

Viral and *Mycoplasma pneumoniae* community-acquired pneumonia and novel clinical outcome evaluation in ambulatory adult patients in China

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Abstract Few studies have addressed the etiology and clinical outcomes of community-acquired pneumonia (CAP) treated in an ambulatory setting. We investigated the etiology by the culture of *Mycoplasma pneumoniae*, urine antigen testing of *Streptococcus pneumoniae* and *Legionella pneumoniae*, and DNA or RNA determination of eight kinds of respiratory virus DNA or RNA. An etiological diagnosis was made in 51.8% of 197 patients. The most common pathogens were *M. pneumoniae* (29.4%) followed by influenza virus A, parainfluenza virus, adenovirus, human metapneumovirus (9.6%), and *S. pneumoniae* (4.1%). Patients with mycoplasma infections were younger, less likely to have comorbidities,

and less likely to have adequate sputum for gram stain and culture. Patients with viral infections were older and more likely to have poorly defined nodules on chest X-ray (CXR) or computed tomography (CT) scan. Among patients infected with *M. pneumoniae*, those with quinolones as initial prescriptions had shorter duration of fever after the initiation of antibiotics than patients with β -lactams, macrolides, or β -lactams + macrolides ($p < 0.05$). This study suggests that *M. pneumoniae* and respiratory viruses were the most frequent pathogens found in ambulatory adult CAP patients and quinolones were better than β -lactams, macrolides, or β -lactams + macrolides in the resolution of fever of *M. pneumoniae* pneumonia.

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Community-acquired pneumonia (CAP) is one of the most clinically important diseases in adults, affecting 5 to 20 per 1,000 adults per year [1]. Fifty to eighty percent of patients with CAP are treated on an ambulatory basis [2]. However, most of our knowledge about the clinical manifestations and outcomes of CAP comes from studies among patients requiring admission to the hospital and CAP management guidelines have been influenced by these CAP etiology studies [3, 4]. Currently available evidence from randomized-controlled trials (RCT) scanning is insufficient to make evidence-based recommendations for the choice of antibiotic for the treatment of CAP in ambulatory patients [5]. Although CAP guidelines acknowledge respiratory viruses as a ‘cause’ of pneumonia, few recommendations are made regarding the management of viral pneumonia.

From 1st August 2008 to 31st July 2009, consecutive adults and adolescents (≥ 14 years of age) seen in the fever clinic and who did not require hospitalization were prospectively enrolled in a surveillance study. None of the patients were immuno-

compromised: patients with HIV infection, neutropenia, or who were receiving immunosuppressive chemotherapy were excluded. In addition, patients from nursing homes or patients who had been admitted to a hospital within the last 30 days were also excluded. After the first clinic encounter, all patients were followed-up by telephone within 7 to 28 days. Symptoms and signs were recorded daily. All patients suspected to have CAP had a chest X-ray (CXR). Only one patient had a normal CXR but a positive computed tomography (CT) scan. The pneumonia severity index (PSI) was used to assess the severity of illness [6]. Throat swabs were collected for *Mycoplasma pneumoniae* culture and polymerase chain reaction (PCR) assay [7]. Sputum and throat swabs were screened for the presence of respiratory syncytial virus (RSV), influenza virus (IFV) A, B, and C, parainfluenza virus (PIV) 1–4, human rhinoviruses (HRVs), enterovirus (EV), human coronavirus (HCoV 229E, OC43, NL63, and HKU1), human metapneumovirus (hMPV), and adenovirus (AdV), as previously reported [8, 9]. The microbial etiology was classified as ‘definitive’, ‘presumptive’, or ‘unknown’. Bacteria were considered to be definitive causative agents when isolated from blood or pleural fluid cultures. If *M. pneumoniae* was isolated, it was considered to be a definitive pathogen. *Legionella pneumophila* and *Streptococcus pneumoniae* were considered to be a definite agent when the urinary antigen test was positive. The bacterial pathogen was considered to be ‘presumptive’ if a respiratory pathogen was isolated from purulent sputum (defined as an adequate quality sputum sample with >25 leukocytes and <10 epithelial cells per×100 magnification field). The presence of nucleic acids of *M. pneumoniae* and respiratory viruses from sputum or throat swabs by molecular methods was considered to be ‘presumptive’. Comparisons of clinical characteristics and clinical outcomes were conducted between patients with known causative pathogens and without, using an unpaired Student’s *t*-test, the Mann–Whitney test, or the Chi-square test (SPSS for Windows 13.0).

