Conferences and Reviews

Fulminant *Mycoplasma pneumoniae* Pneumonia

EDWARD D. CHAN, MD, *and* CAROLYN H. WELSH, MD, *Denver, Colorado*

The frequency of fulminant pneumonia due to *Mycoplasma pneumoniae* is relatively rare despite the high prevalence of *Mycoplasma* species infection in the general population. We recently encountered such a case and have reviewed the English-language literature on cases of *M pneumoniae* pneumonia that have resulted in respiratory failure or death. Due to host factors or on epidemiologic grounds, fulminant cases seem to be more common in young healthy adults, in males, and possibly in smokers among the 46 patients we found. An enhanced host cellular immune response may be responsible for the development of severe cases. A spectrum of small airways disease is characteristic, including cellular bronchiolitis and bronchiolitis obliterans with and without organizing pneumonia. Based largely on anecdotal experience, corticosteroid use may be salutary in patients with respiratory failure. For reasons that are not well known, the incidence of pulmonary thromboembolism is increased in fatal cases.

(Chan ED, Welsh CH: Fulminant *Mycoplasma pneumoniae* pneumonia. West J Med 1995; 162:133-142)

The vast spectrum of diseases caused by *Mycoplasma pneumoniae* includes pharyngitis, sinusitis, tracheobronchitis, pneumonia, myocarditis, pancreatitis, hepatitis, arthritis, and meningoencephalitis. Associated findings are equally diverse and include intravascular hemolysis and coagulation and skin eruptions.[1-5] The protean respiratory complications of *M pneumoniae* pneumonia have included cases of cellular bronchiolitis,[6] bronchiolitis obliterans with or without organizing pneumonia,[6-8] bronchiectasis,[9] pneumatoceles,[10] Swyer-James syndrome,[11] pleural effusion,[2,12] the adult respiratory distress syndrome,[13,14] pulmonary embolism,[15] chronic interstitial fibrosis,[16,17] and lung abscess.[18]

As noted in a review of human mycoplasmal diseases,[3] the current literature stresses the benign and often subclinical nature of such infections, even when pneumonia has occurred. Indeed, it is estimated that clinically apparent pneumonia develops in only 3% to 10% of those infected with *M pneumoniae*[3] and that less than 5% of cases of pneumonia are severe enough to require admission to a hospital.[1,19]

A singular case of severe respiratory insufficiency in a previously healthy young man with *M pneumoniae* pneumonia was recently encountered. A literature search was undertaken to characterize patients in whom this disorder resulted in hypoxic respiratory failure or death. This information is reported because it emphasizes that life-threatening, defined here as "fulminant," *M pneumoniae* infections attack mostly previously healthy people, that empiric antibiotic therapy for community-acquired pneumonia should include coverage for both "typical and atypical" organisms, and that thromboembolism is common in fatal cases.*

Case Presentation

The patient, a 19-year-old male college student who was previously in excellent health, had myalgias eight days before admission, followed by fever, chills, and a nonproductive cough. Over the next few days, he was twice seen in the emergency department and was treated symptomatically for a presumed viral upper respiratory tract infection. He was subsequently admitted because of progressive shortness of breath; on examination, the temperature was 38.1°C, pulse 140 per minute, blood pressure 150/70 mm of mercury, and respiratory rate 32 per minute. Notable findings included cyanosis with bilateral crackles on lung examination. The sputum was mucoid and blood-tinged, and Gram's stain showed abundant neutrophils without a predominant organism. The leukocyte count was 5.6×10^9 per liter (5,580 per mm^3) with 0.80 neutrophils (80%), 0.14 lymphocytes (14%), and 0.03 monocytes (3%); the hemoglobin level was 141 grams per liter (14.1 grams per dl), and the platelet count was 224×10^9 per liter (224,000 per mm^3). The serum sodium level was 128 mmol per liter, and the phosphorus level was 0.52 mmol per liter (1.6 mg per dl). Arterial blood gas values with the patient breathing room air at 2,135 m (7,000 ft) elevation were a pH of 7.46, P_{CO_2} 28 mm of mercury, P_{O_2} 31 mm of mercury, and an oxygen

*See also the editorial by G. H. Cassell, PhD, "Severe Mycoplasma Disease—Rare or Underdiagnosed?" on pages 172-175 of this issue.

From the Divisions of Pulmonary Sciences and Critical Care Medicine, University of Colorado Health Sciences Center (Drs Chan and Welsh) and the Department of Veterans Affairs Medical Center (Dr Welsh), Denver.

Reprint requests to Edward D. Chan, MD, Box C272, Division of Pulmonary Sciences, University of Colorado Health Sciences Center, 4200 East Ninth Ave, Denver, CO 80262.

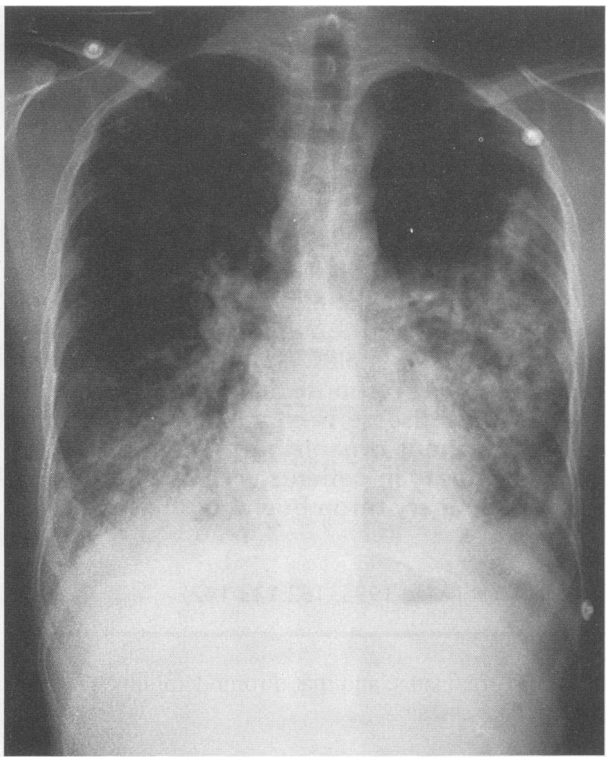

Figure 1.—The admission chest radiograph of the young man with fulminant *Mycoplasma pneumoniae* pneumonia shows diffuse alveolar infiltrates, particularly in the lower lung fields.

saturation of 0.62 (62%). A chest roentgenogram showed diffuse air-space consolidation largely in the lower lung fields (Figure 1).

Although a four-drug antibiotic regimen was begun that included erythromycin, 500 mg given four times a day intravenously, hypercarbia and progressive hypoxemia developed, necessitating mechanical ventilation on the fifth hospital day. A bronchoalveolar lavage specimen was negative for *Pneumocystis carinii*, and all antibiotics except the erythromycin were discontinued. Blood and sputum cultures, human immunodeficiency virus antibody test, and paired serologic titers for *Legionella pneumophila*, respiratory syncytial virus, adenovirus, influenza types A and B, and parainfluenzae types 1, 2, and 3 were all negative. The complement fixation titer for *M pneumoniae* rose from 1:128 to 1:512, and the cold-agglutinin titer rose from 1:64 to 1:2,048 over a four-day interval. He had a progressively favorable course, and the endotracheal tube was removed after five days of mechanical ventilation. He was discharged to complete a three-week course of erythromycin and has recovered without sequelae.

