Symptom resolution in patients with *Mycoplasma pneumoniae* pneumonia

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BACKGROUND: *Mycoplasma pneumoniae* generally causes pneumonia of mild to moderate severity in adults. However, little is known about the time course of the resolution of symptoms in this illness.
OBJECTIVES: To determine the time course of the resolution of symptoms in M *pneumoniae* pneumonia.
METHODS: The severity of fatigue, cough, dyspnea, sputum and pleuritic chest pain were self-scored and recorded daily for 14 days and on days 30 and 42. Each symptom was scored on a scale of 0 to 5. The sum of the five symptom scores had a range of 0 to 25 and was transformed into a value from zero to 100 by multiplying by four.
RESULTS: The mean composite symptom score for 76 patients was 59 (out of 100) at presentation, which declined to a score of 17 on day 14. Patients with a score of greater than 20 on day 14 had significantly higher scores throughout the course of the illness. Thirty-four per cent of those who were employed did not take time off work.
CONCLUSIONS: Most patients with M *pneumoniae* pneumonia had resolution of their symptoms within two weeks; however, 12.6% were still symptomatic at 42 days.

Key Words: Mycoplasma pneumoniae; *Pneumonia; Resolution; Symptoms*

Résolution des symptômes chez un patient atteint d'une pneumonie à *Mycoplasma pneumoniæ*

HISTORIQUE : En général, *Mycoplasma pneumoniæ* provoque une pneumonie d'intensité légère à modérée chez l'adulte. Par contre, on en connaît peu sur le décours de la maladie.
OBJECTIF : Déterminer les étapes de la résolution des symptômes dans la pneumonie à M. *pneumoniæ*.
MÉTHODE : Le degré de fatigue, l'intensité de la toux, de la dyspnée et des douleurs thoraciques, et le volume des expectorations ont été notés par les patients quotidiennement pendant 14 jours, puis aux jours 30 et 42. Chaque symptôme était évalué sur une échelle de 0 à 5. La somme des cinq indices de symptômes variait donc de 0 à 25 et était transformée en une valeur de 0 à 100 au moyen d'un facteur de 4.
RÉSULTATS : Chez 76 patients, l'indice composite moyen des symptômes a été de 59 (sur 100) au moment où ils consultaient et cet indice était ramené à 17 au jour 14. Les patients dont le score était de 20 au jour 14 présentaient des indices significativement plus élevés tout au long de leur maladie. Trente-quatre pour cent des sujets qui étaient sur le marché du travail n'ont pas eu à s'absenter.
CONCLUSION : La plupart des patients qui souffrent d'une pneumonie à M. *pneumoniæ* ont vu leurs symptômes soulagés en l'espace de deux semaines. Par contre, 12,6 % présentaient toujours des symptômes au 42e jour.

Mycoplasma pneumoniae causes 17% to 34% of cases of community-acquired pneumonia (CAP) treated in an ambulatory setting (1-4) and accounts for 1% to 32% of patients who are hospitalized for the treatment of CAP (5-14). M *pneumoniae* pneumonia is generally mild to moderate in severity. However, the range of extrapulmonary manifestations of this infection are wide. Mansel et al (15) reported on 148 patients in a retrospective review of all cases of M *pneumoniae* pneumonia at the Mayo Clinic over a 14-year period. Cough was the most common symptom, occurring in 97% of patients, followed by fever in 85%; 52% had a sore throat; 22% had rhinorrhea; 25% had chest pain; and 17% complained of dyspnea. Other symptoms included nausea, vomiting, diarrhea and anorexia in 42% of patients; headache in 33%, chills in 32%, myalgia and arthralgia in 24%, night sweats 13% and 7% had one or more symptom of neurological disease including diplopia, syncope, confusion or tinnitus. However, the natural history of the resolution of symptoms of M *pneumoniae* pneumonia in adults has not been well described. A prospective study of the treatment of CAP on an outpatient basis gave us the opportunity to describe the resolution of symptoms in these patients.

