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Empiric treatment of ambulatory community-acquired pneumonia: always include treatment for atypical agents

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In the 1920s during the preantibiotic era, an unusual form of pneumonia was noted in Europe. It was unusual because, unlike the form of pneumonia commonly seen, this variety was milder and was associated with high survival rates. A similar syndrome was noted in American colleges and in the United States Army between 1931 and 1936. It is noteworthy that between 1929 and 1931 a pandemic of psittacosis was recognized. It was not until 1938, however, that Reimann [1] first used the term *atypical pneumonia* in his paper, ''an acute infection of the respiratory tract with atypical pneumonia.'' He was using the term to refer to seven patients who had an unusual form of tracheobronchopneumonia that he saw in 1938. Subsequently, ''atypical pneumonia'' has been used to refer to pneumonia caused by the agents listed in Box 1.

Guidelines for the empiric therapy of community-acquired pneumonia (CAP) differ markedly between North America and Europe. In North America, antibiotic therapy of atypical agents (usually a macrolide, doxycycline, or a respiratory fluoroquinolone) is emphasized for ambulatory and hospitalized patients [2]. In Europe, however, as exemplified by the British Thoracic Society guidelines, amoxicillin (Amoxil) is the drug of choice for treatment of ambulatory pneumonia and also is recommended for mild cases of pneumonia requiring hospitalization [3]. Thus, therapy is not directed toward ''atypical'' agents. As discussed later, there is essentially no difference in the rank order of pathogens causing pneumonia in these locales, so why the major difference in recommendations?

This article provides data on the etiology of CAP, briefly reviews the salient features of pneumonia caused by the major atypical pathogens, and

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Box 1. Microbial agents that cause atypical pneumonia

Mycoplasma pneumoniae
Legionella pneumophila
Legionella species
Chlamydia psittaci
Chlamydia pneumoniae
Chlamydia pecorum
Coxiella burnetii
Hantavirus
Influenza viruses A and B
Parainfluenza viruses 1, 2, 3
Adenovirus
Metapneumovirus
Respiratory syncytial virus
Severe acute respiratory syndrome (SARS) coronavirus

reviews studies that attempt to answer whether it is necessary to include antibiotics that are active against "atypical" pneumonia agents as part of the empiric therapy of CAP.

Because there is a lack of data from randomized trials, this question will be answered by using several strategies:

1. Indicating the frequency with which atypical agents cause pneumonia in ambulatory and hospitalized patients who have CAP.
2. Providing an overview of the epidemiology and outcome data on pneumonia caused by four atypical pathogens, namely *M pneumoniae, L pneumophila, Chlamydia pneumoniae,* and *Coxiella burnetii*.
3. Considering data from observational studies of pneumonia caused by the above agents.
4. Considering data from large retrospective studies of CAP.

Etiologic agents that commonly cause community-acquired pneumonia

Ambulatory pneumonia

Although surprisingly few studies have attempted to define the etiology of CAP treated on an ambulatory basis [4–7], a consistent picture has emerged. The etiology is undefined in 50% of cases. *M pneumoniae* is the most commonly identified agent at 20% to 30%, followed by *Chlamydia pneumoniae* at 2% to 16%, *Streptococcus pneumoniae* at 6% to 10%, *Haemophilus influenzae* at 5%, and *Staphylococcus aureus* and *L pneumophila*, both at 1% to 2%.

Pneumonia requiring admission to hospital

Many studies have defined the etiology of CAP among patients requiring admission to hospital in many countries. Again, it was impossible to define the etiology in many patients [8]. *Streptococcus pneumoniae* is the most commonly identified pathogen in this setting and, depending on the methods used, it can be implicated as the cause of CAP in up to 50% of patients requiring admission to hospital [8]. *Chlamydia pneumoniae* is the most commonly identified atypical agent in these patients. *M pneumoniae* is less common than in patients who have ambulatory pneumonia, but is still implicated in a substantial number of patients—32%, in one study [8]. *Legionella* species are more common among patients who require admission to intensive care, but overall account for approximately 2% of patients requiring admission to hospital for treatment of CAP [8].

Unfortunately, studies such as these do not capture pathogens that may occur in localized outbreaks, such as hantavirus [9], or pathogens that occur worldwide as outbreaks of short duration, such as SARS coronavirus [10].