Methods

A MEDLINE search in the English-language literature was undertaken for the period 1966 to 1991 using the following four paired words: "*Mycoplasma pneumoniae*" paired with "artificial respiration," "respiratory failure," "review," and "deaths." The bibliography of relevant articles was reviewed for all fatal and "severe" cases and those requiring lung biopsies. In addition, prospective studies of community-acquired pneumonia in patients requiring hospital admission, with each study comprising more than 100 patients, were reviewed for cases of fulminant *M pneumoniae* pneumonia and for its frequency. In suitable pneumonia studies, the mortality rate for *M pneumoniae* pneumonia was compared with the total mortality rate for inpatient pneumonia. Criteria for respiratory failure included endotracheal intubation or "respiratory failure" as noted by the authors, a Pao_2 of less than 50 mm of mercury with the patient breathing room air, or a clinical diagnosis of adult respiratory distress syndrome or its pathologic equivalent, "diffuse alveolar damage."

Cases Excluded

A total of 42 cases were excluded from the review: 5 cases of respiratory failure were excluded because of mixed infections.[5,20-22] The cases of 13 patients with "severe" *M pneumoniae* infections were excluded because of an absence of objective criteria for respiratory failure.[23-26] Three patients with Down syndrome, one of whom died and the other two had "profound" hypoxia[27]; three patients with adult respiratory distress syndrome[5,19]; four patients from a community-acquired pneumonia study who died[28]; and nine patients with a Pao_2 of less than 60 mm of mercury[27] were all excluded because of inadequate information about the patients and their courses. Three cases of respiratory failure were rejected because the laboratory diagnoses were based on cold-agglutinin titers alone.[29] Two cases were excluded because of contradictory statements regarding mechanical ventilation requirements.[30]

Results

In the 13 inpatient, prospective studies of community-acquired pneumonia analyzed,[28,31-42] *M pneumoniae* accounted for 0.7% to 18% (mean, 8%) of these presumably more seriously ill patients treated in hospital. In 12 of the evaluable studies,[28,31-37,39-42] the average total mortality rate for community-acquired pneumonia was 12% (range, 2% to 24%), whereas the mortality rates for *M pneumoniae* pneumonia in the two studies[28,40] that reported such deaths were 5% (4/81) and 3% (1/30), respectively.

From our review of fulminant cases of *M pneumoniae* pneumonia, three categories of patients' outcome are recognized (Tables 1, 2, and 3),[43-64] namely nonfatal respiratory failure (26 cases), fatal respiratory failure (13 cases), and fatal without respiratory failure (7 cases). Although many patients in the third group were undoubtedly endotracheally intubated, if respiratory failure was not noted before their cardiopulmonary arrest, they were included in the "without respiratory failure" group.

Nonfatal Respiratory Failure

The average age of the 26 patients summarized in Table 1 was 35 years. Most patients (23 [88%]) were previously healthy. Of the 19 male patients, 12 (63%) required mechanical ventilation compared with 2 of the 7 female patients (28%); in 2 patients, 1 male and 1 female,

TABLE 1.—*Nonfatal Respiratory Failure*

Patient	Age, yr	Sex	Underlying Disease or Risk Factor	Diagnostic Tests	Antibiotics* or Steroids†	Complication or Biopsy Findings	Intubated	Oxygenation (Fio_2), mm of Hg	Source
1.....	6	M	Acute lymphocytic leukemia	CA <1:8→1:128; pos throat culture	Erythromycin (14/4)	Open lung biopsy: cellular bronchiolitis	No	Pco_2 30; Po_2 49	Ganick et al, 1980[43]
2.....	16	M	--	CA 1:256→1:512→ 1:32; CF 1:2,048→ 1:4,096	Erythromycin (10/1); steroids (13/4)	ARDS	Yes	Po_2 35	Dixon, 1981[14]
3.....	18	M	Hemoglobin SC	CF 1:32→1:128	Erythromycin (6/2)	Hemolytic anemia; pleural effusion	Yes	--	Solanki and Berdoff, 1979[12]
4.....	20	M	--	CF 1:4→1:64; pos throat culture	Tetracycline (?/10)	--	No	--	Armstrong, 1969[44]
5‡.....	21	F	--	CF <1:8→≥1:256; CA neg →1:512	Erythromycin (14/12)	Tube thoracostomy for pleural effusion	No	Po_2 50	Gump and Hawley, 1976[45]
6.....	24	F	--	CF 1:8 → 1:128	Tetracycline (2/1); steroids (2/1)	--	No	Po_2 40-50	Mlczoch and Witek, 1976[46]
7.....	25	M	--	CF 1:4 → > 1:128	Erythromycin (10/8); steroids (11/9)	Pleural effusion	No	Po_2 32-43	Noriega et al, 1974[47]
8.....	25	M	--	CF < 1:4 → 1:16	Chloramphenicol (?/8)	ARDS; open lung: "pneumonitis"	Yes	--	Fischman et al, 1978[13]
9.....	27	M	Smoker	CF 1:128 → 1:64; CA 1:512	Tetracycline and steroids (13/3)	"Bronchiolitis"	No	Pco_2 71; Po_2 39	Zack and Kazemi, 1973[48]
10.....	30	M	--	CF 1:8 → 1:64	Erythromycin (?/?)	ARDS; open lung: diffuse alveolar damage, bronchiolitis	Unclear	--	Rollins et al, 1986[6]
11.....	30	M	--	Unclear	--	Pneumothorax; hemolysis	Yes	--	Marrie, 1993[22]
12.....	32	F	--	CF 1:16 →> 1:256	Erythromycin (14/11)	--	Yes	Pco_2 70 → 100; Po_2 45 (10 liters)	Teres et al, 1973[49]
13.....	32	M	Smoker	CF 1:32→1,024; CA 1:256	Chloramphenicol (7/2)	--	Yes	Po_2 44	Cockcroft and Stilwell, 1981[50]
14.....	33	M	--	CF 1:64→ 1:256; CA 1:512	Tetracycline and steroids (?/?)	--	No	Po_2 40	Mlczoch and Witek, 1976[46]
15‡....	36	M	--	CF 1:64→1:2,048; CA 1:256	Tetracycline (14/4)	↑Liver function test values	No	--	Fraley et al, 1979[8]
16.....	37	M	Smoker	CF 1:256→1:128; CA 1:512	Erythromycin (16/6); steroids (4→ 6th hosp day)	Open lung: BO with confluent nodular infiltrate (BOOP)	Yes	Po_2 28	Coultas et al, 1986[7]
17.....	41	M	--	Unclear	--	Guillain-Barré syndrome	Yes	--	Marrie, 1993[22]
18.....	45	F	Smoker	CF < 1:8→1:2,048; CA < 1:8→ 1:256	Tetracycline (6/2)	Tracheostomy	Yes	--	Gump and Hawley, 1976[45]
19‡....	48	F	--	Pos sputum culture	Erythromycin (7/4)	--	No	Po_2 60 (5 liters)	Gump and Hawley, 1976[45]
20.....	48	M	Smoker	CF 1:8→ 1:256; CA 1:160; pos sputum culture	Tetracycline and steroids (≥10/?)	Hemolytic anemia; open lung: BOOP	Yes	--	Fraley et al, 1979[8]
21.....	50	F	--	CF 1:1,280	Tetracycline (9/6); steroid as outpatient	Myocarditis; hemolytic anemia; 49-day hosp stay	No	Pco_2 49 Po_2 38	Holt et al, 1977[51]

