This article summarizes studies published in 2009 that have important implications for the practice of pulmonary and critical care medicine.

In pulmonary medicine, 2 trials provide insight into the management of patients with chronic obstructive pulmonary disease (COPD). Inhaled tiotropium added to standard respiratory therapies reduced mortality during 4 years of therapy in nonsmoking patients. In another study, the combination of inhaled salmeterol plus inhaled fluticasone (which reduces mortality in patients with severe COPD) improved health status and reduced exacerbations in patients with mild COPD. For patients with asthma, inhaled salmeterol without corticosteroids worsened airway hyperresponsiveness (AHR), hospitalizations, and mortality. A short-term study showed that salmeterol increases mononuclear cell levels of brain-derived neurotrophic factor, a mediator of AHR, and that these effects were reversed with fluticasone propionate. For patients with pneumonia, guideline-concordant therapy is correlated with better outcomes for community-acquired pneumonia (CAP). Finally, a multicenter study of patients with pneumonia showed that procalcitonin could reduce rates of antibiotic exposure and antibiotic-associated adverse events.

In critical care medicine, 3 studies shed light on optimal management of critically ill patients with sepsis: NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) showed that intensive glucose control in critically ill patients was associated with increased hypoglycemia and increased mortality, suggesting that this strategy should be discarded. A systematic review of corticosteroids as adjunctive therapy for septic shock showed that low-dose corticosteroids reverse shock and may improve survival. In selected patients, an experienced team of therapists and nurses can mobilize mechanically ventilated patients and improve functional outcomes. With regard to other syndromes seen commonly in the intensive care unit (ICU), an observational study of the timeliness of appropriate antibiotics in patients with pneumonia reinforced the need for prompt operational strategies to choose and deliver appropriate empirical therapy. Many articles emphasized the effect of H1N1 influenza in 2009 on morbidity and mortality, presaging what could occur when a more severe pandemic occurs. A study from Canada emphasized that even with a mild strain of influenza that produced low-severity illness in most patients, a substantial number of patients needed ICU care, raising the question of whether enough ICU resources will be available when a more severe pandemic occurs. A study assessing line-related sepsis showed that using chlorhexidine-impregnated sponges to cover the insertion site can reduce the incidence of infectious complications. New interventions, although effective individually, must be interpreted in the context of other, established beneficial interventions.

**Chronic Obstructive Pulmonary Disease**

**Tiotropium May Reduce Mortality in COPD While Patients Continue Therapy**


**Background:** The long-term effect of pharmacologic therapy for COPD is controversial. The UPLIFT (Mortality in the 4-Year Trial of Tiotropium) study was a 4-year randomized, controlled trial (RCT) reported in 2008. It evaluated the effect of inhaled tiotropium (an anticholinergic agent) on the rate of decline in FEV1 in patients with COPD. Although this rate with tiotropium did not differ from that with placebo, benefits were observed in several secondary end points, including health-related quality of life, risk or hospitalization for a COPD exacerbation, respiratory failure, and all-cause mortality. However, a more complete evaluation of the timing and causes of deaths is needed to better understand the effect of tiotropium therapy.

**Study Design:** An independent adjudication committee evaluated deaths during and after the 4-year study. A total of 5993 patients with COPD from 37 countries were randomly assigned to receive tiotropium or placebo in addition to their usual respiratory medications (except for anticholinergic drugs).

**Findings:** All-cause mortality during drug treatment was 13.6% in the placebo group and 12.8% in the tiotropium group (hazard ratio [HR], 0.84 [95% CI, 0.73 to 0.97]; P = 0.016). At study completion (1440 days), mortality...
was lower in the tiotropium group (14.4% vs. 16.3%; HR, 0.87 [CI, 0.76 to 0.99]; \( P = 0.034 \)). At 1470 days (4 years of treatment plus 30 days), mortality rates were 14.9% and 16.5% with tiotropium and placebo, respectively (HR, 0.89 [CI, 0.79 to 1.02]; \( P = 0.086 \)). The most common cause of death in both groups was lower respiratory disorders.

**Cautions:** The placebo group had more premature discontinuations of the study drug, and patients who discontinued prematurely had more severely depressed FEV\(_1\), which might have biased the results.

