Update in Pulmonary Infections 2010

Richard G. Wunderink¹ and Grant W. Waterer^{1,2}

¹Northwestern University Feinberg School of Medicine, Chicago, Illinois; and ²University of Western Australia, Perth, Western Australia

NOVEL 2009 H1N1 PANDEMIC INFLUENZA A

It is difficult to discuss the year in review for pulmonary infections without starting with the 2009 novel H1N1 influenza pandemic. Although excess deaths were reported for pediatric (1) and pregnant patients (2) from the prior year, the most surprising thing about the year 2010 is actually the lack of clinical infection with influenza. This resulted from a combination of factors. The first is that the novel 2009 H1N1 strain was the only circulating influenza strain during the 2009 to 2010 influenza season. The second is the dramatic effect of large-scale immunization against this particular strain. As can be seen in Figure 1, shortly after the vaccine became available, the rate of positive cultures reported to the CDC dropped dramatically (3). A similar pattern was seen with pediatric deaths, another CDC marker of influenza severity. The combination of vaccination and prior exposure during the spring of 2009 resulted in sufficient herd immunity to almost completely block new cases of influenza. Despite the ominous start, the 2009 to 2010 influenza season was actually associated with fewer deaths than in nonpandemic years. One of the lasting effects of this pandemic is a change in the standards of the Advisory Committee on Immunization Practices regarding eligibility for influenza vaccination; the committee now recommends seasonal influenza vaccination or all persons 6 months of age or older (4).

The lung pathology of fatal cases of the novel H1N1 infections was reviewed by Mauad and colleagues (5). They describe three distinct pathologic findings: diffuse alveolar damage, necrotizing tracheobronchitis, and diffuse alveolar damage with diffuse alveolar hemorrhage. A subsequent letter suggests that most of the patients who had purulent tracheobronchitis also had concomitant bacterial pneumonia (6). This association supports the concept that viral damage to the airway mucosa may be important in the pathogenesis of secondary pneumonia. Documented bacterial pneumonia at onset of the H1N1 infection is uncommon, but ventilator-associated pneumonia (VAP) often occurs as a consequence of the severe acute lung injury and prolonged mechanical ventilation (7). Therefore, the purulent tracheobronchitis may be part of the spectrum of VAP previously described in other autopsy series (8).

COMMUNITY-ACQUIRED PNEUMONIA

Measurement of Pathogen Load as a Measure of Prognosis

Improvements in real-time polymerase chain reaction technology have led to a new avenue of assessing the pathogen load in patients with pulmonary infections. Although routine in chronic infections such as HIV and hepatitis C for nearly a decade, we are now in an exciting period of applying this technology to acute infections. DeVincenzo and colleagues (9) infected 35 healthy volunteers with respiratory syncytial virus (RSV) divided into five cohorts, each cohort receiving a different intranasal dose of RSV. No correlation between the inoculum of RSV and viral load from nasal washings was demonstrated, perhaps reflecting different levels of innate immune response as well as the difficulties in accurately delivering RSV in human subjects. In contrast, the onset of symptoms strongly correlated with the first detection of RSV, the most severe symptoms correlated with peak viral load, and symptoms waned as viral load decreased.

Although the correlation between RSV viral load and disease progression may seem obvious, this study is the first to demonstrate it in human subjects. Although quantitative RSV load has no immediate clinical application, it does provide a very important tool for assessing new antivirals. Future potential uses include determination of resolution of RSV infections in patients with significant immunocompromise in the setting of persistent fever and/or pulmonary infiltrates. As viral load is also a marker of infectivity, it may also be useful in infection control. Finally, this paper adds further momentum to the growing number of studies suggesting that measuring pathogen load, either bacterial (10) or viral, may give extremely useful insights into disease pathogenesis and prognosis.

Treatment

High-dose corticosteroids have come in and out of favor for septic shock and acute respiratory distress syndrome. More recently, steroids were suggested to be of benefit in severe community-acquired pneumonia (CAP), at least in the absence of shock. A Dutch study of corticosteroid use for CAP adds to this ongoing controversy (11). Snijders and colleagues conducted a randomized, placebo-controlled study of 40 mg of prednisolone per day for 7 days in 213 patients with CAP. No benefit of corticosteroid therapy for either mortality or clinical cure rate was found. However, less than half the study patients were in pneumonia severity index grades IV or V, and very few required mechanical ventilation. Therefore, although this study suggests no justification for routine use of corticosteroids in CAP, an effect in patients with severe disease cannot be excluded.