(continued on next page)

Table 1 continued from previous page

Patient	Age, yr	Sex	Underlying Disease or Risk Factor	Diagnostic Tests	Antibiotics* or Steroids†	Complication or Biopsy Findings	Intubated	Oxygenation (Fio_2), mm of Hg	Source
22.....	52	M	--	CF < 1:4→ > 1:128	Tetracycline (?/30)	ARDS; 69-day hosp stay	Yes§	--	Fischman et al, 1978[13]
23.....	62	M	Chronic bronchitis	CF 1:40 → 1:160	Erythromycin (?/?)	Pancreatitis; diabetes mellitus	Yes	Po_2 27	Mardh and Ursing, 1974[52]
24.....	65	F	--	CF 1:8 → 1:64; CA 1:64 → 1:256	Erythromycin (?/?)	Renal failure; open lung: BOOP	Unclear	--	Rollins et al, 1986[6]
25.....	71	M	--	CF 1:2,048 →1:8,192; CA 1:128	Tetracycline and erythromycin (10/1)	↑ Liver function test values	Yes	Po_2 53 (↑↑ Fio_2)	Cockcroft and Stilwell, 1981[50]
26‡....	19	M	--	CF 1:128 → 1:512; CA 1:64 → 1:2,048	Erythromycin (8/1)	--	Yes	Pco_2 25; Po_2 31	Present case

ARDS = adult respiratory distress syndrome, BO = bronchiolitis obliterans, BOOP = BO with organizing pneumonia, CA = cold agglutinin (immunoglobulin M), CF = complement fixation (immunoglobulin G), Fio_2 = fractional concentration of supplemental oxygen, hosp = hospital, neg = negative, pos = positive, ? = not reported or unable to derive, ↑ = elevated

*Antibiotic effective against *Mycoplasma pneumoniae*.

†The numbers in parentheses represent days after symptom onset/day of hospital stay antibiotic or corticosteroid therapy begun.

‡The patient is a nonsmoker.

§The patient was intubated for more than 30 days.

the need for endotracheal intubation was unclear. Of the 4 nonsmokers noted (mean age, 31), only 1 required endotracheal intubation; on the other hand, of the 5 smokers noted (mean age, 38), 4 required mechanical ventilation, and in the 1 patient who did not, the $Paco_2$ reached 71 mm of mercury. A regimen of an antibiotic effective against *M pneumoniae* was begun on an average of 10 days (range, 2 to 16 days) after the onset of symptoms in 17 patients and, similarly, in 19 patients, on an average of the sixth hospital day.

Eight patients received corticosteroid therapy. Of the six male patients who were treated with steroids, three required mechanical ventilation. In one patient, endotracheal intubation was instituted for support during an open lung biopsy, and a brief course of corticosteroids was begun on the fourth hospital day[7]; in the other two patients, corticosteroid therapy was begun late (≥10 days after symptom onset) and only after intubation.[8,14] Open lung biopsies showed a consolidative pneumonitis with bronchiolitis obliterans in one of these patients[8] and a confluent nodular infiltrate with bronchiolitis obliterans in the other.[7] Using a more current classification scheme, the pathologic descriptions of these two cases suggests that they are bronchiolitis obliterans with organizing pneumonia.[65] Although the third intubated male patient received corticosteroids after the development of adult respiratory distress syndrome,[14] clearing of the infiltrate was noted after the administration of steroids. In the other three nonintubated male patients, two received tetracycline and corticosteroids simultaneously, and rapid improvements were noted[46,48]; one of these steroid-responsive patients had a clinical diagnosis of bronchiolitis.[48] In the third patient, prompt recovery from a "moribund" state was noted only after a course of steroids was started.[47] In the two female patients who received steroids, it was evident that steroid administration was salutary, and neither required mechanical ventilation.[46,51]

Open lung biopsies in six patients with nonfatal respiratory failure revealed infiltration of bronchiolar walls with acute and chronic inflammatory cells (cellular bronchiolitis) in two patients,[6,43] bronchiolitis obliterans with organizing pneumonia in three patients,[6-8] and an "active pneumonitis" in one patient.[13] Rollins and co-workers reviewed the open lung biopsies of six patients with *M pneumoniae* pneumonia (2 with nonfatal respiratory failure were mentioned earlier) and noted acute and chronic cellular bronchiolitis in five of them; the sixth patient had bronchiolitis obliterans with organizing pneumonia.[6]

Fatal Respiratory Failure

Among the 13 cases shown in Table 2, the average age was 27 years. A regimen of an antibiotic effective against *M pneumoniae* was begun an average of 15 days after symptom onset (range, 1 to 29 days) and on an average of the eighth hospital day in 7 patients. Two patients received corticosteroids. In one patient, the steroid dosage was unclear, and death was due to multiple pulmonary emboli and *Pseudomonas* species sepsis.[8] The other patient received only one dose of corticosteroid.[17]

Of the 13 patients who died of respiratory failure, 9 (69%) had thromboemboli either strongly suspected or documented; most of these were pulmonary emboli. There were 2 sudden deaths, and autopsies revealed bronchiolitis and purulent bronchiectasis in a 6-year-old boy[9] and bronchiolitis obliterans and pulmonary thrombi in a young man with rheumatic heart disease.[57]

Fatal Cases Without Respiratory Failure

In six of the seven patients in Table 3 for whom data were available, the average age was 45 years. The cause of death included thromboembolism in three patients,[40,62,63] meningoencephalitis in two patients,[55,61] myocarditis in one patient,[64] and "indeterminate" cause in one patient.[60] None of the patients were noted to have received steroids.