**Implications:** Long-term treatment with tiotropium (with or without concomitant respiratory medications) may reduce mortality in patients with COPD. The beneficial effect on mortality observed, however, was no longer significant 30 days after the 4-year treatment period: Statistical significance was observed at the end of the protocol-defined treatment period (\( P = 0.034 \)) but not 30 days thereafter (\( P = 0.086 \)). This difference may have been due to an excess number of deaths in the tiotropium group after discontinuation of therapy. In addition, the benefit of tiotropium on mortality was noted in nonsmokers but not current smokers, suggesting that the noxious effects of smoking may override the benefits of therapy.

**A Post Hoc Evaluation of Salmeterol and Fluticasone for Mild COPD**


**Background:** In 2007, an RCT reported that treatment with inhaled salmeterol (a long-acting \( \beta \)-agonist) together with inhaled fluticasone propionate (an inhaled corticosteroid) decreased mortality in patients with severe or very severe COPD. However, data on the value of this combination in patients with milder COPD are lacking.

**Study Design:** The investigators performed an unplanned (post hoc) analysis of data from the TORCH (Towards a Revolution in COPD Health) study, a 3-year RCT of 6112 patients with moderate to severe COPD (prebronchodilator FEV\(_1\) to <60% predicted) in which patients were randomly assigned to treatment with inhaled salmeterol, fluticasone propionate, both drugs in combination, or placebo. Overall, the patients had a mean age of 65 years and a mean FEV\(_1\) of 44%, 76% were male, and 44% were current smokers. The trial excluded patients with asthma or more than 10% reversibility in airway obstruction. In this secondary analysis, the authors assessed outcomes according to patients’ Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage (a classification of disease severity): moderate (GOLD stage II, FEV\(_1\) \( \geq 50\% \) to \( <80\% \); \( n = 2156 \)), severe (GOLD stage III, FEV\(_1\) \( \geq 30\% \) to <50%; \( n = 3019 \)), and very severe (GOLD stage IV, FEV\(_1\) <30%; \( n = 937 \)).

**Findings:** Compared with placebo, combination therapy improved postbronchodilator FEV\(_1\) by 101 mL in patients with GOLD stage II (CI, 71 to 132 mL), 82 mL in patients with GOLD stage III (CI, 60 to 184 mL), and 96 mL in patients with GOLD stage IV (CI, 54 to 138 mL) disease. Combination therapy reduced the rate of COPD exacerbations by 31% in patients with baseline GOLD stage II disease (CI, 19% to 40%) and by 26% in patients with GOLD stage III disease (CI, 17% to 34%). No reduction in the rate of exacerbation was seen in patients with GOLD stage IV disease (14% [CI, −4% to 29%]). Combination therapy improved patient-reported health-related quality of life in all 3 stages. Finally, in this exploratory analysis, mortality was reduced with combination therapy in patients with baseline GOLD stage II disease (HR, 0.67 [CI, 0.65 to 0.98]) but not in those with GOLD stage III (HR, 0.95 [CI, 0.73 to 1.24]) or IV (HR, 0.70 [CI, 0.4 to 1.05]) disease.

Adverse events were similar across treatment groups and increased with disease severity. The incidence of pneumonia was higher in the fluticasone propionate and combination groups, regardless of GOLD stage, when compared with placebo or salmeterol.

**Cautions:** The analysis was post hoc and must be viewed as hypothesis-generating only. The study was not designed to test for differences between GOLD stages or differences between treatment groups within GOLD stages. The numbers of patients in each group differed, and the analysis of treatment subgroups within stages was underpowered.

**Implications:** According to this hypothesis-generating study, 3 years of treatment with combined inhaled salmeterol and fluticasone propionate may improve health-related quality of life and reduce exacerbations and mortality in patients with moderate (GOLD stage II) COPD. Further prospective studies are required to assess whether combination therapy has a clinically meaningful benefit in patients with moderate COPD.

