

Mycoplasma Pneumoniae Pneumonia: Walking Pneumonia Can Cripple the Susceptible

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Abstract

Background: *Mycoplasma pneumoniae* pneumonia (MPP), or “walking pneumonia,” is an atypical mild disease with varied clinical findings. Specifically, diagnosis is often controversial and understanding of disease presentation is limited. The goal of the study was to evaluate presentation, clinical associations and outcomes of MPP patients admitted to an inner-city hospital.

Methods: This was a retrospective analysis of adult patients diagnosed with MPP from January 2010 to January 2017. Primary outcomes were need for intensive care unit (ICU) care, ICU and hospital length of stay (LOS), presence of shock and need for mechanical ventilation (MV). Predictors of mortality were analyzed.

Results: Of the 203 patients analyzed, 16 (8%) died. Relative to survivors, non-survivors were older (65 ± 21 versus 53 ± 18 , $P = 0.009$) and less frequently had obstructive airway disease (OAD; $P = 0.003$). Non-survivors also had significantly higher serum levels of lactic dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, transaminases and troponins. Finally, non-survivors more commonly exhibited shock, need for MV and bilateral lung infiltrates. There were no group differences in patient comorbidities, symptoms, antibiotic use or LOS. Predictors of mortality included age, OAD, low CD4⁺ T-cell counts in human immunodeficiency virus-infected patients and elevated serum levels of LDH, creatinine, BUN, leukocytes, transaminases and troponins.

Conclusion: Despite the availability of appropriate antibiotics, MPP incurs significant mortality and morbidity. Our study indicated that the recommended treatment includes prompt serological diagnosis, aggressive supportive care and presumptive antibiotics, especially in patients with poor prognosis.

Keywords: Atypical pneumonia; *Mycoplasma pneumoniae*; Walking pneumonia; *Mycoplasma pneumoniae* IgM titers

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Introduction

Mycoplasma pneumoniae (MP) infections can commonly cause *M. pneumoniae* pneumonia (MPP), or “walking pneumonia.” The prevalence of MPP is widely underestimated, largely because disease presentation is usually mild and MPP patients do not always seek medical attention. Furthermore, the lack of accurate diagnostic modalities for MPP makes diagnosis difficult and often controversial. Similar to MPP presentation, reports of mortality from MP infections show wide disparities. Among the elderly, mortality is reportedly around 8.0% [1, 2], while young adults with no underlying disease are primarily affected by fulminant MPP, which accounts for 0.5-2% of all MPP cases [3]. Another study reported an in-hospital mortality of 30% [4].

The objective of this study was to evaluate the clinical presentation, associations and outcomes of patients hospitalized for MPP in an inner-city hospital in New York City.

Materials and Methods

This study was approved by the hospital institutional review board (IRB), and the need for informed consent was waived (IRB number: 09081608).

Study design

This was a retrospective review of all adults admitted and diagnosed with MPP from January 2010 to January 2017 at Bronx Lebanon Hospital Center. Bronx Lebanon Hospital Center is the largest voluntary, not-for-profit health care system serving the South and Central Bronx, with 972 beds at two major hospital divisions. This hospital cares for a large, underserved and poor population with multiple comorbid conditions.

Methods

This study included all adult patients admitted to Bronx Lebanon Hospital Center from January 2010 to January 2017 with the diagnosis of pneumonia and serum MP IgM antibodies ≥ 770 U/mL. Exclusion criteria included: 1) patients without pneumonia as the admitting diagnosis and 2) patients with serum MP IgM antibodies < 770 U/mL.

