Pneumonia – A major clinical challenge

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PNEUMONIA IS AN INFECTION OF THE AIR SPACES OF THE lung. It is a significant cause of morbidity and mortality and represents a major diagnostic and therapeutic challenge.

The attack rates for pneumonia are highest at the extremes of age. The rate of pneumonia per 1000 population ranges from 3/1000 adults in England (1) to 12/1000 in Seattle, Washington (2).

The mortality rate for community-acquired pneumonia requiring hospitalization ranges from 5.7 to 21% (3,4). Such rates are meaningless unless there is a uniform admission policy or a pneumonia-specific severity of illness scoring system that will allow comparison of data from centre to centre. The mortality rate among patients primarily treated as outpatients is much lower – 1.2% (5).

After the physician has made a diagnosis of pneumonia, based on clinical and radiographic criteria, the next step is to make an etiological diagnosis. Many patients cannot produce a sputum sample for culture, or they are already receiving antibiotic therapy at the time of admission. Thus, empiric treatment is often necessary. To make the most appropriate antibiotic choice in this setting it is necessary to know the results of carefully designed and executed studies. In such studies the following criteria for the level of certainty of the etiologic diagnosis of pneumonia should be kept in mind (6).

A. Definitive

- Blood cultures yielding a pathogen
- Pleural fluid yielding a pathogen
- Bronchoalveolar lavage revealing *Pneumocystis carinii*
- Open-lung biopsies yielding a pathogen
- Isolation of *Mycoplasma pneumoniae* from respiratory tract samples or a fourfold rise in antibody titre
- Positive direct fluorescent antibody test for *Legionella* species plus an elevated *Legionella* titre
- A fourfold or greater rise in antibody titre for *Chlamydia pneumoniae*

B. Presumptive

- Heavy or moderate growth of a predominant bacterial pathogen on sputum culture
- Light growth of a pathogen in which the sputum Gram stain revealed a bacterium compatible with the culture results
- Bacterium isolated on multiple sputum cultures within three days of admission

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TABLE 1

Etiology of community-acquired pneumonia requiring hospitalization - North America

	Study (reference)	
	Marrie et al (4)	Fang et al (6)
Number of patients studied	719	359
Number (%) patients with sputum cultured	257 (36)	336 (94)
Time period of study	November 1, 1981 to March 18, 1987	July 1, 1986 to June 30, 1987
Number (%) with pneumonia of:		
Unknown etiology	340 (47)	118 (32.9)
More than one etiology	74 (10.3)	10 (2.8)
<i>Streptococcus pneumoniae</i>	61 (8.5)	39 (10.9)
Aspiration	52 (7.2)	12 (3.3)
<i>Mycoplasma pneumoniae</i>	40 (5.6)	7 (2)
Influenza A	40 (5.6)	Not tested
<i>Staphylococcus aureus</i>	29 (4.0)	12 (3.3)
<i>Haemophilus influenzae</i>	27 (3.7)	39 (10.9)
<i>Coxiella burnetii</i>	22 (3.1)	Not tested
Aerobic Gram-negative bacteria	22 (3.1)	21 (5.9)
Influenza B	17 (2.4)	Not tested
<i>Pneumocystis carinii</i>	14 (1.9)	9 (2.5)
<i>Legionella</i> species	16 (2.2)	24 (6.7)
<i>Mycobacterium tuberculosis</i>	10 (1.4)	4 (1.1)
<i>Chlamydia pneumoniae</i>	18/301 (6)*	22 (6.1)
Postobstructive	13 (1.8)	19 (5.3)

*Only 301 patients had serum samples tested for antibodies to *C. pneumoniae*

- A single elevated titre of 1:320 to *Legionella pneumophila* by enzyme-linked immunosorbent assay (ELISA) or 1:512 or higher titre by indirect immunofluorescence assay
- *C. pneumoniae* IgM antibody titre 1:32 or higher