**A Possible Molecular Link for the Effects of Long-Acting \( \beta \)-Agonists and Corticosteroids in Asthma**


**Background:** Long-term use of inhaled \( \beta \)-agonists without concomitant corticosteroids has been associated with a paradoxical loss of asthma control; worsening AHR; and increases in asthma exacerbations, hospitalizations, and mortality. The mechanisms responsible for these effects are not known. The neurotrophin brain-derived neurotrophic fac-

**Asthma**
Pneumonia

Adherence to Antibiotic Guidelines for Community-Acquired Pneumonia Was Associated With Improved Outcomes


Background: Community-acquired pneumonia remains a major cause of morbidity and mortality worldwide. A 2007 clinical practice guideline from the American Thoracic Society and Infectious Diseases Society of America (ATS/ISDA) recommends specific antimicrobial regimens according to specific risk factors, previous antibiotic use, and resistance patterns. The ATS/ISDA recommendations, however, have not been validated in prospective randomized trials.

Study Design: To assess the effect of therapy according to ATS/ISDA guidelines, the outcomes of adults hospitalized for CAP from 1999 to 2003 at 113 U.S. community and tertiary care centers were assessed according to whether initial antibiotic therapy was concordant with the guidelines.

Findings: Of 54,619 adults, 35,477 (65%) received initial antibiotic therapy concordant with 2007 ATS/ISDA guidelines. Overall, 30-day mortality was 5.8%. Patients who received guideline-concordant therapy had lower mortality than those who did not, even after adjustment for multiple confounding variables (odds ratio [OR], 0.70 [CI, 0.63 to 0.77]). Guideline-concordant therapy was associated with lower rates of sepsis and renal failure but no difference in respiratory failure. Patients receiving guideline-concordant therapy were transitioned from parenteral to oral antibiotics an average of 0.57 days sooner and had a shorter length of stay (LOS) regardless of pneumonia severity (mean reduction, 0.66 days; P < 0.001). In univariate exploratory analyses, the risk for death correlated with the use of specific classes of antimicrobials, with reductions observed in patients receiving initial empirical therapy with second- or third-generation cephalosporins, macrolides, or fluoroquinolones. In addition, even after adjustment for pneumonia severity, antibiotic coverage with activity against Legionella species was less likely to have occurred in patients who received cefepime (OR, 0.26), carbapenems (OR, 0.31), piperacillin–tazobactam (OR, 0.33), or vancomycin (OR, 0.43), and mortality was higher in patients receiving these antibiotics.

Cautions: This was an observational study only. Given the lack of randomization, it is possible that persons receiving guideline-concordant therapy differed fundamentally from those receiving discordant therapy. Furthermore, data on the microbial cause of pneumonia were lacking, making it impossible to determine whether the observed mortality and other outcome differences reflect inadequate coverage of specific pathogens (particularly Legionella species).

Implications: The use of ATS/ISDA guidelines was associated with improved outcomes (mortality, LOS, transition to oral antibiotics) in adults with CAP. The greater mortality observed in patients receiving certain antibiotic regimens may have been explained by a lack of coverage against “atypical” organisms (for example, Legionella, Mycoplasma, and Chlamydia species) with either a macrolide or fluoroquinolone. Although the hypothesis requires validation, adherence to clinical practice guidelines for CAP should be encouraged.
Health Care–Associated Pneumonia: Worse Outcomes Than Hospital-Acquired or Community-Acquired Pneumonia


Background: In 2005, the ATS/IDSA guidelines proposed a new category of pneumonia—health care–associated pneumonia (HCAP)—as an entity distinct from CAP and hospital-acquired pneumonia (HAP). Patients with HCAP include those who have recently been hospitalized, have resided in nursing homes or long-term care facilities, or have received hemodialysis or intravenous chemotherapy. Guidelines for empirical treatment were published but have not been validated in prospective studies.

Study Design: To evaluate the causes and outcomes of CAP, HAP, and HCAP, a prospective observational study of adults with pneumonia admitted to 55 hospitals in Italy was performed during 2 surveillance periods of 1 week each.

