surgical personnel</td>
<td>9.2*</td>
</tr>
<tr>
<td>Antimicrobial prophylaxis only when indicated, with dosing to maintain bactericidal levels throughout surgery</td>
<td>4.3</td>
</tr>
<tr>
<td>Intraoperative ventilation, cleaning and disinfection of environmental surfaces, sterilization of surgical instruments, and use of surgical attire and drapes</td>
<td>2.3</td>
</tr>
<tr>
<td>Intraoperative asepsis and surgical technique</td>
<td></td>
</tr>
<tr>
<td>Postoperative protection of incision with sterile dressing for 24 to 48 h</td>
<td></td>
</tr>
<tr>
<td>Handwashing before and after any contact with surgical site</td>
<td></td>
</tr>
<tr>
<td>Surveillance of surgical patients to identify SSI</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions to be avoided</th>
<th>Infection Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine antibiotic prophylaxis with vancomycin</td>
<td>3.8</td>
</tr>
<tr>
<td>Routine environmental sampling of operating room (acceptable only as part of epidemiologic investigation)</td>
<td></td>
</tr>
</tbody>
</table>

*From Mangram et al.19 Category I = strongly recommended for implementation.

---

### Table 8—Effect of Interventions on SSI

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Before Intervention</th>
<th>After Intervention</th>
<th>Significance</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol-chlorhexidine hand sanitizer, educational brochure</td>
<td>9.2*</td>
<td>3.8</td>
<td>p = 0.04</td>
<td>Le et al66</td>
</tr>
<tr>
<td>National surveillance network in the Netherlands</td>
<td>4.3</td>
<td>1.8</td>
<td>Adjusted risk, 57% (95% CI, 24 to 76%)</td>
<td>Geubbels et al67</td>
</tr>
<tr>
<td>Bundled quality improvement objectives, learning sessions on implementing and measuring change, communication</td>
<td>2.3</td>
<td>1.7</td>
<td>p = 0.0005</td>
<td>Dellinger et al68</td>
</tr>
</tbody>
</table>

*For this study, data are from the control ward that did not receive intervention.
ingestion, primarily through antimicrobial stewardship.\textsuperscript{69} Tactics to be avoided include antimicrobial prophylaxis and treating asymptomatic carriers.\textsuperscript{69}

Popular hospital cleaning agents and alcohol-based hand sanitizers are ineffective against \textit{C difficile}. The preferred alternatives are hypochlorite solution (1:10 mixture of household bleach to water) for environmental disinfection and either soap or chlorhexidine for hand hygiene.\textsuperscript{69} When the rate of \textit{C difficile}-associated diarrhea increased from 5.3 to 16.6 cases per 1,000 patient-days in a medical ICU at my institution,\textsuperscript{70} we implemented intensive entire-unit environmental cleaning; daily cleaning of the nursing station, staff restroom, staff conference room, and waiting room; twice-daily cleaning of patient-care equipment; and monthly infection-rate reports. This bundle reduced the rate to 3.7 cases per 1,000 patient-days (RR, 0.22; 95% CI, 0.09 to 0.56). Next, we simplified the intervention and cleaned infected patient rooms daily, sustaining the reduction for 2 years (RR, 0.17; 95% CI, 0.9 to 0.32). This simpler approach successfully controlled a surgical-ICU outbreak and sustained it for 2 years (RR, 0.22; 95% CI, 0.09 to 0.52).\textsuperscript{70}

Muto and colleagues\textsuperscript{71} recently reported success with a series of practices that were fine tuned following surveillance. The first three had little impact. The next practice was more successful and focused on cleaning patient rooms. Subsequent practices included the following: (1) hand washing with soap and water, (2) infection-control audits, and (3) restricting use of clindamycin, ceftriaxone, and levofloxacin. Collectively, these practices reduced the annual infection rate per 1,000 patient-days from 10.4 in 2000 to 3.0 in 2006 (odds ratio, 3.5; 95% CI, 2.3 to 5.4; \(p < 0.001\)).\textsuperscript{71}

Probiotics are viable microorganisms that colonize the GI tract and are an attractive option because of ease of administration, low cost, and safety profile.\textsuperscript{72} In a metaanalysis,\textsuperscript{73} probiotics reduced the RR of antibiotic-associated diarrhea (RR, 0.43; 95% CI, 0.31 to 0.58; \(p < 0.001\)), but only 13 of 25 randomized, blinded studies had significant between-group differences favoring probiotics. These conflicting results may be attributable to study population differences; concomitant antibiotic use; and probiotic type, dose, and duration. Well-designed multicenter studies are needed to determine the role of probiotics in preventing \textit{C difficile}-associated diarrhea in the ICU.\textsuperscript{72}

**CONCLUSIONS**

Evidence-based guidelines are available to reduce nosocomial ICU infection rates, especially when simple tactics are bundled. To increase the likelihood of success, follow the SMART approach. Choose specific objectives that precisely define and quantify desired outcomes, such as reducing the nosocomial ICU infection rate of an institution by 25%. Avoid unrealistic objectives, such as attempting to completely eliminate nosocomial infections. To measure the objective, monitor both staff adherence to tactics and the infection rate using predefined criteria, and provide feedback to ICU staff. Make objectives achievable and relevant by engaging stakeholders and empowering them to select specific tactics and steps for implementation. Nurses and other stakeholders are in the best position to identify the preventive tactics that are achievable within their busy ICUs. Begin with simple, cost-effective tactics. Anticipate the need to add more tactics to achieve the desired target infection rate; specify which tactics will be added to the bundle, and when and how they will be added. Unburden the bedside provider by taking advantage of new technologies shown to reduce nosocomial infection rates. Objectives should also be relevant to the institution so that administrators provide adequate staffing and other resources. Appoint a team to champion the intervention and collaborate with administrators and ICU staff. Provide ongoing communication to reinforce educational tactics and fine-tune practices over time. Make objectives time bound; set dates for collecting baseline and periodic data, and a completion date for evaluating the success of the intervention.

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**REFERENCES**


Review article

Ventilator-associated pneumonia: A review

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Biomarkers
Treatment

A B S T R A C T

Ventilator-associated pneumonia (VAP) is the most frequent intensive-care-unit (ICU)-acquired infection, with an incidence ranging from 6 to 52% [1,2,3,4]. Several studies have shown that critically ill patients are at high risk for getting such nosocomial infections [3,4]. VAP continues to be a major cause of morbidity, mortality and increased financial burden in ICUs [5,6,7,8]. Over the years there has been a significant advance in our understanding of ventilator associated pneumonia. This article reviews the various aspects of VAP such as definition, risk factors, etiological agents, diagnosis, treatment and prevention with emphasis on the recent advances. © 2010 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.

1. Definition

VAP is defined as pneumonia occurring more than 48 h after the initiation of endotracheal intubation and mechanical ventilation [1]. VAP can also be conceptually defined as an inflammation of the lung parenchyma caused by infectious agents not present or incubating at the time MV was started [7]. Despite the clarity of this concept, numerous operational definitions have been proposed over the decades, none of which is universally accepted [8]. Even definitions based on histopathological examination of biopsy or autopsy tissue may lack precision in diagnosis of VAP. Involvement of focal areas of a lobe may be missed and culture may be negative despite the presence of inflammation in the lung [9–11]. The absence of a “gold standard” for diagnosis continues to fuel controversy about the adequacy and accuracy of these definitions.

Early-onset VAP, which occurs during the first 4 days of MV, usually is less severe, associated with a better prognosis, and is more likely to be caused by antibiotic sensitive bacteria. Late-onset VAP, which develops five or more days after initiation of MV, is caused by multidrug-resistant (MDR) pathogens, and is associated with increased morbidity and mortality [8].

2. Incidence

Ventilator-associated pneumonia (VAP) is the most frequent intensive-care-unit (ICU)-acquired infection, with an incidence ranging from 6 to 52% [1,2]. Several studies have shown that critically ill patients are at high risk for getting such nosocomial infections [3,4]. The incidence of VAP is varied among different studies, depending on the definition, the type of hospital or ICU, the population studied and the level of antibiotic exposure. The lack of consensus regarding the most appropriate method to diagnose VAP also partly explains why incidence rates vary widely from one study to another.

Hospital-acquired pneumonia (HAP) and VAP represented the second most common nosocomial infection affecting approximately 27% of all critically ill patients in the United States National Nosocomial Infection Surveillance involving over 14,000 ICU patients [12]. Nearly 90% of episodes of HAP among the ICU patients occur during mechanical ventilation [13].

In the recent reports the incidence rate of VAP ranges from 13.2 to 51 per 1000 ventilator days [14–16]. The rates of VAP vary from 5 cases per 1000 days in pediatric patients to 35 cases per 1000 days in burn patients [17]. Generally, the surgical ICUs have higher rates of VAP compared to the medical ICUs [17]. The incidence of nosocomial
pneumonia (NP) was reported as 21.6% in patients admitted to a cardiothoracic ICU, 14% in other surgical ICU, and 9.3% in a medical ICU [18].

3. Risk factors

The various risk factors for the development of VAP documented in different studies are listed in Table 1 [5,16,19–24].

In a study involving four multidisciplinary ICUs in Athens, univariate analysis indicated that tracheostomy, bronchoscopy, enteral feeding, duration of mechanical ventilation ≥5 days, mean duration of central vein catheterization, APACHE II score ≥18 on admission, and acute physiology score ≥10 on admission were significantly associated with VAP [19].

The following were demonstrated as independent risk factors for the development of VAP by multivariate analysis in different studies: tracheostomy, multiple central venous line insertions, re-intubation, the use of antacids, length of stay, coma, depressed consciousness, enteral feeding [5,20]. During the first 96 h of mechanical ventilation multiple central venous line insertions, emergency intubation and intravenous sedatives were found to be independent predictors of VAP, while after 96 h of ventilation the predictors of VAP were re-intubation, antacids and tracheostomy [16,20].

4. Etiological agents

The etiological agent varies according to patient population, unit, hospital or country. The organisms causing VAP and their susceptibility pattern may not only vary from unit to unit, but also in a given unit over the course of time [2]. The common and unusual microbial causes of VAP documented by several investigators are listed in Table 2 [7,8,25,26].

These agents may be part of the host's endogenous flora, or may be acquired from other patients, health care workers, devices, or the hospital environment [17]. Early-onset VAP is often caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, while late-onset VAP is more frequently caused by multidrug-resistant *Pseudomonas aeruginosa*, *Acinetobacter* or *Enterobacter* spp., or methicillin-resistant *S. aureus* (MRSA) [6,17].