Therapy for severe CAP remains controversial because no prospective randomized controlled trial has studied or even included these patients. A large multicenter cohort from 27 intensive care units (ICUs) found that only 45.9% of patients received therapy recommended by the most recent Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines (12), but inadequate therapy was only documented in 5% (13). Once again, macrolide combination therapy was associated with lower mortality compared with a quinolone

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Correspondence and requests for reprints should be addressed to Richard G. Wunderink M.D., 676 North St. Clair Street, Suite 14-044, Chicago, IL 60611. E-mail: r-wunderink@northwestern.edu

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Figure 1. Falloff in positive influenza cultures reported to the CDC after the novel 2009 H1N1 influenza vaccine became available (arrow). Screen shot from <http://www.cdc.gov/flu/weekly/>, accessed April 2, 2010.

combination, a consistent finding in almost all large databases of patients with severe CAP. The benefit of a macrolide may also explain the finding of greater clinical relapse in patients randomized to a β -lactam alone if their streptococcal urinary antigen was positive (14).

The pipeline for new antibiotics remains clogged. One of a few new antibiotics to receive Food and Drug Administration (FDA) approval is ceftaroline, a third-generation cephalosporin with activity against multidrug-resistant *Staphylococcus aureus* (MRSA). Combined results of two phase 3 trials were published this year (15). The overall results were that ceftaroline was equivalent to ceftriaxone in patients with mild to moderate CAP and low risk of atypical pathogens (15). Unfortunately, too few patients with MRSA pneumonia were enrolled to assess any differential benefit in this population. Interestingly, ceftaroline provided better cure rates for bacteremic pneumococcal pneumonia than ceftriaxone.

The greatest issue for treatment is the ongoing controversy regarding the classification of some patients with CAP as healthcare-associated pneumonia (HCAP), implying the need for treatment for multidrug-resistant pathogens. The original definition is acknowledged by most to be too broad and is leading to excessive antibiotic use (16). A comparison of culture-positive and culture-negative cases of HCAP confirmed that culture-negative patients were generally less ill and could be treated with conventional CAP therapy without excess length of stay or mortality (17). Because culture results can only distinguish retrospectively, further refinement of the HCAP definition is clearly needed.

Site of Care

In the past decade, substantial research effort has been directed toward determining the most accurate way to triage patients with CAP into outpatient, inpatient, or intensive care. Despite clear advances with the use of validated clinical scoring systems, such as the pneumonia severity index or the CURB-65 score, some patients do not conform to the disease outcomes that their initial assessment suggest they should follow. Restrepo and colleagues studied one group of patients of concern to all physicians, patients triaged to the ward who subsequently deteriorate and require admission to intensive care (18). Not surprisingly, patients admitted to the ICU after initial triage to the ward had substantially poorer outcomes, including 30-day mortality, compared with those sent straight to the ICU from the emergency

department. Almost identical findings were demonstrated in a study from Singapore (19). Mortality was again substantially higher in patients admitted to the floor (72.7%) than those admitted to the ICU initially (33.3%) with more than three IDSA/ATS minor criteria (12). What these and other investigators have not established is what interventions in the ICU ameliorate the course of disease and whether interventions can be used to improve the outcome of high-risk patients with CAP initially triaged to the ward. As the mortality rate in the late ICU transfer group was 47 to 73% and standard scoring systems clearly did not identify these patients in the emergency department, further research is desperately needed help prospectively identify them as well as identify interventions that improve their outcome.

Available simple biomarkers also have prognostic significance. Hypoglycemia on admission is associated with nearly threefold greater inpatient mortality, unaffected by the presence of diabetes (20). However, diabetes is associated with increased acute kidney injury and death from cardiovascular and renal disease (21). Up to 18% of patients with CAP have evidence of acute kidney injury with a strong interaction with severity and mortality (22). Thrombocytosis should be added to thrombocytopenia as a risk for 30-day mortality (23). Hypoglycemia and thrombocytosis are not presently in the list of IDSA/ATS minor criteria for severe CAP, but may need to be considered.