C. Unknown etiology

- Normal flora on respiratory tract culture
- Light growth of multiple organisms on culture
- Cases not fulfilling any of the above conditions

Table 1 shows the results of two studies of community-acquired pneumonia requiring hospitalization performed in Pittsburgh, Pennsylvania (6) and Halifax (4) in the 1980s. Note that most of the patients in Pittsburgh had sputum cultures obtained while only 36% of the Halifax patients had such cultures. The etiology of the pneumonia was undetermined in 33% and 47% of the patients in the two studies. *Streptococcus pneumoniae* was the most common etiologic agent identified although it accounted for only 10.9% and 8.5% of the cases in the two studies, respectively. A wide variety of agents were found (Table 1). *Legionella* was more com-

TABLE 2

Etiology of blood culture positive pneumonia in two studies of community-acquired pneumonia requiring hospitalization

	Study (reference)	
	Marrie et al (4)	Fang et al (6)
Number (%) of patients who had blood cultures done	539 (75)	314 (89.5)
Number (%) with positive blood cultures	48 (8.9)	28 (8.9)
Number (%) with indicated microorganism in blood:		
<i>Streptococcus pneumoniae</i>	28 (58)	16 (57)
<i>Staphylococcus aureus</i>	1 (2)	4 (14)
<i>Haemophilus influenzae</i>	2 (4)	1 (3.5)
<i>Streptococcus</i> species	8 (16)	2 (7)
<i>Legionella pneumophila</i>	0	1 (3.5)
<i>Actinomyces israelii</i>	0	1 (3.5)
<i>Pseudomonas aeruginosa</i>	1 (2)	1 (3.5)
<i>Serratia marcescens</i> and <i>Acinetobacter calcoaceticus</i>	0	1 (3.5)
<i>Bacteroides fragilis</i>	1 (1)	1 (3.5)
<i>Escherichia coli</i>	3 (6)	0
<i>Klebsiella pneumoniae</i>	2 (4)	0
<i>Neisseria meningitidis</i> W135	1 (1)	0
<i>Salmonella montevideo</i>	1 (1)	0
<i>Bifidobacterium</i> species	1 (1)	0
Polymicrobial	4 (8)	1 (3.5)

mon in Pittsburgh than in Halifax. In both centres *C. pneumoniae* accounted for 6% of the pneumonias. With the advent of the acquired immune deficiency syndrome (AIDS), *P. carinii* has become an important cause of community-acquired pneumonia (7). In these two studies it accounted for 2.5% and 1.9% of the cases, respectively. In the Pittsburgh study using the definitions previously outlined, 79 of the 210 (37.6%) with an assigned etiology were classified as definitive and 131 (62.4%) were classified as presumptive.

The results of blood cultures performed in the studies cited in Table 1 are presented in Table 2. Nine per cent of patients in both studies were bacteremic and the pneumococcus accounted for 58% of organisms isolated.

It seems as if the pneumococcus has decreased in importance as a cause of community-acquired pneumonia. In the 16 studies that Fang et al (6) reviewed *S. pneumoniae* was the main causal pathogen, accounting for 12 to 76% of the cases of pneumonia. In a study of 196 patients with community-acquired pneumonia requiring hospitalization in Copenhagen, *S. pneumoniae* accounted for 36% of the cases (8). However, the total number of infections due to *S. pneumoniae* would have been 70% if the diagnosis was based on one positive serological test for *S. pneumoniae* (8).

Since many patients with community-acquired

pneumonia are treated as outpatients (9), it is important to know the cause of pneumonia in this group of patients. Unfortunately, such patients have been inadequately studied. Three studies (5, 10, unpublished data) involving mostly outpatients with community-acquired pneumonia are summarized in Table 3.

There are several subsets of the general population in whom the rank order of the etiology of pneumonia is likely to be different from what has just been described for the group of patients with community-acquired pneumonia as a whole. The subset of patients requiring admission to an intensive care unit for treatment of their pneumonia has been defined in a series of studies (11-14). The results of these studies are shown in Table 4; *S pneumoniae*, *L pneumophila*, *M pneumoniae*, aerobic Gram-negative bacilli, viruses and *Staphylococcus aureus* are found most commonly. Even in this setting a significant percentage of the cases of pneumonia are of unknown etiology.