4.1. Multidrug-resistant (MDR) pathogens

Most of the VAP pathogens, such as *Pseudomonas* species, *Acinetobacter* species, MRSA, and enteric Gram-negative bacilli expressing ESBL and AmpC β-lactamas characteristically display high levels of antibiotic resistance. These bacteria are referred to as “multidrug-resistant” (MDR) pathogens [8,27]. Prior antibiotic therapy or prior hospitalization within the past 90 days predisposes to colonization and infection with MDR pathogens [8]. MDR pathogens are more frequently associated with late-onset VAP. The underlying mechanisms for resistance to β-lactams are production of β-lactamas, lack of drug penetration due to mutation in porins, presence of efflux pumps and changes in penicillin-binding proteins (PBPs) that prevent their action [28]. Extended spectrum β-lactamas (ESBL) and AmpC β-lactamas primarily confer resistance to penicillins and cephalosporins, while metallo-β-lactamas (MBL) contribute to carbapenem resistance [29–31]. Modified Hodge test and EDTA disk synergy (EDS) test are the commonly used phenotypic methods for detection of carbapenemases and MBL respectively [32,33]. AmpC disc test and Kirby-Bauer disc approximation (KBDA) method are used frequently to detect stably derepressed and inducible AmpC β-lactamas respectively [34,35]. Oxacillin resistance screening agar containing 4% Sodium chloride and 6μg/ml oxacillin in Mueller-Hinton agar (MHA) is a reliable method for screening of MRSA [36].

4.2. Polymicrobial infection

VAP caused by more than one microorganism was identified in around 30–70% of the cases [37]. In a study by Combes et al., polymicrobial infections were diagnosed in 48% cases of VAP [38]. In two Indian studies, 12.3% and 16.3% of VAP cases were polymicrobial [39,40]. It was also observed that the epidemiology and outcomes of patients with monomicrobial and polymicrobial VAP did not differ significantly [38].

### Table 1

<table>
<thead>
<tr>
<th>Risk factors for VAP.</th>
<th>Intervention factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oro-pharyngeal colonization</td>
<td>Emergency intubation</td>
</tr>
<tr>
<td>Gastric colonization</td>
<td>Re-intubation</td>
</tr>
<tr>
<td>Thermal injury (Burns)</td>
<td>Tracheostomy</td>
</tr>
<tr>
<td>Post-traumatic</td>
<td>Bronchoscopy</td>
</tr>
<tr>
<td>Post-surgical</td>
<td>Nasogastric tube</td>
</tr>
<tr>
<td>Impaired consciousness</td>
<td>Duration of hospital stay/ICU stay</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Multiple central venous line insertions</td>
</tr>
<tr>
<td>Organ failure</td>
<td>Sedatives</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>Stress ulcer prophylaxis</td>
</tr>
<tr>
<td>Severity of underlying illness</td>
<td>Prior antibiotics/no antibiotic prophylaxis</td>
</tr>
<tr>
<td>Old age (≥60 years)</td>
<td>Immunosuppressives (Corticosteroids)</td>
</tr>
<tr>
<td>Presence of comorbidities</td>
<td>Supine head position</td>
</tr>
</tbody>
</table>

MV = mechanical ventilation; ICU = intensive care unit.

### Table 2

Microbial agents causing VAP.

<table>
<thead>
<tr>
<th>Common causes</th>
<th>Rare/unusual causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram positive cocci</td>
<td>Gram positive bacilli</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>Corynebacterium species (diptheroids)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>Nocardia species</td>
</tr>
<tr>
<td>Coagulase negative staphylococci</td>
<td>Aerobic Gram-negative bacilli</td>
</tr>
<tr>
<td>Enterococci</td>
<td>Serratia species</td>
</tr>
<tr>
<td>Aerobic Gram-negative bacilli</td>
<td>Haemophilus alvei</td>
</tr>
<tr>
<td>Enteric Gram-negative bacilli</td>
<td><em>Stenotrophomonas maltophilia</em></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Burkholderia cepacia</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td><em>Gram-negative cocci</em></td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>Neisseria species</td>
</tr>
<tr>
<td>Proteus species</td>
<td>Moraxella species</td>
</tr>
<tr>
<td>Citrobacter species</td>
<td>Anaerobic bacteria</td>
</tr>
<tr>
<td>Non-fementative</td>
<td>Bacillae</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>Bacteroides species</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
<td>Fusobacterium species</td>
</tr>
<tr>
<td><em>Acinetobacter</em> spp.</td>
<td>Prevotella species</td>
</tr>
<tr>
<td><em>Haeomophilus influenzae</em></td>
<td>Actinomyces species</td>
</tr>
<tr>
<td>Fungi</td>
<td>Cocci</td>
</tr>
<tr>
<td><em>Candida</em> species</td>
<td>Veillonella species</td>
</tr>
<tr>
<td><em>Aspergillus</em> species and other molds</td>
<td>Peptostreptococci</td>
</tr>
<tr>
<td><em>Pneumocystis jirovecii</em></td>
<td>Atypical bacteria</td>
</tr>
<tr>
<td><em>Legionella</em> species</td>
<td><em>Mycoplasma pneumoniae</em></td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td><em>Fungi</em></td>
</tr>
<tr>
<td><em>Viruses</em></td>
<td><em>Cocci</em></td>
</tr>
<tr>
<td><em>Influenza</em> and other respiratory viruses</td>
<td><em>Vermecogalovirus</em></td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td><em>Mycoplasma pneumoniae</em></td>
</tr>
</tbody>
</table>

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5. Pathogenesis

Pneumonia represents the overwhelmed host's inflammatory response to the microbial invasion of the normally sterile lung parenchyma [41]. The magnitude of this response is dependent on the type of the inoculum and its size, the virulence of the pathogen, and the competence of the host's immune system [41].

Normally, the host defence mechanisms, including filtration and humidification of air in the upper airways, non-immune antimicrobial agents in saliva, an intact cough reflex, mucociliary clearance, phagocytes and opsonins in lung, and systemic cell mediated and humoral immunity, prevent bacterial invasion [14,41]. In critically ill ICU patients, these host defences are usually altered because of the underlying diseases, comorbidities, malnutrition sedation, and devices like endotracheal tube [14,42]. Once the pathogens reach the distal lung, they multiply and cause invasive disease.

5.1. Role of oropharyngeal colonization

Numerous studies have shown that, upon admission to the ICU, in the critically ill patients, the oral flora shifts dramatically to a predominance of enteric Gram-negative bacilli, Staphylococcus and P. aeruginosa [42,43]. In the mechanically ventilated patient bacterial adherence is favoured by reduced immunoglobulin A, augmented protease production, denuded mucous membrane, elevated airway pH and increased numbers of airway receptors for bacteria, due to acute illness [42]. Ewig et al. proved that oropharyngeal colonization was a powerful independent predictor of subsequent tracheobronchial colonization [43].

5.2. Role of gastric colonization

The chief predisposing factors for gastric colonization include conditions that reduce the gastric pH, such as, achlorhydria, stress ulcer prophylaxis (H$_2$ antagonists or proton-pump inhibitors), or enteral nutrition [42]. Recumbency and the presence of naso-gastric tube may favour reflux of the gastric microorganisms, which can later be aspirated into the trachea, despite the presence of an endotracheal cuff [42]. The stomach has been implicated as a potential reservoir for antibiotic-resistant bacteria particularly in late-onset VAP [13]. But the current view is that, though the stomach is often heavily colonized by enteric Gram-negative bacilli, the gastro-pulmonary route may not be a major route for the development of VAP [7,44].

6. Source of VAP pathogens

There are various sources from which the microorganisms can gain access to the lungs and eventually cause VAP. The source of infection can be endogenous or exogenous [42,45]. The endogenous and exogenous sources of VAP pathogens are depicted in Fig. 1. The oropharyngeal colonization and gastric colonization can act as the endogenous source of microorganisms [7,8,42,46]. Contaminated respiratory instruments (bronchoscopes, ventilator circuits, humidifiers and suction catheters), infective aerosols from the ICU environment and contaminated hands and apparels of the health care workers (e).

Fig. 1. Source of VAP pathogens. The endogenous sources are oropharyngeal colonization (a) and gastric colonization (b). The exogenous sources are aerosols from contaminated ambient air (c), contaminated respiratory instruments (d) and contaminated hands and apparels of health care workers (e).
workers (due to contact with other patients, contaminated taps, medicine trolley and other fomites) are the major exogenous sources of infection [8,42,45].

7. Diagnosis of VAP

There is no gold standard for diagnosis of VAP. However, a combination of clinical, radiological and microbiological criteria can be used effectively for early and accurate diagnosis of VAP. A simple algorithm for the diagnosis of VAP is depicted in Fig. 2, based on the recommendations by several authors [7,8,37,47–54].

8. Clinical diagnosis

VAP is clinically suspected usually based on the presence of fever (temperature >38.3 °C), blood leukocytosis (>10,000/mm³), or leukopenia (<4000/mm³), purulent tracheal secretions, and the presence of a new and/or persistent radiographic infiltrate. However, these clinical parameters individually have limited diagnostic value [55,56,57]. Although this definition is highly sensitive, its specificity is low [56,57]. It has been shown that only as few as one third of clinically diagnosed VAP cases were confirmed microbiologically using quantitative cultures [7]. Fagon et al. have reported that the clinical diagnosis of VAP is associated with 20–25% false-positive and 30–35% false-negative results [14]. Postmortem studies in a series of patients with acute lung injury demonstrated that clinical criteria alone led to an incorrect diagnosis of VAP in 29% of clinically suspected cases [58].

The clinical diagnosis of VAP is overly sensitive because there are other potential causes of fever, leukocytosis, purulent tracheal secretions and pulmonary infiltrates [59].

The systemic signs of VAP, such as fever and leukocytosis, are non-specific and can be caused by any condition that releases cytokines like, interleukin-1, interleukin-6, tumor necrosis factor alpha, and gamma interferon [2,7]. The conditions that induce cytokine release as an inflammatory response are trauma, surgery, deep vein thrombosis, pancreatitis, pulmonary embolism, pulmonary edema, and pulmonary infarction [2,7]. In a prospective study by Meduri et al. 24% of fevers were found to be due to one of these non-infectious causes [80]. In the critically ill ICU patients, underlying diseases like immunosuppression, chronic renal failure may suppress the systemic signs of infection, accounting for the false negativity of these clinical parameters for diagnosis of VAP [14]. Purulent sputum can also be attributed to tracheobronchitis and does not always indicate pulmonary parenchymal involvement [61].

The only alternative approach to the clinical diagnosis of VAP is the Clinical Pulmonary Infection Score (CPIS), which was proposed by Pugin et al., based on 6 clinical assessments, each worth 0–2 points, including: fever, leukocyte count, quantity and purulence of tracheal secretions, oxygenation, type of radiographic abnormality, and results of sputum culture and Gram stain [37,47]. In their study, Pugin et al. showed that the correlation between the CPIS and the bronchoalveolar lavage (BAL) bacterial index was 0.8, proving that clinical diagnosis can be as accurate as microbiologic diagnosis based on quantitative culture of BAL [56]. In addition, a CPIS >6 as a clinical definition of VAP, was associated with a high likelihood of pneumonia with a sensitivity of 93% and a specificity of 100% comparing quantitative BAL culture [56]. In a prospective post mortem study Clinical Pulmonary Infection Score (CPIS) at a threshold of 6 achieved a sensitivity of 72% and a specificity of 85% [62].

