Pneumococcal Pneumonia*
Diagnostic, Epidemiologic, Therapeutic and Prophylactic Considerations
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The past 50 years have witnessed striking changes in the physician's perceptions of the clinical syndrome of pneumonia in general and of pneumococcal pneumonia in particular. Advances in basic and applied microbiology have contributed to increased awareness of the diversity of infectious agents which may invade the lung and of the complex interactions of viruses and bacteria in the pathogenesis of pneumonia. Concomitant with these increments to knowledge, the introduction of potent antimicrobial drugs which have dramatically reduced the morbidity and mortality of many forms of pneumonia has had a profound effect on professional attitudes. Paradoxically, because of the improved prognosis of such illnesses, there has been a diminution of effort on the part of many physicians to seek their cause routinely and, thereby, to maintain knowledge of their clinical and epidemiologic features. In the late 1930s, the simple step of substituting sulfonamides, effective against pneumococci of any capsular type, for treatment with type-specific antisera, which required the isolation and capsular typing of the inciting organism for its rational and effective use, had an initially negative impact on the bacteriologic diagnosis of pneumococcal pneumonia. This trend was heightened greatly a few years later by the introduction of penicillin as the drug of choice for treating pneumococcal infections. For those desirous of continuing to study the causes and epidemiology of pneumonia, the problem was compounded by the increasing difficulty in obtaining for the laboratory the necessary pneumococcal typing sera, which had been by-products of the now discarded therapeutic antisera. This combination of circumstances, together with the markedly improved prognosis of many bacterial infections brought about by new drugs introduced at mid-century, led many physicians to believe that, in most uncomplicated cases of pneumonia, studies to establish their cause were of doubtful value. An example of this outlook may be found in the following statement published in 1956: "In cases of pneumonia in the age group 15-60 without significant coexistent disease, it is felt that routine bacteriologic studies are unnecessary." Similar views were voiced a decade later in the Lancet: "Few physicians order a blood-culture on all patients with pneumonia—and this is probably for patients' good—and no one, so far as we know, types pneumococci routinely." These comments suggest a nihilistic view of the potential benefit that might accrue from studies of the etiology and epidemiology of pneumonia.

Establishment of the cause of the individual case of bacterial pneumonia is fraught with difficulty in a significant proportion of such illnesses. Many of the bacterial species potentially capable of invading the lung are frequent or occasional components of the oro-nasopharyngeal flora in states of good health as well as of disease; and their recovery from cultures of expectorated respiratory secretions does not establish with certainty their causal role in infections of the lower respiratory tract in the absence of additional findings. The problem is exemplified well by the pneumococcus.

Colonization of the human upper respiratory tract with pneumococci of the same capsular type as that carried by the newborn's mother has been observed in the first days of life. A high proportion of children carry pneumococci of one or more types, and simultaneous colonization with as many as four capsular types has been detected. This last finding is consistent with the observation that in 19 (21.3 percent) of 89 cases of bacteremic pneumococcal infection, pneumococcus of a type differing from that isolated from the blood was recovered simultaneously from the patient's respiratory secretions. In order to establish with certainty the causal role of a pneumococcus (or of another bacterium) in a case of pneumonia, one or more of the following criteria must be met:

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1. Isolation of the organism by transthoracic needle aspiration of the lung or by a technically satisfactory transtracheal puncture.

2. Isolation of the organism from cultures of blood.

3. Isolation of the organism from a complicating metastatic focus of infection such as the pleura, pericardium, subarachnoid space or a joint cavity.

4. Immunologic demonstration of the capsular polysaccharide of the organism isolated from sputum in blood, urine or other internal body fluid.

5. Demonstration in two or more samples of serum obtained at appropriate times during the acute and convalescent phases of illness of a rise in antibodies to the capsular antigen of the organism isolated from sputum or of the presence of circulating antigen-antibody complexes.

With the exceptions of routine culture of blood of the patient with pneumonia before initiation of antimicrobial therapy or of recovery of the infecting organism from a metastatic focus of infection, none of the procedures cited is accomplished readily without unacceptable risk to the patient, significant expense or both. For these reasons, rigorous data on the incidence of any bacterial pneumonia are difficult to obtain; and, for practical reasons, reliance on attack rates of bacteremic infection has become the simplest and most readily obtainable index of the continuing incidence of bacterial pneumonia in a given population.