Data from 197 adult CAP outpatients were available for analysis. Convalescent serum samples were not obtained in all patients. Overall, the median age of the patients was 32.5 years (range, 14 to 89 years), 49.7% were male, and 95.2% had mild CAP (PSI<90). A microbiological diagnosis was established in 102 patients (51.8%). The most common pathogens were *M. pneumoniae* (29.4%), followed by respiratory viruses (9.6%) and *S. pneumoniae* (4.1%). Influenza virus A (IFVA) was the most common respiratory virus identified (6.1%), followed by parainfluenza virus (PIV), adenovirus (AdV), and human metapneumovirus (hMPV). The presence of two or three pathogens was detected in ten outpatients (5.1%). Five patients had co-infections with *M. pneumoniae* and respiratory virus; four had co-infections with bacteria and virus. One patient had three pathogens: *Haemophilus influenzae*, *M. pneumoniae*, and IFVA. Two (1%) of them were diagnosed as pulmonary

tuberculosis by the positive culture of *Mycobacterium tuberculosis* from sputum (Table 1). None of the patients were tested positive for *L. pneumoniae* by urine antigen testing. Urinary antigen testing was positive for *S. pneumoniae* in four patients (two sputum and one blood culture positive for *S. pneumoniae*, the other was sputum culture negative).

Patients with mycoplasma infections were younger than those with bacterial and viral infections ($p<0.001$), had lower PSI score ($p<0.001$), were less likely to have comorbidities ($p=0.003$), and were less likely to have adequate sputum for gram stain and culture ($p<0.001$). Patients with bacterial infections were more likely to have underlying diseases ($p<0.001$) and had higher leukocyte count ($p<0.001$). Patients with viral infections were older and more likely to have poorly defined nodules on CXR or CT scan ($p<0.001$). Patients with mycoplasma infections had longer total duration of fever (T1) than those with bacterial infections ($p=0.031$) and those with no pathogens found ($p=0.009$). Patients with bacterial infections had longer duration from the onset of illness to the resolution of respiratory symptoms

Table 1 Etiology of patients with ambulatory community-acquired pneumonia (CAP)

	<i>n</i>	%
Bacteria	13	6.6
<i>Streptococcus pneumoniae</i>	8	
<i>Escherichia coli</i>	2	
<i>Klebsiella pneumoniae</i>	2	
<i>Pseudomonas aeruginosa</i>	1	
Virus	19	9.6
IFVA	9	
PIV	4	
AdV	4	
hMPV	2	
<i>Mycoplasma pneumoniae</i>	58	29.4
Mycoplasma + virus	5	2.5
RSV	2	
HRV	2	
COV	1	
Bacteria + virus	4	2.1
<i>Streptococcus pneumoniae</i> + PIV	1	
<i>Klebsiella pneumoniae</i> + IFVA	1	
<i>Streptococcus</i> spp. + AdV	1	
<i>Ralstonia pickettii</i> + IFVA	1	
<i>Haemophilus influenzae</i> + Mycoplasma + IFVA	1	0.5
<i>Mycobacterium tuberculosis</i>	2	1
Unknown	95	48.2
Total	197	100

IFVA: influenza virus A; PIV: parainfluenza virus; AdV: adenovirus; hMPV: human metapneumovirus; RSV: respiratory syncytial virus; HRV: human rhinovirus; COV: coronavirus