Findings: A total of 362 patients with pneumonia were evaluated: 223 patients (61.6%) had CAP, 90 patients (24.9%) had HCAP, and 49 patients (13.5%) had HAP. The mean age was 75.5 years, and 48.6% had at least 2 comorbid conditions at the time of diagnosis of pneumonia. Compared with patients with CAP, patients with HCAP had higher mean Sequential Organ Failure Assessment scores (3.0 vs. 2.0), were more frequently malnourished (11.1% vs. 4.5%), and had more frequent bilateral (34.4% vs. 19.7%) and multilobar (27.8% vs. 21.5%) involvement on chest radiography. Patients with HCAP also had higher mean Sequential Organ Failure Assessment scores (3.0 vs. 2.0), were more frequently malnourished (11.1% vs. 4.5%), and had more frequent bilateral (34.4% vs. 19.7%) and multilobar (27.8% vs. 21.5%) involvement on chest radiography. Patients with HCAP also had higher mortality rates (17.8% [CI, 10.6% to 24.9%] vs. 6.7% [CI, 2.9% to 10.5%]) and longer mean LOS (18.7 days [CI, 15.9 to 21.5 days] vs. 14.7 days [CI, 13.4 to 15.9 days]). Logistic regression analysis revealed that depressed consciousness (OR, 3.2), leukopenia (OR, 6.2), and receipt of antimicrobial therapy not recommended by the 2005 ATS/IDSA guidelines (OR, 6.4) were independently associated with increased hospital mortality. Of note, patients with HCAP were more likely to receive empirical therapy inconsistent with the 2005 ATS/IDSA guidelines (P < 0.001): Adherence to guideline recommendations was 58.7% for CAP, 69.4% for HAP, and only 26.7% for HCAP (P < 0.001).

Caution: The number of patients with HCAP was relatively small, and microbiological data were not provided. The study included only patients requiring hospitalization; therefore, the results may not apply to outpatients. Given the observational nature of this study and the lack of randomization, additional studies are required to determine optimum therapy for HCAP.

Implications: Clinicians should recognize HCAP as a distinct form of pneumonia because it is associated with higher mortality and increased LOS compared with other types and is frequently managed inadequately with potentially inappropriate initial antibiotic therapy. Selection of antibiotics for HCAP should include coverage of methicillin-resistant Staphylococcus aureus and multidrug-resistant gram-negative rods, as recommended in a 2008 consensus statement by the IDSA.

Critical Care Medicine

Using Serum Procalcitonin Levels to Guide Antibiotic Use in Lower Respiratory Infections


Background: Because symptoms and signs are frequently unreliable in distinguishing bacterial from viral lower respiratory tract infection (LRTI), unnecessary antibiotic use is common. Higher and protracted elevations in serum procalcitonin levels correlate with more severe systemic infections, bacteremic CAP, and slower bacterial clearance. Small (often single-center) studies have suggested that procalcitonin-based clinical algorithms reduce antibiotic use but have not been sufficiently powered to assess whether such algorithms are associated with adverse outcomes.

Study Design: An RCT done in the emergency departments of 6 Swiss tertiary care hospitals assessed the noninferiority of a procalcitonin-based algorithm to guide antibiotic therapy. The investigators randomly assigned 1359 consecutive patients with LRTIs to antibiotic care guided by a procalcitonin-based algorithm (procalcitonin group) or standard guidelines (control group). Serum procalcitonin level was measured locally at each hospital, and results were available within 1 hour. In the procalcitonin group, the initiation or continuation of antibiotics was discouraged for patients with procalcitonin levels less than 0.25 \( \mu \)g/L and was strongly encouraged for patients with procalcitonin levels greater than 0.25 \( \mu \)g/L. Initiation or continuation of antibiotics was not recommended for patients with procalcitonin levels between 0.25 and 0.50 \( \mu \)g/L.

Findings: The rates of overall adverse outcomes were similar in the procalcitonin and control groups (15.4% vs.
18.9%; difference, −3.5 percentage points [CI, −7.6 percentage points to 0.4 percentage points]. The mean duration of antibiotic exposure was shorter in the procalcitonin group than the control group (5.7 vs. 8.7 days; relative change, −34.8% [CI, −40.3% to −28.7%]), with significant reductions in the subgroups of patients with CAP (7.2 vs. 10.7 days), exacerbation of COPD (2.5 vs. 5.1 days), and acute bronchitis (1.0 vs. 2.8 days). Antibiotic-associated adverse effects were less frequent in the procalcitonin group (19.8% vs. 28.1%; difference, −8.3 percentage points [CI, −12.7 to −3.7 percentage points]).

