metric study results have been found in individuals with a high score (3.8 ± 1.3, mean ± SD), while the score is low (2.5 ± 0.6) in the truly negative.21

Because of the potential impact of unrecognized significant sleep-disordered breathing, every effort must be made to identify those affected as well as to define more completely the natural history. To do so will require a tool simpler than polysomnography. In the early days the observation of apneas in a sleeping patient sufficed,22 but this specific and sensitive method would be too dependent on wake-sleep schedules (the physician's as well as the patient's), and a consensus about screening must be achieved.

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Antibiotic Studies in Pneumonia

Pitfalls in Interpretation and Suggested Solutions

Pneumonia continues to offer a major diagnostic and therapeutic challenge for the clinician. Lower respiratory tract infections constitute a major usage group for antibiotics, and the commercial success of a new agent virtually requires that it carries an indication for these infections. Consequently, many new antimicrobial agents continue to be introduced for lower respiratory tract infections with a corresponding number of clinical studies being performed, making it increasingly difficult for the practicing physician to select the appropriate antimicrobial with confidence.

The readers of Chest are well aware of the difficulty in conducting antibiotic studies in pneumonia. The clinical diagnosis is often not straightforward. Fever, chills, and cough do not always signify pneumonia. Markings on chest x-ray films can suggest infection but may also be consistent with congestive heart failure, pulmonary embolus, tumor, old scarring, or an immunologic process.

The major problem is that the determination of the etiologic agent in pneumonia is fraught with difficulty. The most commonly used criterion is the isolation of a microorganism from the sputum culture. However,
the problems of an expectorated sputum are well-known. Because of the sputum's passage through the oropharynx, a "pathogen" isolated from culture may be merely a colonizer. Multiple bacterial species may be cultured, making it difficult to determine the true pathogen. Concomitant corroboration of the sputum culture results with sputum Gram stains would be valuable, but this is often not performed. Also, sputum is often simply not available. Although transtracheal aspirate would overcome many of these problems, this procedure has fallen out of favor with most practicing physicians. Finally, other etiologic agents, including Legionella, Mycoplasma, and TWAR, a newly-discovered Chlamydia species,1 require specialized diagnostic laboratory tests that are not always readily available.

The quinolones are a new group of antimicrobial agents that have been proposed for the treatment of pneumonia because of their activity against Gram-positive and Gram-negative aerobic bacteria, relatively high penetration into lung tissue, small number of serious side effects, and convenience of oral therapy. They also have activity in vitro against Mycoplasma, Chlamydia, and Legionella. Although it has been emphasized that the spectra of quinolones do not include anaerobic bacteria, evidence exists that they may be active against oropharyngeal flora (which may be pathogenic in the context of aspiration pneumonia).2 Preliminary studies suggest that quinolones are efficacious for pneumonia, but there have been few comparative studies.

Khan et al (see page 528) make a promising start in this direction with a prospective, randomized, comparative study of ciprofloxacin vs ceftazidime for pneumonia in 122 patients. The authors are to be commended for the effort that went into a study of this magnitude. Gram stains were done on all sputum samples, patients were followed up carefully on a daily basis, every patient received follow-up chest x-ray films, and in vitro microbiologic studies were performed for sputum isolates. The authors also provide valuable details of the cases that failed therapy. Ciprofloxacin produced a 90.9 percent cure rate and appeared to be as effective as ceftazidime with its 89.3 percent cure rate.

However, their study contains some flaws that deserve mention. Although it is reasonable to summarize the data from all patients, as they have done, a separate analysis for patients with community-acquired and nosocomial pneumonias should have been made available to the reader. The patient populations of these two types of pneumonia are dissimilar, and the common organisms that cause these pneumonias are also different. We also question the use of ceftazidime as a comparative standard for community-acquired pneumonia, since this antibiotic would not be optimally effective against many of the common etiologies of community-acquired pneumonia, including Legionella, Mycoplasma, and TWAR. (Also, neither ciprofloxacin nor ceftazidime are ideal for Pneumococcus, the most common etiology in community-acquired pneumonia.) The authors make no mention of testing for Legionella or Mycoplasma. Blood culture results were not reported. Their total reliance on results of sputum cultures for all of their patients is understandable, but the weakness of this criterion should be acknowledged. A few patients with nonbacterial etiology were included (eg, patient number 133 in their Table 2). Despite our criticisms, we agree that ciprofloxacin shows promise, since efficacy percentages are so high.

