Pulmonary, Sleep, and Critical Care Updates

Update in Respiratory Infections 2011

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Respiratory tract infections again featured prominently in the *Journal* and other publications in 2011. We will discuss updates in respiratory tract infections, classified by the traditional breakdowns by site of acquisition, type of infection, and to a certain extent, causative organisms. Publications addressing cystic fibrosis are the subject of a separate update.

Full understanding of infections of the lower respiratory tract requires knowledge of the normal flora of the respiratory tract. An extremely careful study of the distal lung microbiota (sampled by bronchoalveolar lavage and protected specimen brush) in healthy volunteers contradicts the general assumption that the distal lung is sterile. After careful control for contamination of the bronchoscope during insertion, Charlson and colleagues found that the distal respiratory tract contained an almost identical spectrum of bacteria as the upper respiratory tract but at roughly 2–4 logs lower quantitative counts (1). Distal lung-only isolates were rare and varied from person to person but did include pathogens associated with nosocomial pneumonia. Although study of the lung microbiome is just beginning, changes in the microbiome at this site are likely to have important effects on risk of pneumonia and possibly other respiratory illnesses, similar to those demonstrated for alterations in the gut microbiome (2).

COMMUNITY-ACQUIRED PNEUMONIA

In the era of government and public emphasis on evidence-based medicine encouraged by public reporting of outcomes and pay-for-performance, an appraisal of the evidence supporting the Joint Commission and Centers for Medicare and Medicaid Services community-acquired pneumonia (CAP) performance measures is enlightening. Wilson and Schunemann systematically reviewed the literature and performed meta-analyses for the six main CAP core measures (3). Estimated effects of these interventions were favorable for five of the six core measures, although only influenza vaccination was supported by high-quality evidence. Moderate-quality evidence actually suggested one-step smoking cessation counseling was contraindicated. Their analysis would suggest that two of the performance measures—influenza vaccination and guideline-compliant antibiotics—are reasonable performance measures (3). This disconnect between core measures and high-quality evidence may partially explain the discordance between

improving core measures and documented improvements in actual clinical outcomes.

The largest randomized controlled trial in severe CAP to date, the CAPTIVATE (*Community-acquired Pneumonia Tifacogin Intravenous Administration Trial for Efficacy*) trial of tissue factor pathway inhibitor for severe CAP, was clearly negative (4). However, the study demonstrated the feasibility of a large clinical trial focused solely on one form of severe sepsis. CAPTIVATE was the first to use the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) criteria for severe CAP to define patients appropriate for a clinical trial. The presence of only three minor criteria for severe CAP was associated with 10% mortality, with 25% subsequently developing septic shock or acute respiratory failure. This subgroup of severe CAP therefore warrants inclusion in future trials of severe CAP.

Recombinant surfactant protein C aerosols also demonstrated no effect on mortality, oxygenation, duration of ventilation, or nonpulmonary organ failure-free days in patients with severe direct lung injury, predominantly pneumonia and aspiration (5). Unfortunately, the negative results may have resulted from partial inactivation of the surfactant by the aerosol generator, which may explain the lack of oxygenation benefit consistently seen in other studies of pulmonary deposition of surfactant.

These two negative clinical trials, combined with the negative PROWESS (Recombinant Human Activated Protein C World-wide Evaluation in Severe Sepsis)-Shock trial, leave clinicians and clinical investigators attempting to explain the negative results despite positive preliminary trials (6, 7). But more importantly, the need for adjunctive or supplemental therapy in addition to antibiotics, to reduce the mortality rate in patients with severe CAP, is once again demonstrated in these trials (8).

Viral Pneumonia

Although the pandemic has abated, observations from 2009 H1N1 influenza A infections may have lessons for seasonal cases or future epidemics. Wanzeck and colleagues demonstrate that glycosylation of the hemagglutinin of influenza results in lower antibody responses, lack of neutralizing antibodies, and inability to protect mice from subsequent challenge with less glycosylated strains (9). The clinical relevance is that the recent seasonal H1N1 strain was heavily glycosylated and, in this same mouse model, prior infection did not protect against the pandemic 2009 H1N1 influenza A strain. This may be a partial explanation for the preponderance of severe disease in young adults.