Community-acquired pneumonia in the elderly occurs in two settings – at home and in a nursing home. Nursing home-acquired pneumonia accounts for up to 18% of all cases of community-acquired pneumonia requiring admission to hospital (4). The mortality rate among this group of patients is high – 40% in our study (4). When we compared nursing home-acquired pneumonia with age and marked patients with community-acquired pneumonia, we found that aspiration pneumonia and pneumonia of unknown etiology were significantly more common among patients with nursing home-acquired pneumonia (4).

The major problem when dealing with this group of patients is to distinguish colonization from infection. In one study 23% of nursing home patients had colonization of the oropharynx with aerobic Gram-negative bacilli (15). In a study by Carr et al (16) involving 127

TABLE 3
Etiology of community-acquired pneumonia among patients who were not usually admitted to hospital

	Study (reference)		
	Erard (5)	Woodhead (10)	Marrie*
Number of patients studied	161	236	75
Location of study	Switzerland	United Kingdom	Nova Scotia
Number (%) hospitalized	14 (8.7)	55 (22)	26 (35)
Number (%) died	2 (1.2)	7 (3)	3 (4)
Number (%) with pneumonia of:			
Unknown etiology	76 (47)	107 (45)	43 (57)
<i>Streptococcus pneumoniae</i>	17 (10.5)	83 (36)	–
<i>Haemophilus</i> species	3 (1.8)	24 (10)	–
<i>Moraxella catarrhalis</i>	2 (1.2)	–	–
<i>Streptococcus</i> species	1 (0.6)	–	–
<i>Legionella</i> species	3 (1.8)	1 (0.5)	2 (3)
Chlamydia	9 (5.5)	3 (1)	1†
<i>Mycoplasma pneumoniae</i>	28 (17.3)	3 (1)	22 (29)
<i>Coxiella burnetii</i>	3 (1.8)	–	2 (3)
Influenza viruses	19 (11.8)	20 (8.5)	5 (7)
Other respiratory viruses	7 (4.3)	10 (4.2)	–
<i>Escherichia coli</i>	–	2 (1)	–
<i>Staphylococcus aureus</i>	–	2 (1)	–
<i>Proteus mirabilis</i>	–	1 (0.5)	–
<i>Actinomyces israelii</i>	–	1 (0.5)	–
<i>Mycobacterium tuberculosis</i>	–	3 (1)	–
Adenovirus	–	–	2 (3)

*Unpublished data; †Only 19 patients tested for antibodies to this agent

TABLE 4
Etiology of community-acquired pneumonia requiring admission to intensive care

	British Thoracic Society (11)	Study (reference)		
		Torres (12)	Pachon (13)	Ortquist (14)
Number of patients studied	60	92	67	53
Mean age (years)	54	53	56.8	52
Number (%) died	29 (48)	18 (20)	14 (21)	13 (25)
*Number (%) with pneumonia due to:				
Unknown etiology	25 (42)	44 (48)	45 (67)	25 (47)
<i>Streptococcus pneumoniae</i>	11 (18)	13 (14)	12 (17)	15 (28)
<i>Haemophilus influenzae</i>	7 (12)	–	–	–
<i>Legionella pneumophila</i>	7 (12)	13 (14)	7 (10)	–
<i>Mycoplasma pneumoniae</i>	4 (7)	6 (7)	–	3 (5)
Influenza virus	3 (5)	–	–	2 (4)
<i>Staphylococcus aureus</i>	2 (3)	1	–	2 (4)
Aerobic Gram-negative bacilli	2 (3)	5 (5)	8 (12)	–
Streptococci	–	3 (3)	–	–
<i>Chlamydia psittaci</i>	–	–	–	2 (4)