Vaccine Prevention

Although clearly effective for invasive disease, the efficacy of the 23-valent pneumococcal vaccine in preventing pneumonia has been questioned by large metaanalyses, particularly in the elderly. In a randomized, controlled study of the 23-valent vaccine in 1,006 nursing home residents over 3 years in Japan, Maruyama and colleagues (24) found all-cause pneumonia mortality substantially reduced in the vaccine group (0%) compared with the placebo group (35%).

The efficacy of the 23-valent vaccine in patients with compromised immunity has also been questioned, and, immunologically, the conjugate vaccines may be more effective. In keeping with this hypothesis, French and colleagues (25) studied the efficacy of the 7-valent conjugate pneumococcal vaccine in a randomized, double-blind, placebo-controlled study of 496 adolescents and adults in Malawi, 89% of whom were infected with HIV. The primary endpoint of the study, infection due to serotype 6A covered by the 7-valent vaccine, showed a substantial reduction in events in the vaccine group (5 vs. 19). The overall value of the

vaccine was limited by the finding that 64% of pneumococcal infections were by nonvaccine serotypes; it is hoped that coverage will improve as higher-valent conjugate vaccines become available.

Biomarkers

Despite a number of publications, the role of biomarkers such as procalcitonin (PCT) in the management of patients with pneumonia remains unclear (26). Muller and colleagues (27) conducted a prospective cohort study of 925 patients with CAP to assess the usefulness of PCT as a predictor of bacteremia. Overall, PCT performed better than conventional markers such as peripheral blood white cell count, C-reactive protein (CRP), or clinical parameters. Their analysis showed that if they had only performed blood cultures on patients with a PCT greater than 0.1 µg/L, the total number of cultures would have been reduced by 12.6%, yet all but one of the proven bacteremias would still have been identified. Various other cutoffs were assessed, with a cutoff of 0.5 µg/L, reducing the number of cultures by more than 50% but still capturing 88% of cases of bacteremia. Given the potential economic savings, further studies are definitely warranted.

The last several years have seen a proliferation of potential biomarkers to compete with PCT. Kruger and colleagues (28) studied five different biomarkers as well as CRP and white blood cell count in 728 patients with CAP. The discriminating value of these biomarkers as predictors of 28-day or 180-day mortality was poor, although midregional proadrenomedullin appeared to have better performance than the others (including PCT). Further biomarker comparison studies are expected over the coming years, each arguing for their favorite assay. Given the difficulties in determining exactly how valuable PCT or any other biomarkers is (or is not), a clear consensus is likely to take some time to emerge.

VAP

Prevention

Prevention of hospital-associated pneumonia (HAP)/VAP has drawn increasing attention, likely due to the threat of pay for performance and public reporting. One of the more controversial studies published in 2010 is a prospective blinded randomized trial of probiotic prophylaxis for VAP (29). In a highly selected group of ventilated patients, oropharyngeal and gastric administration of *Lactobacillus rhamnosus* was associated with approximately half the incidence of VAP as the control group. A corresponding decrease in the need for antibiotics, including fewer antibiotics for *Clostridium difficile* colitis and a lower rate of oropharyngeal colonization with pathogenic bacteria, supports the primary endpoint of VAP incidence. Although intriguing, this study needs further confirmation in a more general ICU population.

Use of silver-coated endotracheal tubes was also demonstrated to decrease the incidence of VAP and delayed the time to onset (30). Retrospective analysis of the North American Silver-Coated Endotracheal Tube (NASCENT) study suggested that the silver-coated endotracheal tubes were also associated with decreased mortality (31). Conversely, early tracheostomy (32) and completely withholding sedation in ventilated patients (33) were associated with insignificant trends toward lower VAP incidence.

Treatment

The issue of the appropriate therapy for MRSA VAP/HAP/HCAP remains controversial due in part to the poor clinical

efficacy of vancomycin. Jung and colleagues (34) studied the effect of vancomycin with or without rifampicin in a randomized, open-label study of 83 patients with MRSA VAP. Although the results need to be confirmed by a blinded study, both clinical cure rate at Day 14 (53.7 vs. 31.0%, $P = 0.047$) and 60-day mortality (26.8 vs. 50.0%, $P = 0.41$) favored the rifampicin arm. Haque and colleagues (35) studied 158 patients and found that isolates with minimal inhibitory concentrations between 1 and 2 mg/ml were associated with increased 28-day mortality. Both studies add further weight to the need to consider combination therapy or alternative agents in patients with MRSA isolates that are not fully sensitive to vancomycin.