Table 2 Comparison between CAP patients with different causative pathogens. The data are presented as means±standard deviations, no./total no. (%), or median (range)

	Bacteria group* n=18	Virus group n=19	Mycoplasma group* n=63	Unknown group n=95	p-value
Age (years)	45.1±15.4	51.6±20.1	28.6±11.0	41.2±20.6	<0.001 ^a
Male gender	11/18 (61.1)	12/19 (63.2)	27/63 (42.9)	47/95 (49.5)	0.350
Comorbidities	7/18 (38.9)	2/19 (10.5)	3/63 (4.8)	16/95 (16.8)	0.003 ^b
PSI	61.4±34.4	59.3±24.5	24.8±11.8	39±24.5	<0.001 ^c
Symptoms					
Tmax (°C)	39±1.1	39.1±1.1	38.9±0.8	38.8±0.8	0.527
Cough	17/18 (94.4)	19/19 (100)	60/62 (96.8)	82/89 (92.1)	0.323
White sputum	10/18 (55.6)	10/19 (52.6)	36/62 (58.1)	55/89 (61.8)	0.899
Yellow or bloody sputum	6/18 (33.3)	8/19 (42.1)	16/62 (25.8)	15/89 (16.9)	0.101
Shortness of breath	3/18 (16.7)	3/19 (15.8)	3/62 (4.8)	5/89 (5.6)	0.159
Chest pain	3/18 (16.7)	1/19 (5.3)	6/62 (9.7)	7/89 (7.9)	0.619
Adequate specimen for gram stain or culture	11/18 (61.1)	10/19 (52.6)	13/62 (21.0)	38/87 (43.7)	0.001 ^d
Radiology					
Patchy	15/18 (83.3)	13/19 (68.4)	50/63 (79.4)	84/95 (88.4)	0.142
Poorly defined nodules	0/18 (0)	5/19 (26.3)	0/63 (0)	0/95 (0)	
Consolidation	2/18 (11.1)	4/19 (21.5)	10/63 (15.9)	0/95 (0)	
Bilateral infiltrate	4/18 (22.2)	5/19 (26.3)	13/63 (20.6)	15/95 (15.8)	0.676
Plural fluid	1/18 (5.6)	1/19 (5.3)	3/63 (4.8)	1/95 (1.1)	0.5
Leukocyte count (×10 ⁹ /L)	12.6±8.2	7.9±4.3	7.4±2.2	9.1±3.6	<0.001 ^e
Granulocyte (%)	82.3±8.5	76.0±13.2	74.0±7.5	78.3±8.3	<0.001 ^f
Initial antibiotic					
β-lactams	2/18 (11.1)	5/19 (26.3)	33/62 (53.2)	29/89 (32.6)	0.004 ^g
Macrolides	1/18 (5.6)	0/19 (0)	8/62 (12.9)	14/89 (15.7)	0.230
Quinolones	8/18 (44.4)	9/19 (47.4)	16/62 (25.8)	33/89 (37.1)	0.186
β-lactams + macrolides	5/18 (27.8)	1/19 (5.3)	4/62 (6.5)	10/89 (11.2)	0.046 ^h
Parenteral antibiotic					
T1 (days)	4 (3–5)	5 (3–9)	6 (4–8)	5 (3–7)	0.036 ⁱ
T2 (days)	3 (2–4)	3 (2–4)	3.25 (2–5)	2 (1–4.5)	0.310
R1 (days)	16 (10–22)	11 (8–16)	10 (7–15.25)	9 (6–13)	0.010 ^j
R2 (days)	12 (8–16)	8 (4–13)	8 (5–13)	6.5 (4–10)	0.043 ^k
Defervescence 24 h after antibiotic therapy	1/16 (5.6)	3/17 (15.8)	7/62 (11.3)	26/85 (29.2)	0.014 ^l
Defervescence 72 h after antibiotic therapy	8/16 (44.4)	9/17 (47.4)	26/62 (41.9)	55/85 (61.8)	0.053
Change of antibiotics	9/17 (52.9)	7/17 (36.8)	43/63 (69.4)	46/89 (51.7)	0.594
Duration of antibiotic therapy (days)	10 (7.25–18.75)	9.5 (7.25–13)	9 (7–11)	9 (7–12)	0.774
Cost (US \$)	196 (111–2097)	170 (122–300)	126 (104–169)	153 (115–238)	0.060