*The six most common causes are listed

TABLE 5
Etiology of pneumonia in the elderly

Study: Venkatesan (17)	
Number of patients studied	73
Location of study	Nottingham, UK
Median age (years)	79
Number (%) died	24 (33)
Sputum cultured	62 (84)
Number (%) with pneumonia of:	
Unknown etiology	42 (57)
<i>Streptococcus pneumoniae</i>	23 (30)
<i>Haemophilus influenzae</i>	5 (7)
<i>Legionella pneumophila</i>	2 (3)
Influenza B virus	5 (7)
Respiratory syncytial virus	1 (1.4)

TABLE 6
Clues to the etiology of community-acquired pneumonia from history

Microorganism	Clue
<i>Legionella pneumophila</i>	Exposure to contaminated water source: air conditioning, cooling tower, grocery shop mist machine
<i>Streptococcus pneumoniae</i>	Shelter for homeless men, jails, South African miners, army barracks
<i>Mycoplasma pneumoniae</i>	Infected family member
<i>Coxiella burnetii</i>	Exposure to infected parturient cats, sheep, cattle, goats
<i>Mycobacterium tuberculosis</i>	Exposure to an infected person (especially one with cavitory disease in a closed setting) – nursing home, shelter for the homeless, HIV-positive patient
<i>Histoplasma capsulatum</i>	Exposure to contaminated bat caves, excavation in endemic areas, fallen trees in endemic areas
<i>Coccidioides immitis</i>	Following a wind storm in an endemic area

elderly patients with lower respiratory tract infection requiring admission to hospital, 79 patients (62%) had pneumonia. Venkatesan and co-workers (17) studied 73 patients 65 years or older with pneumonia (they excluded patients with severe chronic illness in whom pneumonia was an expected terminal event). However, even then the mortality rate was very high – 33%. Table 5 gives the causes of pneumonia in this group of patients. *S pneumoniae* was the most commonly isolated pathogen. No etiological agent was identified for 57% of the patients.

Patients who have AIDS frequently develop pneumonia and account for a significant population of all patients with community-acquired pneumonia. *P carinii* still accounts for a substantial percentage of all cases of pneumonia in this group although now it represents only about 27% of the pneumonias (18). The incidence of pneumococcal pneumonia among patients

with AIDS is 5.5 to 17.5 fold higher than that in the general population (19). A wide variety of pathogens can cause pneumonia in this immunosuppressed population (20).

Chronic obstructive pulmonary disease (COPD) is a frequent co-morbid condition among patients with community-acquired pneumonia; 32% of the Halifax patients (4) and 53% of the patients admitted to the Veterans Administration hospital in Pittsburgh with pneumonia had this condition (6). Twenty-two per cent of the patients with pneumonia at two other Pittsburgh hospitals had COPD (6). Overall 31.4% of the patients in the Pittsburgh study had COPD. Despite the frequent co-existence of these two conditions, studies delineating this subgroup of pneumonia patients are almost nonexistent. Indeed Griffith and Mazurek (21) state "it currently is difficult to establish a clear picture of pneumonia in COPD, including incidence, cause, optimal diagnostic procedures, and treatment". These authors had the impression that there had been a relative decline in importance of pneumococcal disease, more frequent isolation of Gram-negative rods (particularly *Pseudomonas* species) and the emergence of 'new' pathogens such as *Moraxella catarrhalis* (21).

In general terms the approach to the patient with pneumonia should include a careful search for clues to the etiology from the history (Table 6), the physical examination, radiographic features and examination of a Gram stain of the sputum. Often, however, one has to initiate empiric therapy. The best approach then is to tailor treatment to the severity of illness of the patient. If the patient can be treated as an outpatient, a macrolide is probably the best choice. If the patient requires admission to an intensive care unit triple therapy should be used – erythromycin, rifampin and a third generation cephalosporin with activity against *Pseudomonas aeruginosa*. This regimen can be modified as soon as the results of the diagnostic studies are available.

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