Ambiguities in the scoring system or missing data that were required to calculate the CPIS could result in a large interobserver variability [56]. Another drawback of the CPIS is that it is associated with a delay of 24–48 h for the results of tracheal aspirate cultures. Therefore Singh et al. proposed that a modified CPIS with only the first five clinical variables can be used for the initial diagnosis of VAP, followed by calculation of CPIS based on all the 6 variables after 72 h, so that antibiotics can be stopped in patients with a persistent low score (CPIS <6) after 3 days of therapy, avoiding unnecessary use of antibiotics [63]. Fartoukh et al. reported that the modified CPIS had low diagnostic accuracy; however, incorporating Gram stain results into the score (by adding two more points when Gram stain was positive) may increase the sensitivity of the score and help clinical decision making in patients with clinically suspected pneumonia [55]. They also reported that CPIS >6 after incorporation of Gram stain results was still associated with a false-negative rate of 16 to 25% [55].

9. Radiological diagnosis

Numerous studies have shown that certain chest radiograph findings, like progressive rapid cavitation of the pulmonary infiltrate, an air space process abutting a fissure and a single air bronchogram are associated with 96% specificity for diagnosing VAP. But, such specific radiographic abnormalities being uncommon, chest radiographs are mainly helpful in excluding VAP when they are normal [2].

Asymmetric pulmonary infiltrates on chest radiograph consistent with VAP may be caused by various non-infectious conditions, such as atelectasis, emphysema, chemical pneumonitis, asymmetric cardio-

![Fig. 2. The algorithm for the diagnosis of VAP. CPIS—Clinical Pulmonary Infection Score, PCT—procalcitonin, sTREM—soluble triggering receptor expressed on myeloid cells-1, CRP—C-reactive protein, EA—endotracheal aspirate, ICB—intracellular bacteria, CFU—colony forming units, VAP—ventilator associated pneumonia, BAL—bronchoalveolar lavage, PSB—protected specimen brush.](image-url)
pulmonary edema, pulmonary embolism, cryptogenic organizing pneumonia, pulmonary contusion, pulmonary hemorrhage, and drug reaction [2,7,41]. The overall radiographic specificity of a pulmonary opacity consistent with pneumonia is only 27% to 35% [2].

10. Laboratory diagnosis

The microbiological diagnosis of VAP is based on direct microscopic examination, qualitative and quantitative culture of lower respiratory tract secretions obtained bronchoscopically or nonbronchoscopically.

The quality of lower respiratory secretions is of utmost importance for better interpretation of both microscopy and culture [64,65]. Although no absolute guideline exists, the recommendations for ensuring proper quality of the secretions are: 1) Lower respiratory tract secretions should be obtained before antibiotics are started or changed. 2) When collecting BAL, less than 10% return of instilled fluid probably represents inadequate sampling. 3) When protected specimen brush (PSB) is used for lower respiratory tract sampling, the brush must be placed into exactly 1 mL of fluid. 4) Specimens should be processed within 30 min or refrigerated if any further delay is expected [7,64,66].

10.1. Microscopy

10.1.1. Gram’s stain

The Gram’s staining is useful to detect bacteria and yeast cells in the respiratory secretions. The percentages of squamous epithelial or bronchial cells may be used to predict heavy upper respiratory contamination [7]. The presence of more than 1% epithelial cells or 10 epithelial cells per low-power field (magnification, ×100) has been proposed as a rejection criterion [2,7,64]. The number of polymorphonuclear (PMN) leukocytes is generally not predictive of an interpretable specimen in patients with VAP [67]. However, in a postmortem study, BAL fluid with <50% neutrophils had a 100% negative predictive value for histologic pneumonia [68]. The presence of leucocytes was not found to be specific for a positive culture, but in their absence, a positive culture was unlikely as it probably represents inadequate sampling [65,69].

Duflo F et al. showed that in patients with VAP, the correlation between the Gram’s stain and BAL quantitative cultures was complete in 39%, partial in 28%, and absent in 33% [70]. Hence, Gram’s stain is not reliable for the early adaptation of empirical chemotherapy.

10.1.2. Giemsa staining

Giemsa staining is recommended for evaluation of VAP, as it offers a number of advantages over Gram’s staining, including better visualization of host cell morphology, improved detection of bacteria, particularly intracellular bacteria, and detection of some protozoan and fungal pathogens, such as Histoplasma capsulatum, Pneumocystis jirovecii, Toxoplasma gondii, and Candida spp. [7,66].

In a study by Sirvent et al., the cut-off point of >2% of cells containing intracellular bacteria had the highest sensitivity (80%) and specificity (82%) in the microscopic examination of nonbronchoscopic protected bronchoalveolar mini-lavage (mini-PBAL) fluid for the diagnosis of VAP [71]. However, the sensitivity is too low to be clinically useful. The direct examination of mini-PBAL fluid is less accurate when previous antibiotic therapy has been administered [71].

Chastre et al. had shown that the presence of ≥5% intracellular organisms had a sensitivity, specificity, positive predictive value, and negative predictive value of 91%, 89%, 91%, and 89%, respectively [51].

10.2. Culture

The specimen for culture should ideally be collected before starting antibiotics or when there is no change in antibiotic therapy in the past 3 days. The negative predictive value is high (94%) for culture of such appropriately collected specimen [72]. A false-negative rate of 10 to 40% is observed in the presence of prior antibiotic therapy [2].

10.2.1. Qualitative culture

Qualitative tracheobronchial aspirates are highly sensitive (>75%) but poorly specific (<25%) for the diagnosis of VAP [37]. Qualitative cultures of tracheal aspirate (TA) is not a specific diagnostic tool as it is associated with a high percentage of false-positives due to colonization of the lower respiratory tract [14].

Nevertheless, due to the high negative predictive value, they may be useful to exclude VAP, particularly in the patients without prior antimicrobial treatment [37]. As qualitative culture is overly sensitive, continuation of antibiotic therapy based only on a positive qualitative culture report may lead to unnecessary antibiotic use, encouraging bacterial resistance and consequently higher costs [73]. In one study it was observed that 57% patients were overtreated with antibiotics based on qualitative endotracheal aspirate (EA) cultures [74].

In another study, quantitative cultures of tracheal aspirates in selected critically ill patients showed decreased sensitivity when compared with qualitative culture (65% and 81% respectively) [75]. Consequently, qualitative culture though not highly specific, should not be replaced by quantitative culture to confirm a clinical diagnosis of VAP as certain cases of VAP may be missed by the latter.

10.2.2. Semiquantitative culture

Semiquantitative culture is performed based on the four-quadrant streak technique using a calibrated loop. Endotracheal aspirate (EA) cultures are read semiquantitatively by observing the growth in the four quadrants, which suggests the approximate number of CFU/mL of the bacteria in the specimen [74].

In a study comparing the semiquantitative culture (calibrated loop technique) and the quantitative culture (serial dilution technique) of 121 BAL samples, a very good agreement between the techniques was observed with only one discordant result [52].

However, use of semiquantitative cultures for guiding antibiotic therapy may be associated with substantially more patients being overtreated as observed in a study by Brun-Buisson et al., wherein 18% patients were unnecessarily treated with antibiotics based on semiquantitative cultures of EA [74].

10.2.3. Quantitative culture

Quantitative culture is performed by serial dilution of the specimen. Cultures were reported as colony forming units per milliliter (CFU/mL), after correction for the initial dilution. If the number of CFU/mL is equal to or exceeds the threshold values for the particular technique, a diagnosis of pneumonia is made. Threshold values commonly employed for diagnosing VAP by quantitative cultures are ≥10^3, ≥10^4, and ≥10^5 CFU/mL for EA, bronchoscopic BAL, and PSB, respectively [7,54,76].

Quantitative cultures are generally preferred over qualitative culture for making decisions regarding therapy for VAP [73]. The results of quantitative cultures is influenced by various factors, such as the stage of pneumonia, prior antibiotic therapy, the adequacy of the sample, the operator’s skill, method of processing, delay in transport [2]. False-positive quantitative cultures could be secondary to chronic obstructive pulmonary disease (have high bacterial counts without pneumonia) and bronchiolitis [2]. Considering these potential limitations, a quantitative culture that exceeds a threshold value is not always diagnostic of VAP.

10.2.4. Bronchoscopic specimens

The most commonly used bronchoscopic techniques are BAL or protected specimen brushing (PSB) [7]. The average sensitivity and specificity of BAL in several studies are 73% and 82% respectively, while PSB has 89% sensitivity and 94% specificity [41].
Chastre et al. showed that, BAL had a sensitivity of 91%, a specificity of 78%, a positive predictive value of 83%, and a negative predictive value of 87%, while PSB had a sensitivity of 82%, a specificity of 89%, a positive predictive value of 90%, and a negative predictive value of 89% compared to histopathological findings and quantitative culture of lung tissue [51].

Although bronchoscopy has only a low inherent risk even for critically ill patients, it may rarely lead to cardiac arrhythmias, hypoxemia, or bronchospasm [7].

10.2.5. Non-bronchoscopic specimens (endotracheal aspirate)

Quantitative endotracheal aspirate (EA) culture may be an acceptable tool for diagnosing VAP as this approach is non-invasive, inexpensive, and widely available [37]. Quantitative EA also had a high negative predictive (88.9%) value, warranting its early use in diagnosis of VAP [53].

When the diagnosis of VAP was based on postmortem lung examination, the quantitative EA at a threshold of 10^5 CFU/ml had 63% sensitivity and 75% specificity, while a cut-off of 10^6 CFU/ml was 55% sensitive and 85% specific [2].

10.2.6. Non-bronchoscopic vs. bronchoscopic specimens

Quantitatively cultured EA and bronchoscopically collected specimens have a very good correlation [77]. Sanchez-Nieto et al. observed a 10.2.6. Non-bronchoscopic vs. bronchoscopic specimens

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The American Thoracic Society (ATS) guidelines for treatment of VAP recommends that the initial empiric therapy should be based on the presence or absence of risk factors for MDR pathogens such as prolonged hospitalization (5 days or more), admission from a healthcare-related facility, and recent antibiotic therapy [8]. The initial empiric therapy recommended by the American Thoracic Society for treatment of VAP patients with and without risk factors for MDR pathogens are summarized in Table 3 [8].

The selection of specific antibiotics should be dictated by local microbial flora, cost, feasibility and availability. Although the duration of empiric therapy is traditionally 14 to 21 days, in patients with good clinical response with resolution of infection, it can be shortened to 7 days, except when treating P. aeruginosa, Acinetobacter species or other non-fermenters [8].