METHODS

Study design and patient population

This was a prospective, randomized, double-blind, multicentre study to compare the efficacy and safety of moxifloxacin hydrochloride 400 mg (orally, once daily) for 10 days with clarithromycin 500 mg (orally, twice daily) for 10 days in the treatment of nonhospitalized patients with CAP.

Patients 18 years of age or older, with signs and symptoms consistent with bacterial pneumonia of mild to moderate severity, not requiring hospitalization (Fine risk class I to III) participated in the study (16). To be classified as having CAP, patients had to have both radiological evidence (as determined by a radiologist) of a new or progressive infiltrate(s) consistent with pneumonia, and two or more of the following symptoms/physical findings: productive cough, purulent sputum, dyspnea or tachypnea (respiratory rate greater than 20 breaths/min), rigors or chills, or pleuritic chest pain.

Patients were excluded from the trial if they met any of the following criteria: a history of allergy to carboxyquinolone or macrolide derivatives; pregnant or nursing women; severe hepatic impairment (baseline serum glutamic-oxaloacetic transaminase or

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TABLE 1
Assessment of pneumonia symptom severity

Symptom	Score	Severity	Description
Fatigue	0	None/absent	No fatigue
	1	Very mild	No fatigue after a full day of ordinary physical activity; fatigue only on exertion greater than ordinary physical activity; comfortable at rest
	2	Mild	Fatigue with ordinary physical activity; comfortable at rest
	3	Moderate	Fatigue with less than ordinary physical activity; still able to cope with daily work, but needs to rest after work; comfortable at rest
	4	Severe	Feeling tired most of the time; fatigue interferes with regular physical activities; comfortable only at rest
	5	Very severe	Fatigue even at rest; cannot perform ordinary physical activities; fatigue necessitates staying home and sleeping at least once during the day
Cough	0	None/absent	No cough
	1	Very mild	Coughing 4 to 5 times per day; no cough suppressant needed
	2	Mild	Coughing 6 to 12 times per day; no cough suppressant needed
	3	Moderate	Coughing 1 to 2 times per hour; cough suppressant needed
	4	Severe	Coughing several times per hour (>3); cough suppressant needed
	5	Very severe	Coughing several times per hour (>5) with coughing spells; interfering with sleep; cough suppressant needed
Dyspnea	0	None/absent	No shortness of breath (SOB)
	1	Very mild	SOB only on exertion greater than ordinary physical activity; comfortable at rest
	2	Mild	SOB with ordinary physical activity; comfortable at rest
	3	Moderate	SOB with less than ordinary physical activity; comfortable at rest
	4	Severe	SOB most of the time; comfortable at rest
	5	Very severe	SOB all the time, even at rest
Sputum	0	None/absent	No sputum expectorated
	1	Very mild	Mucoid; clear to white
	2	Mild	Mucopurulent; mostly white with some yellow; ≤1 teaspoon per day
	3	Moderate	Purulent; yellow to green; 1 tablespoon per day
	4	Severe	Purulent; yellow to green; 2 to 3 tablespoons per day
	5	Very severe	Purulent and bloody; 1 cup per day
Pleuritic chest pain	0	None/absent	No pain
	1	Very mild	Occasional pain; no pain medication needed
	2	Mild	Pain interferes with coughing; no pain medication needed
	3	Moderate	Pain on coughing and deep breath; over-the-counter pain medication needed
	4	Severe	Pain on normal breathing; interferes with sleep; over-the-counter pain medication needed
	5	Very severe	Pain with every breath; requires prescription pain medication.

serum glutamic-pyruvic transaminase and/or total bilirubin three times the upper limit of normal or higher); coexistent disease considered likely to affect the outcome of the study (eg, lung cancer, lung abscess, collagen vascular disease affecting the lungs, empyema, cystic fibrosis, known or suspected active tuberculosis, or alcoholism); or use of systemic corticosteroids greater than 15 mg/day oral prednisone (or its equivalent).

