Initial Selection of Antibiotic Therapy for Community Acquired Pneumonia in Adults

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Abstract

Patients with community acquired pneumonia must often be treated in the absence of a definitive microbiologic diagnosis. The optimal choice of antibiotic therapy depends on the patient's age, season of the year, onset of symptoms, underlying illnesses, epidemiological features, x-ray patterns, and the local prevalence of pathogens. The issues related to antibiotic cost and toxicity are also important considerations. Streptococcus penumoniae remains the most common etiologic agent among community acquired penumonias, however, in a significant percentage of cases no definite etiologic agent is identified. The incidence of Mycoplasma penumonia is dependent on the occurrence of epidemics and that of Legionnaries' Disease on the geographic area and the time of the year. Community acquired pueumonias may be divided into typical bacterial pneumonias or atypical pneumonias. Patients with a typical bacterial pneumonia and a compatible history, chest radiography, and sputum gram stain for penumococcal pneumonia should be treated with penicillin G. Those who present with atypical pneumonia may be initially treated with Erythromycin to cover both Mycoplasma and Legionella. Risk factors for infection with human immunodeficiency virus should be elicited in every patient since the likely pathogens are very different with Pneumocystis carinii leading the list.

Key words: *Antiobiotics, pneumonia, therapy.*

As we approach the twenty-first century, pneumonia remains a cause of significant morbidity and mortality worldwide. It has been estimated that between two and three million cases of pneumonia occur annually in the United States.[1] Pneumonia was the sixth most common cause of death in the United States in 1986-1988 and the leading cause of infection-related mortality.[2] Although most of the mortality associated with pulmonary infection is due to nosocomial penumonia, community-acquired pneumonia requiring hospitalization has had mortalities of 5-15% in recent series.[3-8] In the elderly mortality may approach 30%,[9] and in patients requiring admission to the Intensive Care Unit, community-acquired penumonia may be fatal in over 50% of individuals.[10]

Patients with community-acquired pneumonia must often be initially treated in the absence of definitive microbiologic information. The optimal choice of antibiotic therapy may vary from one individual to another and in different geographic locales. A number of factors must be considered in the intial selection of antimicrobial chemotherapy. These include the patient's age, season of the year, rapid versus gradual onset of symptoms, associated underlying illnesses, exposure history, radiographic pattern of infiltrate, local prevalence of pathogens and their antimicrobial susceptibilities, and issues related to antibiotic cost and toxicity. This will sum-

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Table 1. Etiology of Community-Acquired Penumonia* 1980– 1989.

Series	No. of Patients	Percent Pneumo-coccus	Percent Legionella	Percent Mycoplasma	Percent Viral	Percent S. aureus	Percent H. influenzae	Percent Gram negative bacilli	Percent Aspiration	Percent Other	Percent No Diagnosis
Elbright 1980[11]	106	36	–	–	–	3	1	10	–	3	47
White 1981[12]	210	12	2	14	15	4	2	2	–	4	52
McFarlane 1982[13]	127	76	15	2	9	2	3	1	–	6	2
Klimek 1983[3]	204	36	14	–	–	8	15	22	4	–	–
McNabb 1984[14]	80	50	1	–	6	4	6	1	–	3	36
Marrie 1988[9]	138	9	1	17	3	9	3	15	18	17	44
Berntsson 1985[15]	127	54	1	14	18	1	5	–	–	4	21
Holmberg 1987[4]	147	47	3	5	11	1	10	–	–	5	30
Marrie 1987[17]	301	9	4	3	16	5	6	2	11	20	37
BritishThoracic Society 1987[5]	453	34	2	18	7	1	6	1	–	7	33
Aubertin 1987[16]	274	25	21	17	5	4	7	6	1	6	49
Levy 1988[1]	116	26	4	4	4	3	12	7	3	14	35
Austina 1988[6]	207	39	6	17	4	1	1	3	–	9	20
Lim 1989[7]	106	42	3	8	18	3	9	8	–	8	23

*In some instances, percentages total 100% due to mixed infections in some patients.

marize the pertinent considerations essential in the initial selection of antimicrobial therapy in the adult patient with community-acquired pneumonia.

Microbiologic considerations

The most important consideration in selecting initial antibiotic therapy for patients with community-acquired pneumonia is the etiologic agent responsible for the infection. Data from 14 series reported in the 1980's regarding the etiology of community-acquired pneumonia are summarized in Table 1.[1,3-7,9,11-17] Although the prevalence of each pathogen varies from one series to another, it is apparent that streptococcus pneumoniae remain the most common etiologic agent. Equally apparent is the significant percentage of cases in most studies in which no etiologic agent was identified.