Two large multicenter studies of the 2009 H1N1 epidemic addressed the effect of corticosteroid therapy on outcomes. Brun-Buisson and colleagues retrospectively analyzed steroid treatment in the prospective French cohort of 2009 H1N1 influenza A patients with acute respiratory distress syndrome (ARDS) (10). Kim and colleagues retrospectively analyzed all patients with the 2009 H1N1 influenza A patients referred to all academic medical centers in Korea (11). Results in both cohorts

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were remarkably similar: neither demonstrated a mortality benefit of corticosteroids and both found a higher rate of secondary bacterial infections, particularly pneumonia. Both studies used a propensity-to-receive-corticosteroid score to adjust for differences in baseline characteristics. In addition, Brun-Buisson and colleagues excluded patients with other indications for corticosteroids, such as asthma or acute exacerbations of chronic obstructive pulmonary disease (AECOPDs), in an effort to isolate the effect on influenza pneumonia specifically (10). Despite several limitations, data from these two studies provide strong evidence against the use of corticosteroids purely for treatment of severe influenza pneumonia, a pattern consistent with corticosteroids in case series of other severe viral pneumonias, such as the avian influenza and severe acute respiratory syndrome (SARS) epidemic (12). Although proponents are not ready to abandon steroid treatment for heterogeneous groups of patients with ARDS (13), the results of these two studies suggest that inclusion of severe viral pneumonia in these heterogeneous ARDS studies may actually blunt evidence for a beneficial corticosteroid effect in the rest of the population.

An animal study suggests a potential alternative treatment for severe influenza pneumonia (14). Transgenic mice that with increased granulocyte-macrophage colony-stimulating factor (GM-CSF) expression in the lungs were protected from an influenza challenge lethal in wild-type mice. Intranasal GM-CSF after influenza inoculation also rescued the wild-type mice. Depletion of alveolar macrophages, but not T cells, B cells, or neutrophils, in the transgenic mice resulted in the loss of the protective effect of GM-CSF, suggesting enhanced alveolar macrophage function contributes to protection against influenza. The significant barriers to clinical use of GM-CSF for severe viral pneumonia were discussed in the accompanying editorial (15).

Inhaled Steroids and CAP Outcomes

A number of studies have suggested that inhaled steroid use in patients with COPD increases the risk of pneumonia. Although the risk remains controversial and the mechanism(s) unclear (16), concern has been raised about this possibility. Two publications addressed this issue. Using adverse event reporting from industry-sponsored clinical trials, O'Byrne and colleagues could not demonstrate an increased risk in patients with asthma who were using inhaled corticosteroids compared with placebo (17). They also found no difference in pneumonia risk between budesonide and fluticasone or by dose of budesonide. Chen and colleagues reported on the flip side of the coin (18). Using the Veterans Administration administrative database, they found that prior use of inhaled steroids in patients with COPD admitted with CAP was associated with a significantly lower risk of mortality (odds ratio [OR], 0.80) and need for mechanical ventilation (OR, 0.83). No difference in need for vasopressors was demonstrated. Their results may explain why no increase in all-cause mortality has been seen despite the increased risk of developing CAP in patients with COPD who are receiving inhaled corticosteroids.

PNEUMONIA IN THE IMMUNOCOMPROMISED HOST

The changing spectrum of pulmonary disease in patients with HIV disease is documented in a matched cohort of veterans (19). Bacterial pneumonia was still four to five times more likely in HIV-positive veterans less than 50 years old than HIV-negative patients, with lower ratios for older patients. Bacterial pneumonia remains the second most common pulmonary diagnosis in patients with HIV disease, but rates are significantly

decreased compared with historical cohorts. Despite this, HIV-positive patients may still benefit from conjugate pneumococcal vaccination (20). A similar pattern is seen for tuberculosis. *Pneumocystis* pneumonia remains many times more likely in patients with HIV disease but is no longer the most common pulmonary diagnosis. This study clearly documents the increased burden of noninfectious pulmonary disorders in patients with HIV disease, including lung cancer, COPD, pulmonary hypertension, and a new association with pulmonary fibrosis. The shifting spectrum of pulmonary disorders in the era of highly active antiretroviral therapy and aging of the HIV-positive population parallels other indicators that HIV disease has now become a chronic disease affecting multiple organs (21).