In a study by Porzecanski it was observed that a guideline-based approach using the antibiotic susceptibility pattern of the local hospital or ICU pathogens, can increase the likelihood of adequate initial antibiotic therapy and reduce the overall use of antibiotics and the associated selection pressure for MDR bacteria [59].

Recently a new approach known as ‘de-escalation’ strategy has been suggested for effective delivery of appropriate empiric therapy for VAP, without the overuse of antibiotics [86]. De-escalation refers to use of microbiologic and clinical data to change from an initial broad-spectrum, multi-Drug empiric therapy regimen to a therapy with fewer antibiotics and agents of narrower spectrum [86]. This is a promising approach for optimizing the use of antibiotics while permitting administration of prompt and appropriate empiric therapy of VAP.

In a study evaluating the role of nebulized colistin, it was shown to be reasonably efficacious and safe for treatment of MDR P. aeruginosa and Acinetobacter baumannii with an overall clinical and microbiologic response rates of 57.1% and 85.7% respectively [89].

Despite the fact that the use of aerosolized antibiotics can effectively kill the bacteria limited to the airway epithelium in the early stage of infection, the clinical evidence to support this approach for treatment of VAP is lacking [90]. Several evidence-based consensus groups recommend against routine use of aerosolized antibiotics for VAP prevention due to concerns about the high cost and possible development of antibiotic resistance [90].

### 14. Prevention

The important measures for prevention of VAP include implementation of hand hygiene using alcohol rubs, reduction of duration of mechanical ventilation as far as possible, maintenance of semi-recumbent position and avoidance of the modifiable risk factors such as tracheostomy, re-intubation, corticosteroid therapy, stress ulcer prophylaxis and contaminated respiratory equipment, water or environment [2,91].

To conclude, VAP continues to be a major challenge to the critical care physicians. Most of the risk factors of VAP are preventable. VAP is increasingly associated with MDR pathogens. The multi-drug resistance of these pathogens was mainly due to production of ESBL, AmpC β-lactamases and metallo β-lactamases. VAP should be diagnosed based on a combination of different clinical and laboratory criteria such as CPIS ≥6, qualitative and quantitative culture of lower respiratory tract secretions collected bronchoscopically or nonbronchoscopically. VAP is associated with increased morbidity and imposes significant financial burden on the health care system. The initial empiric therapy of VAP should be based on the presence or absence of risk factors for MDR pathogens. Awareness of the important risk factors of VAP is essential for implementation of simple and effective preventive measures.

### 15. Learning points

- The incidence rate of VAP ranges from 13 to 51 per 1000 ventilator days
- VAP is increasingly associated with MDR pathogens
- The source of infection can be endogenous or exogenous

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**Table 3**

<table>
<thead>
<tr>
<th>VAP with no risk factors for MDR pathogens</th>
<th>VAP with risk factors for MDR pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>Antipseudomonal cephalosporin (cefepime, ceftazidine)</td>
</tr>
<tr>
<td>or Levofoxacin, moxifloxacine, or ciprofloxacine</td>
<td>or Antipseudomonal carbapenem (imipenem or meropenem)</td>
</tr>
<tr>
<td>or Ampicillin/sulbactam or Ertapenem</td>
<td>or β-Lactam/β-lactamase inhibitor (piperacillin–tazobactam) plus Antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or Aminoglycoside (amikacin, gentamicin, or tobramycin) plus Linezolid or vancomycin (if risk factors for MRSA are present)</td>
</tr>
</tbody>
</table>

MDR = multidrug-resistant.  
MRSA = methicillin-resistant Staphylococcus aureus.

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Fig. 3. The algorithm for the treatment of VAP. VAP—ventilator associated pneumonia, MDR—multidrug resistant, CPIS—Clinical Pulmonary Infection Score, PCT—procalcitoni- 

n, CFU—colony forming units, BAL—bronchoalveolar lavage, PSB—protected specimen brush.
• The quality of lower respiratory secretions is of utmost importance for better interpretation
• Both the clinical criteria (CPIS) and the microbiological criteria (quantitative culture) are essential for diagnosis
• Gram's stain is not reliable for the early adaptation of empirical chemotherapy
• Biomarkers are an indispensable tool for the diagnosis and prognosis of VAP
• Empirical treatment of VAP is based on the presence or absence of risk factors for MDR pathogens
• The choice of the antibiotics is based on the susceptibility pattern of local microbial flora, cost, feasibility and availability
• 'De-escalation' strategy is a promising approach for effective delivery of appropriate empiric therapy for VAP, without the overuse of antibiotics
• The mortality rates for VAP range from 20% to 76% in various studies
• Implementation of simple preventive measures is important.

References

Diagnosis of ventilator-associated pneumonia
Robert P. Baughman

Purpose of review
This review examines the various techniques used to diagnose ventilator-associated pneumonia. The ideal diagnostic test not only helps the clinician to recognize whether pneumonia is present, but also to influence clinical outcome.

Recent findings
Several studies have suggested that the clinical pulmonary infection score can be used to detect the onset of ventilator associated pneumonia. Serial clinical pulmonary infection scores have also been useful in helping to decide when to stop therapy. Semiquantitative culture methods have been used for nonbronchoscopic and bronchoscopic samples. Adequate initial empiric therapy for those organisms identified in these samples has been associated with improved survival. This supports the use of these culture techniques to diagnose patients with ventilator-associated pneumonia.

Summary
Diagnostic testing for ventilator-associated pneumonia can identify those patients at risk for a poor clinical outcome.

Keywords
bronchoalveolar lavage, CPIS, endotracheal aspirate, bronchoscopy

Introduction
The diagnosis of ventilator-associated pneumonia (VAP) remains one of the most controversial points of the management of ventilated patients [1••]. A consensus conference on intensive care unit acquired pneumonia highlighted many of the problems with diagnosis [2•]. Much of the controversy arose over the role of various diagnostic techniques used by different centers around the world. Everyone had a reason for their particular method, but everyone could agree that no perfect technique exists.

Investigators have chosen several different ways of deciding which patient has pneumonia. This includes the clinical criteria and ultimate outcome of the patient based on antibiotic therapy and failure to identify an alternative cause. Another mechanism is to use the results of an immediate post mortem examination, using histology and cultures, as originally reported by Chastre et al. [3], and confirmed by others [4,5]. These immediate post mortem studies verified that bronchoscopic samples such as bronchoalveolar lavage (BAL) could also be used as the standard for diagnostic testing [4,5]. In an evidence-based review of the literature, there was no significant difference between the results of VAP diagnostic techniques whether one used bronchoscopic sampling, immediate post mortem examination, or careful clinical criteria with follow-up of patients [6,7]. In the past few years, there has been a general agreement that any of these three criteria are acceptable in studies trying to study new diagnostic tests for VAP.

The attributes of the perfect diagnostic test are listed in Table 1. Most of the techniques used to diagnose VAP have been described more than 10 years ago, with clinical criteria in use for more than 40 years. The last few years have brought some clarity on the relative role of these techniques. The ability to influence survival based on the results of the testing is the ultimate goal of any diagnostic test. In the area of VAP, it appears that knowing what organism is causing the pneumonia in a timely manner may influence survival. Other tests are being proposed as useful in identifying patients with a worse prognosis.

The diagnostic approaches to VAP can be broadly classified in three general categories: clinical criteria, nonbronchoscopic sampling, and bronchoscopic-directed sampling. We will discuss the changes in these areas.

Clinical criteria
The traditional clinical criteria for diagnosis of VAP include those used for diagnosing pneumonia in nonventilated patients. These include the presence of fever or
Infectious diseases

In 1990, Pugin et al. proposed a clinical pulmonary infection score (CPIS), which gave points for the temperature, quantity of secretions, leukocyte count changes, changes in chest roentgenogram, hypoxemia, and the results of BAL Gram stain and culture [11]. Using post mortem examination as the gold standard, CPIS was more sensitive and specific than clinical criteria alone [5]. In a subsequent study using post mortem examination as the standard to diagnose pneumonia, using only the clinical criteria of CPIS alone had a specificity of 85% [12]. Adding the results of culture increased the specificity to 95%. The CPIS have a sensitivity and specificity similar to that reported for bronchoscopic-derived cultures [8].

A clinical trial of treatment of VAP by Singh et al. used the CPIS to identify low-risk patients with VAP [13]. In addition, the CPIS was recalculated at day 3. For patients with a stable or falling CPIS, antibiotics were discontinued in one group. The early discontinuation of antibiotics in patients with an improving CPIS was associated with a lower rate of second infection and a trend to lower mortality. This study suggested that follow-up CPIS studies may provide prognostic information.

In the past year, Luna and his group have examined the value of serial CPIS scores for patients already receiving mechanical ventilation. The authors found an increase in the CPIS at the time of pneumonia, as confirmed by bronchoscopic or blood cultures [14••]. During therapy, the CPIS decreased in some, but not all patients. For those patients who failed to have a decrease in their CPIS over the first week of treatment, there was a significantly higher 28-day mortality. This study confirmed the utility of serial CPIS in predicting clinical outcome of the patient.

In examining components of the CPIS, Luna et al. found that the best single predictor of survival was the resolution of the partial pressure of oxygen divided by the fraction of inspired oxygen (PaO2/FiO2 ratio). Others have shown that PaO2/FiO2 improved significantly with time in patients with resolving VAP [15]. This may mean that oxygenation is the best measure of treatment success for VAP. It could also just mean that patients who are becoming less hypoxic may be weaned from the ventilator more rapidly. The chances of acquiring pneumonia are greater than 1% for every day on the ventilator [16]. Oxygenation is also difficult to evaluate in the patient with acute respiratory distress syndrome (ARDS). In that situation, the hypoxemia is part of the underlying disease. However, nearly 40% of patients with ARDS may have pneumonia as the cause of their ARDS [17]. For the CPIS, the PaO2/FiO2 ratio is not calculated if the patient has ARDS.

Another issue with the CPIS is the Gram stain and culture of the BAL sample. Although BAL culture and Gram stain was in the original Pugin score [11], others have substituted the endotracheal aspirate for the BAL sample [13]. However, the results of culture may still take 2 to 3 days. The culture results do increase the specificity of the CPIS, but only to a minor degree [12]. In addition, to perform daily CPIS scores would require daily cultures, which would add considerably to the cost of the testing.