Table 1. Patient Demographic Characteristics and Comorbid Conditions

	Survivors N = 187 (%)	Non-survivors N = 16 (%)	P value
Age, year (mean ± SD)	53 ± 18	65 ± 21	T = 2.526; P = 0.012
Male sex	86 (46)	7 (44)	1.000
Race/ethnicity			
Black	91 (48.6)	8 (50)	1.000
Hispanic	92 (49.2)	8 (50)	1.000
Others	4 (2.2)	0	1.000
Current smoker	91 (48.6)	7 (43.8)	0.798
Obstructive airway disease	108 (57.8)	3 (18.8)	0.003
Human immunodeficiency virus infection	46 (24.6)	2 (12.5)	0.368
Liver disease	46 (24.6)	4 (25)	1.000
Malignancy	15 (8)	2 (12.5)	0.629
Diabetes mellitus	40 (21.4)	6 (37.5)	0.208

In previous MPP studies, diagnosis modality varies widely and includes cultures, polymerase chain reaction (PCR), serology and antigen detection techniques. Of these, serology has a sensitivity and specificity of approximately 90% for titers above 32 U/mL. Thus, in our study, we used serology as the diagnosis modality with threshold serum MP IgM antibody titers of 770 U/mL to diagnose MPP.

For all patients, we recorded baseline general characteristics and presence of comorbid conditions such as chronic kidney disease, diabetes mellitus, obstructive airway disease (OAD), coagulopathy, malignancy, infection with human immunodeficiency virus (HIV) and liver disease. Data regarding laboratory parameters, chest imaging results and antibiotic management were also collected. Primary outcomes included admission to the intensive care unit (ICU), ICU and hospital length of stay (LOS), presence of septic shock and need for mechanical ventilation (MV). Predictors of inpatient mortality were also analyzed.

Analysis

In this study, we compared survivors with non-survivors. Group differences for continuous variables and proportions were analyzed with a Mann-Whitney *U* test and Fisher's exact test, respectively. A binomial logistic regression model was constructed to test the predictive power of age, OAD, CreatinineMax, BUNMax, Infiltrates, MycAbLevel, ICULOS-Days, Shock, MV and Macrolide use on patient survival. Association significance was measured with a two-tailed *t*-test. All tests were performed using Statistical Package for Social Sciences v.17 (SPSS Inc., Chicago, IL, USA), with a *P* value of ≤ 0.05 considered significant.

Results

During the study period, we identified a total of 203 patients

composed of 54% women and with an average age of 53 years. Of these patients, 24 (12%) were admitted from a skilled nursing facility and the rest came from home. The majority of patients (92%) survived hospitalization. Survivors were significantly younger than non-survivors (53 ± 18 versus 65 ± 21, *P* = 0.012) and more frequently had OAD (*P* = 0.003). In our cohort, there were also frequent comorbidities, particularly OAD and tobacco abuse, but there were no group differences in patient race, smoking, liver disease, malignancy, diabetes or HIV infection (Table 1). Of note, not all the patients had HIV test available.

There were also no group differences in symptoms at disease presentation. Indeed, 91% of patients presented with respiratory and gastrointestinal complaints. However, cough was more frequent among survivors. Furthermore, exacerbation of OAD was seen in 19.7% of patients, and all required systemic steroids (Table 2). For 32 (67%) of the 48 HIV-infected patients, CD4⁺ T-cell counts were available, which revealed that although there were no group differences in this measure, 30% of those patients had acquired immunodeficiency syndrome.

Analysis of different laboratory parameters revealed that non-survivors had significantly higher serum lactic dehydrogenase (LDH; 2,113 ± 1,476 versus 346 ± 227, *P* = 0.0001), blood urea nitrogen (BUN; 54 ± 40 versus 25 ± 20, *P* = 0.0001), creatinine (3.3 ± 3 versus 1.3 ± 1.0, *P* = 0.0001) and leukocyte counts (*P* = 0.0001). Non-survivors also had significantly higher liver function tests and serum troponins (Table 3). Thus, these values may be predictive of patient prognosis.