Because in most studies the diagnosis of *M pneumoniae*, *L pneumophila*, and *Chlamydia pneumoniae* is made using serology, the criteria for a positive test can have a huge impact on the number of cases diagnosed. A fourfold increase in antibody titer between acute and convalescent serum samples generally is considered definite evidence that an infection with the test agent has occurred. A high single or stable titer is often considered diagnostic as well, however. In one study, the incidence of *M pneumoniae* was 6.3 per 100,000 population when criteria for definite infection were used and 38.2 per 100,000 when a titer of 1:64 or higher was used; in the same study when the fourfold increase and single-titer criteria were applied, the incidence of *Chlamydia pneumoniae* was 2.8 per 100,000 and 16.5 per 100,000, respectively, and for *L pneumophila* it was 4.4 per 100,000 and 6.0 per 100,000, respectively [11].

Pneumonia caused by selected atypical agents

Mycoplasma pneumoniae

Mycoplasmas, including *M pneumoniae*, are the smallest free-living organisms with a size (125–150 μm) similar to that of myxoviruses [12]. The genome of *M pneumoniae* consists of 816,394 base pairs and has been sequenced in its entirety [13]. Adherence to host respiratory epithelial cells is mediated by a 169kDa protein (P1) located in the tip-like organelle of *M pneumoniae*. Once *M pneumoniae* adheres to the mucous and ciliated epithelial cells of the respiratory tract, a chemotactic stimulus leads to directed motility of the mycoplasma to the bases of the cilia. This protects the mycoplasma from the clearance action of the ciliary system. A few hours after this contact, loss of ciliary motility is observed, followed by extensive damage to the host cells. It is likely that ciliary stasis and cell damage result from production of hydrogen peroxide and superoxide by *M pneumoniae* [14,15].

Pneumonia is the manifestation of *M pneumoniae* infection most frequently recognized by clinicians. The incubation period is 2 to 3 weeks and the onset is gradual [16]. In a retrospective review of all *M pneumoniae* pneumonia cases at the Mayo Clinic over a 14-year period, Mansel and colleagues [17] reported on 148 patients. Cough was the most common symptom, occurring in 97%, followed by fever in 85%. Fifty-two percent of the patients had sore throat, 22% had rhinorrhea, 25% had chest pain, and 17% complained of dyspnea. Other symptoms included nausea, vomiting, diarrhea, anorexia, headache, chills, myalgia, arthralgia, and night sweats. Seven percent had one or more symptoms of neurologic disease, including diplopia, syncope, confusion, or tinnitus. One patient had severe hemoptysis. The following findings were noted on physical examination: pharyngeal erythema (47%), pulmonary consolidation (26%), cervical lymphadenopathy (26%), otitis media (20%), bullous myringitis (18%), and skin lesions (6%).

Mortality is uncommon in patients who have *M pneumoniae*, as illustrated in a study by Marrie and colleagues [18] where 1 of 64 patients requiring admission to hospital for treatment of *M pneumoniae* pneumonia died. This patient had terminal Shy-Drager syndrome and died of this disease, not *M pneumonia*. In Ali's study [19], 1 of 47 patients died—a 38-year-old woman with Down's syndrome. She was admitted with multilobe pneumonia and hemolytic anemia and died 9 hours after admission. Lind [20] reported that 20 fatal cases of *M pneumoniae* pneumonia had been described up to 1983. Chan and Welsh [21] performed a review of fulminant *M pneumoniae* pneumonia from 1966 to 1991. They found 46 such cases and divided them into three categories: nonfatal respiratory failure (26 cases), fatal cases with respiratory failure (13 cases), and fatal cases without respiratory failure (seven cases).

One noteworthy feature of *M pneumoniae* infections is the variety of extrapulmonary infections. Almost any organ system can be involved. In most series, 2% to 7% of patients who have *M pneumoniae* infection have an extrapulmonary manifestation [20].

Antimicrobial susceptibility of *M pneumoniae* can be determined by agar dilution or by the broth dilution method, usually in the form of the metabolism inhibition test. Using these methods, *M pneumoniae* is susceptible to macrolides, tetracyclines, quinolones, streptomycin, pristinamycin, and ketolides [22]. Erythromycin-resistant strains of *M pneumoniae* have been isolated from treated patients [22]. Such resistance is a result of point mutations in 23rRNA gene.