Luna et al. simplified the CPIS score by removing the evaluation of endotracheal aspirate cultures altogether. Table 2 summarizes the features they studied and the points awarded. In their prospective study, they found that patients receiving mechanical ventilation without pneumonia had a score of 4. When pneumonia developed in the patients, the score rose to 5 or greater in all cases (mean was 6.3). The score has some obvious defects, especially in the patient with ARDS. However, the

<table>
<thead>
<tr>
<th>Component</th>
<th>Value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (C)</td>
<td>≥36.5 and ≤38.4</td>
<td>0</td>
</tr>
<tr>
<td>Blood leukocytes/cubic mm</td>
<td>≥4,000 and ≤11,000</td>
<td>0</td>
</tr>
<tr>
<td>Tracheal secretions</td>
<td>Few</td>
<td>0</td>
</tr>
<tr>
<td>Oxygenation PaO2/FiO2, mm Hg</td>
<td>≥240 or presence of ARDS</td>
<td>0</td>
</tr>
<tr>
<td>Chest roentgenogram</td>
<td>No infiltrate</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Patchy or diffuse infiltrate</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Localized infiltrate</td>
<td>2</td>
</tr>
</tbody>
</table>

ARDS, acute respiratory distress syndrome.

Adapted from Luna et al. [14•].

Table 1. Characteristics of ideal diagnostic test for VAP

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accurate</td>
<td>Yes</td>
</tr>
<tr>
<td>Rapid results</td>
<td>Yes</td>
</tr>
<tr>
<td>Easy to perform</td>
<td>Yes</td>
</tr>
<tr>
<td>Easy to interpret</td>
<td>Yes</td>
</tr>
<tr>
<td>Safe</td>
<td>Yes</td>
</tr>
<tr>
<td>Inexpensive</td>
<td>Yes</td>
</tr>
<tr>
<td>Application of test affects survival</td>
<td>No</td>
</tr>
</tbody>
</table>

VAP, ventilator-associated pneumonia.

hypothermia, leukocytosis or leukopenia, increased pulmonary secretions, and the presence of a new or worsening infiltrate. Each of these criteria alone is not specific in the diagnosis of VAP [8,9]. In part, the failure of these methods is that patients in the intensive care unit (ICU) already have many clinical features suggesting infection [10]. In addition, the chest roentgenogram is less accurate in the ICU for various reasons [9], including the fact that these patients are most likely to have portable films.

Table 2. Simplified clinical pulmonary infection score

In evaluating patients who were being treated for VAP, Singh et al. included and compared CPIS in the patients who resolved VAP with those in whom VAP continued [14]. The CPIS was most helpful in those patients with a higher CPIS at the time of pneumonia, as confirmed by bronchoscopic or blood cultures [14••]. During therapy, the CPIS decreased in some, but not all patients. For those patients who failed to have a decrease in their CPIS over the first week of treatment, there was a significantly higher 28-day mortality. This study confirmed the utility of serial CPIS in predicting clinical outcome of the patient.

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simplicity of the score and the ability to follow it serially is an appealing feature.

Overall, the use of a single clinical criterion alone seems less specific than the CPIS in detecting VAP. The sensitivity and specificity can be enhanced by calculating the score on a daily basis for all patients receiving mechanical ventilation. The use of CPIS to follow patients while receiving therapy may direct therapy and predict survival.

**Nonbronchoscopic sampling**

Endotracheal aspirates are the most commonly performed method of culturing lower respiratory secretions. Although the technique has good sensitivity, it lacks much specificity because of tracheal colonization [18]. The tracheal aspirate specificity can be enhanced considerably by using semiquantitative cultures [4,18,19]. In a recent study by Wu et al. [20•], quantitative culture of endotracheal aspirate had a sensitivity of 93% and specificity of 80%, using bronchoscopically obtained samples as the standard.

The role of serial cultures of endotracheal aspirates is a distinct advantage of this technique over more expensive methods, such as nonbronchoscopic BAL or bronchoscopy-derived samples. Dennesen et al. have shown that bacterial load in the endotracheal aspirates decreases during treatment [15]. However, that study did not investigate the role of surveillance endotracheal cultures before pneumonia.

In a prospective study of 125 consecutive patients in whom VAP developed, Hayon et al. examined all prior cultures to determine their value in directing empiric therapy [21•]. All patients had an organism determined by bronchoscopic BAL at the time of their pneumonia. Of the 220 organisms that were greater than 10,000 cfu/mL, BAL at time of pneumonia, only 33% were recovered before the episode of VAP. However, more than half of the organisms isolated before the pneumonia were not considered as causative for the episode of pneumonia. The authors did note that an organism isolated within 72 hours of the episode of pneumonia was more likely to be the cause of the pneumonia (56%) than an organism only found at a time greater than 72 hours before the episode (13%). The more troublesome multidrug-resistant bacteria *Pseudomonas aeruginosa*, Acinetobacter baumannii, and methicillin resistant *Staphylococcus aureus* were more readily identified in prior cultures, especially in the 72 hours before development of pneumonia. The negative predictive value for these three agents was greater than 80%. Surveillance cultures may be useful in directing empiric therapy, but only to a limited degree. The most useful surveillance culture is that obtained within 72 hours of the episode. The authors of this study calculated that the cost of cultures was approximately 20,000 euros. If one were to do surveillance cultures every 3 days for patients receiving ventilator assistance, the price would be higher.

Although surveillance cultures may not be cost effective, they are one mechanism of knowing the flora in one’s ICU. Another method is keeping track of the organisms isolated from patients with VAP. Knowing what bacteria are present in one’s ICU is needed as one tries to establish guidelines for empiric therapy in the ICU. Ibrahim et al. developed a clinical guideline for management of VAP in one ICU [22]. This included analysis of culture results of 50 cases of VAP. They then used these results to develop a subsequent guideline for empiric therapy of the next 50 cases of VAP. They found that this method significantly increased the percentage of pneumonia cases receiving adequate empiric therapy from 48% to 94%.

Nonbronchoscopic or blind BAL has grown in popularity over the past 10 years based on several studies showing that results are similar to the bronchoscopic technique in most clinical settings [4,23,24]. Another key factor in its wide acceptance is the ability to have the technique performed by respiratory therapists using an established protocol [25,26]. The use of nonphysicians allows for the procedure to be more widely applied, for example, at nighttime when a patient’s antibiotics are being initiated. This freedom to perform the procedure by nonphysicians may lead to a wider application of BAL sample at the institution. However, the procedure does incur a cost of the catheter itself as well as the performance of semiquantitative cultures. In addition, one should recognize that the procedure has to be done correctly to be useful. In one study, predefined criteria for an acceptable sample were established: greater than or equal to 10% of instilled fluid being aspirated and less than 5% bronchial epithelial cells in the retrieved sample. Patients who had this type of sample had a higher probability of a positive BAL culture than those in whom an inadequate sample was obtained [25].

The question of whether to perform endotracheal aspirate or nonbronchoscopic BAL was addressed by Arora et al. [27•]. They studied 100 episodes of possible VAP in 82 patients. They found the nonbronchoscopic BAL more specific compared with the endotracheal aspirate. The endotracheal aspirate was associated with a high rate of colonization of bacteria in patients not thought to have pneumonia.

**Bronchoscopic sampling**

Bronchoscopic sampling for BAL and PSB are still commonly employed to diagnose VAP. Over the years, both techniques have been found to have good sensitivity and specificity for the diagnosis of VAP [6,7]. Use of semi-
quantitative cultures enhances the sensitivity and specificity of these samples [1,28].

With the original description of the semiquantitative BAL culture technique, there were BAL samples that identified some bacteria thought to be nonpathogens at high concentrations [29]. Referred to as commensal organisms, these include coagulase-negative Staphylococcus and alpha-Streptococcus. In some cases, these commensals were identified from healthy volunteers and assumed to be aspirated into the lung during the bronchoscopy itself [30]. Although some groups thought these organisms could be ignored [30], others were concerned that they represented possible pathogens [29]. In a careful review of 369 episodes of VAP, Lambotte et al. found that 9% of all cases of VAP were associated with isolation of only commensal bacteria at significant levels in the BAL fluid [31•]. The authors found that these commensal organisms were associated with the development of worsening clinical status for the patient. They concluded that these organisms could not be ignored in the ventilated patient with symptoms consistent with pneumonia.

Another area that has been difficult to interpret is the number of bacteria causing pneumonia. In early studies of dogs receiving mechanical ventilation, it was clear that pneumonia could be caused by more than one bacterium at a time. Johanson et al. developed a bacterial index score, reflecting the total bacterial burden for these multiple organisms [32]. For humans, the presence of more than one bacterium causing VAP has been noted [33]. At the same time, some patients have only one pathogen identified. Combes et al. examined 124 episodes of VAP [34••]. They found that half of the cases were caused by a single pathogen, the rest were polymicrobial. The authors could not find a difference in the types of bacteria identified, duration of ventilation, the use of prior antibiotics, or mortality of the two groups.

**Effect of diagnostic test on clinical outcome**

The goal of diagnostic testing is to change the clinical outcome of the patient. For the various techniques I have discussed, there is increasing evidence that the tests may help the clinician predict or even improve the clinical outcome.

Improving oxygenation in the non-ARDS patient is the only single clinical criterion that appears to predict outcome [14••,15]. Serial CPIS has been used as a means to identify which patients can have early discontinuation of their antibiotics [13]. Serial studies can also help identify which patients are failing to respond appropriately to therapy [14••]. These patients may be failing to respond because they have a resistant bacterium or an alternative cause of their apparent pneumonia, such as a pulmonary embolism.

To determine the role of bronchoscopic BAL, Fagon et al. studied 413 patients with possible VAP [35]. The study compared clinical criteria and nonquantitative endotracheal aspirates to patients undergoing bronchoscopic diagnostic testing. The investigators found that the invasive group had a reduced mortality at 14 days and more antibiotic-free days within the 28 days of the study. One criticism of this study was that of the 24 patients in the clinical group who initially received inadequate antibiotics, 10 grew methicillin-resistant S. aureus (MRSA). Although this study was published in 2000, it was performed during a time when routine coverage for MRSA was not widely used. It is unclear whether such a difference in outcome would be seen if the same study were to be done currently, when antistaphylococcus empiric therapy is more widely used.

In the surgical and trauma intensive care units, there have been two studies to determine the role of bronchoscopic BAL in evaluating VAP. In an interesting study by Croce et al. [10], bronchoscopic BAL was used to distinguish between pneumonia and a systemic inflammatory response caused by other factors in trauma patients. In that study, patients with negative BAL cultures were not treated with antibiotics. There appeared to be no untoward outcome for the patients who had the clinical appearance of pneumonia but had negative cultures and therefore were not treated with antibiotics. Most other VAP studies will still treat these patients because of the concern about false negatives [6].

In a recent study, Wahl et al. examined whether bronchoscopic BAL impacted on the outcome of pneumonia in a trauma/burn unit [36•]. The authors found that there was no advantage of bronchoscopic versus endotracheal aspiration analysis. It is interesting to note that in this study, the bronchoscopic BAL was performed with only 50 mL, not the usual 100- to 120-mL sample usually used for bronchoscopic BAL. This smaller volume bronchoscopic BAL is associated with a higher proportion of bronchial sampling [37]. On the other hand, the endotracheal aspirate was described by the authors as often performed as part of a “small-volume saline lavage.” Therefore, the failure to show a difference may be because the sampling procedures were very similar. Also, the use of continued empiric antibiotics for patients with negative cultures appeared to be much more common than in the Croce study.