Comparisons of chest imaging results also revealed group differences. In the initial chest roentgenogram, lung infiltrates were observed in only 80% of survivors but in 100% of non-survivors, and non-survivors more commonly had bilateral infiltrates (10 versus 57, *P* = 0.0128). Normal chest X-rays (CXRs) were observed in 18% of patients, primarily in survivors. Relatively few patients (33%) underwent a chest computerized tomography (CT) scan to evaluate respiratory symptoms, but all that did, had abnormal scans (Table 4). Thus, the results of chest imaging varied among MPP patients, including

Table 2. Symptoms and Extrapulmonary Involvement of Patients With MPP

Symptom(s)	Survivors N = 187 (%)	Non-survivors N = 16 (%)	P value
Chest pain	23 (12.3)	0	0.23
Dyspnea	126 (67.3)	8 (50)	0.17
Cough	133 (71.1)	5 (31.2)	0.003
Gastrointestinal	35 (18.7)	4 (25)	0.51
Headache	25 (13.3)	6 (37.5)	0.02
Weight loss	6 (3.2)	0	1.00
Fever	100 (53.4)	10 (62.5)	0.60
Musculoskeletal	2 (1)	3 (18.7)	0.003
Exacerbation of obstructive airway disease (OAD)	39 (20.8)	1 (6.2)	0.204
Patients given systemic steroids for OAD	39 (20.8)	1 (6.2)	0.204
Extrapulmonary involvement of MP			
Renal	81 (43.3)	15 (93.8)	0.0001
Gastrointestinal	169 (90.4)	16 (100)	0.0001
Cardiovascular	39 (20.8)	11 (68.8)	0.0001
Hematological	29 (15.5)	3 (18.8)	0.72
Musculoskeletal	106 (56.7)	16 (100)	0.0003
Pulmonary involvement	150 (80.2)	16 (100)	0.047

some that had initially normal CXRs, but bilateral infiltrates were associated with non-survivors. Multi-organ involvement, primarily of the liver, lung, kidney or cardiovascular system, was common, particularly in non-survivors (Table 2).

We then compared antibiotic management strategies to determine if this predicted patient survival. Appropriate and timely (within 24 h of admission) antibiotics were received by 160 (79%) patients, which corresponded to 82% of survivors and 38% of non-survivors (Table 5). This highlights the importance of antibiotic treatment to MPP patient survival.

Finally, we compared outcomes in survivors and non-survivors. Eighty (39%) patients required ICU care, most of them

in the non-survivor group. Non-survivors were more likely to experience shock (5 versus 13, $P = 0.007$) and require MV (11 versus 16, $P = 0.0001$). However, there were no group differences in the ICU or hospital LOS (Table 6). Of the survivors, discharge dispositions were as follows: 22 (12%) patients to a skilled nursing facility, 12 (6%) to hospice, 4 (2%) to a tertiary care center and the remaining 149 (80%) to home.

Discussion

We first analyzed common MPP patient demographics and co-

Table 3. Laboratory Parameters

Laboratory parameters Mean \pm SD (n) (units)	Survivors N = 187	Non-survivors N = 16	P value
Serum lactic dehydrogenase (unit/L)	346 \pm 227 (N = 81)	2,113 \pm 1,476 (N = 4)	T = 9.627; P = 0.0001
Serum haptoglobin (mg/dL)	169 \pm 126 (N = 29)	132 \pm 120 (N = 3)	T = 0.486; P = 0.631
Serum creatinine kinase (unit/L)	558 \pm 1,645 (N = 106)	1,029 \pm 2,780 (N = 16)	T = 0.962; P = 0.338
Serum blood urea nitrogen	25 \pm 20	54 \pm 40	T = 5.032; P = 0.0001
Serum creatinine (mg/dL)	1.3 \pm 1.0	3.3 \pm 3	T = 6.076; P = 0.0001
White blood cells (k/ μ L)	13.7 \pm 7.0	22.7 \pm 9.1	T = 4.814; P = 0.0001
Platelets (k/ μ L)	269 \pm 134	241 \pm 126	T = 0.806; P = 0.421
Serum aspartate transaminase (unit/L)	84 \pm 260 (N = 169)	1,789 \pm 305 (N = 16)	T = 7.179; P = 0.0001
Serum alkaline transaminase (unit/L)	59 \pm 203 (N = 169)	566 \pm 936 (N = 16)	T = 5.853; P = 0.0001
Troponin T (ng/mL)	1.0 \pm 0.3 (N = 39)	0.45 \pm 0.64 (N = 11)	T = 2.591; P = 0.013
Mycoplasma IgM titers (U/mL)	1,555 \pm 1,127	1,366 \pm 582	T = 0.662; P = 0.509

