Oral Therapy for Pneumonia: Who, When, and With What?

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Introduction

Sir William Osler called pneumonia the "captain of the men of death." Although the advent of the antimicrobial age has somewhat reduced this rank, pneumonia remains the sixth leading cause of death in the United States. In 1993, the age-adjusted death rate due to pneumonia was 13.5 per 100,000 persons, reflecting a 20.5% rise between 1979 and 1993 [1]. Estimates of the incidence of pneumonia range from 3 to 4 million cases per year, with about 20% of cases requiring hospitalization [2]. The heterogeneity of pneumonia patients and their underlying diseases, as well as the variation in clinical syndromes caused by different pathogens, has always made the selection of agents to treat pulmonary infections a complex decision. The simultaneous rise of pathogens resistant to the antimicrobial agents traditionally used in pneumonia therapy and arrival of a plethora of new, broad-spectrum antibiotics has further complicated the difficult issues surrounding antimicrobial selection and treatment setting. This has forced a reevaluation of pneumonia therapy, manifested in the medical literature as major new reviews from authoritative sources, including 1998 guidelines by the Infectious Diseases Society of America (IDSA) [3].

Factors Complicating Therapy Selection

Microbial Factors

Among the factors complicating choice of antimicrobial therapy for pneumonia has been the emergence of pathogens falling outside the traditional list of etiologic organisms. In the past, therapies were geared toward *Streptococcus pneumoniae* and *Haemophilus influenzae* as primary community-acquired pathogens. In this model, β-lactams, such as the penicillins and cephalosporins, usually were used as first-line agents. Many older studies of pneumonia found no pathogen in up to 50% of cases [4], which may be partly explained by failure to collect an adequate sputum specimen before the initiation of therapy. The past 2 decades, however, have seen a rise in bacterial agents of pneumonia that are both difficult to culture and inherently resistant to β-lactams. The emergence of *Legionella pneumophila* (2% to 8% of U.S. cases), *Chlamydia pneumoniae* (4% to 6% of cases), and *Mycoplasma pneumoniae* (1% to 6% of cases) as prevalent causes of community-acquired pneumonia [5] has contributed significantly to the explosive development and wide use of newer members of the macrolide and fluoroquinolone families of antibiotics. Also more fully appreciated in recent years is the role of viruses in community-acquired pneumonia, with various studies implicating viruses as the primary pathogens in 2% to 15% of cases [5]. With these data in hand, IDSA guidelines now recommend that an oral tetracycline, macrolide, or fluoroquinolone be used as first-line therapy of pneumonia in the outpatient setting.

Paralleling new discoveries in pneumonia etiology and therapy has been the development of a worldwide rise in antimicrobial resistance among bacteria. A case in point is the most common etiology of pneumonia, *S. pneumoniae.* Estimated to occur in 14 to 46 cases per 1000 person-years in the the U.S. elderly population, pneumococcal pneumonia is associated with an estimated 30% mortality when left untreated [6]. While pneumococci have traditionally been exquisitely sensitive to penicillin, strains of the organism possessing intermediate- or high-level resistance to penicillin have established endemicity in several communities. A recent report from the Centers for Disease Control and Prevention [7] found that a full 25% of pneumococcal isolates exhibited penicillin resistance, 7% with high-level resistance. Many of these strains are resistant to multiple cephalosporins, erythromycin, and trimethoprim/sulfamethoxazole. In the article by Bittner et al [8] in this issue of *JCOM, S. pneumoniae* isolates were fully resistant to cefpodoxime in 15% of cases and resistant to ceftriaxone in 11% of cases. It is clear that local patterns of antimicrobial resistance can have a significant impact in the selection of antimicrobial agents, and culture confirmation of susceptibility must be diligently sought.

Other gram-positive pathogens, such as enterococci and staphylococci, also have grown more resistant. To be sure, the epidemiology of such resistance is complex and not yet fully elucidated. However, there is a clear sense in the infectious disease community that the inappropriate initiation of broad-spectrum antibiotics and failure to appropriately narrow

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therapy to target culture isolates, both in the hospital and the community, has exerted selective pressure favoring resistant pathogens. Ongoing failure to recognize these influences further threatens the fragile gains of modern medicine in the war against microbes.