Cautions: Patients with severe immunosuppressive or life-threatening comorbid conditions were excluded. Use of a composite end point (combined adverse outcomes) can complicate interpretation. The rate of combined adverse outcomes tended to be lower in the procalcitonin group, but the mortality rate was slightly higher.

Implications: In patients with LRTIs, the use of serum procalcitonin levels to guide antibiotic use results in lower rates of antibiotic exposure and antibiotic-associated adverse effects without an increase in overall adverse outcomes compared with standard management. Algorithms based on serial procalcitonin levels can reduce antibiotic use and antibiotic resistance.

Intensive Glucose Control in Critically Ill Patients Was Associated With Hypoglycemia and Increased Mortality at 90 Days

Background: After a study reported decreased mortality and other benefits with an intensive glucose-control protocol in postoperative patients in the ICU, many professional organizations recommended tight glucose control as routine in ICUs. The study, however, was done at a single center, did not study medical patients in the ICU definitively, and routinely administered substantial amounts of glucose as part of postoperative care. Although a benefit of intensive glucose control was not seen in multiple subsequent studies or in a meta-analysis, an increased risk for hypoglycemia was found, and the relative risks and benefits of aiming to maintain normoglycemia in critically ill patients are debated.

Study Design: A multicenter, international RCT of 6104 critically ill medical and surgical patients compared insulin infusion protocols aimed to achieve intensive glucose control (target blood glucose level, 4.5 to 6.0 mmol/L [81 to 108 mg/dL]) or conventional glucose control (target <10.0 mmol/L [<180 mg/dL]). The primary end point was death from any cause at 90 days.

Findings: The groups were similar at baseline and included patients with a range of medical and surgical problems (37% were surgical patients, 20% had diabetes, 31% had an Acute Physiology and Chronic Health Evaluation II score greater than 25, 21% had severe sepsis, and 93% received mechanical ventilation). At 90 days, 27.5% in the intensive-control group had died, compared with 24.9% in the conventional-control group (OR for intensive control, 1.14 [CI, 1.02 to 1.28]; P = 0.02). Subgroup analysis suggested that the results did not differ between surgical or medical patients or whether the patient had diabetes or severe sepsis. The median survival time was lower in the intensive-control group than in the conventional-control group (HR, 1.11 [CI, 1.01 to 1.23]; P = 0.03). Severe hypoglycemia (≤2.2 mmol/L [≤40 mg/dL]) occurred in 6.8% of patients in the intensive-control group and 0.5% in the conventional-control group (OR, 14.7 [CI, 9 to 25]; P < 0.001).

Cautions: The intensive-control group had more premature discontinuations from the assigned treatment protocol, and more intensive-control patients received corticosteroids.

Implications: Despite earlier enthusiasm and recommendations for widespread implementation, intensive glucose control has not been substantiated as beneficial in critically ill patients. Insulin therapy aiming to achieve normoglycemia results in increased mortality compared with a goal of less than 10.0 mmol/L (<180 mg/dL) and an increased risk for hypoglycemia. The study reminds us of the need for a more cautious approach to the adoption of widespread recommendations, including awaiting confirmation of preliminary findings from additional studies.

Early Physical and Occupational Therapy in Critically Ill Patients May Improve Long-Term Functional Status

Background: Patients with critical illness frequently develop neuromuscular dysfunction, including weakness, fatigue, and muscle atrophy, which compromises the quality of life of long-term survivors. Multiple factors occurring during acute illness, such as prolonged immobilization, probably contribute to such disability. Nutritional support, daily interruption of sedation to facilitate removal from mechanical ventilation, and avoidance of neuromuscular blockade may help reduce these adverse consequences of life-threatening illnesses. In addition, small, uncontrolled observational studies suggest that exercise and mobilization in the ICU may improve long-term recovery and quality-of-life outcomes.