Clinical evaluation

The primary efficacy variable was clinical improvement measured by a change in the sum of five pneumonia symptom scores (fatigue, cough, dyspnea, sputum and pleuritic chest pain) from baseline to day 14. The severity scale for each of the five symptoms was a six-point scale from 0 (no symptom) to 5 (very severe symptom) (Table 1). The sum of the five severity scales had a range of 0 to 25, and was transformed into a 0 to 100 scale through direct multiplication by four. Untransformed scores were used for the analysis of resolution of individual symptoms.

These individual symptoms were assessed by a clinician (site assessment) at baseline (0 h to 48 h pretherapy office visit), on day 7 of treatment (phone call), at the end of therapy (day 14 office visit), on day 30 (phone call) and at the follow-up visit (day 42 after onset of treatment; office visit). Individual patient diaries (self-assessment) were also used to record symptom resolution data (days 0 through 14, 30 and 42).

Symptom resolution was defined as a total symptom score of 20 or less at day 14. A score of 20 or less was chosen because it indicated very mild individual symptoms (eg, an untransformed score of 1 for each symptom). For individual symptoms, a score of less than 1 at day 14 was termed resolution.

Etiological diagnosis

Serum samples (acute phase, day 14 and day 42) were received frozen on dry ice. Before testing, samples were thawed and centrifuged at 3000 *g* for 10 min.

M pneumoniae immunoglobulin G and immunoglobulin M

Serum samples were tested using a semiquantitative enzyme-linked immunosorbent assay (Savyon Diagnostics Ltd, Israel) according to the manufacturer's instructions. A standard curve was generated for each assay using the calibrators provided by the manufacturer. The absorbance values of the patient samples were then plotted on the standard curve and the concentration of antibodies interpolated and expressed as binding units/mL

TABLE 2
Interpretation of the serum immunoglobulin (Ig) G and IgM results at prestudy, day 14 and the six-week follow-up

IgG	IgM	Interpretation
Negative	Negative	No evidence of infection
Negative	Positive	Recent/current infection
Positive	Positive	Recent/current infection
Positive	Negative	Past infection

TABLE 3
Characteristics of patients with *Mycoplasma pneumoniae* pneumonia

Patient population	
Total, n	76
Female, n (%)	46 (60.5)
Mean age (years ± SD)	38.1±14.4
Pneumonia-specific severity of illness class, n (%)	
I	57 (75)
II	17 (22.4)
III	2 (2.6)
Chest radiograph (number of lobes involved), n (%)	
1	59 (77.6)
2	15 (19.7)
Physical measurements (mean ± SD)	
Diastolic blood pressure (mmHg)	73.3±10.6
Systolic blood pressure (mmHg)	121.4±18.9
Heart rate (beats/min)	90.1±15.7
Respiratory rate (breaths/min)	21.2±3.7
Oral temperature (°C)	37.5±1.0

(BU/mL). Patient samples with BU/mL values of greater than 15% BU/mL were considered positive. Results of prestudy, day 14 and six-week follow-up serum were interpreted based on both the immunoglobulin (Ig) G and IgM results (Table 2).

Patients with negative serology at prestudy but whose IgG and/or IgM became positive at day 14 or the six-week follow-up were considered as having recent/current infection.

Statistical methods

The two-sample unpaired Student's *t* test was used to test significant differences between the two groups. The significance level was 0.05.

RESULTS

Five hundred eighteen patients were enrolled in the present study, of whom 76 (14.6%) were diagnosed as having M *pneumoniae* pneumonia. Because these patients were a small subset of the original study, the influence of antibiotic choice on the outcome for patients with M *pneumoniae* was not analyzed. Sixty-four of the patients with M *pneumoniae* had blood cultures done at the time of enrollment and all were negative for a pathogen – one patient had yeast isolated but this was felt to be a contaminant. Thirty-eight of the 64 patients had a sputum specimen processed for culture at the time of enrollment. Twelve (31.5%) were positive for a respiratory pathogen. These were: three *Staphylococcus aureus* isolates; two *Haemophilus influenzae*; two *Streptococcus pneumoniae*; two *Streptococcus* species; and one each of *Moraxella catarrhalis*, group G streptococcus and *Acinetobacter* species.