T1: total duration of fever; T2: duration of fever after antibiotic therapy; R1: duration from the onset of illness to the resolution of respiratory symptoms; R2: duration of respiratory symptoms after antibiotic therapy

*Including bacteria as a single pathogen (n=13), bacteria + virus (n=4), bacteria + virus + mycoplasma (n=1)

**Including mycoplasma as a single pathogen (n=58), mycoplasma + virus (n=5)

^a Viral group vs. mycoplasma group (p<0.001); viral group vs. unknown group (p=0.046); no statistically significant difference between other groups (p>0.05)

^b Bacterial group vs. viral group (p=0.044); bacterial group vs. mycoplasma group (p<0.001); bacterial group vs. unknown group (p=0.043); unknown group vs. mycoplasma group (p=0.017); no statistically significant difference between other groups (p>0.05)

^c Bacterial group vs. mycoplasma group (p<0.001); bacterial group vs. unknown group (p=0.001); viral group vs. mycoplasma group (p=0.001); no statistically significant difference between other groups (p>0.05)

^d Bacterial group, viral group, and unknown group vs. mycoplasma group (p=0.001); no statistically significant difference between other groups (p>0.05)

^e Bacterial group vs. viral group (p=0.036); bacterial group vs. mycoplasma group (p<0.001); bacterial group vs. unknown group (p=0.004); unknown group vs. mycoplasma group (p=0.001); no statistically significant difference between other groups (p>0.05)

^f Bacterial group vs. mycoplasma group (p<0.001); unknown group vs. mycoplasma group (p=0.001); no statistically significant difference between other groups (p>0.05)

ⁱ Bacterial group vs. mycoplasma group (p=0.031); unknown group vs. mycoplasma group (p=0.009); no statistically significant difference between other groups (p>0.05)

^j Bacterial group vs. mycoplasma group (p=0.031); bacterial group vs. unknown group (p=0.002); no statistically significant difference between other groups (p>0.05)

^k Bacterial group vs. unknown group (p=0.005); no statistically significant difference between other groups (p>0.05)

^l Bacterial group vs. unknown group (p=0.045); unknown group vs. mycoplasma group (p=0.006); no statistically significant difference between other groups (p>0.05)

(R1) than those with mycoplasma infections ($p=0.020$) and those with no pathogens found ($p=0.002$). Patients with bacterial infections also had longer duration of respiratory symptoms after the initiation of antibiotics (R2) than those with no pathogens found ($p=0.005$) (Table 2).

There were no significant differences between the outcomes in patients with bacterial infections according to the initial prescription of antibiotics (β -lactams or β -lactams + macrolides vs. quinolones, $p>0.05$). Among patients infected with mycoplasma, those with quinolones as initial prescriptions had shorter duration of fever after the initiation of antibiotics (T2) than patients with β -lactams, macrolides, or β -lactams + macrolides ($p<0.05$) (Table 3).

The main findings of this prospective cohort study were: (1) *M. pneumoniae* was the most frequent pathogen found in ambulatory adult CAP patients, followed by respiratory viruses and *S. pneumoniae*; (2) patients with different causative pathogens had different clinical features: patients with mycoplasma infections were younger, had lower PSI score, and were less likely to present with purulent sputum; patients with bacterial infections were more likely to have underlying diseases and had higher leukocyte count; patients with viral infections were more likely to have poorly defined nodules on CXR or CT; (3) quinolones seemed to be better than β -lactams, macrolides, or β -

lactams + macrolides in the resolution of fever of *M. pneumoniae* pneumonia.