Shames and colleagues [23] evaluated the response to therapy in 317 military trainees with *M pneumoniae* pneumonia. They noted that patients treated with demeclocycline (Declomycin) were febrile for 1.8 days compared with 2.4 days for those treated with tetracycline (Achromycin V) or erythromycin stearate (Erythrocin). Control subjects were febrile for 4.2 days. The mean duration of hospitalization was 6.6 days and 7.6 days for demeclocycline and tetracycline, respectively, versus 14 days for control subjects. Those who were treated with erythromycin stearate were

hospitalized a mean of 7.0 days and those treated with erythromycin ethyl succinate (EES) were hospitalized a mean of 9 days. These investigators also noted that clinical cure did not equate with eradication of *M pneumoniae* from the respiratory tract. At followup, 33% of the control subjects were culture-positive for *M pneumoniae*, compared with 5% to 20% of the subjects treated with various antibiotics.

Kingston and colleagues [24] treated 59 patients who had *M pneumoniae* pneumonia with demethylchlortetracycline and 50 patients with placebo. The mean number of days the treated patients had an oral temperature above 99°F was 3.02 days versus 10.04 days for the placebo-treated group.

M pneumoniae infections tend to peak every 4 to 7 years [25]. Outbreaks can occur in schools, military bases, and summer camps [26–28].

Legionella infections

From July 21 to 24, 1976, the 58th Annual Convention of the American Legion was held at a hotel in Philadelphia. One hundred eighty-two of the attendees at the convention developed pneumonia [29]. One hundred forty-seven (81%) were hospitalized, and 29 (16%) died. This outbreak of pneumonia of apparent unknown cause triggered an exhaustive epidemiologic and microbiologic investigation by the Centers for Disease Control and Prevention (CDC), culminating in the isolation of a new microorganism, *Legionella pneumophila*, approximately 6 months later [30].

In 1981, just 4 years after the initial outbreak, 1000 cases of sporadic legionnaires' disease (LD) had been diagnosed in the United States [31]. Most cases occurred between June and October; 71% of patients were male, and 88% were white. During the 2 weeks before onset of this illness, 37% had traveled overnight, 29% had visited a hospital, and 5% had been hospitalized 2 days before onset of illness. Twenty-three percent lived within sight of a construction or excavation site and 32% had been exposed to a construction or excavation [31].

Marston and colleagues [32] analyzed *Legionella* surveillance data on 3254 patients reported to the CDC from 1980 through 1989. Disease rates did not vary by year but were higher in the northern states and during the summer. The mean age of patients who had LD was 52.7 years compared with 34.7 years for the United States population. In contrast to the earlier reports, persons who had LD were more likely to be nonwhite. They were also more likely to be smokers, have diabetes, cancer, AIDS, or end-stage renal disease. The observed number of cases among patients who had AIDS was 42-fold higher than expected [32]. Risk factors for mortality in the study by Marston and colleagues included older age, male sex, nosocomial acquisition of disease, immunosuppression, end-stage renal disease, and cancer [32]. Twenty-three percent of the cases were acquired nosocomially.

Two recent large outbreaks of LD have taught additional lessons about this fascinating disease. An explosive outbreak of LD occurred in Murcia,

Spain in July 2001 with over 800 suspected cases, 449 of which were confirmed as LD [33]. Most noteworthy was the low mortality rate of 1% [33]. The outbreak was caused by a contaminated cooling tower, and cases occurred up to 1.3 km downwind [33]. The other major outbreak occurred in March 1999 in the Netherlands at a flower show [34]. Of the 77,061 persons attending the flower show, 181 developed LD [34]. The source of the outbreak was a contaminated decorative fountain. This outbreak allowed investigators to determine the risk factors for intensive care unit (ICU) admission and death, and the impact of adequate therapy on ICU survival for 141 hospitalized patients [35]. ICU mortality was 36% and overall mortality was 13%. Starting adequate therapy within 24 hours of admission was associated with significantly higher ICU survival: 78% versus 54% for those who started therapy more than 24 hours after admission. This finding did not apply to patients with negative urinary antigen, suggesting that bacterial load plays a role in outcome [35].

Heath and colleagues [36] studied 39 patients who had LD (36 were community-acquired) and found that the mortality rate was 26%. These investigators noted that survivors had therapy with erythromycin started a median of 6 days from onset of symptoms compared with 11 days from onset for those who died.