Two official ATS statements that deal with pneumonia in the immunocompromised host were published this year (22, 23). The official ATS statement on the treatment of fungal disease in adults distinguishes carefully between immunocompetent and immunosuppressed patients in recommendations for antifungal treatment and other management strategies (23). The official ATS Research Statement reviewed the current state of knowledge regarding the idiopathic pneumonia syndrome after stem cell transplantation, which has frequently been treated as infectious (22). A better understanding of the pathogenesis is likely to lead to new potential interventions since the benefit of corticosteroid therapy remains controversial.

Novel treatment modalities are clearly needed in immunocompromised patients. Respiratory syncytial virus (RSV) infection is an independent risk factor for bronchiolitis obliterans syndrome (BOS), acute rejection, graft failure, and death in lung transplant recipients. Aerosolization of a small interfering RNA, which binds to messenger RNA for the nucleocapsid gene of RSV and induces cleavage, was studied in a small randomized placebo-controlled trial in lung transplant recipients with RSV-only infections (24). Both clinical symptom scores and, more importantly, incidence of new BOS were lower in treated patients than in patients receiving placebo (6.3 vs. 50%; $P = 0.027$). Astor reviews this promising new therapeutic approach and discusses why use for RSV in transplant recipients appears to be a model infection for this new class of therapeutic agents (25).

NOSOCOMIAL PNEUMONIA: HOSPITAL-ACQUIRED PNEUMONIA, VENTILATOR-ASSOCIATED PNEUMONIA, AND HEALTHCARE-ASSOCIATED PNEUMONIA

Host Defenses

Nosocomial pneumonia remains a common concern in hospitalized patients, and several investigations of the inflammatory response to lung infection have helped us better understand how gram-negative pneumonia can lead to adverse consequences such as acute lung injury (ALI). Herold and colleagues (26) observed that CC-chemokine receptor-2 (CCR2)-deficient mice had a lack of exudate macrophages, leading to more ALI after LPS challenge. However, intratracheal IL-1 receptor antagonist (IL-1ra) enhanced survival after experimental gram-negative pneumonia. The findings indicate that exudate macrophages protect the lung from injury through the up-regulation of IL-1ra. On the other hand, in studies of sepsis other than pneumonia, CCR2-deficient animals also had less of an inflammatory response, which was protective against mortality (27).

A benefit of understanding the host inflammatory response in pneumonia is the potential discovery of novel biomarkers of infection and infection prognosis. Serkova and colleagues reviewed the field of metabolomics to examine the importance of metabolite detection, gene function, and protein production, using methods such as mass spectroscopy (28). This type of approach may be

useful for the determination of etiology in pneumonia, because different bacterial pathogens may have different metabolic profiles with even greater differences in viral infection. For example, *Pseudomonas aeruginosa* pathogenesis is particularly mediated by exoproduct production. Wargo and colleagues demonstrated that phospholipase C/sphingomyelinase (PC-PLC/SMase) led to loss of lung function in a mouse model of *P. aeruginosa* pneumonia (29), which was reduced in animals infected with exoproduct-deficient strains. Systemic miltefosine, which acts as a substrate for phospholipase C, also protected against this exoproduct-induced loss of lung function. These findings may lead to therapies that ameliorate the development of ALI in patients with *P. aeruginosa* pneumonia, a common cause of ventilator-associated pneumonia (VAP).

Risk Factors and Natural History

One of the current controversies is whether we have already been so effective at identifying risk factors for VAP that we have been able to devise prevention strategies that lead to “zero VAP.” However, prevention of VAP may not be as important for the outcome of patients in the intensive care unit (ICU) as previously thought, because data suggest no impact on mortality when it does occur (30). A French multicenter study of 4,479 ventilated patients compared the outcome of the 685 (15.3%) who acquired VAP with those who did not. The 30-day mortality rate for patients with VAP was 24.1 versus 23.1% for the patients without VAP, thus showing the mortality impact of VAP to be small. The authors differentiated their study results from others by accounting for a change in severity of illness over time, using a marginal structure model in their survival analysis. Although provocative, the findings do not answer a number of questions, particularly concerning the impact of therapy on mortality. No information on the rate of appropriate therapy is provided for a population that had little methicillin-resistant *Staphylococcus aureus* (MRSA) but nearly 30% non-fermenting gram-negatives. If these pathogens were all treated effectively, then to say that VAP did not impact mortality would be misleading, because mortality would certainly occur if no therapy, or the wrong therapy, were given. In the accompanying editorial, other deficiencies were noted, including the lack of a diagnostic “gold standard,” so that some patients with VAP may have been misclassified as not having VAP, thus underestimating the attributable mortality of the disease (31).

