Severe Community-Acquired Pneumonia

The Need To Customize Empirc Therapy

Even with extensive diagnostic regimens, most studies of community-acquired pneumonia (CAP) fail to determine the etiology in $\geq$ 50% of cases. In usual clinical practice, the diagnostic rate is closer to 15%, which results in most patients with CAP receiving an empiric antibiotic regimen rather than individualized therapy. The choice of empiric antibiotic agents is often guided by consensus guidelines.1,2 These guidelines are in turn based on covering the majority of pathogens identified in published findings from groups of patients with CAP.

Empirc therapy that does not cover the infecting pathogen is an independent predictor of poor outcome,3-5 and patients with subsequent changes in antibiotic therapy based on culture results still have a significant mortality.6,7 The adverse implications for inadequate empiric therapy make it imperative that the antibiotic regimen chosen has as few “holes” as possible, especially in patients with severe CAP, where the mortality is $\geq$ 20%. As the study by Chen and colleagues in this edition of CHEST demonstrates (see page 1072), significant holes in antibiotic coverage may result when the local etiology of CAP differs from the etiology in “standard” populations (predominantly North American and Western European) on which the guidelines are based. To achieve the best outcome, physicians need to have knowledge of local variations in the etiology of CAP, and they must be aware of which pathogens may not be covered by standard empiric regimens, and the risk factors for infection with these pathogens.

Deficiencies in empiric antibiotic coverage can result from either unexpected antibiotic resistance in the common pathogens or because unusual pathogens are the cause of CAP. The impact of antibiotic resistance is dependent on the empiric antibiotic regimen used. In the case of penicillin-resistant Streptococcus pneumoniae infection, the impact is relatively small because empiric regimens in areas with a high prevalence of penicillin resistance are designed to cover this eventuality. Conversely, while Staphylococcus aureus is not an unexpected pathogen, the presence of methicillin resistance in community-acquired infections is increasing8 and the inadequacy of usual empiric regimens may significantly impact outcome.4

The occurrence of etiologies other than the usual pathogens, S pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella spp, and respi-
ratory viruses, increases the complexity of CAP management. It is reassuring that aggressive diagnostic procedures, such as percutaneous needle aspirations and preantibiotic bronchoscopy, or research protocols, such as polymerase chain reaction testing regularly find that the pneumococcus is the most common etiology for these otherwise undiagnosed cases. Convalescent serologic studies also consistently confirm that the usual “atypical” microorganisms cause another large percentage of cases, although the relative frequency of each varies depending on the geographic location of the study.

However, a disturbing percentage of patients with CAP, particularly those with severe CAP, are infected with pathogens not covered by the usual empiric antibiotic regimens. The more serious of this second tier of causative microorganisms are the Gram-negative bacilli. A study by Ruiz and coworkers found that Gram-negative bacilli (other than Haemophilus spp) caused 11% of CAP in patients requiring ICU admission. The mortality of severe Gram-negative CAP was 55.5%, the highest case fatality rate for any etiology.9 Gram-negative pathogens, particularly Klebsiella pneumoniae and Pseudomonas aeruginosa, are also frequently identified in patients presenting with CAP and shock,10 where the mortality is >50%.

In this issue of CHEST, Chen and colleagues present a case series of severe CAP due to another Gram-negative bacillus, Acinetobacter baumannii. While usually considered a nosocomial pathogen, numerous cases of A. baumannii CAP have been reported over many years, particularly in patients with severe CAP.10,11 One of the most helpful hints from the series reported by Chen et al is the geographic and temporal distribution of Acinetobacter CAP cases to areas and seasons of heat and humidity. The other helpful hint on diagnosis is that Acinetobacter CAP often has a presentation similar to the alcoholism, leukopenia, and pneumococcal bacteremia syndrome.11,12

Obviously, the greatest concern when unusual pathogens cause CAP is whether they are susceptible to the usual empiric antibiotic regimens. Although not as active as ciprofloxacin, empiric use of the newer quinolones for empiric therapy of CAP may provide some coverage of Pseudomonas, while the other common regimen of a nonpseudomonal cephalosporin and a macrolide would not. Acinetobacter CAP presents an even greater challenge because even antipseudomonal cephalosporins are infrequently effective. Carbapenems (imipenem and meropenem), seldom used but mentioned as an alternative by both American Thoracic Society and Infectious Disease Society of America guidelines, are the most reliable antibiotic agents for Acinetobacter pneumonia. However, Chen et al found that the addition of an aminoglycoside to a β-lactam was associated with better outcome.