Table 4. Comparison of Chest Imaging Results

Chest X-ray (CXR) on admission	Survivors N = 187 (%)	Non-survivors N = 16 (%)	P value
CXR-unilateral infiltrates	93 (50%)	6 (37.5)	0.438
CXR-bilateral infiltrates	57 (30.5)	10 (62.5)	0.0128
CXR-normal	37 (19.8)	0	0.047
Chest computed tomography (CT) scan on admission			
Number of patients with chest CT scan	64 (34.2)	3 (18.7)	0.27
Ground-glass opacification/airspace consolidation	22 (34.4)	1 (33.3)	1.000
Nodules/masses	8 (12.5)	1 (33.3)	0.355
Bronchovascular thickening/linear opacities	13 (6.9)	0	1.000
Pleural effusion(s)	15 (23.4)	0	1.000
Lymphadenopathy	4 (6.3)	0	1.000
Bronchiectasis	7 (10.9)	0	1.000
Cavitary lesions	2 (3)	0	1.000
Acute pulmonary embolism	1 (1.5)	1 (33.3)	0.08
Normal CXR with abnormal chest CT	8 (12.5)	0	1.000

Table 5. Comparison of Antibiotic Management

Treatment characteristics	Survivors N = 187 (%)	Non-survivors N = 16 (%)	P value
Macrolides	124 (66.3)	3 (18.8)	0.0003
Quinolones	14 (7.5)	1 (6.2)	1.000
Both: macrolides and quinolones	16 (8.5)	2 (12.5)	0.639
Either	138 (73.8)	6 (37.5)	0.007
No antibiotics to cover for mycoplasma	33 (17.6)	10 (62.5)	0.0002
Appropriate antibiotic	154 (82.3)	6 (37.5)	0.0002
Appropriate antibiotics after 24 h	14 (7.5)	1 (6.2)	1.000
Days of appropriate antibiotic	5.82 ± 3.45 (N = 154)	6.33 ± 5.47 (N = 6)	T = 0.347; P = 0.729

morbidities. Our study supports the concept that among adults, illness severity increases in the elderly population [1, 2]. For example, a prospective analysis of 64 MP patients older than 65 years showed that 9% of patients were admitted to the ICU, and one-third of these patients required MV [1]. Similarly, in our cohort, non-survivors were significantly older than survivors (Table 1). Previous reports also indicate that MPP is more common in patients with an underlying OAD, such as

bronchial asthma or chronic obstructive pulmonary disease (COPD) [5-8]. In our study, 55% of our cohort had history of OAD, supporting that OAD increases MPP incidence. Recent studies suggest a strong association between MP infections and exacerbation of asthma [9-12]. For example, asthmatics hospitalized for an exacerbation are six times more likely to have an MP infection [13], and refractory asthma is associated with the CARDS toxin assay [14]. Furthermore, PCR of

Table 6. Comparison of Outcomes Between Survivors and Non-Survivors

Outcomes	Survivors N = 187 (%)	Non-survivors N = 16 (%)	P value
Intensive care unit (ICU) admission	68 (36.3)	12 (75)	0.003
Septic shock	13 (6.9)	5 (31.2)	0.007
Mechanical ventilation	16 (8.5)	11 (68.8)	0.0001
ICU length of stay (days)	5.6 ± 10	6.0 ± 8.2	T = 0.155; P = 0.877
Hospital length of stay (days)	7.3 ± 8.0	9.4 ± 10	T = 0.987; P = 0.325

upper airway samples revealed that 40% of controlled asthma adults had an MP infection, although none had MP antibodies. Together, these data suggest that allergic airway inflammation predisposes the host response to MP infections, implicating MP prevalence in chronic asthma and its role in inflammatory respiratory disease. Interestingly, Kraft et al showed that among asthmatics with MP infections, 6 weeks of clarithromycin treatment improved lung function [15]. In the context of COPD, Smith et al demonstrated that irrespective of COPD severity, the number of exacerbations was higher in patients with MP infections relative to un-infected individuals [5]. Finally, a retrospective study by Lieberman et al showed that MP was the only atypical infection associated with hospitalization for exacerbation of bronchial asthma or COPD [6, 13]. In total, these data coincide with our study results demonstrating that more than 50% of MP patients had concomitant OAD.