Contemporary information on the incidence of pneumococcal bacteremia and of bacteremic pneumococcal pneumonia is relatively limited and has been obtained largely through retrospective studies and "passive" surveillance. Data regarding pneumococcal bacteremia collected in this fashion suggest minimal attack rates of 8.5 to 9.5 per 100,000 persons per annum.6,7 These figures clearly underestimate its actual incidence, for they fail to take into account cases from which blood cultures were not obtained at all or those cases which were treated with antimicrobial drugs before blood was obtained for culture. Data collected more recently by passive prospective surveillance in the state of Connecticut suggest an incidence of bacteremic pneumococcal infection not less than 25 per 100,000 persons per annum (Shapiro ED, Austrian R. Unpublished observations). It is not unlikely that the true attack rate is two to four times this value. An incidence of pneumococcal bacteremia of 50 to 100 per 100,000 persons per annum would fit well with other estimates of the incidence of pneumococcal pneumonia of one to five per 1,000 persons per annum,8 a ratio of one bacteremic case of pneumococcal pneumonia to four cases of putative nonbacteremic infection having been observed in a number of earlier studies.9

While the criteria set forth above provide those necessary for monitoring, with some degree of accuracy, the incidence of bacterial pneumonia and an example of their application to pneumococcal pneumonia, they are not intended to serve as a deterrent to the examination of a suitably collected specimen of respiratory secretions from the patient with pneumonia.10 The statements of several authors cited earlier notwithstanding, it remains of considerable importance to the diagnosis, treatment and prognosis of the individual patient that microscopic and cultural examinations of the sputum and cultural examinations of the blood be made routinely before initiation of antimicrobial therapy in all cases of pneumonia where circumstances permit; and, in some patients, more invasive procedures may be required to establish a diagnosis. The reasons for these approaches are several:

1. Diagnosis of the presumptive cause of pneumonia cannot be made with sufficient accuracy on the basis of clinical findings alone. Microscopic examination of the sputum may provide the first clue as to the cause of bacterial pneumonia. Failure to detect large numbers of Gram-positive cocci in clusters or of Gram-negative bacilli may jeopardize the chances of recovery of a patient with staphylococcal or with Friedländer's pneumonia by delaying the institution of appropriate antimicrobial therapy.

2. Microscopic examination of the sputum permits assessment of the suitability of the specimen as an aid in diagnosis. The presence of a predominant bacterial form together with significant numbers of polymorphonuclear leukocytes and alveolar macrophages and the absence of large numbers of nasopharyngeal epithelial cells suggest that the organism identified by culture is the likely cause of the infection. In addition, utilization of the quelling reaction, for the performance of which sera are available commercially,* may permit recognition of an invasive pneumococcal capsular type more likely to be associated with infection than the carrier state, and, in some areas, a type with the attribute of resistance to one or more antimicrobial drugs.

3. All the bacterial species which cause significant numbers of pneumonic illnesses may give rise to mutants resistant to one or more antimicrobial drugs. In the absence of cultures of blood and of sputum to isolate the proved or putative cause of infection, it may be impossible to make the necessary modifications in therapy dictated by its susceptibilities to these agents. The substitution of immunologic methods, such as tests for cap-

*Typing sera from the Danish Statens Serum Institut may be purchased in the United States from DAKO Corp., 22 North Milpas Street, Santa Barbara, CA 93103.
sular polysaccharides by counterimmunoelectrophoresis or by latex agglutination, for bacteriologic procedures as a means of attempting to identify the inciting organism is less than optimal for the same reasons. In addition, because of the production of highly cross-reactive or identical antigens by diverse bacterial species, it may be impossible to reach even a reasonable presumptive identification of the inciting organism. For example, the capsular polysaccharides of *Escherichia coli K1* and of the group B meningococcus are nearly identical, if not identical.11