TABLE 4
Symptoms and mean severity score of five symptoms at time of presentation and at 14 days

	Presentation	14 days
Symptoms, n (%)		
Fatigue	71 (94.6)	23 of 68 (33.8)
Cough	68 (90.6)	17 of 65 (26.1)
Dyspnea	55 (73.3)	11 of 52 (21.2)
Chest pain	50 (66)	8 of 47 (17)
Sputum	48 (64)	12 of 45 (26.7)
Severity of indicated symptom (mean ± SD)		
Fatigue	3.7±1.3	1.1±1.1
Cough	3.7±1.3	1.1±1.0
Dyspnea	2.3±1.5	0.5±0.8
Chest pain	2.3±1.7	0.5±0.9
Sputum	2.2±1.5	0.7±0.9

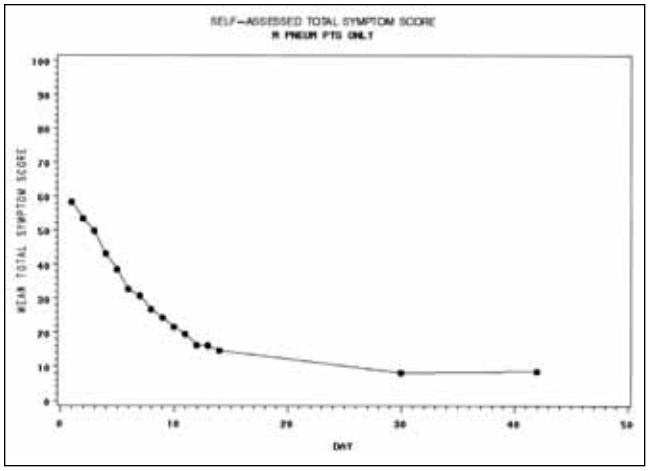

Figure 1) *Mean self-assessed daily total symptom scores for 76 patients with* Mycoplasma pneumoniae *pneumonia*

Sixty per cent of the patients were female (Table 3) and most had mild pneumonia. The symptoms reported by these patients are given in Table 4. Cough and fatigue were the most frequent and most severe symptoms. At 14 days, the symptoms had almost completely resolved. Figure 1 shows the time course of the resolution of symptoms for the entire patient group. Note that the symptom score decreased by 50% within six days. Sixty patients could be divided into two populations based on a total symptom score of 20 or less, or greater than 20 at day 14. The majority (97.3%) had a total symptom score of greater than 20 at the time of enrollment while 19 of these 60 patients (31.6%) had a score greater than 20 on day 14. Those with a score of greater than 20 on day 14 had a higher mean total score at the time of presentation than those with a day 14 score of 20 or less (70 versus 52, respectively; $P<0.001$). Figure 2 shows the time course of symptom resolution for patients with a total symptom score of greater than 20 at day 14 compared with those with a score of 20 or less at day 14. At all time points, those patients with a score greater