In terms of disease presentation, most of our patients presented with non-specific respiratory symptoms, which is consistent with the results from previous studies. Respiratory symptoms associated with MP infections ranged from minor issues such as productive or dry cough secondary to tracheobronchitis to more serious symptoms like exacerbation of OADs or respiratory failure. Other reported symptoms include lung abscess, bronchiectasis, organizing pneumonia, cellular bronchiolitis, pulmonary embolism, pleural effusion and empyema, chronic interstitial fibrosis, diffuse alveolar damage and adult respiratory distress syndrome [9, 16, 17].

Almost 90% of our patients also had some extrapulmonary finding, as demonstrated by symptoms or laboratory findings. This is unsurprising, as MP infections can affect the cardiovascular, digestive, neurological, hematological and dermatological systems [16-19]. Indeed, extrapulmonary involvement associated with MPP typically results from three mechanisms: direct, indirect or vascular occlusion triggered by infection. Fatal complications of MP infection include acute respiratory distress syndrome, disseminated intravascular coagulation, hemophagocytic syndrome, acute disseminated encephalomyelitis, thrombotic events and Stevens-Johnson syndrome [16].

In general, features of MPP in chest imaging are non-specific, although four of the most common patterns are peribronchial and perivascular interstitial infiltrates (49%), airspace consolidation (38%), reticulonodular opacification (8%) and nodular or mass-like opacification (5%). More uncommon findings are pleural effusion and hilar lymphadenopathy [20]. Interestingly, of the 64 patients in our study that underwent chest CTs, cavities were seen in two (3%) patients and lung masses/nodules in seven (10%). In our patients, the most common findings in chest CTs were airspace consolidation, ground-glass opacification and pleural effusions. These features correspond to those previously reported in the literature. For example, Reittner et al observed that among 28 MPP patients undergoing high-resolution chest CTs, the most common patterns were airspace consolidation and ground-glass attenuation [20]. In the pediatric population, however, focal or bilateral reticulonodular opacification are most indicative of MPP [21]. Additionally, normal CXRs have been previously reported in less than 5% of MPP cases [21]. By contrast, 18% of our patients presented with normal CXRs. We suspect that this discrepancy was due to earlier disease presentation in our

study than in previous reports.

MP infections are primarily managed using antibiotics that act on the bacterial ribosome to either inhibit protein synthesis or DNA replication. Effective antibiotics against MP include macrolides, ketolides, streptogramins, tetracyclines and fluoroquinolones [9]. Our study suggests that appropriate and timely antibiotic administration could increase chance of survival; however, this conclusion is limited by the low number of non-survivors in our cohort and the presence of acute respiratory failure and shock among those patients. Interestingly, 10% of our patients survived despite not receiving appropriate antibiotics. This is not entirely surprising, as previous reports suggest that some MP infections can spontaneously resolve within 7 - 10 days of disease manifestation [22]. In general, though, antibiotics seem to be important for MPP patient outcomes. Indeed, a prospective epidemiological study of 343 patients with community-acquired pneumonia showed that identification of the etiological microorganism did not affect the mortality rate, but delays in antibiotic treatment increased mortality [23]. Miyashita et al further emphasized the importance of early antibiotic administration and the positive outcomes associated with systemic corticosteroid treatment, as delayed administration of appropriate antibiotics exacerbated MPP severity [24]. Together, these findings highlight the importance of early and appropriate antibiotic administration.