Study Design: The investigators randomly assigned 104 critically ill adults who had received less than 72 hours of mechanical ventilation at 2 university hospitals to either early exercise and mobilization during periods when sedation was interrupted or routine physical and occupational
therapy. The primary outcome was the number of patients returning to independent functional status at hospital discharge. A physical therapist blinded to treatment allocation assessed this outcome.

**Findings:** Forty-nine patients were randomly assigned to the early exercise and mobilization intervention, and 55 patients were randomly assigned to routine care. The overall premorbid Barthel score (a measure of performance of basic activities of daily living) was high (≥85), and more than 80% of patients had sepsis complicating their condition. In the intervention group, several activities were achieved during mechanical ventilation, including standing at bedside, marching in place, chair transfers, or walking 2 or more steps. Intensive care unit and hospital LOS and quantitative measures of extremity strength did not differ between the groups. The intervention group had marginally less ICU-acquired paresis at hospital discharge (31% vs. 49%; P = 0.09). Despite these findings, the primary end point of return to an independent functional status at hospital discharge was achieved in 29 patients (59%) in the intervention group compared with 19 patients (35%) in the control group (P = 0.02).

**Caution:** Patients who were not functionally independent before their critical illness were excluded, so the results may not be generalizable to all critically ill patients. Safe application of physical and occupational therapy in critically ill patients requires appropriate patient selection and experienced personnel.

**Implications:** Prolonged immobilization is not a requisite consequence of critical illness and mechanical ventilation in the ICU. A skilled team of therapists and nurses can intervene with early graded exercise and mobilization in selected mechanically ventilated patients. Addressing multiasystem recovery, including neuromuscular function, may contribute to improved functional outcomes in patients in the ICU.

**Low-Dose Corticosteroids as Adjunctive Therapy in Septic Shock**


**Background:** Studies performed in the 1960s to 1980s showed that short courses of high-dose steroids in sepsis and septic shock either had minimal effects or were harmful. During the past decade, interest has been renewed in the use of lower (“physiologic”) doses of corticosteroids as therapy for patients with septic shock, but results from clinical trials and meta-analyses have been inconsistent.

**Study Design:** A systematic review was performed to identify randomized and quasi-randomized, placebo-controlled trials of corticosteroid treatment for septic shock, and a meta-analysis was performed to assess the effect according to the dose and duration of corticosteroid treatment.

**Findings:** In all, 17 randomized trials (with a total of 2138 patients) and 3 quasi-randomized trials (with a total of 246 patients) of either high- or low-dose steroids were analyzed in a meta-analysis. Analysis of the data from randomized trials found that the 28-day mortality rate was 35.3% in the corticosteroid group compared with 38.5% in the control group (HR, 0.84 [CI, 0.71 to 1.00]; P = 0.05), but heterogeneity among the trials was substantial (I² = 53%). Mortality was not reduced in the quasi-randomized trials. Analysis of data from 12 trials of low-dose, prolonged corticosteroid therapy (≥5 days at doses ≤300 mg hydrocortisone or its equivalent) found a beneficial effect on 28-day mortality (HR, 0.84 [CI, 0.72 to 0.97]; P = 0.02, I² = 15%). Meta-regression analysis confirmed the positive interaction between dose and duration of corticosteroid treatment and survival. Shock reversal with low-dose corticosteroids was improved at 7 days (P < 0.001) and 28 days (P = 0.02). An interaction with mortality rates in the control group (an indicator of the severity of illness in the population) was observed (P = 0.06), suggesting that steroids might be more beneficial in sicker patients. Corticosteroid treatment was associated with an increased risk for hyperglycemia and hypernatremia but not with an increased risk for gastroduodenal bleeding, superinfection, or acquired neuromuscular weakness. The latter events, however, may have been underreported.

**Caution:** Other meta-analyses of these studies have observed publication bias, with a greater likelihood of small trials reporting a beneficial effect of steroids. Furthermore, others have noted an even stronger interaction between control-group mortality and the benefit from steroids. Finally, it is unclear whether these findings are generalizable to settings in which the supportive care provided to patients with septic shock might differ from that of the clinical trials evaluated (for example, in the developing world). Until new data are available, the decision to administer low-dose steroids for septic shock should be made on an individual basis, with consideration of the severity of illness and the potential risks of corticosteroid administration.