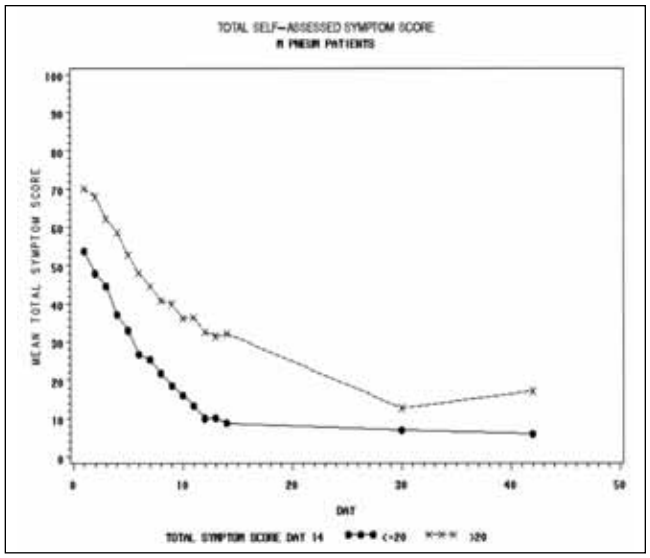

Figure 2) *Time course of symptom resolution when patient were divided into two groups according to a symptom score of 20 or less at day 14 (n=41) versus a score of greater than 20 on day 14 (n=19)*

TABLE 5
Comparison of the *Mycoplasma pneumoniae* patients at day 14 who had a symptom score of 20 or less versus those patients with a symptom score of greater than 20

	Score ≤20	Score >20	P
Number	41	19	
Mean age (± SD)	39.4±14	35.9±12	0.33
Male	22	7	0.76
Fine Class			
I	36	18	0.055
II	16	1	
III	2	0	
Any comorbidity	13	2	0.20

than 20 had a significantly higher score (P<0.001). At day 42, 12.6% of these patients still had a score greater than 20.

The M *pneumoniae* patients who had a symptom score of 20 or less at day 14 were compared with those who had a symptom score of greater than 20 (Table 5). There were no statistically significant differences between the two groups.

Patients with M *pneumoniae* were compared with the 442 patients who had pneumonia due to agents other than M *pneumoniae* (Table 6). The M *pneumoniae* patients were more likely to be female and younger, and less likely to have comorbid illnesses.

The mean symptom scores at presentation were essentially identical for the M *pneumoniae* patients and patients with pneumonia caused by other agents (Table 6 and Figure 3). However, after day 8, symptom resolution was slower among the M *pneumoniae* patients (P<0.01).

One of the most important findings in the present study was that 22 of 64 (34.3%) patients with M *pneumoniae* who were employed at the time of onset of pneumonia did not take time off work.

TABLE 6
Comparison of *Mycoplasma pneumoniae* patients with patients with pneumonia due to agents other than *M pneumoniae*

	M pneumoniae	Others	P
Number	76	442	
Male, n (%)	30 (37)	238 (54)	0.020
Mean age, years (SD)	38.1 (13.4)	49.3 (16.2)	<0.0001
Fine class, n (%)			
Class I	57 (75)	236 (53)	
Class II	17 (22)	136 (31)	0.001
Class III	2 (3)	63 (14)	
Any comorbidity, n (%)	15 (20)	135 (31)	0.05
Cough day 1 mean score (SD)	3.9 (1.2)	3.4 (1.5)	0.06
Cough day 14 mean score (SD)	1 (0.8)	1.1 (1.1)	0.69
Fatigue day 1 mean score (SD)	3.8 (1.1)	3.5 (1.4)	0.06
Fatigue day 14 mean score (SD)	0.9 (0.9)	1.2 (1.2)	0.09
Pleuritic chest pain day 1 mean score (SD)	2.2 (1.6)	2.1 (1.6)	0.46
Pleuritic chest pain day 14 mean score (SD)	0.4 (0.7)	0.5 (0.7)	0.68
Sputum day 1 mean score (SD)	2 (1.6)	2.1 (1.6)	0.47
Sputum day 14 mean score (SD)	0.6 (0.8)	0.7 (0.9)	0.57
Dyspnea day 1 mean score (SD)	2.5 (1.5)	2.6 (1.6)	0.27
Dyspnea day 14 mean score (SD)	0.6 (0.7)	0.9 (1.1)	0.001