Unfortunately, outcomes analyses of CAP treatment have cast aminoglycoside use in a bad light. A large study14 of CAP treatment regimens suggested the inclusion of an aminoglycoside was associated with an increased risk of death. Rather than substandard empiric therapy, the association between mortality and aminoglycosides may be due to physicians correctly suspecting a Gram-negative pathogen with its attendant greater mortality. Combination therapy with a β-lactam and an aminoglycoside has been demonstrated to lead to improved mortality in Klebsiella CAP,14 and aminoglycosides are routinely used in combination therapy for suspected pseudomonal infections.

Physicians want to select empiric antibiotic therapy that is likely to cover all likely pathogens, particularly in patients with severe CAP. How then should physicians select antibiotic regimens in patients with severe CAP in order to plug the occasional holes in standard empiric therapy? Indiscriminate use of a carbapenem or addition of an aminoglycoside to all patients with severe CAP is clearly not appropriate. However, the epidemiologic clues for unusual etiologies of CAP can justify selective use of these agents. Severe CAP occurring during hot, humid weather probably is an adequate indication for empiric carbapenem use for suspected Acinetobacter CAP, particularly if occurring in an active alcoholic or associated with neutropenia.

Most importantly, physicians need to be aware of the local differences in the etiology of CAP and the risk factors for pathogens likely to be resistant to standard empiric antibiotic regimens. When very broad-spectrum empiric therapy is selected to cover for drug-resistant pathogens, adequate blood and respiratory specimens must be collected to maximize the possibility of converting to specific therapy as soon as possible. Empirc therapy is indicated for infections in which the diagnostic yield is low or until diagnostic culture results are available. The success of empiric therapy in a majority of cases also does not justify laxity in diagnostic efforts in individual high-risk, high-yield cases.

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Hypersensitivity Pneumonitis

Just Think of It!

Ambient air contains variable amounts of respirable foreign substances. Some of these substances are capable of inciting immune responses in the host inhaling them. Hypersensitivity pneumonitis (HP) represents one possible response of the lung to the inhalation of these antigenic substances. Subjects who are exposed to respirable antigens occasionally react to this by a complex immune response, involving both T-lymphocyte and B-lymphocyte activation in the lower respiratory tract. Disease resulting from antigen exposure is uncommon, even among subjects with similar exposures to the relevant antigens. This variability in disease expression following exposure suggests that the genetic background of affected individuals or other factors such as concomitant viral infection may be responsible for disease expression.

Although the exact pathogenesis of HP is not known, patients with the disease have several characteristic features that allow a firm diagnosis in most cases. These features include a history of exposure to respirable antigens, the relief of symptoms with antigen avoidance, and a recrudescence of symptoms with re-exposure. The symptom complex can be quite variable and includes severe presentations that are similar to that of ARDS, subacute presentations with malaise, cough, and weight loss, and the development of chronic fibrosis. These variable forms of presentation pose a considerable challenge to the clinician. The clinician must first consider the possibility that HP may be causing the disease. Then the physician must question the patient about exposure to relevant antigens. Unfortunately, the spectrum of potential antigens is quite broad, and these antigens may be concealed in the environment. However, in most cases the amount of antigen in the inhaled air is quite large. Thus, affected patients usually have an idea that they are being exposed to something. They may notice that the air that they breathe is dusty or has an objectionable odor. In some cases, the patient's occupation is a powerful clue to a potential exposure.

Once the possibility of exposure has been determined, support of the diagnosis may be provided by a CT scan of the chest and by lung function tests. HP is associated with the combination of ground glass changes and small nodular lesions that are visible on the CT scan. Pulmonary physiology usually shows a mixture of restrictive and obstructive changes. Neither a CT scan nor a lung function test provides a diagnosis, but both provide soft support. Subsequently, the clinician may proceed by attempting to identify immune responses against the probable antigens. The easiest test to perform is the search for precipitating antibodies. The antigens responsible for common forms of HP such as farmer's lung and pigeon-breeder's disease are well-characterized and can be tested by commercial laboratories. In other cases, antibodies may be difficult to detect, and previously unknown antigens cannot be assessed by standard antibody methods in commercial laboratories. If antibodies cannot be detected, the patient...