Little attention has been paid to the etiology and clinical outcomes of ambulatory adult CAP patients. Similar to reports from Roux et al. [10] and Johnstone et al. [11], we demonstrated the significant potential contribution of respiratory viruses in patients presenting with pneumonia. Of 29 viral pneumonia, IFVA ($n=13$), PIV ($n=5$), AdV ($n=4$), and hMPV ($n=2$) were most commonly seen. We also found that the clinical features and outcomes of viral CAP were comparable to bacterial and atypical bacterial pathogens, except that patients with viral infections were older and more likely to have poorly defined nodules on CXR or CT scan (Table 2). It is the well-accepted standard that every CAP patient should receive an antibacterial agent [3, 4]. Based on the findings, we suggest that, if no bacteria or atypical pathogens are detected, antibacterial agents should not be routinely given. More clinical trials are indicated to confirm our suggestion and to select a targeted patient population in whom antibacterial agents can be safely withheld.

Based on the prospective data from 4,532 patients with CAP (CAPNETZ), *M. pneumoniae* pneumonia was found significantly more often in younger patients who had less comorbidity, presented with a less severe

Table 3 Initial prescription and clinical judgment of ambulatory CAP caused by *Mycoplasma pneumoniae*. The data are presented as means \pm standard deviations, no./total no. (%), or median (range)

	β -lactams $n=33$	Macrolides $n=8$	Quinolones $n=16$	β -lactams + macrolides $n=4$	p -value
Age (years)	26.8 \pm 8.7	22.3 \pm 6.5	34.6 \pm 13.9	30.0 \pm 16.1	0.039*
Male gender	13 (39.4)	5 (62.5)	10 (62.5)	3 (75%)	0.358
Comorbidities	1 (3.0)	0 (0)	1 (6.3)	1 (25)	0.243
PSI	22.9 \pm 10.2	18.5 \pm 7.9	30.8 \pm 13.9	30.0 \pm 16.1	0.048*
Tmax ($^{\circ}$ C)	39 \pm 0.9	38.9 \pm 0.7	38.8 \pm 0.8	38.8 \pm 0.7	0.936
White blood cell count	7.8 \pm 2.1	7.3 \pm 2.1	7.2 \pm 2.6	6.5 \pm 1.3	0.606
GR	74.1 \pm 8.4	71.5 \pm 7.0	76.2 \pm 6.2	70.1 \pm 5.9	0.361
T1 (days)	6.5 (4.25–8.75)	6.5 (3.25–7)	5.5 (3.25–7)	7 (4.5–9.5)	0.602
T2 (days)	4 (2–5)	4 (2.4–5.75)	2 (1.25–3)	4.5 (2.5–5)	0.018** ^a
R1 (days)	10 (6.5–18.5)	9 (7–13.25)	9.5 (7.5–13.75)	11 (9–14.5)	0.915
R2 (days)	8 (4–16)	7 (5.25–12.25)	7 (3.5–10)	7.5 (5–11.5)	0.801
Duration of antibiotic therapy (days)	9 (7–11.5)	10 (7.25–10)	7 (6–14)	9.5 (6.75–10)	0.494
Cost (US \$)	132 (103–168)	121 (94–152)	121 (104–221)	131 (96–166)	0.954
Defervescence 24 h after antibiotic therapy	3 (11.1)	0 (0)	4 (25%)	0 (0)	0.202
Defervescence 72 h after antibiotic therapy	12 (36.4)	2 (25)	10 (62.5)	1 (25)	0.200
Change of antibiotics	25 (75.8)	6 (75)	8 (50)	3 (75)	0.779

T1: total duration of fever; T2: duration of fever after antibiotic therapy; R1: total duration of respiratory symptoms; R2: duration of respiratory symptoms after antibiotic therapy