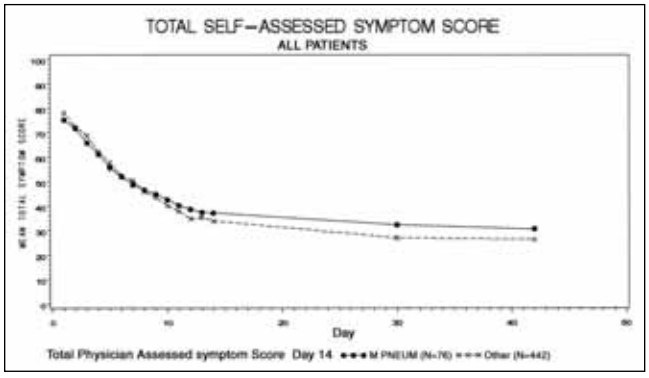

Figure 3) *Time course of resolution of total symptom score for patients with* Mycoplasma pneumoniae *pneumonia* (•) *compared with 442 patients with pneumonia due to other etiological agents* (×)

DISCUSSION

There have been few studies examining the time required to recover from M *pneumoniae* pneumonia. Marrie et al (2) studied 31 patients with pneumonia of unknown etiology and 38 patients with atypical pneumonia (the majority of whom had M *pneumoniae* pneumonia). Both groups of patients completed the short form-36 health survey at presentation and again 30 days after presentation. Both groups of patients suffered a severe deterioration of physical function at the time of presentation with marked but incomplete recovery at 30 days. It is noteworthy that the group with atypical pneumonia had higher physical functioning and mental health scores at 30 days than those with pneumonia of unknown etiology. Benusiglio et al (17) measured pulmonary function in 21 patients suffering

from atypical pneumonia during the acute illness and during convalescence (two to 18 months). Seven of the patients had M *pneumoniae* pneumonia. At the time of admission, 75% of the patients had abnormalities of gas exchange, 52% had a restrictive pattern and 52% had an obstructive pattern. The frequency of abnormalities in the pulmonary function tests decreased dramatically after two to four weeks, and nearly disappeared in all patients during convalescence. However, the mid-maximum expiratory flow rate was abnormal for all patients except those who had M *pneumoniae* infection. The authors concluded that small airway involvement could not be demonstrated during convalescence in patients with M *pneumoniae* infection. Macfarlane and Morris (18) studied 10 patients with M *pneumoniae* pneumonia and found that the diffusion capacity was reduced for a mean of 21 weeks.

Our study indicates that the time course for symptom resolution in adults with M *pneumoniae* pneumonia was related to the severity of the symptoms at the time of presentation. Patients with a mean total symptom score of 70 at the time of presentation had a mean total symptom score of 32 at day 14 compared with a mean score of 8 for patients who had a mean total symptom score of 52 at the time of presentation. We also noted that 12.6% of patients still had a score of greater than 20 at 42 days.

Increasing age is associated with a decrease in the number and severity of symptoms reported by patients with CAP (19). Metlay et al (20) had patients rate the severity of cough, fatigue, dyspnea, myalgia and fever on a scale from 0 (absent) to 5 (severe) on days 0 to 7, 14, 21 and 28 from the time of presentation. They studied 126 ambulatory patients and defined cure as the time to resolution for all five symptoms. The median time to symptomatic cure was 21 days (interquartile range 21 to 28 days). Thirty-five per cent had unresolved symptoms at the end of the study period. However, all of our patients were relatively young, and based on Metlay's data (20) might be expected to have more severe symptoms.

One of the noteworthy findings from the present study was that 34.3% of patients who were employed at the time of diagnosis of the pneumonia did not take time off work.

Eight of our patients had a respiratory pathogen isolated from a sputum specimen and, hence, may have had a dual infection. We did not exclude these patients from the analysis because in any population of patients with M *pneumoniae* pneumonia there may be some patients with polymicrobial infection.

When the speed of symptom resolution for M *pneumoniae* pneumonia patients was compared with the other 442 patients in our study (Figure 3), we noted that the mean total symptom scores were identical for the first eight days, after day 8, the patients with M *pneumoniae* showed slower resolution.

CONCLUSION

The majority of patients with M *pneumoniae* pneumonia have resolution of symptoms within two weeks; however, most (65%) do take some time off work.

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