The incidence of mycoplasma pneumonia is variable with epidemics occurring every four to eight years.[18] Sporadic disease may occur throughout the year, but epidemic mycoplasma pneumonia occurs more commonly in the summer and fall. The variability in the prevalence of Legionellosis from one geographic area to another is striking. Legionnaires' disease occurs predominantly in late summer and early autumn. Sporadic Legionnaires' disease occurs with higher frequency in males; alcoholics; and in patients with underlying COPD, diabetes mellitus, renal failure, and malignancy.[19] Residents near excavation sites or occupational exposure as construction work are also predisposing factors.[20] Staphylococcus aureus is an uncommon cause of community-acquired pneumonia, accounting for 1-8% of cases. It is most commonly encountered in patients with recent influenza or in intravenous drug users with right-sided bacterial endocarditis. Haemophilus influenzae is responsible for 1-15% of cases is a frequently recognized cause of pneumonia in patients with underlying chronic obstructive pulmonary disease.[21] Uncommon causes of community-acquired pneumonia include Chlamydia psittaci, Coxiella burnettii, fungi, and Mycobacterium tuberculosis. Of note is the observation that Mycobacterium tuberculosis accounted for 10% of cases of community-acquired pneumonia in one recent series from France.[3]

Mixed aerobic and anaerobic pneumonia arising in the setting of aspiration may be encountered in elderly or debilitated patients. Residents of chronic care facilities may be colonized with enteric gram negative bacilli in their oropharynx and present with necrotizing gram negative penumonia following aspiration.[22] Gram negative bacilli are relatively uncommon causes of community-acquired pneumonia in healthy immunocompetent individuals in most series in the past decade. Chlamydia TWAR and Branhamella catarrhalis are recently recognized causes of community-acquired pneumonia.[17,23,24] The precise prevalence of these infections remains to be determined. They are probably uncommon, although in one recent study Chlamydia TWAR accounted for 6% of cases of community-acquired pneumonia.[17] Epidemics have been described in military conscripts in Scandinavia.[25]

Clinical manifestations

The clinical features of patients with community-acquired pneumonia may provide useful information in the selection of empiric antibiotic therapy. Community-acquired pneumonia may be divided into typical bacterial penumonia and atypical pneumonia. The major differences between these two syndromes are summarized in Table 2.

Typical bacterial pneumonia is unsually charcterized by the sudden onset of fever, chills, pleuritic chest pain, and a producitve couth. Streptococcus pneumoniae is the most common etiologic agent, although other potential pathogens include

Table 2. "Typical" Bacterial Pneumonia vs. "Atypical" Pneumonia Distinguishing Features

	"Typical" Bacterial Pneumonia	"Atypical" Pneumonia
Onset	Sudden	Gradual over several days
Host	Middle aged or elderly	Child, adolescent or young adult
Constitutional sympstoms	Less prominent	May overshadow respiratory symptoms
Respiratory symptoms	Prominent Productive cough	Less prominent. Cough dry at outset but may become productive
	Pleurisy common	Pleurisy uncommon
Radiographic findings	Lobar consolidation Bronchopneumonia	Patchy infiltrates, often lower lobe
Leukocytosis	Common	$<10,000$ in 80%

Haemophilus influenzae (especially in the elderly patient with COPD), Legionella species, gram negative bacilli, and Staphylococcus aureus (often in the setting of previous influenza). Aspiration pneumonia may also present as a "typical" bacterial penumonia.

By contrast, the atypical pneumonia syndrome usually presents with subacute onset of fever, constitutional symptoms, and non-productive cough. Headache may be prominent and cough is a minor complaint at the outset, but predominates with time. The most common pathogens include Mycoplasma pneumoniae, numerous viruses, and Legionella species. Uncommon causes include Chlamydia psittaci, Chlamydia TWAR, Coxiella burenetii (the etiologic agent of Q Fever), Mycobacterium tuberculosis, and several fungi including Histoplasma capsulatum and Coccidioides immitis.

A number of epidemiologic factors in a patient's history may provide clues to the etiologic diagnosis of community-acquired pneumonia. A careful travel, occupational, and exposure history is essential in every patient presenting with pneumonia, since this may reveal exposure to unusual pathogens such as Chlamydia psittaci and Coxiella burnetii. Psittacosis is acquired through exposure to infected birds such as parrots, turkeys, cockatiels, and canaries. Q fever is contracted from the secretions of infected cattle, sheep, or goats.