Host Factors

A variety of host factors also can impact the selection of antimicrobial agent and route of administration. In aspiration-prone patients, empiric pneumonia therapy must take into account the polymicrobial oral and gastric anaerobic flora that are frequently present. *M. catarrhalis, H. influenzae,* and *S. pneumoniae* are identified in the setting of chronic obstructive pulmonary disease. Patients living in nursing homes are more likely than patients living at home to have pneumonias due to *Staphylococcus aureus* or gram-negative bacilli and can be unwilling participants in institutional outbreaks of atypical bacterial or viral respiratory infections. HIV infection and corticosteroid therapy increase the risk of pneumonia due to opportunistic pathogens such as *Pneumocystis carinii,* cytomegalovirus, and several species of fungi and mycobacteria. Neutropenic patients are especially prone to fungal pneumonias, such as those caused by *Aspergillus* species. Diabetics are more prone to staphylococcal infections. Patients with functional or surgical asplenia are especially susceptible to infection with encapsulated organisms such as *S. pneumoniae* and *H. influenzae.*

Cost Issues and Patient Preferences

With an annual treatment cost estimated at more than $20 billion, pneumonia is clearly a diagnosis targeted for cost-containment [5]. As traditional treatment regimens are based on inpatient parenteral antibiotic therapy, there has been growing interest in oral regimens that could reduce or obviate the need for hospitalization, with its attendant costs of personnel and intravenous administration, risk of venous access complications and noscomial infections, and disruption of activities for patient and family. A considerable cost savings could be realized with oral therapy: Chan et al [9] predicted a cost savings of £176,000 if 800 patients were treated with oral therapy over a single year. Cunha [10] showed that drugs administered in their oral rather than in their parenteral form produced a cost savings of at least ten-fold. Further, patients support the notion of outpatient treatment: 74% of those surveyed by Coley et al [11] preferred home therapy.

Mortality Risk and the Decision to Admit

The complex interplay among these factors makes the decision regarding site of care for pneumonia challenging indeed. Several recent studies have attempted to risk stratify patients on the basis of objective clinical findings. Most notable is the prediction rule of Fine et al [12], which builds upon the findings of the multicenter Patient Outcomes and Research Team (PORT). Studying a large cohort of patients with pneumonia, the PORT investigators established a list of underlying host factors, examination findings, laboratory values, and radiographic features disproportionately associated with morbidity and mortality. These factors were then prioritized in a point system, with patients assigned to 1 of 5 risk classes (5 being highest risk) on the basis of total risk score. This system was then validated in a cohort of 2287 patients. Patients in classes 1 through 3 had less than 3% mortality, and less than 6% of these patients required admission to an intensive care unit. Fewer than 10% of patients in risk classes 1 and 2 who were treated as outpatients eventually required hospitalization. Patients in risk classes 4 and 5 experienced a steep rise in mortality (8% and 29%, respectively). On the basis of this information, the authors recommend that while patients in risk classes 4 and 5 should routinely be hospitalized, patients in risk classes 1 and 2 can routinely be treated as outpatients. Patients falling into the middle zone of risk class 3 can be treated either as outpatients or briefly in the hospital, depending on clinical judgement. The authors point out, however, that the decision to admit should be individualized.

Who Should Get Oral Therapy?

The PORT study has important implications for oral therapy for pneumonia. By defining a low-risk group of pneumonia sufferers who can safely be treated as outpatients, the PORT risk-scoring system shines the light on the patients who, in most instances, are excellent candidates for oral antibiotic treatment.

The landscape changes dramatically in the inpatient setting. Implementation of oral regimens has been limited, in part, by a peculiarity of the American third-party health care payer system that holds that a patient sick enough to be admitted to the hospital should be treated with intravenous medication. Many physicians, encouraged by institutional and third-party utilization reviewers, feel obligated to meet hospitalization criteria for pneumonia by ordering intravenous antibiotics. The same economic pressures have tended to slow conversion to oral antibiotic therapy for some patients, as physicians struggle to justify ongoing hospitalization for those they do not yet feel comfortable discharging. Further discomfort stems from fear of legal retribution for poor outcomes. Most physicians lose less sleep over the prospect of criticism for use of unneeded parenteral antibiotics than over the prospect of having a plaintiff's attorney ask why "gold standard" parenteral therapy was not used. A portion of this discomfort must certainly stem from a dearth of well-designed studies proving safety and efficacy of oral antibiotics in this setting.