One feature of VAP in the trauma unit is the overall better outcome of the patients. For the trauma patient, the overall mortality is 15 to 20% [10,36•]. This is significantly less than the mortality noted in medical intensive care units, where the mortality is between 30 and
40% for patients receiving adequate initial antibiotics [33,38]. A recent large epidemiologic study of VAP was performed in surgical patients (Eole study). Bronchoscopy was used to confirm the diagnosis of VAP in most cases. This study confirmed the overall lower rate of mortality from VAP for the surgical versus medical patients. The investigators attributed the death of their patients to complications of pulmonary infection in less than 10% of cases of pneumonia [39•]. These observations highlight the need to identify the population being studied. In the Eole study, most cases were early-onset pneumonias with a lower rate of multidrug-resistant bacteria [39•]. The studies of medical ICU patients are characterized by a large proportion of multidrug-resistant bacteria being identified in the BAL samples [33,35,38].

In the medical ICU, the culture results of the BAL have proved useful in diagnosis of pneumonia. In a study examining the importance of initial empiric therapy, it was found that if initial therapy did not treat the bacteria recovered by BAL, there was a doubling of the mortality rate. This was true if the sample was obtained by a bronchoscope [33] or by a nonbronchoscopic catheter [38]. However, this important feature requires the culture results, which are not available for 48 to 72 hours. There have been some attempts to improve the diagnostic value at the time of the procedure.

Microscopic examination for intracellular organisms in the BAL sample may provide a rapid indication of culture results. Originally proposed by Chastre et al. [3], the method has not been widely adapted because of the required additional expertise required in analyzing the sample. However, two recent articles suggest that the effort may be worthwhile. In the study by Brasel et al., serial examination of the endotracheal aspirate for presence of intracellular organisms (ICOs) was as predictive as semiquantitative cultures in identifying patients in whom pneumonia had developed [40•]. In that study, antibiotic use did not affect the results. In a study of nonbronchoscopic BAL, Sirvent et al. found that the cutoff of greater than or equal to 2% ICOs differentiated VAP and non-VAP cases [41•]. However, that study found that prior antibiotic use decreased the sensitivity of the microscopic examination for ICOs. Sirvent et al. also looked at the value of Gram stain for the BAL specimen and found an 83% sensitivity and 64% specificity. Although not as good as looking for ICOs, the Gram stain is certainly more widely applied in examining respiratory samples.

Another technique is the use of polymerase chain reaction analysis of the sample. There are two genes that are important. Methicillin resistance is associated with the mecA gene for both S. aureus and S. epidermis [42]. The gene femA has a different sequence for S. epidermis compared with S. aureus [42]. Multiplex polymerase chain reaction looking for both mecA and the S. aureus femA was used to detect MRSA in endotracheal aspirates [43].

In the past year, a modification of this technique was made, by adding the femA gene from S. epidermis [44••]. With this triple polymerase chain reaction on samples from the various clinical sites (lung, nose, inguinal area), one could detect MRSA with high specificity. The technique was rapid, with the results available within 6 hours, rather than the 2 to 3 days required of culture techniques. A major limitation may be how to quantify the amount of bacteria present. One would have to be careful to separate the colonizer from the truly infected patient.

**Conclusion**

The diagnosis of VAP remains difficult. During the last few years, it has become clear that diagnostic tests may help guide clinical outcome. The clinical status, as measured by the CPIS, may prove to be a reliable way to detect pneumonia and monitor therapy. The best culture technique remains unclear. However, whichever culture method is used, it is clear that one needs to be aware of what the flora are in the ICU, to determine the best empiric therapy.

**References and recommended reading**

Papers of particular interest, published within the period of review, have been highlighted as:

- Of special interest
- Of outstanding interest


Study that failed to demonstrate a benefit for bronchoscopic BAL versus endotracheal aspirate in managing VAP in trauma/burn unit.


A large trial looking at various aspects of VAP in a surgical ICU. Many of patients were diagnosed using bronchoscopic sampling.


Found examination of BAL sample for intracellular organisms predictive of culture results.


Found examination of BAL sample for intracellular organisms predictive of culture results only in patients not taking antibiotics. They also examined Gram stain, which was not as sensitive.


Rapid technique to detect MRSA in respiratory secretions.
Antimicrobial Pharmacokinetic and Pharmacodynamic Issues in the Critically Ill with Severe Sepsis and Septic Shock

Julie M. Varghese, BPharm (Hons)\textsuperscript{a}, Jason A. Roberts, PhD, BPharm (Hons), FSHP\textsuperscript{a,b,c}, Jeffrey Lipman, MBCh, FCICM, MD\textsuperscript{a,b,*}

Severe sepsis and septic shock are a major challenge for critical care clinicians because of the associated high rates of morbidity and mortality. In the United States, the estimated incidence of severe sepsis is \( \sim 3 \) cases per 1000 population with mortality of 28.6\% (215,000 deaths from 750,000 patients diagnosed) per year.\textsuperscript{1} Septicemia was listed as the 10th leading cause of death in the United States in 2007.\textsuperscript{2}

In critically ill patients with sepsis and septic shock, early and appropriate antimicrobial therapy has been shown to be the predominant factor for reducing mortality.\textsuperscript{3,4}

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Severe sepsis is defined as sepsis with the failure or dysfunction of more than 1 organ; septic shock is defined as hypotension in the setting of severe sepsis that is unresponsive to fluid resuscitation. The pathophysiologic changes that occur during sepsis, severe sepsis, and septic shock can lead to changes in pharmacokinetic parameters that affect the achievement of pharmacodynamic targets for antimicrobial therapy. This may adversely affect efficacy of antimicrobial therapy in this group of critically ill patients.

This article provides a systematic review of the data on the effect of severe sepsis and septic shock on the pharmacokinetics of antimicrobials and the likely consequences for antimicrobial effect. A rational framework for antimicrobial dosing in these complex patients is also provided.

INTERRELATIONSHIP BETWEEN PHARMACOKINETICS AND PHARMACODYNAMICS

An understanding of pharmacokinetics (PK) and pharmacodynamics (PD) is essential to understand the effect of the many pathophysiologic changes in critically ill patients on antimicrobial concentrations, both in blood and in tissues. Knowledge of PK and PD can be used to personalize dosing to achieve optimized antimicrobial therapy.

PK describes the relationship between the dose administered and the changes in the drug concentration in the body with time. PD, on the other hand, describes the relationship between drug concentration and its pharmacologic effect. Fig. 1 highlights the relationship between PK and PD. The relevant pharmacokinetic parameters for drug dosing are defined in Table 1.

Clearance (CL) and apparent volume of distribution (Vd) can be considered the 2 pharmacokinetic parameters that influence drug dosing most. Half-life ($t_{1/2}$) is related to CL and Vd as represented in the following equation:

$$t_{1/2} = \frac{0.693 \times V_d}{CL}$$

(1)

First principles suggest that initial dosing of a drug is determined by Vd, whereas maintenance dosing should be based on clearance. Alterations in CL and Vd of a drug can occur as a result of the pathophysiologic changes during severe sepsis.
and septic shock. An understanding of the interrelationship between pathophysiology and PK is of importance to adjust empiric dosing to meet the specific needs of the individual patient to achieve the pharmacodynamic targets associated with maximal antimicrobial efficacy.

Different antimicrobial classes have different PK/PD indices correlated with optimal antimicrobial activity. These are summarized in Table 2. Drug dosing regimens should take into consideration the different pharmacodynamic kill characteristics and PK/PD targets for the prescribed antimicrobial, as well as the susceptibility of the organism(s) targeted, to achieve optimal antimicrobial activity.

A general understanding of the physicochemical properties of antimicrobials (eg, degree of hydrophilicity) is useful to further explain the likely pharmacokinetic and pharmacodynamic changes in critically ill patients. Table 3 provides a summary of the general characteristics of hydrophilic antimicrobials compared with lipophilic agents.

### Table 1
Relevant PK parameters for drug dosing

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Definition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance (CL)</td>
<td>The volume of blood cleared of drug per unit time</td>
<td>CL measures the irreversible elimination of a drug from the body by excretion and/or metabolism</td>
</tr>
<tr>
<td>Volume of distribution (V_d)</td>
<td>Apparent volume of fluid that contains the total drug dose administered at the same concentration as in the plasma</td>
<td>V_d is the parameter that relates the total amount of drug in the body to the plasma concentration</td>
</tr>
<tr>
<td>Half-life (t_1/2)</td>
<td>Time required for the plasma drug concentration to decrease by half</td>
<td>Half-life is dependent on CL and V_d; half-life is increased with a decrease in CL or an increase in V_d</td>
</tr>
<tr>
<td>C_max</td>
<td>Peak drug concentration during a dosing interval</td>
<td></td>
</tr>
<tr>
<td>C_min</td>
<td>Minimum drug concentration during a dosing interval</td>
<td></td>
</tr>
<tr>
<td>AUC_0–24</td>
<td>Area under the concentration-time curve from 0 to 24 h</td>
<td></td>
</tr>
</tbody>
</table>

### Changes in Distribution

#### Volume of Distribution and Fluid Shifts

The pathogenesis of sepsis is complex and involves the release of endotoxins and exotoxins from pathogens. Endotoxins such as lipopolysaccharides (gram-negative organisms) and lipotechoic acid (gram-positive organisms) are structural components of the bacterial cell wall. Exotoxins are actively secreted toxins mainly produced by gram-positive organisms. These toxins result in the production of various endogenous mediators that can cause endothelial damage and thus increased capillary permeability. This capillary leak results in fluid shifting from the intravascular space into the interstitial space in a phenomenon described as third spacing. This process serves to increase the V_d for hydrophilic antimicrobials, thus resulting in lower plasma and tissue antimicrobial concentrations. Lipophilic drugs, on the other hand, distribute to a greater extent intracellularly and/or into adipose tissue, and
therefore generally have larger $V_d$ to start with and are not greatly influenced by these fluid shifts.