Pneumonia presenting in the peak of influenza season in the winter should alert one to the possibility of Staphylococcus aureus. Pneumonia in a young person in an institutional setting, such as a military barracks or school dormitory, should raise the possibilities of Mycoplasma pneumoniae or Chlamydia TWAR pneumonia. Nursing home patients or other individuals with obtundation or impaired gag reflexes are predisposed to aspiration pneumonia with aerobic and anaerobic mouth flora.

Risk factors for infection with the human immunodeficiency virus (HIV) should be elicited in every patient presenting with community-acquired pneumonia, since the differential diagnosis of likely pathogens and empiric therapy are very different in patients with suspected AIDS. This is especially important in young and middle-aged individuals presenting with community-acquired pneumonia. In homosexual males, hemophiliacs, intravenous drug users, and sexually promiscuous individuals, Pneumocystis carinii associted with HIV infection must be entertained in the differential diagnosis. The clinical presentation of pneumocystis pneumonia in AIDS is highly variable and may range from subacute and indolent nonproductive cough and dyspnea on exertion, to a fulminant illness with high fever, constitutional symptoms, cough, and dyspnea.

Certain findings on physical examination may also be helpful in assessing the likelihood of a specific pathogen in patients with community-acquired pneumonia. Relative bradycardia in the absence of underlying heart disease or beta-blockade suggests agents such as Mycoplasma pneumoniae, Legionella species, virus, Chlamydia psittaci, or Chlamydia TWAR. Asplenic or splenectomized patients are predisposed to overwhelming infection with encapsulated organisms such as Streptococcus pneumoniae or Haemophilus influenzae.[25] Splenomegaly with pneumonia should suggest psittacosis or Q Fever. Signs of intravenous drug use in a patient with penumonia should prompt consideration of Staphylococcus aureus or gram negtive bacilli such as Pseudomonas aeruginosa with concomitant right-sided bacterial endocarditis and septic pulmonary emboli. In addition, Pneumocystis carinii pneumonia in association with underlying HIV infection should

Table 3. Therapeutic Recommendations for Adults with Community-Acquired Pneumonia Requiring Parenteral Therapy*.

Suspected Pathogen	Recommended Regimen	Alternative	Estimated Daily Cost of Recommended Regimen***
Streptococcus pneumoniae	PCN G 600,000 U IV Q12H	Erythromycin 500 mg IV Q6H	$ 17.18
Haemophilus influenzae	3rd generation cephalosporin (e.g. Ceftizoxime, Cefotaxime, or Ceftriaxone)	Bactrim 5 mg/kg IV Q12H	$ 70.62##
Legionella species	Erythromycin 1 gm IV Q6H	Doxycycline 100 mg IV Q12H + Rifampin 600 mg po QD	$ 39.88
Mycoplasma pneumoniae	Erythromycin 500 mg IV Q6HD	Doxycycline 100 mg IV Q12H	$ 36.94
Staphylococcus aureus	Oxacillin or Nafcillin 2 gm IV Q4H (use vancomycin if methicillin resistance suspected)	Vancomycin 1 gm IV Q12H	$ 63.12
Aspiration Community-acquired	Clindamycin 600 mg IV Q6H	Penicillin G 2 M U IV Q4H	$ 38.48
Nursing home	Clindamycin 600 mg IV Q6H + 3rd genertion cephalosporin##	Penicillin G 2 M U IV Q4H + Gentamicin 1.5 mg/kg IV Q8H	$109.10
Pneumocystis carinii	Trimethoprimsulfamethoxazole 10 mg/kg IV Q12H	Pentamidine 4 mg/kg IV QD	$ 88.28 + +
Chlamydia TWAR**	Doxycycline 100 mg IV Q12H		$ 18.30

* Based on normal renal and hepatic function.
** Efficacy of antibiotic therapy not established.
*** Based on 1990 formulary prices at the Cleveland Clinic Founation and an administrative charge of $8.50 per infusion.
Ceftizoxime 2 gm IV Q8H.
+ + *Based on therapy of 70 kg patient.*

be considered in such individuals. Bullous myringitis has been associated with mycoplasma pneumonia,[27] although this association has been disputed in recent years.[28] The presence of Kaposi's sarcoma, thrush, or oral hairy leukoplakia should suggest the presence of underlying infection with the human immunodeficiency virus. If any of these physical findings are present, the differential diagnosis should include Pneumocystis carinii, cytomegalovirus, and mycobacterial infection as potential causes of penumonia.