What is the evidence? Parenteral-to-oral "switch" therapy has been attempted in a number of studies and found to be safe and effective, provided the patient has good social supports and the ability to take and absorb oral medication. Cassiere and Fein [13], in their excellent recent review of the existing literature on switch therapy, provide a common-sense algorithm for its use. To this author's knowledge, there are no large studies proving improved clinical outcomes when intravenous therapy is used instead of oral therapy. Chan et al [9], in an open study of 541 pneumonia patients, found no difference in outcomes between groups receiving oral amoxicillin/clavulanate, intravenous followed by oral amoxicillin/clavulanate, or oral followed by intravenous cephalosporins. Unfortunately, even rarer are studies that attempt a direct, double-blind, randomized comparison of oral and intravenous antimicrobial therapy in the appropriate patient population. In this clinical setting, the appropriate study population would likely be members of PORT risk classes 3 and 4 — sick enough to be hospitalized, but not too sick to swallow and absorb oral medications.

In this issue of *JCOM*, Bittner and colleagues show that a randomized, double-blind comparison of oral and intravenous antibiotic therapy is possible. Cefpodoxime is a newer oral cephalosporin with a spectrum of activity that includes most of the "typical" bacterial causes of community-acquired pneumonia. As a comparator agent, the authors chose ceftriaxone, an intravenous cephalosporin with a spectrum of activity similar to cefpodoxime. Patients received both an oral and a parenteral medication, 1 of which was a placebo. All patients in both groups had bacteriologic cures. Clinical cures were achieved in approximately 60% of patients in both groups. One patient in each group discontinued therapy for a drug-related adverse event. Only 1 patient (cepodoxime group) had a clinical relapse at the time of the 2- to 4-week follow-up visit. From these data, the authors infer that oral cefpodoxime can replace parenteral ceftriaxone in treating hospitalized patients with pneumonia.

This assertion seems true enough, but there are several important limitations to the study. The most important limitation is in the area of patient selection. For instance, it is not known how many patients were residents of nursing homes, where *S. aureus* (2 of 6 isolates susceptible to cefpodoxime) and gram-negative bacilli are more prevalent. Patients were excluded for, among other factors, organ failure, leukopenia, adult respiratory distress syndrome, HIV infection, and treatment for neoplastic disease. All but 10 of the patients who received cefpodoxime and 12 of the patients who received ceftriaxone were retrospectively categorized as being in PORT risk classes 1, 2, or 3. Such patients have a low mortality rate and might not be hospitalized in the PORT algorithm, although the treating physicians judged the patients sick enough to admit. These patients are likely ideal

candidates for oral therapy, but in some cases may have missed the group targeted for study—those with risk factors that suggest a benefit to hospital care.

Secondly, it is important to highlight some practical truths about pneumonia care in 1999. As discussed above, many pneumonias are caused by pathogens that would not be treated by any cephalosporin—namely, *Legionella* species, *M. pneumoniae*, *Chlamydia pneumoniae*, and viruses. Given the frequent difficulty in obtaining sputum specimens, the relatively poor sensitivity of sputum Gram stain and culture, and overlap in clinical syndromes between "typical" and "atypical" pathogens, many clinicians feel compelled to empiric antimicrobial coverage for atypical bacteria. These facts have led the IDSA to recommend that outpatient oral therapy provide such coverage, with tetracyclines, macrolides, and newer fluorquinolones recommended. β-Lactams enter IDSA guidelines in the inpatient setting and may, with clinician judgement, be combined with atypical bacterial coverage.

Conclusion

What is the role of oral therapy in community-acquired pneumonia? In their study, Bittner and colleagues provide a good study mechanism and some tantalizing data indicating that outcomes with oral therapy may be as good as those with parenteral therapy in some patient populations. The devil is in the details, and the details are yet to come. Larger studies comparing oral and parenteral therapy, with patients stratified by risk group, would help further shape guidelines for induction treatment of pneumonia. In the interim, the suggestions of the PORT group provide a reasonable guideline. In addition, stratification with regard to microorganism may create a list of pathogens as amenable to oral therapy as parenteral therapy in appropriate circumstances. Already available are data that support switch therapy. As clinical common sense dictates, oral therapy is only possible when the patient is hemodynamically stable, clinically improving, and capable of taking and absorbing oral medication. Choice of agents must be made with a working knowledge of clinical syndromes, local resistance patterns, and drug bioavailability. Therapy should be narrowed whenever microbiologic profile allows to retard the development of antimicrobial resistance. By combining these factors, the astute clinician can help the pneumonia patient recover from the illness with minimum cost and inconvenience and maximum success.

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