By definition, septic shock is associated with hypotension and initial management is by administration of boluses of intravenous fluids to increase blood pressure. In the presence of increased capillary permeability, administration of large volumes of fluid

<table>
<thead>
<tr>
<th>Table 2</th>
<th>PK/PD indices of significance for antimicrobials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic Classification</td>
<td>PK/PD Index</td>
</tr>
<tr>
<td>Time-dependent</td>
<td>T&gt;MIC</td>
</tr>
<tr>
<td>Concentration-dependent</td>
<td>$C_{\text{max}}$/MIC</td>
</tr>
<tr>
<td>Concentration-dependent with time dependence</td>
<td>AUC$_{0-24}$/MIC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>PK characteristics of antimicrobials based on classification according to hydrophilicity and lipophilicity in general ward patients (General PK) compared with altered PK observed in critically ill patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>General PK</td>
<td>Altered PK in Critically Ill</td>
</tr>
<tr>
<td>Hydrophilic antibiotics</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>$V_d$</td>
</tr>
<tr>
<td>Predominantly renal</td>
<td>CL</td>
</tr>
<tr>
<td>Poor intracellular penetration</td>
<td>Distribution</td>
</tr>
<tr>
<td>Examples: Beta-lactams, carbapenems, aminoglycosides, glycopeptides, linezolid</td>
<td></td>
</tr>
<tr>
<td>Lipophilic antibiotics</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>$V_d$</td>
</tr>
<tr>
<td>Predominantly hepatic</td>
<td>CL</td>
</tr>
<tr>
<td>Good intracellular penetration</td>
<td>Distribution</td>
</tr>
<tr>
<td>Examples: fluoroquinolones, macrolides, tigecycline, lincosamides</td>
<td></td>
</tr>
</tbody>
</table>
can lead to an expansion of fluid volume in the interstitial space and an increase in the 
$V_d$ for hydrophilic antimicrobials. Other possible reasons for edema and fluid retention 
in critically ill patients may include cardiac failure or renal failure, both of which may 
also serve to increase $V_d$ of hydrophilic antimicrobials.

Tissue Perfusion, Tissue Penetration, and Target Site Distribution of Antimicrobials

Most infections occur in the interstitial fluid of tissues and may be considered the site 
of most infections. During septic shock, microvascular perfusion is diminished 
which, in turn, leads to impaired distribution of drugs to sites of infection, such as 
soft tissue.

Impaired tissue penetration in patients with severe sepsis and septic shock can be 
attributed to capillary leakage, tissue edema, and microvascular failure. Several 
studies have utilized an in vivo sampling technique known as microdialysis in critically 
ill patients with sepsis and septic shock to measure antimicrobial concentrations in 
interstitial fluid. A study by Joukhadar and colleagues showed that in patients 
with septic shock, the concentration of piperacillin in interstitial fluid was 5 to 10 times 
lower than the corresponding plasma concentrations. In this study, interstitial fluid 
concentrations in healthy volunteers was observed to be 3- to 4-fold higher compared 
with interstitial fluid concentrations in patients with septic shock. Roberts and 
colleagues studied piperacillin penetration into interstitial fluid in patients with sepsis 
and observed subcutaneous tissue concentrations to be 1 to 5 times lower than 
plasma concentrations. The difference in the level of sickness severity (septic shock 
vs sepsis) may explain the observed difference in the tissue interstitial fluid concentra-
tions in these studies for piperacillin, where the greater impairment of microvascular 
perfusion in patients with septic shock is associated with much lower tissue antimicro-
bial concentrations compared with that observed in patients with sepsis. Higher 
plasma concentrations may be required to achieve the target concentrations needed 
in tissues, especially when poor tissue penetration is suspected, such as during septic 
shock.

Selection and dosing of antimicrobials in patients with severe sepsis and septic 
shock should consider the potential sites of infection and whether adequate concen-
trations will be achieved at the focus of infection. For example, in the treatment of 
bacterial meningitis, penetration of most antimicrobials, including beta-lactams, into 
the cerebrospinal fluid is limited and high-dose therapy is recommended for this 
reason.

Protein Binding and Hypoalbuminemia

Albumin, the predominant plasma protein that binds to acidic drugs, is a negative 
acute phase protein and is often low in critically ill patients. Hypoalbuminemia in crit-
ically ill patients with sepsis is mainly caused by increased capillary permeability and 
leakage into extravascular space, as well as decreased synthesis in the liver. Low 
plasma albumin levels cause an increase in the unbound (ie, free) fraction of drugs 
that are usually bound to this protein. Increased unbound concentrations result in 
increased tissue distribution because it is only the unbound drug that distributes. 
However, the increased fluid loading that is required in critically ill patients in response 
to fluid shifts during an acute phase response, means that the interstitial fluid volume in 
tissues increases. This causes the tissue concentration of antibiotic to remain low, 
despite the increased amount of drug that has distributed. This effect is particularly 
significant for highly protein-bound antimicrobials such as ceftriaxone, ertapenem, tei-
coplanin, and flucloxacillin. The increased $V_d$ is associated with low plasma 
concentrations, in which case, larger, or more frequent doses, or modified dosing
regimens such as continuous infusion may be required to meet pharmacodynamic targets for these highly protein-bound agents. An initial loading dose may also be required in this situation to account for the increased V_d and ensure adequate drug concentrations are achieved early during antimicrobial therapy.

A recent study examining the PK of flucloxacillin in critically ill patients with hypoalbuminemia observed subtherapeutic unbound plasma levels of flucloxacillin.23 This highlights the importance of measuring unbound concentrations of highly protein-bound antimicrobials, rather than total concentration alone, as the unbound fraction can change during severe sepsis and septic shock and only the unbound drug confers antimicrobial effect.

**CHANGES IN CL**

**Increased Cardiac Output and Increased CL**

The initial hyperdynamic state of sepsis is associated with a high cardiac output and, thus, increased renal blood flow resulting in increased CL of drugs eliminated by glomerular filtration. The administration of fluid as well as the use of inotropes during severe sepsis and septic shock can also lead to an early increase in cardiac output and increased glomerular filtration rate. Hydrophilic antimicrobials are predominantly cleared by the kidneys and increased renal CL results in lower plasma concentrations. Septic shock with renal dysfunction, on the other hand, translates to lower glomerular filtration rates and decreased CL.

Only the unbound or free fraction of a drug can be cleared by the body. Hypoalbuminemia as previously discussed results in an increase in the unbound fraction of highly protein-bound drugs. This translates to an increased renal CL particularly for highly protein-bound hydrophilic antimicrobials.

**End-Organ Dysfunction and Decreased CL**

Decreased organ perfusion that occurs with sepsis can lead to the development of organ dysfunction including renal and/or hepatic dysfunction. In general, decreased CL and/or metabolism of drugs will result in accumulation of drugs and/or metabolites with the possibility of increased risk of toxicity. It follows that dose reductions need to be considered for these patients, taking into consideration possible alternative mechanisms of CL that may be upregulated in the presence of isolated organ dysfunction.

**Renal Replacement Therapy**

Sepsis is the most common cause of acute kidney injury and continuous renal replacement therapy (RRT) is often prescribed to remove fluid and wastes from the body. There are different forms of RRT available and different centers use different modes of RRT with different settings. The principles of antimicrobial dosing during continuous renal replacement therapy (CRRT) have recently been reviewed.24 Multiple factors including the physicochemical properties of the drug, dialysis settings, and patient-related factors can influence the PK of antimicrobials in patients undergoing RRT.25

Extended daily dialysis (EDD) is a hybrid form of dialysis that generally runs for 8–12 hours a day and has the combined advantages of intermittent hemodialysis (IHD) and CRRT. This form of dialysis is increasingly being used in some centers and a few recent studies have examined antimicrobial PK in EDD.26–28 Additional factors that need to be considered include the timing of antimicrobial dosing in relation to EDD treatment and the possible need for supplemental antimicrobial dosing after an EDD session.29
Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) may influence antimicrobial kinetics through increasing the V_d for a drug as well as through possible binding of drugs in the ECMO circuit.\textsuperscript{30,31} In practice, in the absence of informative data, therapeutic drug monitoring of antimicrobials is recommended where possible in critically ill patients treated with ECMO.

Plasma Exchange

Plasma exchange is a treatment modality that may influence antimicrobial concentrations as a result of extracorporeal removal of drugs.\textsuperscript{32} During the procedure, plasma proteins are removed from the body and plasma losses are replaced with donor human albumin. Drugs with a low V_d (<0.3 L/kg) and high protein binding are most likely to be removed during plasma exchange and may require dose adjustments.\textsuperscript{33,34} Highly protein-bound drugs such as ceftriaxone and teicoplanin, for example, have been shown to be significantly affected by plasma exchange.\textsuperscript{35,36}

Changes in Metabolism

Decreased hepatic blood flow as a result of sepsis may cause a decrease in drug metabolism.\textsuperscript{37} Hepatic metabolism of drugs with a high extraction ratio is primarily dependent on the blood flow. For drugs with a low extraction ratio, metabolism is dependent on the unbound fraction and/or the activity of hepatic enzymes. Clindamycin, for example, has a low extraction ratio and has been shown to have decreased clearance during the hyperdynamic state of sepsis.\textsuperscript{38} This antimicrobial is highly bound to alpha\textsubscript{1}-acid glycoprotein, an acute phase protein that is increased in critical illness. The observed decreased hepatic clearance of clindamycin in sepsis/septic shock is possibly caused by a decrease in enzyme activity or a decrease in fraction unbound considering only the unbound fraction of drug can be cleared heptically. Decrease in CYP3A4 activity has also been observed in animal models of endotoxin-induced shock.\textsuperscript{39}

Changes in Absorption

Critically ill patients with sepsis are not normally administered drugs via the oral route, but if the oral route is used absorption into the systemic circulation is expected to be low. During septic shock, blood flow is directed preferentially to vital organs such as the brain, heart, and lungs. Organs such as the kidney and the gastrointestinal tract become less well perfused. Poor blood perfusion to the peripheries also impairs the systemic absorption of drugs from muscles and subcutaneous tissues. The intravenous route of administration is thus preferred because of the unreliable systemic drug absorption by other routes.