**Implications:** Low-dose, prolonged corticosteroid therapy may have a beneficial effect on the survival of patients with septic shock. Short courses of high-dose corticosteroids are not supported by available data.

**Failure to Choose Appropriate Initial Antibiotics for Septic Shock Is Associated With Substantially Increased Mortality**

**Background:** Failure to initiate the appropriate treatment promptly can have irreversible and sometimes fatal consequences, particularly in critically ill patients. Although it is intuitively obvious, clinicians may not appreciate the magnitude of this harm (for example, when choosing an initial antibiotic regimen for patients with severe infections and septic shock).

**Study Design:** A retrospective chart review was done to assess the effect of inappropriate initial antibiotic regimens in patients with severe sepsis in 5715 patients from 22 institutions in 3 countries who met consensus criteria for septic shock.

**Findings:** The initial antimicrobial regimen had no activity against the causative organism in 19.9% of patients. A total of 55% of the infections were community-acquired, and a causative organism was identified in 82% of all cases. Patients with *Staphylococcus aureus*, enterococcal, and fungal or yeast infections were most likely to receive inappropriate antibiotic regimens initially. Pneumonia, intra-abdominal, catheter-related, and bloodstream infections were most likely to be treated with inappropriate empirical coverage initially. The hospital mortality of patients receiving appropriate antibiotic regimens initially was 10.3% compared with 52.0% in patients receiving inappropriate antibiotic regimens initially ($P < 0.001$). The high mortality rate associated with an inappropriate initial antibiotic choice is particularly striking, because appropriate antibiotics were eventually administered in three quarters of cases. After adjustment for baseline severity of illness, comorbid conditions, and epidemiologic risk factors, inappropriate initial antibiotic therapy remained the most significant factor associated with death (OR, 8.99 [CI, 6.60 to 12.23]).

**Cautions:** This was an observational rather than a prospective, randomized study and was therefore subject to bias. The interpretation of antibiotic appropriateness was in part determined subjectively. The overall results included both culture-positive and culture-negative cases, although the results were similar.

**Implications:** Clinicians must recognize that initial antibiotic therapy for life-threatening infections must be sufficiently broad and carefully chosen, particularly because the range and antibiotic susceptibility of pathogens causing life-threatening infection continues to increase in the community and the hospital. Choosing the correct therapy requires knowledge of the underlying disease, the previous patient colonization, and the microbial trends in the community, as well as the specific health care facility. The use of guidelines to inform initial antibiotic choices may be the most effective way to ensure such care (as shown, for example, in the previously described study assessing the use of ATS/IDSA guidelines for pneumonia). These efforts should be coupled with changes to the system to ensure the timely administration of initial antibiotic dose and narrowing of the antimicrobial spectrum when a causative organism is identified.

**Critical Care Services Vital in the Response to 2009 Influenza A (H1N1), an Outbreak Clinically Distinct From Recent Seasonal Flu and Other Pandemics**


**Background:** Seasonal influenza causes 30 000 to 40 000 deaths in the United States yearly. Although viral mutations are known to alter the host immune response and vaccine efficacy, less is known about the effect of viral mutations on the clinical manifestations of human disease.

**Study Design:** To study the clinical characteristics and outcomes of critically ill patients with H1N1 influenza infection, the Canadian Critical Care Trials Group performed an observational study of patients admitted to 30 adult and pediatric ICUs between April and August 2009.

**Findings:** A total of 168 critically ill patients with confirmed or probable H1N1 influenza were identified. The population was relatively young (mean age, 32.3 years) and predominantly female (67%). Common comorbid conditions included diabetes, obesity, smoking, and chronic lung disease; 30.4% of patients had “major” comorbid conditions, such as immunosuppression, congestive heart failure, and renal insufficiency. Sixteen cases resulted from nosocomial transmission. The median time from onset of illness to hospital admission was 4 days, and the median time from hospitalization to ICU admission was 1 day. Mechanical ventilation was required by 81% of patients for a median of 12 days. The 28-day mortality rate was 14.3%, and the 90-day mortality rate was 17.3%. Bacterial superinfections (for example, with *S. aureus* or *Streptococcus pneumoniae*) were documented in 24% of patients.