Several investigators have expanded our understanding of VAP risk factors by examining the role of the gastropulmonary route of pathogen acquisition (32), by trying to interrupt this route via maintenance of endotracheal tube cuff pressure (33), and by trying to prevent prolonged intubation by using noninvasive ventilation to facilitate weaning (34). Although noninvasive ventilation was effective at reducing postextubation respiratory failure and death, it did not significantly reduce the incidence of nosocomial pneumonia compared with conventional weaning (34). Interest in endotracheal tube cuffs has renewed, not only with maintenance of adequate pressure to avoid aspiration of oropharyngeal secretions into the lung, but with attention to composition (polyurethane being preferable to polyvinylchloride) and shape (with a possible value to a tapered cuff shape) (35).

One interesting risk factor for early-onset VAP that has emerged is the use of therapeutic hypothermia following out-of-hospital cardiac arrest (OHCA) (36, 37). French investigators examined the incidence of pneumonia within 3 days of OHCA in a population with widespread use of therapeutic hypothermia (500 of 641 with OHCA). The incidence of early-onset pneumonia (EOP) was 65% in the patients with OHCA (using microbiological sampling in all but 15 patients), and therapeutic

hypothermia was the single independent risk factor for EOP in a multivariate analysis, raising the risk almost twofold. Although EOP did not increase the risk of subsequent VAP, poor neurologic outcome, or mortality, duration of mechanical ventilation, and ICU length of stay increased (36). The accompanying editorial noted that although the bacteriology commonly involved community pathogens, some patients surprisingly harbored resistant pathogens (37). Because pneumonia incidence was so high in this population, the value of a short course of prophylactic antibiotics in patients with OHCA treated with hypothermia may be worth studying. We also need greater understanding of the biological effects of hypothermia. Although hypothermia can predispose to pneumonia, hypothermia protected against bacterial dissemination when applied after the onset of pneumococcal pneumonia in an animal model, by preventing sepsis-induced mitochondrial dysfunction (38).

Etiologic Pathogens

Most episodes of pneumonia result from microaspiration of bacteria present in the oropharynx into the lung. As demonstrated, the healthy lower respiratory tract contains the same organisms as the oropharynx, only in lower numbers (1). The situation in illness may vary, as pointed out in studies of the stomach as a source of pathogens that can reach the lung and cause pneumonia (32), and the possibility that ventilated patients can have organisms directly inoculated into the lung from the surrounding environment. The organisms that cause nosocomial pneumonia are increasingly multidrug-resistant (MDR) pathogens. In a study of the bacteriology of hospital-acquired pneumonia (HAP) and VAP from 10 Asian countries, involving 73 hospitals, MDR pathogens were common, and if treated incorrectly, led to increased mortality (39). The most common pathogen was *S. aureus*, followed by *Acinetobacter* species, *P. aeruginosa*, and *Klebsiella pneumoniae*. Resistance was common in all countries studied, with unique bacteriologic features in each. In VAP, *Acinetobacter* (36% of patients) was the most common, followed by *P. aeruginosa* (26%) and *S. aureus* (12.2%). MDR pathogens occurred in and outside the ICU, and were even present in patients with EOP and no identified MDR risk factors. Methicillin resistance was present in 82% of *S. aureus* isolates, and 67% of *Acinetobacter* species and 37% of *P. aeruginosa* were resistant to carbapenems. These alarming data indicate that not only does each country, but each ICU, needs to know their local microbial pathogens to design effective empiric therapies, especially because discordant therapy increases mortality. Unfortunately, the only effective agent for pathogens such as *Acinetobacter* species was colistin, emphasizing the urgent need for new agents active against MDR gram-negatives.