Diagnosis

The diagnosis of pneumonia is supported by the radiographic demonstration of pulmonry infiltration. The radiographic pattern of the infiltrate is sometimes helpful in predicting the likely pathogens.[3] The presence of a lobar infiltrate, large pleural effusion, or cavitation favors a diagnosis of bacterial pneumonia. Pneumococcal pneumonia usually presents as bronchopneumonia or lobar consolidation. Staphylococcal and gram negative pneumonias may present with consolidation and small areas of cavitation. Mycoplasma pneumonia frequently produces patchy lower lobe infiltrates. Legionella penumonia often exhibits lobar disease which progresses to involve several additional lobes. Diffuse interstitial infiltrates should suggest viral or Pneumocystis carinii pneumonia.

The initial diagnostic evaluation is dictated by the

clinical setting, severity of illness, and presence of underlying disease. Gram stain examination of an adequate sputum specimen is crucial in patients with community-acquired pneumonia. An adequate specimen is defined as one which contains more than 25 white blood cells and fewer than 10 epithelial cells per low powered microscopic field.[29] If necessary, sputum should be induced by inhalation of nebulized hypertonic saline. If this is unsuccessful, additional invasive diagnostic procedures may be necessary to obtain an adequate specimen of lower respiratory tract secretions.

Empiric antibiotic therapy

The selection of an empiric antibiotic regimen in patients with community-acquired pneumonia depends upon the certainty of the diagnosis and the severity of the illness. Treatment recommendations for respective etiologies of community-acquired pneumonia are summarized in Table 3. Hospitalized patients with a compatible history, chest radiograph, and sputum gram stain for pneumococcal pneumonia should be treated with penicillin G. Those with uncomplicated pneumonia may receive 600,000 units intravenously Q12 hours. Patients with complicating meningitis, septic arthritis, empyema, or endocarditis required high-dose therapy with 20 million units of intravenous penicillin G per day in divided doses. The penicillin-allergic patient with uncomplicated pneumonia may be treated with erythromycin. Those with concomitant meningitis who are penicillin-allergic should receive chloramphenicol or a third generation cephalosporin. In some areas of the world, penicillin-resistant pneumococci are prevalent.[30,31] This is fortunately quite uncommon in the United States at present. For patients with suspected penicillin-resistant pneumococci, vancomycin appears to be the drug of choice.[31]

Young otherwise healthy patients who present with the atypical pneumonia syndrome may be treated with erythromycin, since this covers mycoplasma and Legionella, as well as the pneumococcus. Patients with mild illnesses may be treated on an outpatient basis if they are compliant and reliable. Sicker patients should be admitted to the hospital for parenteral antibiotic therapy.

Empiric therapy in patients with suspected Haemophilus influenzae pneumonia depends upon the local susceptibility pattern of H. influenzae. In areas where beta-lactamase producing strains of H. influenzae are extremely uncommon, ampicillin is an appropriate empiric choice. On the other hand, in some geographic locales the incidence of beta-lactamase producing H. influenzae has approached 25%. In such settings, third generation cephalosporins are appropriate choices and are preferable to second generation drugs such as cephamndole, since they are more resistant to bacterial beta-lactamases. Of the third generation cephalosporins, cefotaxime, ceftriaxone, and ceftizoxime have comparable in vitro activity against Haemophilus influenzae. The major differences between these three antibiotics are in their pharmacokinetics. Differences in cost may also vary from one institution to another. Any of these drugs would be appropriate empiric choices in patients with sustected H. influenzae pneumonia in areas where beta-lactamase producing strains are commonly encountered.

Patients with post-influenza staphylococcal pneumonia may be treatred with a penicillinase-resistant penicillin such as oxacillin or nafcillin, or a first generation cephalosporin. Vancomycin is the preferred treatment in the penicillin-allergic patient. Parental drug users with pneumonia should be treated with broad spectrum coverage if a bacterial etiology is suspected. An appropriate empiric regimen would include vancomycin for potential methicillin-resistant Staphylococcus aureus, as well as a third generation cephalosporin, such as ceftazidime, or an aminoglycoside with anti-pseudomonal activity. If Pneumocystis carinii is a differential diagnostic possibility, trimethoprim-sulfamethoxazole or pentamidine should be employed as discussed below.