The emergence of pneumococci with clinically significant levels of resistance to penicillin and to other antimicrobial drugs in current use is a relatively recent phenomenon, although information pointing to the ultimate development of such drug-resistant mutants has been long extant. In fact, if not the first, one of the first isolates of a drug-resistant bacterium from man during the course of antimicrobial therapy was the finding of an optochin-resistant pneumococcus in the blood of a patient treated with that drug in 1916.12 Strains of pneumococci showing increased resistance to penicillin were isolated in the laboratory in 1945 after serial passage of the organism in increasing concentrations of the drug,13 a harbinger of their recovery from patients two decades later.14 Unlike the determinants of resistance to antimicrobial drugs in many bacterial species, those of the pneumococcus appear to be associated with the bacterial chromosome rather than with a plasmid (episome). The higher levels of pneumococcal resistance to penicillin result from the cumulative effect of multiple mutations affecting the penicillin-binding proteins of the organism,15 a finding consistent with the relatively late appearance of such strains in man. The production of beta lactamases by the pneumococcus has not been recognized to date.

Although not yet numerically a major threat to the successful treatment of pneumococcal infection, strains of pneumococci resistant to one or more of the antimicrobial drugs employed usually to treat such infections have been recognized with increasing frequency in the past decade. Strains resistant to antimicrobial drugs tend to emerge when one or more such agents is administered widely in an entire population or to a specific segment thereof.16 Because of the frequent prescription of antibacterial agents for children with respiratory ailments, capsular types commonly infecting those in this age group (types 6A, 6B, 14, 19F, 19A, and 23F) are often among the first discovered in a given area to be manifesting resistance. Limited initially in some instances to institutional settings, singly and multiply resistant pneumococci may spread to healthy contacts who in turn become carriers of such organisms in the community. The occurrence of community-acquired infection with such organisms resulting in fatal bacteremic illness has been reported recently,17 and the possibility of similar infections in the future cannot be disregarded. In South Africa, where monitoring of pneumococcal isolates from blood and cerebrospinal fluid for resistance to penicillin in sentinel laboratories has been carried out since 1980, the proportion of strains isolated from blood and showing increased resistance to penicillin exceeds 4 percent.18 Analogous observations have been made in Israel.19 In the United States, 5-15 percent of pneumococcal isolates tested showed relative resistance to penicillin.20

Vancomycin currently remains the drug of choice for the treatment of infections caused by multiply resistant pneumococci. Preliminary data suggest, however, that some of the newer cephalosporins such as ceftriaxone may also prove useful in the management of infections caused by some strains resistant to penicillin G, although currently available data in man are limited.21

A review of the outcome of bacteremic pneumococcal infections caused by penicillin-sensitive strains carried out 25 years ago showed that the case fatality rate among those over 12 years of age with treated uncomplicated bacteremic pneumococcal pneumonia was 17 percent.22 In addition, it was possible to identify subsets of the population whose members, because of advanced age or the presence of complicating underlying disease, suffered case fatality rates in excess of 25 percent even with the best available treatment. As indicated in Table 1, these findings have been confirmed repeatedly in the ensuing decades, although, in the data from some geographic areas, the higher case-fatality rates reflect in part the inclusion of cases with metastatic foci of infection. Because no therapeutic measures were available to reduce the unacceptably high case fatality rates observed at the time the initial study was done, prophylaxis appeared to offer a desirable and acceptable alternative for those at high risk of death if infected, and measures were initiated in the

Table 1—Case Fatality Rates of Pneumococcal Bacteremia in Different Geographic Areas, 1952-1984