Therapy and Prevention

As mentioned, HAP and VAP are often due to MDR gram-negatives, and treatment of these pathogens with existing agents is limited. In this setting, the use of adjunctive aerosolized antibiotics may be valuable. One bold study compared aerosol therapy of VAP (ceftazidime and amikacin without intravenous therapy) with intravenous ceftazidime and amikacin therapy in a randomized study of 40 patients (40). All patients had susceptible or intermediately sensitive *P. aeruginosa*. Efficacy of both regimens was comparable, with more early eradication of the pathogen and greater ability to eradicate intermediately susceptible pathogens in the aerosol group. Recurrence of infection did occur in 3 of 20 aerosol-treated patients versus 1 of 20 comparator patients. Use of a vibrating mesh plate nebulizer

led to greater than 60% retention in the lungs, but the expiratory line filter became obstructed in three patients, and one had a transient cardiac arrest. Although the findings are promising, given current challenges with MDR pathogens, aerosol therapy is likely to be most useful as an adjunct to intravenous therapy, as suggested by results of another blinded study (41).

In the past year, several studies examined the impact of the ATS/IDSA guidelines for managing HAP, VAP, and healthcare-associated pneumonia (HCAP) (42). One controversial study of VAP ($n = 132$) and HAP/HCAP ($n = 171$) concluded that patients who received therapy “compliant” with the guidelines had increased mortality (43). A number of issues limit full acceptance of this conclusion, including the observation that appropriate therapy did not lead to improved survival for patients infected with *P. aeruginosa* or MRSA (44). In addition, the definition of compliant therapy did not consider deescalation (which was often not done) or the timing and dosing of appropriate therapy. Controversy regarding use of the nosocomial pneumonia antibiotic regimen in patients with HCAP also amplified in the last year, with studies from the United States, Canada, and the United Kingdom indicating that many patients with HCAP can be successfully treated with a CAP regimen, and that a broader spectrum regimen may be harmful (45–47). The heterogeneity of patients with HCAP is increasingly clear, and the correct approach probably depends on each patient’s risk factors for MDR pathogens (48).

The fact that ventilator bundles, although useful, may not realistically lead to “zero VAP” indicates the need for additions to these routine measures. Maintenance of cuff pressure above 25 cm H₂O with a continuous control device was effective in reducing VAP (33), as was use of intermittent, rather than continuous, subglottic secretion drainage (49). However, it is important to note that, although both interventions were beneficial, VAP rates were not reduced to zero. Subglottic secretion drainage reduced late-onset VAP rates to 18.6% (49), and continuous maintenance of cuff pressure reduced VAP rates to 9.8% (33). When using a bundle or other methods to reduce VAP, a robust method to implement and monitor the use of these interventions is important. Prompting to enhance adherence to use of a daily checklist for recommended processes of care may improve use of antibiotics and impact mortality (50).

ACUTE EXACERBATION OF COPD

AECOPDs have too often been treated as a single entity (51). Using unbiased statistical tools, Bafadhel and coworkers were able to classify AECOPDs into four biological clusters—bacterial, viral, eosinophilic, and paucinflamatory—and define biomarkers characterizing each cluster (52). Baseline biomarker data predicted both eosinophilic and bacterial exacerbations but not viral exacerbations. These clusters could not be distinguished by the Anthonisen criteria (53), which have been used extensively in registration trials to indicate bacterial AECOPDs. The easiest clinical biomarker was peripheral eosinophilia ($>2\%$), which defines eosinophilic exacerbations. Although some of the other biomarkers used to define clusters are not easily obtained currently, the ability to distinguish types of AECOPD is likely to increase correct management (51), although these trials to demonstrate this approach are yet to be completed.

Rhinovirus was the most common documented cause of the 29% of AECOPDs that were virus-predominant in the study by Bafadhel and colleagues (52). Experimental exposure studies have documented that rhinovirus can clearly cause all the symptomatology of an AECOPD (54). Patients with COPD appear to have impaired IFN- γ responses from BAL cells compared with normal people exposed to rhinovirus. Patients with asthma

also have increased risk of exacerbation with rhinovirus infection (55). Even infants with increased airway resistance were more likely to wheeze when infected with rhinovirus (56). Thus, rhinovirus joins RSV as a major cause of worse bronchospasm in patients with underlying obstructive lung disease. In contrast, viruses do not appear to play a major role in acute exacerbations of pulmonary fibrosis, despite an extensive search (57).

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