Erythromycin appears to be the drug of choice for patients with suspected Legionellosis. Doses of 2-4 grams intravenously per day are appropriate, but seriously ill patients with suspected Legionnaires' disease should be treated with erythromycin 1 gm IV Q6H. Some patients will experience tinnitus or impaired hearing on this dose, but this is reversible with dosage reduction or discontinuation of the medication. Rifampin may be added in critically ill patients, although no data clearly demonstrate superior efficacy of two-drug versus single-drug therapy. Doxycycline or tetracycline are alternative agents for the therapy of Legionnaires' disease. Comparative studies have not been done, however, comparing erythromycin with doxycycline or tetracycline.

Community-acquired aspiration pneumonia may be treated with parenteral penicillin or ampicillin in patients who have not been on recent antibiotics or in an institutional setting. Nursing home residents or recently hospitalized patients, in whom oropharyngeal colonization with gram negative bacilli may occur, should receive empiric coverge directed at mouth flora and enteric gram negative bacilli. An appropriate regimen would include penicillin or clindamycin plus a third generation cephalosporin or aminoglycoside. Such a regimen covers Streptococcus pneumoniae, Haemophilus influenzae, mouth anaerobes, and most enteric gram negative rods.

Patients with Pneumocystis carinii penumonia in the setting of AIDS may be treated with either

trimethoprim-sulfamethoxazole or pentamidine. Most studies have suggested comparable efficacies of these agents, although a recent randomized prospective trial demonstrated improved survival in trimethoprim-sulfamethoxazone recipients compared with patients receiving pentamidine.[32] Trimethoprim-sulfamethoxazone should be adminstered parenterally to patients with moderate or severe Pneumocystis pneumonia at a dose of 15-20 mg/kg/day in two divided doses. Oral therapy is appropriate in patients with mild Pneumocystis or to complete a three week course of therapy in those with more serious disease requiring initial parenteral therapy. Pentamidine is administered at a dose of 4 mg/kg/day by slow intravenous infusion. Side effects are unfortunately common with both medications. Up to 50% of AIDS patients may experience adverse side effects with trimethoprim-sulfamethoxazole, which most commonly consist of fever, rash, leukopenia, or hepatitis.[33] Pentamidine may also produce significant toxicity, including intractable hypoglycemia, renal dysfuncion, hyperglycemia, leukopenia, fever, and hypotension.[34]

The selection of empiric therapy is most difficult in the seriously ill patient with community-acquired pneumonia in whom the diagnosis is uncertain. Such individuals require broad spectrum therapy. A regimen of erythromycin and a third generation cephalosporin provides excellent coverage against the pneumococcus, Mycoplasma pneumoniae, Legionella species, and Haemophilus influenzae. The third generation cephalosporins also provide reasonable coverage against many enteric gram negative bacilli, although Pseudomonas aeruginosa is not optimally covered by ceftriaxone, cefotaxime, or ceftizoxime. Pseudomonas aeruginosa is an extremely uncommon cause of community-acquired pneumonia, except in patients with underlying cystic fibrosis. If Pseudomonas aeruginosa is a concern, however, an anti-pseudomonal penicillin or third generation cephalosporin, such as ceftazidime, should be employed together with an aminoglycoside. Erythromycin does have some activity against Staphylococcus aureus, although is not a first line drug. If Staphylococcus aureus is in the differential diagnosis, a semi-synthetic penicillin or vancomycin should be added pending definitive microbiologic information.

The efficacy of newer antibiotics such as imipenem/cilastatin and ciprofloxacin in the treatment of community-acquired pneumonia has been confirmed in several studies.[35-38] The major drawbacks of imipenem/cilstatin are its cost and extremely broad spectrum of antimicrobial activity. Most patients with community-acquired pneumonia do not require such broad spectrum therapy. Ciprofloxacin is a potentially attractive agent, since oral therapy is feasible. In vitro testing against Streptococcus pneumoniae and anaerobic mouth flora has disclosed relatively high MICs, raising concern about the utility of ciprofloxacin for penumococcal penumonia or aspiration penumonia.[39] Although published studies have suggested favorable results with ciprofloxacin in the treatment of pneumococcal pneumonia, it is our opinion that penicillin or erythromycin remain the agents of choice. The precise role of ciprofloxacin as empiric therapy for community-acquired bacterial pneumonia remains to be defined.

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