Reports of mortality from MP infections vary widely, ranging from less than 5-30% [4, 9, 24, 25]. In the elderly specifically, mortality occurs in approximately 8.0% of cases, which is similar to our findings [24, 25]. Khoury et al reported that for patients with MP infections, there was an overall ICU mortality rate of 26.5% and a hospital mortality of 29.4% [4]. For patients over 65 years specifically, the ICU mortality rate was 38.8% relative to 18% in the 19- to 64-year-age group. By contrast, for our patients, ICU mortality was lower at 15. Furthermore, in the Khoury et al.'s study, overall patient mortality correlated with higher APACHE II scores and multiple comorbidities. Extrapulmonary complications of MPP may also contribute to mortality, especially serious cardiovascular and thrombotic complications for which antibiotic therapy would have no effect. Smoking may also lead to fulminant MP and adverse outcomes [3].

There were few limitations to our study. First, this was a single-center, retrospective study that captured adults with MP infections severe enough to require hospitalization. Thus, conclusions from our study must be restricted to patients requiring hospitalization. Second, our description of extrapulmonary involvement was restricted to complications severe enough to be captured in the medical records. Third, we analyzed only short-term all-cause hospital mortality, and few of our patients required transfer to hospice or tertiary center, so it is possible that long-term mortality rates would be higher. Lastly, we did not exclude patients with co-infections of the lung.

Strengths of our study include having a large cohort in an underserved urban population with multiple comorbidities. Furthermore, in our study, diagnosis of MP infections was based mainly on serology. Most studies diagnosed MP infections using serology. Cultures are rarely used, while PCR is expensive and not readily available. PCR results also become negative sooner than serological ones once antibiotic therapy

commences [9]. Alternatively, IgM assay sensitivity increases with the duration of symptoms, approaching more than 70% sensitivity and a positive predictive value close to 80% after 16 days of symptoms [26]. Interestingly, in the adult population, results from PCR and serology correlate well, and using both techniques together improves the reliability and accuracy of MPP diagnosis [27-29]. It is clear that in symptomatic adults, detection of MP would be considered an infection [9]. Hence, our study represents real-world diagnostic modalities for MP infection, making it more translatable to everyday medical practice.

In conclusion, MPP that requires hospitalization is associated with patient mortality and morbidity, particularly in patients with poor prognostic features. MPP patients requiring hospitalization are usually middle-aged with associated comorbidities such as OAD. However, accurate diagnostic tools and understanding of MPP presentation are still limited. In particular, the myriad of clinicoradiological presentations for this disease make diagnosis difficult. Recognition of the different imaging features, including normal radiological findings, cavities and nodules, is required for prompt and specific disease treatment. Our study revealed that such treatment should include an early, empirical antibiotic regimen including coverage for possible MPP, prompt serological diagnosis and careful evaluation for extrapulmonary involvement. Aggressive care is recommended, especially for elderly patients and those with poor prognostic features. Our study contradicts the belief that MPP is a “benign” disease, as 12% of our patients were disabled enough to require transfer to a skilled nursing facility. Ultimately, our study highlights the morbidity and mortality of patients suffering from MPP.

Disclosure

All authors have nothing to disclose.

Author Contributions

All authors were involved in design of the study as well as data acquisition, analysis and interpretation of data.

Definitions

Mechanical ventilation (MV): invasive mechanical ventilation; septic shock: a patient requiring vasopressor to maintain mean arterial pressure > 65 mm Hg despite adequate fluid resuscitation; mortality: in-hospital all-cause mortality; CreatinineMax: highest serum creatinine recorded during admission; BUNMax: highest serum BUN recorded during admission; MycAbLevel: serum mycoplasma IgM antibody.

Abbreviations

MPP: *Mycoplasma pneumoniae* pneumonia; MP: *Mycoplasma*

pneumoniae; HIV: human immunodeficiency virus; LDH: lactic dehydrogenase; BUN: blood urea nitrogen; ICU: intensive care unit; LOS: length of stay; MV: mechanical ventilation; OAD: obstructive airway disease; COPD: chronic obstructive pulmonary disease; CXR: chest X-ray; CT: computed tomography

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