Effect of PK/PD on Specific Antimicrobial Classes

Beta-lactams

Beta-lactams are the most commonly prescribed class of antimicrobials and include penicillins and cephalosporins. In general, beta-lactams are hydrophilic in nature and thus predominantly renally cleared with the exception of ceftriaxone and oxacillin, which undergo biliary clearance. Variability exists in terms of protein binding, with high protein binding (~90%) well recognized for ceftriaxone and flucloxacillin. Beta-lactam antimicrobials have a slow concentration-independent continuous kill characteristic and the time for which the free (or unbound) antimicrobial concentration...
is maintained above the minimum inhibitory concentration (MIC), \( \text{fT}_{>\text{MIC}} \) is the PK/PD index best correlated to efficacy.\(^7\) A recent study with cefepime and ceftazidime has suggested that a \( \text{fT}_{>\text{MIC}} \) of 100\% is associated with better clinical and microbiological cure in serious bacterial infections.\(^40\) Changes in \( V_d \) and CL that occur in patients with sepsis can influence the maintenance of adequate \( \text{fT}_{>\text{MIC}} \) for beta-lactams. Some studies of beta-lactams in critically ill patients with sepsis have observed an increased \( V_d \) compared with patients who are not critically ill.\(^12,13\) Pharmacokinetic studies of cefepime and ceftipime in critically ill patients with normal serum creatinine levels have shown subtherapeutic plasma levels and high antimicrobial CL with renal elimination linearly related to creatinine clearance.\(^41\) Some patients with normal serum creatinine levels may have large creatinine clearances (more than the generally reported maximum of 120 mL/min) and creatinine clearance was shown to be an independent predictor of antimicrobial clearance.\(^41\) In these patients, measured creatinine clearances may be useful to identify or predict patients who are at risk of underdosing because of increased renal CL. An 8-, 12- or 24-hour creatinine clearance collection\(^42,43\) is the most practical and accurate method to measure renal function in these cases, although a 2-hour creatinine clearance has been shown to be an appropriate substitute.\(^44\)

Pharmacokinetic modeling and dosing simulation indicate that an improved pharmacodynamic profile is achieved with more frequent dosing or extended or continuous infusion (for a fixed total dose) of beta-lactams in critically ill patients.\(^45–49\) This is of particular value for patients with increased renal CL and/or large \( V_d \) especially when targeting bacteria with high MICs and subtherapeutic antimicrobial concentrations are likely to result from the pathophysiologic changes that occur during sepsis.\(^13,19,45,50,51\)

### Carbapenems

Carbapenems generally have similar kill characteristics to other beta-lactams although the carbapenems do exhibit some postantimicrobial effects (PAE).\(^7\) In vitro data for carbapenems suggest that \( \text{fT}_{>\text{MIC}} \) of at least 40\% is required for antibacterial activity. Increased \( V_d \) and CL has been observed for carbapenems in critically ill patients.\(^52,53\) Pharmacokinetic studies along with pharmacodynamic modeling indicate that PK/PD targets are better achieved through administration as an extended or continuous infusion.\(^54–56\)

### Aminoglycosides

Aminoglycosides have concentration-dependent kill characteristics where a \( C_{\text{max}}/\text{MIC} \) of at least 10 is the PK/PD index related to clinical success.\(^57\) This class also displays a PAE whereby antibacterial activity is prolonged even when drug concentrations decrease to less than the MIC.\(^58\) These PK/PD characteristics support the recommendation for extended interval dosing of aminoglycosides. High trough concentrations of aminoglycosides are related to toxicity with increased risk of toxicity associated with increased drug exposure.

Critically ill patients often display increased \( V_d \) for aminoglycosides\(^59–61\) and this translates to decreased \( C_{\text{max}} \). Increased sickness severity as measured by the APACHE II score has been shown to be related to higher \( V_d \) for aminoglycosides.\(^62\) Weight-based initial dosing of 7 mg/kg for gentamicin and tobramycin, and 20 mg/kg for amikacin is recommended and therapeutic drug monitoring should be performed after the first dose. Once available, the MIC for the pathogen(s) allows further dose adjustments to achieve PK/PD targets.
**Glycopeptides**

Vancomycin displays moderate protein binding, whereas teicoplanin is highly protein bound. In patients with hypoalbuminemia, increased $V_d$ and CL are possible for teicoplanin because of an increase in the unbound fraction of the drug. A teicoplanin loading dose of 6 mg/kg every 12 hours for at least 3 doses followed by once-daily dosing is recommended.

Increased capillary permeability and fluid shifts in the critically ill can lead to increased $V_d$ for vancomycin. The optimal PK/PD target for optimal antibacterial activity of vancomycin is not well understood. In vitro and animal studies demonstrate that bacterial killing of vancomycin is time dependent ($T>MIC$). A neutropenic mouse model demonstrated that area under the curve AUC/MIC ratio is the best predictor of antibacterial activity although a non-neutropenic mouse model demonstrated that $C_{max}/MIC$ was the PK/PD index determining efficacy.

In practice, therapeutic drug monitoring of vancomycin in the form of trough concentration monitoring is recommended aiming for $C_{min}$ of between 15 and 20 mg/L to achieve a target AUC/MIC ratio of at least 400 for eradication of *Staphylococcus aureus*. Maintenance doses of up to 30 to 40 mg/kg/d may be required in critically ill patients with increased $V_d$ and/or increased CL to achieve adequate antimicrobial concentrations. Vancomycin can be administered by continuous infusion to improve the PD and to minimize the risk of toxicity associated with the use of large intermittent doses. In patients with renal impairment, dose reduction of glycopeptides is warranted to minimize the risk of toxicity.

**Fluoroquinolones**

Fluoroquinolones are lipophilic antimicrobials and fluid shifts in critically ill patients have minimal effect on the $V_d$ of this class of antimicrobials. Fluoroquinolones display concentration-dependent kill characteristic with time-dependent effects. In vitro studies have shown that a $C_{max}/MIC$ ratio of 10 is the PK/PD parameter correlated to bacterial eradication. Peak drug concentration may be decreased as a result of fluid shifts in critically ill patients. An AUC/MIC>125 has been shown to be the PK/PD target for ciprofloxacin against gram-negative pathogens for clinical and microbiological cure in critically ill patients.

The results from several pharmacokinetic studies of ciprofloxacin in critically ill patients suggest that a total daily dose of 1200 mg is required in patients with normal renal function to achieve the PK/PD targets that maximize bacterial kill. High doses of intravenous ciprofloxacin of up to 1200 mg per day (ie, 600 mg every 12 hours or 400 mg every 8 hours) in patients with normal renal function seem to be safe. Subtherapeutic fluoroquinolone concentrations, on the other hand, have been associated with the emergence of resistance. Selection of antimicrobial resistance is associated with suboptimal drug exposure as defined by AUC/MIC<100. The goal for dosing fluoroquinolones is to ensure maximal antimicrobial exposure to maximize achievement of PK/PD target as well as minimize the development of resistance.

**Lincosamides**

Clindamycin and lincomycin are lipophilic in nature and $fT>MIC$ is the PK/PD index related to efficacy. Unbound drug concentrations should exceed the MIC for at least 40% to 50% of the dosing interval for optimal antimicrobial activity. In critically ill patients with sepsis, hepatic CL of clindamycin has been shown to decrease. Decreased doses are required for clindamycin and lincomycin in patients with hepatic dysfunction. Lincomycin requires dose adjustment in renal impairment.
**Linezolid**

Linezolid is an oxazolidinone antibacterial that has a weak, reversible, nonselective monoamine oxidase inhibitory activity and the potential for drug interactions should be considered when prescribing this agent. Linezolid is predominantly metabolized in the liver and the metabolites and parent drug are renally cleared.\(^83\) Although hydrophilic in nature, linezolid penetrates well into tissues and has been shown to achieve adequate concentrations in epithelial lining fluid in patients with ventilator-associated pneumonia.\(^84\) The AUC/MIC ratio is the PK/PD index associated with antimicrobial efficacy.\(^85\) Oral bioavailability of linezolid is 100% and a dose of 600 mg every 12 hours is adequate to achieve a pharmacodynamic target of AUC/MIC between 80 and 100 against susceptible organisms with MICs up to 2 to 4 mg/L.\(^85\)

**Tigecycline**

Tigecycline is a glycycline antimicrobial that has broad spectrum activity including gram-positive, gram-negative, and anaerobic cover.\(^86\) It is lipophilic in nature and has a large V\(_d\) indicating extensive distribution into tissues.\(^87\) The AUC/MIC ratio is the PK/PD index that is correlated with efficacy as tigecycline has a long half-life and exhibits a prolonged PAE.\(^88\) The primary route of elimination is biliary excretion.\(^87\) No dosing adjustment is required for tigecycline in renal dysfunction or mild to moderate hepatic dysfunction.

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**HYDROPHILIC ANTIBIOTICS**

![Flow diagram summarizing the effects of pathophysiologic changes on PK/PD parameters of hydrophilic antibiotics. AUC, area under the curve; C\(_{\text{max}}\), maximum drug concentration; C\(_{\text{min}}\), minimum drug concentration; CL, clearance; CO, cardiac output; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; V\(_d\), volume of distribution.](image-url)

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SUMMARY

In critically ill patients with severe sepsis and septic shock, altered pathophysiology can have a significant influence on pharmacokinetic parameters, particularly $V_d$ and $CL$, which can then further affect the achievement of pharmacodynamic targets for antimicrobial agents. Failure to achieve pharmacodynamic targets for antimicrobials can result in poor clinical outcomes. Knowledge of the physicochemical properties and PK/PD index associated with maximal activity of an antimicrobial can help clinicians determine if dosage adjustments need to be made. The flow diagrams in Figs. 2 and 3 summarize the effects of pathophysiologic changes on PK/PD parameters for the different hydrophilic and lipophilic antimicrobials and provide suggested dosage adjustments.

**LIPOPHILIC ANTIBIOTICS**

- **AUC/MIC**
  - PK/PD index
  - $T > MIC$

**Lincosamides**

- Hepatic dysfunction
  - $\downarrow CL$
  - $\uparrow C_{\text{min}}$
  - Decrease dose of clindamycin & lincomycin in hepatic failure
  - Decrease dose of lincomycin in renal impairment

**Fluoroquinolones**

- Fluid shifts
  - $\leftrightarrow V_d$
  - $\downarrow C_{\text{max}}$

  **Renal dysfunction**
  - $\downarrow CL$

  Use high doses (e.g., ciprofloxacin 400mg every 8 hours in normal renal function)

  Aim to achieve AUC/MIC 125 for Gram negatives, and 30 for Gram positive organisms

  Decrease dose of ciprofloxacin, levofloxacin, and gatifloxacin.

  Note: In renal failure, ciprofloxacin displays increased hepatic and transintestinal $CL$

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**Fig. 3.** Flow diagram summarizing the effects of pathophysiologic changes on PK/PD parameters of lipophilic antibiotics. AUC, area under the curve; $C_{\text{max}}$, maximum drug concentration; $C_{\text{min}}$, minimum drug concentration; $CL$, clearance; $CO$, cardiac output; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; $V_d$, volume of distribution.
dosing recommendations for the different antimicrobial classes. Hydrophilic time-dependent antimicrobials such as beta-lactams may display decreased C\textsubscript{min} as a result of large V\textsubscript{d} and/or increased CL, whereas hydrophilic concentration-dependent antimicrobials such as the aminoglycosides may display decreased C\textsubscript{max} as a result of higher V\textsubscript{d} in the critically ill patient with sepsis.

Antimicrobial dosing adjustments should take into considerations these potential changes in pharmacokinetic parameters and careful dosage adjustments need to be made particularly in patients with renal and/or hepatic dysfunction. The effect of any extracorporeal treatment modalities on antimicrobial pharmacokinetics also needs to be considered by clinicians. Knowledge of PK/PD properties of antimicrobials can be used to personalize dosing regimens for critically ill patients with sepsis and septic shock not only to maximize antimicrobial activity but also to minimize toxicity and reduce the development of antimicrobial resistance.89

REFERENCES