Although the initial recommendations for the treatment of LD were high-dose intravenous erythromycin, Edelstein [37] found that azithromycin (Zithromax) is more active against intracellular *L pneumophila* than erythromycin. He recommends treatment of LD with a fluoroquinolone (which, in contrast to erythromycin, can kill intracellular legionella) or azithromycin [38]. Plouffe and colleagues [39] in an open-label study treated 25 hospitalized patients who had LD. The overall cure rate among 21 clinically evaluable patients was 20 (95%).

Chlamydia pneumoniae *pneumonia*

In 1986, Grayston and colleagues [40] described a new *Chlamydia* species as a cause of respiratory tract infections. This organism was later named *Chlamydia pneumoniae* [41]. Subsequent studies have shown that this microorganism is implicated frequently as a cause of CAP [42]. In many careful studies of *Chlamydia pneumoniae*, it has not been the sole cause of the pneumonia. Almirall and colleagues [43] studied 105 patients who had CAP and found that 16 had *Chlamydia pneumoniae* pneumonia. Seven of the 16 had a copathogen demonstrated, including adenovirus in three, parainfluenza virus in two, *L pneumophila* in one, and respiratory syncytial virus in one. File and colleagues [44] found that 21 of 47 (44.6%) patients who had *Chlamydia pneumoniae* pneumonia had a copathogen. Marrie and colleagues [45] studied 539 patients who had CAP requiring hospitalization and found that 2.2% had acute *Chlamydia pneumoniae* infection and an additional 5.9% had possible acute infection. The mortality rate for the

patients who had *Chlamydia pneumoniae* was 4.9%, lower than the 9.4% for the patients who did not have this infection. The results of this study have led some to question the importance of *C pneumoniae* as a cause of CAP [46]. No randomized trials have evaluated the treatment of *Chlamydia pneumoniae* pneumonia.

Coxiella burnetii *(Q fever pneumonia)*

Q fever, a zoonosis, was described in 1935 as an outbreak of febrile illness among abattoir workers in Brisbane, Australia [47]. Q fever usually is transmitted by aerosols generated during parturition of an infected animal [48,49]. Cattle, sheep, and goats are the usual reservoirs, but cats, dogs, and pigeons also have been infected and served as sources of outbreaks of this infection [48,50–52]. Infection may be acute (self-limited fever, pneumonia, hepatitis, central nervous system infection) or chronic (endocarditis, hepatitis, osteomyelitis, intravascular infection) [53]. Q fever accounts for approximately 1% to 2% of ambulatory pneumonia in endemic areas [3].

In general, tetracyclines, quinolones, rifampin (Rifadin), telithromycin (Ketek), and clarithromycin (Biaxin) are active against *Coxiella burnetii* [54]. Some strains are susceptible to erythromycin; others are not [54]. Sobradillo and colleagues [55] performed a prospective randomized, double-blind study of doxycycline (Doryx) and erythromycin in the treatment of 48 patients who had Q fever pneumonia. Twenty-three patients received doxycycline, 100 mg, twice daily, and 25 received erythromycin (500 mg every 6 hours) for 10 days. Resolution of fever occurred more rapidly in the doxycycline-treated group (3 ± 1.6 days versus 4.3 ± 2 days for erythromycin-treated patients; $P = .05$). By day 40, the chest radiograph was normal in 47 of the 48 patients.

Kuzman and colleagues [56], in a study of 64 patients who had Q fever pneumonia, treated 22 patients who had azithromycin (total dose 1.5 g administered over 3 to 5 days, 15 with doxycycline (100 mg twice a day for 10–14 days), and 15 with a variety of other antibiotics. The azithromycin-treated group had fever for a mean of 2.5 days, the doxycycline-treated group for 2 days, and the patients who received other antibiotics for 3.5 days. Kofterids and colleagues [57], in a retrospective review of 100 patients who had Q fever pneumonia, noted that 11 patients who were treated with tetracycline became afebrile in a mean of 3 days, the 42 patients treated with erythromycin were afebrile in a mean of 4.26 days, and the 28 patients treated with β-lactam agents required 6.8 days to become afebrile. Fifteen percent of the clarithromycin-treated patients were febrile at 5 days compared with 35% of the erythromycin-treated patients and none of the tetracycline-treated patients. In a retrospective review of 19 patients who had Q fever pneumonia, 11 patients were treated with erythromycin and eight with β-lactam antibiotics. The erythromycin-treated group was afebrile by day 3, whereas only two of the β-lactam-treated group were afebrile by day 3 ($P < .005$) [58].