TABLE 2.—*Fatal Respiratory Failure*

Patient	Age, yr	Sex	Underlying Disease or Risk Factor	Diagnostic Tests	Antibiotics* or Steroids†	Complication/ Autopsy Findings	Intubated	Oxygenation (Fio_2), mm of Hg	Source
1.....	3	F	--	CF 1:8→1:64	Erythromycin (23/21)	Hemolytic anemia; DIC, renal failure; candida sepsis; ? thromboembolism	Yes	--	Nilsson et al, 1971[53]
2.....	6	M	--	CF 1:1,024; CA 1:512	Erythromycin (29/12)	Bronchiolitis; bronchiectasis	Yes	Pco_2 125; Po_2 158 (100%)	Halal et al, 1977[9]
3.....	8	F	Silent atrial septal defect	"Serologic evidence"	Erythromycin (?/?)	Stevens-Johnson syndrome; obliterative bronchitis; pericarditis	Unclear	--	Edwards et al, 1983[54]
4.....	13	M	--	CF 1:10,000; CA 1:128	No appropriate antibiotics	Multiple thrombi in leptomeninges; bilateral pneumonia	Unclear	--	Dorff and Lind, 1976[55]
5.....	20	M	--	CF 1:8→1:64; pos DNA probe	Erythromycin (10/1)	DIC/ARDS; open lung: pulmonary thrombosis, diffuse alveolar damage	Yes	--	Donat, 1992[56]
6.....	23	M	Rheumatic heart disease	CF 1:32 → > 1:256; CA 1:40 → 1:160	Erythromycin (17/10)	CHF, sudden death; interstitial pneumonitis; BO, PE	Yes	--	Benisch et al, 1972[57]
7.....	28	F	Nonsmoker, pregnant	CF 1:2,048; CA 1:4 → 1:16	Erythromycin/ steroids (?/?)	Multiple PE; pseudomonas pneumonia/sepsis	Yes	Po_2 52 (28%)	Fraley et al, 1979[8]
8.....	30	F	--	Postmortem tissue culture	No appropriate antibiotics	Shock, PE; DIC	Yes	--	Koletsky and Weinstein, 1980[15]
9.....	31	F	Postpartum	CF 1:4 → 1:128	Doxycycline (6/1); 1 dose of steroid	Interstitial fibrosis	Yes	Pco_2 90	Kaufman et al, 1980[17]
10.....	31	M	--	CF 1:4 → 1:64	Erythromycin (1/1)	CHF; PE	Yes	--	Sands and Rosenthal, 1982[58]
11.....	37	M	Diabetes mellitus; cirrhosis	CF 0 → 1:256	No appropriate antibiotics	DIC, shock, myocarditis; hemorrhagic pneumonia	Yes	--	DeVos et al, 1974[59]
12.....	55	F	--	CF < 1:8 →1:32	No appropriate antibiotics	Interstitial pneumonitis; left main pulmonary artery embolus	Unclear	--	Meyers and Hirschman, 1972[60]
13.....	68	F	--	CF 1:10→1:320	Tetracycline (18/7)	Pancreatitis/diabetes; PE, DIC	Yes	--	Mardh and Ursing, 1974[52]

ARDS = adult respiratory distress syndrome, BO = bronchiolitis obliterans, CA = cold agglutinin (immunoglobulin M), CF = complement fixation (immunoglobulin G), CHF = congestive heart failure, DIC = disseminated intravascular coagulation, Fio_2 = fractional concentration of supplemental oxygen, PE = pulmonary thromboembolism, pos = positive

*Antibiotic effective against *Mycoplasma pneumoniae*.

†The numbers in parentheses represent days after symptom onset/day of hospital stay antibiotic or corticosteroid therapy started.

Discussion

Nearly 50 years ago, a filterable agent was described from the sputum of patients with atypical, cold-agglutinin–positive pneumonia, and the pneumonia was duplicated in laboratory animals.[66] In 1962 Eaton's agent, subsequently characterized as *M pneumoniae*, was grown on agar.[67] It is one of the smallest free-living organisms known, and it lacks the cell wall of most bacteria.

According to epidemiologic studies regarding this agent, *M pneumoniae* infections are common. Most of the illnesses are mild, and the patients are never seen by practitioners. It is estimated that *M pneumoniae* accounts for as many as 20% of all cases of community-acquired pneumonia in the general population and for as many as 50% in closed populations such as students and military recruits living in dormitories.[3] In a community survey performed in Seattle, Washington, spanning 11 years, it was determined that *M pneumoniae* accounted for 30% to 60% of all cases of pneumonia in the 5- to 20-year age group.[68] In the subgroup of 15- to 19-year-olds, it was the most common cause of pneumonia.

Unfortunately, the diagnosis of *M pneumoniae* pneumonia is often delayed and retrospective because of the

lack of a rapid, accurate, and widely available diagnostic test. More specialized tests, such as culture, detecting antigen in sputum by the use of indirect immunofluorescence with monoclonal antibodies and enzyme-linked immunoassay, complementary DNA probes for ribosomal RNA detection, and polymerase chain reaction for detecting DNA are done only in specialized laboratories.[69] Diagnostic testing is also complicated by the fact that a prolonged nasopharyngeal carriage for *M pneumoniae* may exist even after successful treatment with antibiotics[70] and may account for relapses.[71]

A bias for the most critically ill patients to be seen at referral centers[30] or possible differences in virulence between strains[45] may account for the higher rate of fulminant cases reported by some authors. Such reasoning, however, would not likely explain the greater incidence of severe cases reported in young healthy adults, as many are single case reports. Because *M pneumoniae* pneumonia is endemic, with epidemics occurring every two to six years,[4] the disparity in the number of severe cases collected by different workers may reflect this cycle. The possibility that such epidemics account for the greater incidence in young men due to the greater clustering of young men in organizations such as the military can only be conjectured. Although it has been suggested that a correlation exists between severe respiratory involvement and high cold-agglutinin titers,[8] a perusal of our list does not support this observation.

Surprisingly, in the studies of community-acquired pneumonia examined, the mortality rate for patients admitted to a hospital with *M pneumoniae* pneumonia (3% to 5%) is lower than that for all etiologic agents combined (mean, 12%). The frequency with which mycoplasmal infection results in respiratory failure or death is therefore probably low, but given the high estimated incidence of *M pneumoniae* infections, sporadic cases are not unusual. Most fulminant cases are essentially documented as case reports, of which we found only 46 to be evaluable.

Nonfatal Respiratory Failure

In the group of 26 patients listed in Table 1, most had no underlying disease and were previously healthy. In light of this, it is ironic that two groups reported "unusually severe" cases of *M pneumoniae* infections in immunocompromised hosts and yet none of these patients had respiratory failure or death.[25,26] In one such report,[25] "severe" infections occurred in four teenagers with immunodeficiency syndromes in whom there were minimal or no changes on chest radiographs and in whom rapid improvement occurred with antibiotic therapy. In the other report, "severe" *M pneumoniae* pneumonia was described in five children with sickle cell anemia, all of whom had uneventful recoveries.[26]

Most of the reported patients were young adults. Whether this is due to a lower suspicion for *M pneumoniae* pneumonia in elderly patients with chronic disease