Coloring the findings of excess mortality in these clinical trials, Nguile-Makao and colleagues published a more sophisticated analysis of the attributable mortality of VAP (36). Their analysis adjusted for the well-known fact that the risk of VAP increases with increasing duration of mechanical ventilation. Use of a time-dependent model demonstrated somewhat lower 8.1% attributable mortality for VAP compared with the 10.4% attributable mortality found with more traditional logistic regression. Resistant isolates of *S. aureus* and *Pseudomonas aeruginosa* did not increase the attributable mortality in their study, although intermediate-level severity of illness scores and late-onset VAP did. These findings had important implications within this FDA registration trial because the FDA now mandates mortality as the primary endpoint for comparison of new antibiotics for HAP/VAP (37, 38).

One of the assumptions about VAP has been that bypassing the normal upper respiratory tract defense mechanisms with an endotracheal tube plays a key role in the pathogenesis. The findings of Esperatti and colleagues (39) are therefore somewhat surprising. In this multicenter European study of 315 episodes of ICU-acquired pneumonia, no significant differences were found in the spectrum, proportion of pathogens, and most importantly, mortality between cases acquired on or off mechanical ventilation. Interestingly, approximately half of all the episodes of non-VAP subsequently required mechanical ventilation. This study supports the argument that patient comorbidities and immune status, as well as the nosocomial infection-prone environment of the ICU, are much more important drivers of the outcome of VAP than simply the presence of an endotracheal tube.

ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

One of the most controversial aspects of the management of chronic obstructive pulmonary disease (COPD) is the benefit of either corticosteroids or antibiotics in acute exacerbations. The FDA has determined that placebo-controlled trials are mandated for new antibiotic approval for this indication. Daniels and colleagues published a landmark study addressing this issue (40). They randomized 223 patients with 265 exacerbations to either oral doxycycline or placebo. A major strength of this randomized controlled trial is that all patients received corticosteroid therapy in a standardized manner. Doxycycline was superior to placebo in clinical success, symptom scores, microbiologic outcome, and need for open-label antibiotics at Day 10. Importantly, clinical success at Day 30 was the same. The study has important implications for the design of antibiotic trials in acute exacerbations of COPD. Clearly, an early endpoint is required to demonstrate any effect of antibiotics. Spontaneous resolution in placebo-treated and/or new exacerbations in patients initially given antibiotics will decrease the separation in clinical responses if assessed later. In contrast to previous literature, PCT did not predict patients more likely to respond

to antibiotic therapy (41). A substantial number of patients with low PCT levels benefited from doxycycline. One explanation may be that atypical pathogens did not significantly increase PCT levels and yet would be adequately treated with doxycycline. CRP appeared to be a better predictor of response to antibiotics, although the correlation was weak. Clearly, further studies are needed before we can be clear about what role, if any, PCT may have in helping clinicians manage acute exacerbations of COPD.

BRONCHIECTASIS

Although a common condition, bronchiectasis remains relatively understudied compared with most pulmonary infectious diseases. Frustratingly for patients and physicians, the cause of bronchiectasis is only infrequently identified. An increased frequency of cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations has been reported in patients with bronchiectasis. However, proof that heterozygotes for these mutations have abnormal protein function has been lacking. Bienvenu and colleagues (42) conducted a study of 122 patients with diffuse bronchiectasis and a normal sweat test and then characterized them according to whether they had two, one, or no identifiable CFTR mutations. The range of the nasal potential difference studies in the patients with bronchiectasis varied from the normal range to close to that seen in mild cystic fibrosis. Furthermore, the number of mutations in CFTR carried by a patient strongly correlated with the nasal potential difference results. These findings strongly suggest that abnormalities of the CFTR gene are a cause of diffuse bronchiectasis. Although no therapeutic intervention is currently available, screening patients with idiopathic disease may be justified to enable appropriate genetic counseling.

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