Although the evidence is sparse, it seems that the treatment of choice for Q fever pneumonia is doxycycline for 10 days. Alternative therapies are a fluoroquinolone or a macrolide plus rifampin (Rifadin). Substitution of Glu for Lys at the position corresponding to amino acid 87 of *Escherichia coli* results in quinolone resistance in *Coxiella burnetii* [59]. In a real-time polymerase chain reaction assay using a murine macrophage cell line after 6 days of treatment, tetracycline, rifampin, and ampicillin (Amoxil) significantly inhibited the replication of *Coxiella burnetii,* whereas chloramphenicol (Chloromycetin) and ciprofloxacin did not [60]. The observations in this study regarding ampicillin do not fit with the clinical observations outlined above. It is possible that the strain used was resistant to ciprofloxacin.

If one had to contend only with ''atypical'' agents as a cause of ambulatory CAP, the treatment of choice would be a macrolide or doxycycline. *Streptococcus pneumoniae* is a major cause of ambulatory pneumonia, however [61,62], and the incidence of pneumococcal macrolide resistance in the United States doubled between 1995 and 1999 [63]. Currently, approximately 32% of pneumococcal isolates are resistant to erythromycin [64]. This would leave amoxicillin or the new fluoroquinolones as first-line therapy for ambulatory CAP. The CDC working group recommends use of fluoroquinolones only for cases that have failed other agents, however, because of the concern for the emergence of fluoroquinolone-resistant *Streptococcus pneumoniae* [65].

In North America, efflux is the mechanism whereby most *Streptococcus pneumoniae* are resistant to penicillin and it is presumed that the newer macrolides, clarithromycin and azithromycin, can overcome this [66]. In Europe, most macrolide resistance is a result of target–site alteration and hence is absolute [66]. This, therefore, is the reason for the difference in recommendations for first-line therapy for ambulatory CAP between North America and Europe. It is possible that the ketolides will become the agents of choice for the treatment of ambulatory CAP on both sides of the Atlantic [67]. A double–blind, randomized, controlled trial comparing amoxicillin with telithromycin is needed to determine the optimal agent for the treatment of ambulatory CAP.

Pneumonia requiring hospitalization: data from large retrospective studies and from observational studies

Oosterheert and colleagues [68] performed a systematic review to determine the evidence for the current recommendations for the empiric antimicrobial therapy of patients hospitalized with CAP. They included original peer-reviewed articles published between January 1997 and April 2003 regarding adult patients hospitalized because of CAP and dealing with the question of whether treatment with a β-lactam plus macrolide or quinolone monotherapy reduces mortality or length of stay compared with β-lactam treatment alone. They found only eight of the 139 articles met the

criteria for inclusion [69–76]. Six studies found a significant reduction in mortality for patients treated with combinations of β-lactams plus macrolides or a fluoroquinolone alone [68]. Three of these six studies involved patients who had bacteremic pneumococcal pneumonia exclusively, and mortality was reduced with the combination of a macrolide and a β-lactam [68]. In two of the eight studies, a reduced length of stay was noted for patients treated with a macrolide in combination with another agent [68]. Some have attributed the favorable effect of the macrolide combination to the coverage of atypical agents [68]. Only one study was prospective, and all were level-III evidence [77]. The beneficial effect of combination therapy with a β-lactam and a macrolide may not be found in randomized trials.

Bjerre and colleagues [78] set out to summarize the evidence from randomized clinical trials concerning the efficacy of antibiotic treatment for CAP in ambulatory patients 12 years of age and older. They did a comprehensive search to identify relevant studies. Thirty-four articles met the screening criteria, but only three trials met the inclusion criteria. These three trials involved 622 patients. None of the three studies clearly stated the randomization method. Two trials involved a comparison of clarithromycin and erythromycin and the other sparfloxacin (Zagam) versus clarithromycin. Thus, none of the three are suitable for answering our question of the importance of therapy directed against atypical agents. Nevertheless, the authors of the meta-analysis concluded that, ''current evidence for randomized clinical trials is insufficient to make evidence-based recommendations for the choice of antibiotic to be used for the treatment of CAP in ambulatory patients'' [78].

Summary

There are no data from proper studies to answer whether it is necessary to include antibiotics that are active against atypical pneumonia agents as part of the empiric therapy of CAP. Until such data are available, clinical judgment and severity of the pneumonic illness are the best guides to empiric antimicrobial therapy.

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