Given the proliferation of antibiotic studies reported in peer-review journals, "throw-away" journals, and pharmaceutical-produced literature, how does one evaluate the relative merits of these studies? We offer some guidelines for consideration by practicing physicians to use in evaluating studies of this type.

First, prospective, randomized, comparative trials of the new agent to an established standard is an obvious minimal requirement. This separates Khan's study from other "open" studies of ciprofloxacin in pneumonia. A double-blind format would be ideal, since criteria for cure in pneumonia includes subjective evaluation.

Patient entry should be stratified by severity of illness to decrease the possibility that ill patients with a correspondingly poor prognosis would be disproportionately randomized to one arm of the study. Presence of mental status changes, severe vital sign abnormality, underlying neoplasm, and age greater than 65 have been shown to be significant predictors of mortality in patients with community-acquired pneumonia.3,4 The definition of pneumonia should be clearly stated. Signs and symptoms such as fever, cough, purulent sputum, shortness of breath, and chills are important but not sufficient. Objective evidence in the form of a new pulmonary infiltrate on chest x-ray film should be required. Eleven patients in the Khan study had normal chest x-ray film findings and should have been excluded; these patients with bronchitis would artifactually increase the efficacy of both agents studied, since outcome in bronchitis can be expected to be uniformly favorable.

Having an appropriate comparative standard to the test antimicrobial is essential and the Achilles heel of many comparative studies. Since so much therapy for pneumonia is empiric, consideration must obviously be given to the likely etiologic organisms. The two most common treatable etiologies of community-acquired pneumonia are Pneumococcus and Hemophilus influenzae,4 while Legionella and TWAR have been implicated with increasing frequency.5,8 For nosocomial pneumonias, aerobic Gram-negative bacilli and
staphylococci emerge as important pathogens; 

Legionella would be a nosocomial pathogen for those hospitals with a contaminated water supply. 

For nursing home pneumonias, the organisms are similar to those of nosocomial pneumonias, but coverage for oropharyngeal anaerobic bacteria should be included, considering the frequency of aspiration in this debilitated population.

Given the difficulties in interpretation of sputum culture, we suggest subclassifying etiologies into two categories: "definitive" and "presumptive." Definitive etiology might include any of the following: (a) blood or pleural fluid cultures yielding a pathogen; (b) open lung biopsy results yielding a pathogen; (c) bronchoalveolar lavage findings revealing Pseudomonas aeruginosa; (d) positive sputum culture for Legionella, Mycoplasma, or TWAR; or (e) fourfold rise in antibody titer for Legionella, Mycoplasma, TWAR, Q-fever or influenza A.

Presumptive etiology might include growth of a bacterial pathogen in sputum culture in which Gram stain revealed a predominant bacterium compatible with the culture result. Even when the sputum is considered to be an excellent specimen, any organism isolated cannot be considered as the "definitive" etiology, since the specimen may still fail to yield the actual pathogen.

For most cases, the etiology could be expected to be "presumptive," since in the real world sputum culture remains the primary method for diagnosis despite its problems. The "presumptive" category would acknowledge the tentativeness of the etiology while using the culture specimens available. Should newer agents be discovered or diagnostic criteria changed, the data published could be reevaluated in the future. This classification also allows readers to confine the analysis for efficacy to the more rigorously-defined group of patients classified as "definitive."

Although blood cultures are usually negative, when positive they provide definitive evidence of etiology. Thus, obtaining blood cultures prior to therapy should be an integral part of any pneumonia protocol. The problem of small numbers of patients can be alleviated somewhat by combining all bacteremic patients in a meta-analysis from numerous studies—a capability of the sponsoring pharmaceutical firm that has access to data from many studies.

As previously mentioned, community-acquired and nosocomial pneumonias must be evaluated separately. The etiologies of these two types of pneumonia differ greatly, and as a result, empiric therapy is different for the two.

The end points for the classification of cure should be explicit. We suggest a new criterion: clinical cure is defined as resolution of presenting symptoms and signs (for example, defervescence, return of normal respiratory rate, clearing of cough and sputum, etc) at a fixed time (for example, five-seven days) following discontinuation of the test antibiotic. Bacteriologic eradication based on post-therapy sputum cultures would be of secondary importance given the aforementioned difficulties in interpretation. The current requirement of the Food and Drug Administration for sputum sterilization by the antibiotic in declaring a patient as "cured" should be re-evaluated.