^a Quinolones vs. macrolides ($p=0.018$); quinolones vs. β -lactams ($p=0.006$); quinolones vs. β -lactams + macrolides ($p=0.027$); there were no statistically significant differences between β -lactams, macrolides, and β -lactams + macrolides ($p>0.05$)

disease, showed a lower inflammatory response in terms of leukocyte counts and C-reactive protein (CRP) values, and had had better outcomes [12]. We also demonstrated that, compared with bacterial and viral pneumonia, CAP patients infected with *M. pneumoniae* were younger, had lower PSI score, and were less likely to have adequate sputum for gram stain and culture (Table 2). The Japanese Respiratory Society (JRS) guidelines on CAP included five parameters for differentiation between atypical (*M. pneumoniae*) and bacterial (*S. pneumoniae*) pneumonia. These parameters were: (1) persistent cough; (2) limited auscultatory findings on chest examination; (3) minimal sputum production; (4) a peripheral white blood cell count below 10,000/mm³; (5) nonsevere comorbid illnesses [13].

In older CAP clinical evaluation studies, efficacy was usually defined as the composite endpoint of clinical cure, pneumonia-associated complications, and mortality [14]. But for ambulatory CAP patients, the total duration of fever is only 4–6 days, and there are no pneumonia-associated complications or death [15]. To evaluate the outcomes for the various pathogens, we used the surrogate endpoints of the rapidity of the resolution of clinical manifestations of pneumonia (fever and respiratory tract symptoms). We found that, although patients with CAP caused by *M. pneumoniae* had less severe illness (as measured by the PSI), they had longer duration of fever than patients infected by the common bacterial pathogens. For bacterial pneumonia, the clinical outcome was comparable in patients treated with β -lactams and/or macrolides and respiratory quinolones. But, for *M. pneumoniae*, quinolones appeared to have superior efficacy compared to β -lactams for the resolution of fever (Table 3). The trend in favor of quinolones in the treatment of CAP caused by *M. pneumoniae* can be explained by the high prevalence of macrolide resistance in *M. pneumoniae* isolates from adult and adolescent patients with respiratory tract infections [16].

Serological methods are now frequently used for the diagnosis of *M. pneumoniae* infections. But the reliable diagnosis of *M. pneumoniae* infections still cannot be made on the basis of single acute-phase sera. Paired sera should be obtained during acute and convalescent phases in order to demonstrate rises in antibody titers; a fourfold increase is thought to be significant [17]. Cold agglutinins are IgM antibodies that may appear in the second week of illness. They are detected at a titer of greater than 1:64 in 50–75% of patients with pneumonia due to *M. pneumoniae*, but the test is nonspecific, rendering it more of historical value than of clinical utility.

PCR diagnosis is already available in some centers, will become increasingly available, and is likely to replace serodiagnosis in the longer term. Real-time PCR has both high sensitivity and high specificity and can detect pathogen

DNA even when damaged by the empirical administration of antibiotics. The sensitivity (60–100%) and specificity (96.7–100%) of real-time PCR are both higher than those of serologic assays for *M. pneumoniae* [18]. Almost all PCR-positive cases (>90%) were also confirmed serologically. Where available, the PCR of sputum or lower respiratory tract sample should be the method of choice for the diagnosis of *M. pneumoniae*. In the absence of sputum, a throat swab for *M. pneumoniae* PCR is recommended.

Limitations of this study include the following. (1) This is a single-center study, with only 197 cases in one year. The conclusions about the effect of antibiotics should be made carefully, as the numbers of patients in each subgroup was small and statistical significance does not mean that it is necessarily clinically relevant. (2) The culture of *Legionella* spp. and paired serology were not performed in this study.

In conclusion, we found that *M. pneumoniae* and respiratory viruses (IFVA, PIV, AdV, hMPV) were the most frequent pathogens found in ambulatory adult CAP patients. We also observed that quinolones were better than β -lactams, macrolides, or β -lactams + macrolides in the resolution of fever of *M. pneumoniae* pneumonia.

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Conflicts of interests None.

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