TABLE 3.—*Fatal Nonrespiratory Failure*

Patient	*Age, yr*	*Sex*	*Underlying Disease or Risk Factor*	*Diagnostic Tests*	*Antibiotics*†*	*Complication or Cause of Death*	*Source*
1	Unknown	Unknown	Unknown	Unknown	Unknown	PE	White et al, 1981[40]
2	17	M	- -	CF 1:1,000; CA 1:256	Antibiotics (?/?)	Bilateral pneumonia; meningoencephalitis; brain edema	Dorff and Lind, 1976[55]
3	29	M	- -	CF 1:32 → 1:256	Erythromycin (15/10)	Cerebritis, meningitis; cerebrovascular thrombi	Weinblatt and Caplan, 1980[61]
4	39	F	- -	CF 1:64 → 1:128	Tetracycline and erythromycin (7/3)	Pleural effusion; "indeterminable cause of death"	Meyers and Hirschman, 1972[60]
5	45	M	- -	Pos throat culture; CA 1:64	Tetracycline (7/1)	Psychosis; bilateral PE/ infarctions	Sterne and, Biberfeld, 1969[62]
6	70	F	- -	Pos postmortem tissue culture	Tetracycline (8/?)	Diffuse thrombo-emboli; hemolytic anemia; interstitial pneumonitis; bronchiolitis, bronchitis	Maisel et al, 1967[63]
7	71	M	- -	Pos blood/peri-cardial fluid culture	Antibiotics (?/?)	Myocarditis; pleuritis; minimal consolidation	Naftalin et al, 1974[64]

CA = cold agglutinin (immunoglobulin MG), CF = complement fixation (immunoglobulin MG), PE = pulmonary thromboembolism, pos = positive

*Antibiotic effective against *Mycoplasma pneumoniae*.

†The numbers in parentheses represent days after symptom onset/day of hospital stay antibiotic or corticosteroid therapy begun.

or a greater prevalence and severity of the disease in younger persons is unknown. There were nearly three times as many male as female patients in the sample analyzed.

It is premature to comment on the use of tobacco and the need for mechanical ventilation in this series despite the suggestive association, because only nine patients had their smoking status documented. Nevertheless, smokers have a substantial increase in neutrophils in their lungs,[72] and these cells may play a crucial role, by the release of proteolytic enzymes or oxidants, in the pathogenesis of lung injury caused by this disorder. Similarly, it is inappropriate to construe that the untimely administration of antibiotics was associated with adverse outcomes. In many instances, however, antibiotic therapy was delayed and often started after agents ineffective against *M pneumoniae*, such as a β-lactam, were tried. We support the observation made recently that it is clinically difficult to predict the etiologic agent of a community-acquired pneumonia[31] and that empiric antibiotic therapy should initially include coverage for both "typical" (such as *Streptococcus pneumoniae*) and "atypical" (such as *M pneumoniae*) organisms. The fulminant cases of *M pneumoniae* pneumonia we have reviewed emphasize the point that classifying a case of pneumonia as either a typical or atypical form, based on the abruptness of onset, severity of symptoms, and purulence of sputum, is an unreliable method on which to base empiric antibiotic therapy. Moreover, we stress that empiric monotherapy with the newer cephalosporins or penicillins for community-acquired pneumonia, increasingly popular in the United States,[31] has no scientific basis because these agents are not effective against *M pneumoniae*, *Legionella pneumophila*, or *Chlamydia pneumoniae*. Similarly, the fluoroquinolones are being increasingly used to treat bronchitis and community-acquired pneumonia, but their efficacy against *S pneumoniae* is doubtful.

Immune mechanisms may be important in the pathogenesis of *M pneumoniae* pneumonia. Active *M pneumoniae* infection has been shown to transiently depress cell-mediated immunity, as demonstrated by a decrease in skin and lymphocyte stimulation responses to purified-protein derivative of tuberculin.[73] On the other hand, protein antigens on the cell surface of *M pneumoniae* have been shown to induce cellular immunity, as confirmed by both lymphocyte transformation in vitro and enhancement of delayed cutaneous hypersensitivity.[74] Noriega and co-workers suggested that a host-cellular immune response to *M pneumoniae* played a central role in the severe pneumonitis that occurred in a patient.[47] The proposed hypothesis was that previously sensitized lymphocytes from an earlier infection are activated during a subsequent infection and release supranormal levels of "mediators" that cause local tissue destruction and precipitate a cascading inflammatory response. This postulate was supported by later investigators in a case report[51] and by a laboratory experiment in which hamsters pretreated with antithymocyte globulin, which decreases the number of lymphocytes, showed less severe pneumonia than control animals.[75] These studies suggest that indeed an excessive host-cellular response to the organism may be responsible for the lung injury.

Clinical studies also corroborate a role for the cellular immune system in the pathogenesis of *M pneumoniae* pneumonia. It has been suggested that a lack of an immune response accounted for the absence of pneumonic infiltrates in four children with immunodeficiency syndromes.[25] Perez and Leigh commented on the underwhelming incidence of *M pneumoniae* infection in children with cancer.[76] In a review of the immunology of *M pneumoniae* infection, it was noted that there was no convincing evidence that cell-mediated immunity played a direct role in resistance to *M pneumoniae* respiratory infections, but experiments showed that hamsters challenged intranasally with *M pneumoniae* had T cells accumulate in the peribronchiolar and perivascular spaces of their lungs with a secondary outpouring of phagocytic cells into their bronchial lumina.[77] The time required for such a host response to develop may be the basis for one author's observation that respiratory failure in his patients developed 7 to 14 days after the onset of their illnesses.[29] The fact that severe *M pneumoniae* pneumonia is not seen with increased frequency in patients with the acquired immunodeficiency syndrome also lends credence to a cellular immunologic basis in the pathogenesis of fulminant cases,[70] although this has not been systematically evaluated.

In contrast to the deleterious role that the cellular immune response may have in patients with *M pneumoniae* pneumonia, local humoral immunity may have an important role in the resistance to mycoplasmal respiratory infections.[77] There is evidence that immunoglobulin levels in respiratory secretions correlate better with resistance to such infections than do circulating antibody levels.[73] Enhanced antibody response in the bronchial lumen may inhibit *M pneumoniae* attachment to the respiratory epithelium and may also, by opsonization, increase phagocytosis of the organism by mononuclear cells. Immunization with the Pi surface protein, the specialized surface structure of *M pneumoniae* that serves as the attachment site to host cells, may also confer protective local humoral immunity.[73]

The stimulation of autoimmune antibodies by *M pneumoniae* antigens cross-reactive with host tissue has been proposed as an explanation for the extrapulmonary manifestations of *M pneumoniae* infections.[78] Except for hemolytic anemia where nonspecific immunoglobulin M interacts with the I antigen of erythrocytes, direct evidence of antibody-mediated injury is lacking.[79] Similarly, there is no evidence that autoantibodies are involved in the lung injury. Although it has been shown that circulating immune complexes are increased in patients with *M pneumoniae* pneumonia and that high levels correlate with the severity of the pneumonia, it is unclear whether they have a pathogenic role or are the result of the disease.[80]