When the above criteria are applied to previously published studies of antimicrobial agent efficacy in pneumonia, it is clear that most studies fall short of our ideal. Although it may not be realistic to expect complete conformity to these standards, attempts to adhere to these criteria would enable more valid comparisons of different studies and give greater support for recommended antibiotic usage in specific clinical settings. Studies which approach this ideal should be submitted to peer-review journals. Studies which fall short of this ideal could still be published in literature sponsored by pharmaceutical firms. However, the critical reader should realize that reports in "throw-away" journals and symposia (even if published as a supplement in peer-review journals) are only marginally peer-reviewed and generally carry a bias favorable to the study drug. Our suggested criteria will require greater detail and refinements in individual studies. Nevertheless, the overview expressed in this editorial may be helpful in elucidating common problems in interpretation of pneumonia studies. The goal for both investigators and pharmaceutical firms is to critically and objectively determine the efficacy of any new antimicrobial agent. The formulation of uniform and rigorous criteria should ultimately prove valuable to assessment of therapy in pneumonia.

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References

 Bronchial Infusion Therapy (BIT)

A Bit of Caution

Of the many vexations facing chest physicians, certainly one of the more problematic and occasionally dramatic is the patient with persistent hemoptysis, particularly of the massive variety. What constitutes "massive" varies: in a respiratory cripple a small amount of blood may asphyxiate, whereas a previously healthy individual may tolerate hundreds of milliliters of respiratory blood loss. Besides therapies directed at the underlying disease process, a variety of nonsurgical interventions have evolved over the years with the primary aim of stopping the bleeding. These include IV pitressin,1,2 double-lumen endotracheal tubes,3 Fogarty-type endobronchial balloon catheters,4 iced saline solution,5 iced saline solution with thrombin,6 laser therapy,7 endobronchial irradiation,8 external beam irradiation,9 and endovascular therapy, which comprises primarily bronchial artery embolization (BAE).10 The wide variety of therapies available leads one to conclude no therapy is uniquely efficacious, safe, available and durable, but BAE has the largest experience and is generally the procedure of choice, particularly when critical volumes of hemoptysis are present in a poor surgical candidate. However, BAE is "high tech," has some infrequent but serious risk (spinal artery embolization) and requires an invasive radiologist who is readily available and experienced in the technique.

The article in this issue of Chest by Tsukamoto and colleagues (see page 473) describes a simple technique of instilling thrombin alone or fibrinogen followed by thrombin through the channel of a fiberoptic bronchoscope directly into a bleeding bronchus. The appeal of this technique of bronchial infusion therapy (BIT) lies in the more widespread availability of bronchoscopes and bronchoscopists than invasive radiologists and the well-established record of fiberoptic bronchoscopy for ease and safety. However, a few cautionary notes are needed.

First, commercial fibrinogen has not been available in this country since 1978,13 because of the hepatitis risk then and the added risk of human immunodeficiency virus (HIV) now. Thus, the fibrinogen followed by thrombin method described as more effective than thrombin alone is not readily available to bronchoscopists here. This should not be a major problem, since thrombin alone should be effective if fibrinogen-containing blood is present in the bronchus. Alternatively, cryoprecipitate, with a lessened risk of hepatitis and HIV transmission, could be used if necessary.14 Second, it may be overstating the obvious to say that BIT should subvert the smallest order bronchus possible in order to maximize respiratory function. Third is the question of what role BIT will play in the diagnosis and therapy of patients with hemoptysis. In my practice and that of my colleagues, the patient with refractory hemoptysis of whatever amount is not seen very often. Over an eight-year period at my institution, there have been two patients referred for BAE, out of some 3,200 bronchoscopies of which approximately 10 percent were done for hemoptysis. In contrast, the authors had 33 cases in five years, probably reflecting a higher incidence of suppurative lung disease in their practice. Most hemoptysis simply stops if the patient is put at rest and effective therapy for his underlying condition is given. Even with idiopathic hemoptysis this occurs, and the prognosis is excellent.15 These considerations aside, I concur with the authors’ conclusion that BIT should be considered an effective alternative to BAE, but I would reserve its use for those refractory cases in which routine measures have failed. This approach potentially represents a standard primary therapy and may complement other medical, endobronchial, endovascular, and surgical therapies. However, the urgency of massive hemoptysis, the multiple etiologies thereof, and the varying availability of the differing therapies will limit attempts to prospectively establish what constitutes “optimal” primary treatment for persistent hemoptysis.

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