<table>
<thead>
<tr>
<th>Location</th>
<th>Dates</th>
<th>Patient Group</th>
<th>Case Fatality (%)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston</td>
<td>1952-72</td>
<td>All ages</td>
<td>23%(734)</td>
<td>23</td>
</tr>
<tr>
<td>Boston</td>
<td>1977-81</td>
<td>Adults</td>
<td>31%(138)</td>
<td>24</td>
</tr>
<tr>
<td>Chicago</td>
<td>1967-70</td>
<td>Adults</td>
<td>26%(325)</td>
<td>25</td>
</tr>
<tr>
<td>New York</td>
<td>1952-62</td>
<td>Adults</td>
<td>25%(529)</td>
<td>22</td>
</tr>
<tr>
<td>New York</td>
<td>1972-82</td>
<td>Adults</td>
<td>26%(170)</td>
<td>26</td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>1975-80</td>
<td>Adults</td>
<td>43%(72)</td>
<td>27</td>
</tr>
<tr>
<td>Seattle</td>
<td>1974-80</td>
<td>Adults</td>
<td>30%(134)</td>
<td>28</td>
</tr>
<tr>
<td>London, England</td>
<td>1970-84</td>
<td>All ages</td>
<td>26%(325)</td>
<td>29</td>
</tr>
<tr>
<td>Birmingham, England</td>
<td>1974-81</td>
<td>All ages</td>
<td>34%(103)</td>
<td>30</td>
</tr>
<tr>
<td>Rouen, France</td>
<td>1972-82</td>
<td>Adults</td>
<td>45%(92)</td>
<td>31</td>
</tr>
<tr>
<td>Tel Aviv, Israel</td>
<td>1975-82</td>
<td>Adults</td>
<td>33%(24)</td>
<td>32</td>
</tr>
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1960s to develop a suitable vaccine. In 1977, a 14-valent vaccine containing 50 µg of each of the capsular polysaccharides of the pneumococcal types most commonly responsible for bacteremic infections was licensed. The history of its development has been reviewed elsewhere. Since that time, the formulation of the vaccine has been expanded to include 25 µg each of the capsular polysaccharides of 23 pneumococcal types which together account for approximately 90 percent of all bacteremic pneumococcal infection.

Utilization of pneumococcal vaccine, like that of influenza viral vaccines, has been limited, seemingly for a variety of reasons. Unlike pediatricians, physicians caring for adults have been relatively unconcerned about routine immunoprophylaxis except when travel to a poorly sanitized area was planned by the patient. The licensure of pneumococcal vaccine in 1977, the year after problems arose in connection with the program for universal immunization with the swine strain of influenza A vaccine, had, in all likelihood, an inhibiting effect on use of the newly released agent. In addition, the questioning of the vaccine's efficacy by some in immunocompetent persons at highest risk of serious or fatal pneumococcal infection served as an additional deterrent to its administration.

As noted earlier, unequivocal demonstration of the cause of a bacterial pneumonia is difficult to achieve. To establish without question the efficacy of pneumococcal vaccine required that trials be conducted in a population with a high attack rate of pneumococcal infection and under conditions when obtaining blood and sputum for culture before the initiation of antimicrobial therapy could be assured. Such criteria can be met in very few places, but were present in populations of gold mining novices in South Africa. The attack rate of putative and proved pneumococcal pneumonia in these subjects exceeded 100 per 1,000 persons per annum. It was possible, therefore, in a randomized double blind controlled trial, to demonstrate unequivocally the 80 percent aggregate efficacy of the vaccine in reducing bacteremic infection in recipients of the vaccine and a 50 percent reduction in all pneumonic illness associated with a radiologically demonstrable lesion in the lung. When the vaccine was being considered for licensure, the data resulting from these trials provided solid evidence of its utility.

In the United States, trials of similar design were carried out with results concordant with those of the African studies, although, for a variety of reasons, they were less definitive. To begin, the attack rate of proved and putative pneumococcal pneumonia in most populations in the United States is less than one tenth that in African gold mining novices. Although more than 13,000 persons over the age of 45 took part in the American trials, and although all cases of bacteremic pneumococcal infection caused by types represented in the vaccine occurred in unvaccinated control subjects, the number of such illnesses was too small to permit establishment of the vaccine's efficacy with certainty. Serologic studies of those vaccinated and of unvaccinated control subjects with putative nonbacteremic pneumococcal pneumonia were also consistent with earlier findings of the vaccine's efficacy. The interpretation of these last findings is rendered moot, however, because it is not known how a vaccinated person with nonbacteremic pneumococcal pneumonia caused by a pneumococcal type represented in the vaccine will respond serologically to such infection. To obtain the desired information would require a study that included routine efforts to isolate the pneumococcus directly from the lower respiratory tract either by transthoracic or transtracheal puncture. Because a protocol including the routine employment of these invasive procedures cannot be justified on ethical grounds, the interpretation of serologic data obtained from studies of patients with nonbacteremic infection remains uncertain.

To obtain data from randomized double-blind controlled trials based solely on bacteremic infection in the United States would pose formidable problems involving logistic, financial and ethical issues. Populations of 100,000 persons or more would have to be enrolled, annual costs would probably exceed $2,000,000, and the ethical issue of withholding a licensed vaccine from the control subjects would have to be addressed. Such considerations make the conduct of additional randomized double-blind controlled trials of pneumococcal vaccine in this country unlikely.