Pathologic support for a cellular immunologic response in *M pneumoniae* pneumonia comes from Rollins

and co-workers in their description of a lymphoplasmacytic bronchiolar wall infiltrate with a neutrophil-rich intraluminal exudate[6]—that is, a cellular bronchiolitis. They emphasized that *M pneumoniae* is often omitted from the differential diagnosis even when this characteristic bronchiolitis is seen on lung biopsy specimens, but underscored that this pathologic appearance may be seen with viral, other bacterial, and allergic disorders as well. A case of bronchiolitis obliterans with organizing pneumonia from an open lung biopsy was also described by these authors.[6] Typically in these cases, polypoid masses of granulation tissue are found filling the respiratory bronchioles and alveolar ducts with a lymphoplasmacytic infiltration of the adjacent alveolar interstices.[65] Unfortunately, interpreting much of the pathologic literature regarding *M pneumoniae* pneumonia is difficult because the classification and nomenclature of bronchiolitis, which is increasingly described in various lung diseases, are rapidly evolving.[65]

Of the six nonfatal, fulminant cases of pneumonia we found reported in which lung biopsies were done, two had a cellular bronchiolitis[6,43] and three others had pathologic descriptions that are consistent with bronchiolitis obliterans with organizing pneumonia.[6-8] Cellular bronchiolitis is usually self-limiting, but a chronic cough may persist and require the use of corticosteroids for resolution.[65] In the eight patients with nonfatal respiratory failure who received corticosteroids, six were specifically noted to have responded favorably to steroid therapy.[14,46-48,51] Given the frequent recognition of bronchiolitis and bronchiolitis obliterans with and without organizing pneumonitis in this series of patients, one must question whether steroid responsiveness relates to the presence and extent of these pathologic lesions. Bronchiolitis was diagnosed in a patient with severe obstructive and ventilatory defects who, despite considerable hypoxemia and hypercarbia, responded well to steroids and avoided mechanical ventilation.[48]

In contrast to the mild course of bronchiolitis, postinfectious bronchiolitis obliterans may have a malignant and fatal course with irreversible and extensive scarring of the bronchioles. The early use of corticosteroids is considered the treatment of choice.[65] Two of the three patients with bronchiolitis obliterans with organizing pneumonia due to *M pneumoniae* were smokers, and both required mechanical ventilation despite steroid administration.[7,8] Either late[8] or brief[7] administration of steroids is a plausible explanation for its ineffectiveness. In the third patient with bronchiolitis obliterans with organizing pneumonia,[6] smoking status and steroid usage were unclear. It is interesting that in patients in whom bronchiolitis obliterans with organizing pneumonia develops in the setting of chronic graft-versus-host disease after allogeneic bone marrow transplantation, there is a similar lymphoplasmacytic infiltration of the bronchioles, and early treatment with high-dose corticosteroids has been emphasized to resolve the lung disease.[81] The early administration of corticosteroids was recommended to stave off fibroblast proliferation in severe cases of *M pneumoniae* pneumonia that do not show improvement after a few days from symptom onset.[17] Pulmonary fibrosis developed in a patient with a well-documented case of *M pneumoniae* pneumonia and who responded dramatically to a course of corticosteroids a year after her initial pneumonia.[16] Additional cases of *M pneumoniae* pneumonia were reported in which fulminant evolution into diffuse interstitial fibrosis occurred.[82] Whether these patients had a component of bronchiolitis obliterans with organizing pneumonia or bronchiolitis obliterans early in the clinical course is unclear.

Fatal Cases

The incidence of fatal *M pneumoniae* pneumonia is low, especially in outpatient series. The relatively young age of the fatal cases in the cases summarized in Tables 2 and 3 (mean, 33 years) is intriguing in light of the fact that age is often regarded as an independent risk factor for increased morbidity and mortality in pneumonia.[83] In a five-year prospective study of community-acquired pneumonia, an overall mortality rate for all etiologic agents of 8.5% was documented for those younger than 60 years and 28.6% for those 60 and older.[41] As previously noted, whether this increase in the severity of *M pneumoniae* pneumonia in younger and presumably more immunocompetent hosts is a true risk and due to host factors or whether the collecting of cases is biased because of greater prevalence or greater awareness in younger patients is unresolved.

In an earlier review of 11 fatal cases of *M pneumoniae*, it was noted that vascular thromboses with associated infarctions occurred in nearly half of the patients.[15] In our more current review of 20 fatal cases, thromboembolism was a salient feature and was either suspected (1 case) or documented (12 cases) in 65% of the patients. In the latter 12 cases, pulmonary embolism was diagnosed in 10 and was either the direct cause[40,57,60,62] or a facilitator of death. The unanswered question is whether the thromboemboli are provoked by the *M pneumoniae* or whether they are the result of venous stasis in very ill patients. It has been suggested that a cold agglutinin-induced hemolysis precipitated a hypercoagulable state in a patient, leading to widespread thromboembolism.[63] Although disseminated intravascular coagulation has been associated with both fatal and nonfatal cases of *M pneumoniae* infection, cases of pulmonary emboli have occurred in the absence of this complication.[40,57,60,62] It is unclear to us why there were no cases of pulmonary emboli noted in the patients with nonfatal respiratory failure. Because most of the fatal cases with thromboembolism were diagnosed at autopsies, a possible explanation for this discrepancy is that nonfatal thromboembolism also occurred, but was simply not suspected in some of those patients who recovered.

Summary

This review of fulminant *Mycoplasma pneumoniae* infections confirms the widely held belief that the etiologic diagnosis of community-acquired pneumonia is

frequently putative and treatment empirical. It also emphasizes that empiric therapy based on the conventional scheme for dividing community-acquired pneumonia into typical and atypical forms is deceptive and unreliable. Because of the high frequency of infections with *M pneumoniae*, severe cases of *M pneumoniae* pneumonia are not rare, but are probably underdiagnosed owing to unawareness or to an underestimation of such cases and to the lack of a rapid method to diagnose *M pneumoniae*. Because of host factors or on epidemiologic grounds, fulminant cases seem to be more common in young healthy adults, in males, and possibly in smokers. Enhanced host-cellular immune response and cytokine elaboration, increasingly implicated in the pathogenesis of various diseases, may be involved in fulminant cases of *M pneumoniae* pneumonia as well. Rarely, fatal cases may show little or no pulmonary involvement. Because of the high frequency with which inflammatory injury to the bronchioles is observed, empiric corticosteroid therapy should be considered in cases of respiratory failure. Prophylaxis against and investigation for thromboembolism should be strongly considered in life-threatening cases.

Acknowledgment

Rebecca L. Mortenson, MD, reviewed this article in manuscript form.