**Cautions:** The study patients may not represent the presentation of patients with less severe H1N1 infection. A total of 25% of the study patients were aboriginal Canadians, which might limit the generalizability of the findings, although characteristics and outcomes of other study subpopulations did not differ substantially. Clinicians used antibiotics aggressively in these patients, and even more bacterial superinfection may have occurred if less prophylactic antibiotic therapy had been used.

**Implications:** Unlike most previous pandemics, this outbreak involved relatively healthy adolescents and young adults while sparing older persons. Bacterial superinfections were common, which emphasizes the importance of careful, regular evaluations for bacterial complications and of prompt institution of antibiotics when suggestive evidence first emerges. Supportive critical care services seemed to be life saving. Regional capacities for such services might be perilously inadequate if a pandemic larger than that experienced thus far in North America occurs with this current strain of influenza.
Determining Which Component of a “Bundle” Improves Outcomes: Benefit of Chlorhexidine-Impregnated Sponge Dressings for Venous Catheter Sites


Background: Device-related infections are well-recognized causes of morbidity, mortality, and increased hospital LOS and costs. Although standardized clinical protocols and checklists to reduce catheter-related infections are being embraced nationally, additional preventative strategies are needed to effect further improvements and changes in bacterial and fungal characteristics.

Design: A prospective randomized trial was performed in 7 ICUs at 5 hospitals to assess the effect of 2 practices on the incidence of arterial and central venous catheter-related infections: frequency of dressing change (3 vs. 7 days) and type of dressing (standard vs. chlorhexidine-impregnated sponges). Assessors of infection were blinded to treatment allocation.

Findings: The study included 1636 patients with 28,931 catheter-days (median duration, 6 days). The use of chlorhexidine-impregnated sponges decreased the rate of major catheter-related infections (0.6 per 1000 catheter-days; vs. 1.4 per 1000 catheter-days; HR, 0.39 [CI, 0.17 to 0.93]; \( P = 0.03 \)) and catheter-related bloodstream infections (0.40 per 1000 catheter-days vs. 1.3 per 1000 catheter-days; HR, 0.24 [CI, 0.09 to 0.65]) without an increase in the rate of resistant organisms cultured. The chlorhexidine-impregnated sponges were associated with severe contact dermatitis occurred in 8 patients. Changing catheter dressings every 7 days was not inferior to changing every 3 days in terms of rate of colonization.

Cautions: Caregivers were not blinded to the patients’ treatment allocation. This protocol used povidone-iodine for skin antisepsis, whereas many U.S. hospitals now follow guidelines for use of chlorhexidine skin antisepsis. Whether chlorhexidine sponges add efficacy to chlorhexidine skin antisepsis is not known. The prolonged use of chlorhexidine might result in resistant microbial flora and an increasing incidence of contact dermatitis.

Implications: Health care providers should recognize the importance of standardized protocols when performing procedures to help minimize complications. This study provides convincing evidence that chlorhexidine-impregnated sponges can be effective at reducing the incidence of catheter-related infection in the ICU. Although standardized practice “bundles” have been developed by various professional organizations, teasing out which elements are responsible for improving outcomes remains important, as illustrated by these findings. The efficacy of each intervention, moreover, must be monitored prospectively. Chlorhexidine might lose its efficacy if resistant organisms emerge.

From the National Institutes of Health, Bethesda, Maryland, and David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, California.

Potential Conflicts of Interest: None disclosed. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M10-0261.

Requests for Single Reprints: Henry Masur, MD, National Institutes of Health, Clinical Center, Critical Care Medicine Department, 10 Center Drive, Room 2C145, Bethesda, MD; e-mail, hmasur@nih.gov.

Current author addresses are available at www.annals.org.
Current Author Addresses: Drs. Suffredini and Masur: National Institutes of Health, Clinical Center, Critical Care Medicine Department, 10 Center Drive, Room 2C145, Bethesda, MD 20892.
Dr. Lynch: David Geffen School of Medicine, University of California, Los Angeles, 200 Medical Plaza, Suite 365B, Los Angeles, CA 90095.