Alternative methods do exist, however, to assess the efficacy of pneumococcal vaccine in preventing bacteremic infection in immunocompetent subsets of the population at increased risk of death if infected. The immunocompetence of vaccinees is emphasized because no vaccine designed to stimulate the production of humoral antibodies essential to defense against infection will be effective in a subject incapable of making such antibodies.

One method which has been used to assess the efficacy of polyvalent pneumococcal vaccine in preventing bacteremic infection is that of the so-called "quasi-cohort" analysis. It is based on the proposition that the ratio of pneumococcal infections caused by types represented in the vaccine to those caused by types excluded from the vaccine will be lower in vaccinated individuals than in control subjects. To use this approach meaningfully, it is essential that vaccinees and control subjects have similar attributes with regard to age, state of health and immunocompetence. In a recent analysis by the Centers for Disease Control of 92 bacteremic infections in vaccinated individuals, the aggregate efficacy of the 14-valent vaccine was calculated to be 64 percent. In vaccinees over two
years of age, efficacy appeared comparable in all age groups including those 65 years of age and older. No significant diminution in efficacy was observed in adults vaccinated three to five years earlier when compared with those receiving the vaccine more recently; and, at present, there is no indication for the readministration of the same pneumococcal vaccine. Estimated efficacy appeared somewhat lower in those with renal failure, alcoholism and chronic pulmonary disease, although the numbers of patients were small and confidence intervals wide. From studies of patients with chronic obstructive respiratory disease, it appears unlikely that vaccination will effectively prevent colonization or infection of the lower respiratory tract, although it may prevent bacteremic infection with a newly acquired pneumococcal type represented in the vaccine. Pneumococci have been isolated by transtracheal puncture from the lower respiratory tract of patients with chronic obstructive pulmonary disease who have high levels of circulating antibody to the homologous capsular type. This finding suggests the presence in some forms of chronic pulmonary disease of an anatomic and/or physiologic defect in the clearance of bacteria from the lower respiratory tract related to host defenses other than antibodies.

The results cited are concordant with those of an earlier analysis of the efficacy of pneumococcal vaccine employing another method, that of the case-control study. In that investigation, the vaccine was found to be 77 percent effective in preventing bacteremic infection by pneumococci in immunocompetent individuals, but to have 0 percent efficacy among those who were severely immunocompromised. Among patients over 55 years of age, the vaccine’s efficacy was 70 percent.

The results of the two studies cited are consistent with the findings regarding the vaccine’s aggregate efficacy in young adults as assessed in randomized double-blind trials, although the confidence intervals in each are still rather wide because of their limited size. Each study is being extended, and additional data will be forthcoming eventually to refine estimates of the efficacy of the 23-valent vaccine now available.

In assessing the aggregate efficacy of polyvalent pneumococcal vaccine, it is essential that its unique complexity be kept in mind. Pneumococcal vaccine, as currently formulated, is designed to prevent 23 immunologically distinct infections, a greater number of infections than all the vaccines mandated for entry to elementary school are employed to prevent. It is evident that the aggregate efficacy of a combination of 23 vaccines administered simultaneously is unlikely to equal that of a monovalent vaccine, even though the former is misperceived by many as a “single vaccine.” If one assumes that the efficacy of each component of pneumococcal vaccine is 90 percent and that, over a two-year period, an individual is exposed to four of the pneumococcal types represented in it, then the maximum achievable efficacy of the vaccine for such an individual will be 0.94 or 65 percent, a figure concordant with those observed in several of the studies cited. The evidence now available suggests that pneumococcal vaccine is performing with an efficacy comparable to that of other licensed vaccines. These conclusions are recognized in the latest statements of the Advisory Committee on Immunization Practices of the Centers for Disease Control and the Health and Public Policy Committee of the American College of Physicians. To facilitate the immunization of those at high risk of serious or fatal pneumococcal infection, several programs for hospital-based vaccination have been proposed and their institution is to be recommended highly. Both the inability of physicians to reduce the continuing significant case fatality rate of established bacteremic pneumococcal infection and the slow but steady increase in the number of pneumococcal isolates resistant to one or more antimicrobial drugs should serve as stimuli to the wider use of routine immunophrophylaxis.

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