REFERENCES

1. Couch RB: *Mycoplasma pneumoniae* (primary atypical pneumonia), *In* Mandell GL, Douglas RG, Bennett JE (Eds): Principles and Practice of Infectious Diseases, 3rd edition. New York, NY, Churchill Livingstone, 1990, pp 1451-1453

2. Murray HW, Masur H, Senterfit LB, Roberts RB: The protean manifestations of *Mycoplasma pneumoniae* infection in adults. Am J Med 1975; 58:229-242

3. Cassell GH, Cole BC: Mycoplasmas as agents of human disease. N Engl J Med 1981; 304:80-89

4. Levine DP, Lerner AM: The clinical spectrum of *Mycoplasma pneumoniae* infections. Med Clin North Am 1978; 62:961-978

5. Mansel JK, Rosenow EC, Smith TF, Martin JW: *Mycoplasma pneumoniae* pneumonia. Chest 1989; 95:639-646

6. Rollins S, Colby T, Clayton F: Open lung biopsy in *Mycoplasma pneumoniae* pneumonia. Arch Pathol Lab Med 1986; 110:34-41

7. Coultas DB, Samet JM, Butler C: Bronchiolitis obliterans due to *Mycoplasma pneumoniae*. West J Med 1986; 144:471-474

8. Fraley DS, Ruben FL, Donnelly EJ: Respiratory failure secondary to *Mycoplasma pneumoniae* infection. South Med J 1979; 72:437-440

9. Halal F, Brochu P, Delage G, et al: Severe disseminated lung disease and bronchiectasis probably due to *Mycoplasma pneumoniae*. Can Med Assoc J 1977; 117:1055-1056

10. Kawata K, Sumino Y, Kikuchi Y, Nukada H, Watanabe Y: Two cases of *Mycoplasma pneumoniae* with cavity formation. Jpn J Med 1978; 17:144-147

11. Stokes D, Sigler A, Khouri NF, Talamo RC: Unilateral hyperlucent lung (Swyer-James syndrome) after severe *Mycoplasma pneumoniae* infection. Am Rev Respir Dis 1978; 117:145-152

12. Solanki DL, Berdoff RL: Severe mycoplasma pneumonia with pleural effusions in a patient with sickle cell-hemoglobin C(SC) disease—Case report and review of the literature. Am J Med 1979; 66:707-710

13. Fischman RA, Marschall KE, Kislak JW, Greenbaum DM: Adult respiratory distress syndrome caused by *Mycoplasma pneumoniae*. Chest 1978; 74:471-473

14. Dixon C: Mycoplasmal pneumonia and adult respiratory distress syndrome: A complication to be recognized. J Natl Med Assoc 1981; 73:549-552

15. Koletsky RJ, Weinstein AJ: Fulminant *Mycoplasma pneumoniae* infection. Am Rev Respir Dis 1980; 122:491-496

16. Tablan OC, Reyes MP: Chronic interstitial pulmonary fibrosis following *Mycoplasma pneumoniae* pneumonia. Am J Med 1985; 79:268-270

17. Kaufman JM, Cuvelier CA, Van der Straeten M: Mycoplasma pneumonia with fulminant evolution into diffuse interstitial fibrosis. Thorax 1980; 35:140-144

18. Siegler DIM: Lung abscess associated with *Mycoplasma pneumoniae* infection. Br J Dis Chest 1973; 67:123-127

19. Foy HM, Nolan CM, Allan ID: Epidemiologic aspects of *M pneumoniae* disease complications—A review. Yale J Biol Med 1983; 56:469-473

20. Sutherland GE, Schlichtig R: Acute respiratory failure due to atypical pneumonia. Mo Med 1983; 80:144-145

21. Oldenburger D, Carson JP, Gundlach WJ, Ghaly FI, Wright WH: Legionnaires' disease: Association with Mycoplasma pneumonia and disseminated intravascular coagulation. JAMA 1979; 241:1269-1270

22. Marrie TJ: *Mycoplasma pneumoniae* pneumonia requiring hospitalization, with emphasis on infection in the elderly. Arch Intern Med 1993; 153:488-494

23. Singer JI, DeVoe WM: Severe *Mycoplasma pneumoniae* infection in otherwise healthy siblings. J Pediatr 1979; 95:999-1001

24. Chusid MJ, Lachman BS, Lazerson J: Severe Mycoplasma pneumonia and vesicular eruption in SC hemoglobinopathy. J Pediatr 1978; 93:449-451

25. Foy HM, Ochs H, Davis SD, Kenny GE, Luce RR: *Mycoplasma pneumoniae* infections in patients with immunodeficiency syndromes: Report of four cases. J Infect Dis 1973; 127:388-393

26. Shulman ST, Bartlett J, Clyde WA, Ayoub EM: The unusual severity of mycoplasmal pneumonia in children with sickle-cell disease. N Engl J Med 1972; 287:164-167

27. Ali NJ, Sillis M, Andrews BE, Jenkins PF, Harrison BDW: The clinical spectrum and diagnosis of *Mycoplasma pneumoniae* infection. Q J Med 1986; 58:241-251

28. British Thoracic Society and Public Health Laboratory Service: Community-acquired pneumonia in adults in British hospitals in 1982-1983: A survey of aetiology, mortality, prognostic factors and outcome. Q J Med 1987; 62:195-220

29. Jastremski MS: Adult respiratory distress syndrome due to *Mycoplasma pneumoniae* (Letter). Chest 1979; 75:529

30. Linz DH, Tolle SW, Elliot DL: *Mycoplasma pneumoniae* pneumonia. West J Med 1984; 140:895-900

31. Fang GD, Fine M, Orloff J, et al: New and emerging etiologies for community-acquired pneumonia with implications for therapy. Medicine (Baltimore) 1990; 69:307-316

32. Macfarlane JT, Finch RG, Ward MJ, Macrae AD: Hospital study of adult community-acquired pneumonia. Lancet 1982; 2:255-258

33. Sullivan RJ, Dowdle WR, Marine WM, Hierholzer JC: Adult pneumonia in a general hospital. Arch Intern Med 1972; 129:935-942

34. Dorff GJ, Rytel MW, Farmer SG, Scanlon G: Etiologies and characteristic features of pneumonias in a municipal hospital. Am J Med Sci 1973; 266:349-358

35. Fekety FR, Caldwell J, Gump D, et al: Bacteria, viruses, and mycoplasmas in acute pneumonia in adults. Am Rev Respir Dis 1971; 104:499-507

36. Levy M, Dromer F, Brion N, Leturdu F, Carbon C: Community-acquired pneumonia: Importance of initial noninvasive bacteriologic and radiographic investigations. Chest 1988; 92:43-48

37. Aubertin J, Dabis F, Fleurette J, et al: Prevalence of legionellosis among adults: A study of community-acquired pneumonia in France. Infection 1987; 15:328-331

38. Berntsson E, Blomberg J, Lagergård T, Trollfors B: Etiology of community-acquired pneumonia in patients requiring hospitalization. Eur J Microbiol 1985; 4:268-272

39. Holmberg H: Aetiology of community-acquired pneumonia in hospital treated patients. Scand J Infect Dis 1987; 19:491-501

40. White RJ, Blainey AD, Harrison KJ, Clarke SKR: Causes of pneumonia presenting to a district general hospital. Thorax 1981; 36:566-570

41. Marrie TJ, Durant H, Yates L: Community-acquired pneumonia requiring hospitalization: 5-Year prospective study. Rev Infect Dis 1989; 11:586-599

42. Lim I, Shaw DR, Stanley DP, Lumb R, McLennan G: A prospective hospital study of the aetiology of community-acquired pneumonia. Med J Aust 1989; 151:87-91

43. Ganick DJ, Wolfson J, Gilbert EF, Joo P: Mycoplasma infection in the immunosuppressed leukemic patient. Arch Pathol Lab Med 1980; 104:535-536

44. Armstrong D: Virus and Mycoplasma respiratory infections. Adv Cardiopulm Dis 1969; 4:175-197

45. Gump DW, Hawley HB: Severe *Mycoplasma pneumoniae* pneumonia. Respiration 1976; 33:475-486

46. Mlczoch F, Witek F: Miliary mycoplasmal pneumonia: A report of six cases. Infection 1976; 4(suppl 1):64-67

47. Noriega ER, Simberkoff MS, Gilroy FJ, Rahal JJ: Life-threatening *Mycoplasma pneumoniae* pneumonia. JAMA 1974; 229:1471-1472

48. Zack MB, Kazemi H: Carbon dioxide retention in Mycoplasma pneumonia. Am Rev Respir Dis 1973; 107:1052-1054

49. Teres D, Roizen MF, Bushnell LS: Successful weaning from controlled ventilation despite high dead space-to-tidal volume ratio. Anesthesiology 1973; 39:656-659

50. Cockcroft DW, Stilwell GA: Lobar pneumonia caused by *Mycoplasma pneumoniae*. Can Med Assoc J 1981; 124:1463-1468

51. Holt S, Ryan WF, Epstein EJ: Severe Mycoplasma pneumonia. Thorax 1977; 32:112-115

52. Mardh PA, Ursing B: The occurrence of acute pancreatitis in *Mycoplasma pneumoniae* infection. Scand J Infect Dis 1974; 6:167-171

53. Nilsson IM, Rausing A, Denneberg T, Christensson P: Intravascular coagulation and acute renal failure in a child with Mycoplasma infection. Acta Med Scand 1971; 189:359-365

54. Edwards C, Penny M, Newman J: Mycoplasma pneumonia, Stevens-Johnson syndrome, and chronic obliterative bronchitis. Thorax 1983; 38:867-869

55. Dorff B, Lind K: Two fatal cases of meningoencephalitis associated with *Mycoplasma pneumoniae* infection. Scand J Infect Dis 1976; 8:49-51

56. Donat WE: Case records of the Massachusetts General Hospital. N Engl J Med 1992; 326:324-336

57. Benisch BM, Fayemi A, Gerber MA, Axelrod J: Mycoplasmal pneumonia in a patient with rheumatic heart disease. Am J Cardiovasc Pathol 1972; 58:343-348

58. Sands MJ, Rosenthal R: Progressive heart failure and death associated with *Mycoplasma pneumoniae* pneumonia. Chest 1982; 81:763-765

59. DeVos M, Van Nimmen L, Baele G: Disseminated intravascular coagulation during a fatal *Mycoplasma pneumoniae* infection. Acta Haematol 1974; 52:120-125

60. Meyers BR, Hirschman SZ: Fatal infections associated with *Mycoplasma pneumoniae*: Discussion of three cases with necropsy findings. Mt Sinai J Med (NY) 1972; 39:258-264

61. Weinblatt ME, Caplan ES: Fatal *Mycoplasma pneumoniae* encephalitis in an adult. Arch Neurol 1980; 37:321

62. Sterner G, Biberfeld G: Central nervous system complications of *Mycoplasma pneumoniae* infection. Scand J Infect Dis 1969; 1:203-208

63. Maisel JC, Babbitt LH, John TJ: Fatal *Mycoplasma pneumoniae* infection with isolation of organisms from lung. JAMA 1967; 202:139-142

64. Naftalin JM, Wellisch G, Kahana Z, Diengott D: *Mycoplasma pneumoniae* septicemia (Letter). JAMA 1974; 228:565

65. King TE: Bronchiolitis, *In* Schwarz MI, King TE (Eds): Interstitial Lung Disease, 2nd edition. St Louis, Mo, Mosby-Year Book, 1993, pp 463-495

66. Eaton MD, Meiklejohn G, Van Herick W: Studies on the etiology of primary atypical pneumonia: A filterable agent transmissible to cotton rats, hamsters, and chick embryos. J Exp Med 1944; 79:649-668

67. Chanock RM, Hayflick L, Barile MF: Growth on artificial medium of an agent associated with atypical pneumonia and its identification as a PPLO. Proc Natl Acad Sci USA 1962; 48:41-49

68. Foy HM, Kenny GE, Cooney MK, et al: Long-term epidemiology of infections with *Mycoplasma pneumoniae*. J Infect Dis 1979; 139:681-687

69. *Mycoplasma pneumoniae* (Editorial). Lancet 1991; 337:651-652

70. Luby JP: Pneumonia caused by *Mycoplasma pneumoniae* infection. Clin Chest Med 1991; 12:237-244

71. Foy HM, Kenny GE, Sefi R, Ochs HD, Allan ID: Second attacks of pneumonia due to *Mycoplasma pneumoniae*. J Infect Dis 1977; 135:673-677

72. Hunninghake G, Crystal R: Cigarette smoking and lung destruction: Accumulation of neutrophils in the lungs of cigarette smokers. Am Rev Respir Dis 1983; 128:833-838

73. Biberfeld G, Sterner G: Effect of *Mycoplasma pneumoniae* infection on cell-mediated immunity. Infection 1976; 4(suppl):17-20

74. Lin JSL: Human Mycoplasmal infections: Serologic observations. Rev Infect Dis 1985; 7:216-231

75. Taylor G, Taylor-Robinson D, Fernald GW: Reduction in severity of *Mycoplasma pneumoniae* induced pneumonia in hamsters by immunosuppressive treatment with antithymocyte sera. J Med Microbiol 1974; 7:343-348

76. Perez CR, Leigh MW: *Mycoplasma pneumoniae* as the causative agent for pneumonia in the immunocompromised host. Chest 1991; 100:860-861

77. Taylor G: Immunity to Mycoplasma infections of the respiratory tract: A review. J R Soc Med 1979; 72:520-526

78. Fernald GW: Immunologic mechanisms suggested in the association of *M pneumoniae* infection and extrapulmonary disease: A review. Yale J Biol Med 1983; 56:475-479

79. Alshafi KM, Ironton R: Unusual presentation of *Mycoplasma pneumoniae* infection (Letter). Lancet 1991; 338:1519-1520

80. Mizutani H, Mizutani H: Circulating immune complexes in patients with Mycoplasmal pneumonia. Am Rev Respir Dis 1984; 130:627-629

81. Chan CK, Hyland RH, Hutcheon MA: Pulmonary complications following bone marrow transplantation. Clin Chest Med 1990; 11:323-332

82. Domenighetti G, Perret C: Mycoplasma pneumonia with fulminant evolution into diffuse interstitial fibrosis (Letter). Thorax 1980; 35:960

83. Fine MJ, Singer DE, Hanusa BH, Lave JR, Kapoor WN: Validation of a pneumonia prognostic index using the MedisGroups Comparative Hospital Database. Am J Med 1993; 94:153-159