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Clinical, radiographic and hematological characteristics of *Mycoplasma pneumoniae* pneumonia

Letícia Alves Vervloet,[1] Paulo Augusto Moreira Camargos,[2] Damião Ranulfo Fernandes Soares,[3] Gabriel Antônio de Oliveira,[4] Janúncio Nunes de Oliveira[5]

Abstract

Objective: To describe the clinical, hematological and radiographic characteristics of children hospitalized for *Mycoplasma pneumoniae* pneumonia.

Method: The study population consisted of 190 children between 3 months and 16 years old, hospitalized for radiographically confirmed pneumonia. Patients were divided into two groups, to wit: 95 children with *Mycoplasma pneumoniae* pneumonia, as diagnosed using the enzyme-linked immunosorbent assay (ELISA) method; and 95 children with pneumonia caused by other etiologic agents. Using a validated scoring system, the clinical, hematological and radiographic findings of both groups were compared to differentiate *Mycoplasma pneumoniae* pneumonia (group 1) from pneumonia caused by other etiologic agents (group 2), itself divided into two groups, bacterial (n = 75) and viral (n = 20).

Results: *Mycoplasma pneumoniae* pneumonia was found most often in girls ($p < 0.01$), older children ($p < 0.01$), and patients with dry cough ($p < 0.01$) and extrapulmonary manifestations ($p < 0.01$). The clinical, hematological and radiographic variables of *Mycoplasma pneumoniae* pneumonia (mean score = 6.95) scored between those found in bacterial (mean score = 8.27) and viral pneumonia (mean score = 0.90).

Conclusion: Results suggest that the scoring system can contribute to the presumptive diagnosis of *Mycoplasma pneumoniae* pneumonia and help differentiate pneumonic status caused by other etiologic agents.

J Pediatr (Rio J). 2010;86(6):480-487: Mycoplasma, *Mycoplasma pneumoniae*, pneumonia, radiography, children.

Introduction

Mycoplasma pneumoniae (MP) is a major etiologic agent behind community-acquired pneumonia. The factors include poor familiarity with clinical status, lack of quick and specific exams during the initial stage (often unavailable in most practices), and difficulty culturing said microorganisms in laboratories.[1]

Identifying the etiologic agent is a key challenge for pneumonia. In everyday practice, clinicians usually resort to empirical treatment, since the agent is only identified in 40 to 60% of cases,[2,3] and can sometimes not be the sole case of the pneumonia.[4,5] That's why treatment is based on the epidemiological, clinical (especially age),

1. Doutoranda, Saúde da Criança e do Adolescente. Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil.
2. Professor titular, Departamento de Pediatria, Faculdade de Medicina, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil.
3. Pós-graduado, Radiologia. Hospital Trousseau, Paris, France. Médico Radiologista, Hospital Infantil Nossa Senhora da Glória, Vitória, ES, Brazil.
4. Titular, Colégio Brasileiro de Radiologia. Médico Radiologista, Hospital Infantil Nossa Senhora da Glória, Vitória, ES, Brazil.
5. Especialista, Colégio Brasileiro de Radiologia. Radiologista, Hospital Infantil Nossa Senhora da Glória, Vitória, ES, Brazil.

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radiographic and laboratory characteristics associated with certain microorganisms. One should always include MP in differential etiologic diagnosis of community-acquired pneumonia, including as coinfection, since it does not respond to the antibiotics habitually used in treatment, such as beta-lactam.[6,7]

MP does not grow in the media usually employed for bacterial culture, and does not turn the media opaque when it does grow. Colonies formed in solid media cannot be seen under optical microscopes and, since they are Gram-negative, cannot be detected by sputum bacterioscopy either. Therefore, diagnosis requires specific exams; currently, the most frequent are serological exams and the polymerase chain reaction (PCR), with sensitivity and specificity varying according to the kit used.[1]

The objective of this study is to describe a clinical, hematological and radiographic profile of children hospitalized for MP pneumonia, comparing it to the profile of pneumonia caused by other etiologic agents.

Method

This cross-sectional, observational study recruited in sequence 190 children, ages 3 months to 16 years old, with radiographically proven community-acquired pneumonia, admitted to the pneumology department of Hospital Infantil Nossa Senhora da Glória, Vitória, state of Espírito Santo, Brazil (Figure 1). The public regional hospital is associated with the state department of health, and is a reference for urgent/emergency care and pediatric specialties, including pneumology and infectology.

Patients were divided into two groups, to wit: 1) 95 children with MP pneumonia; 2) 95 children with negative results for the same test, and who therefore were suffering from pneumonia caused by other etiologic agents. Later, the score described by Moreno et al.[8] was used to divide group 2 into two others, one suggestive of bacterial (n = 75) and the other of viral etiology (n = 20).

The study included patients ranging from 3 months to 16 years old, of both genders, suffering from community-acquired pneumonia. Patients were excluded if their clinical and radiographic features suggested or confirmed neurological and/or neuromuscular diseases, congenital malformation, primary or acquired immunodeficiency, cardiopathies, bronchopulmonary dysplasia, neoplasms, Bronchiolitis Obliterans, cystic fibrosis, and other chronic pulmonary diseases with pulmonary sequelae.

Clinical diagnosis of pneumonia was based on the clinical and radiographic criteria proposed by the World Health Organization (WHO).[9] MP pneumonia was defined by the

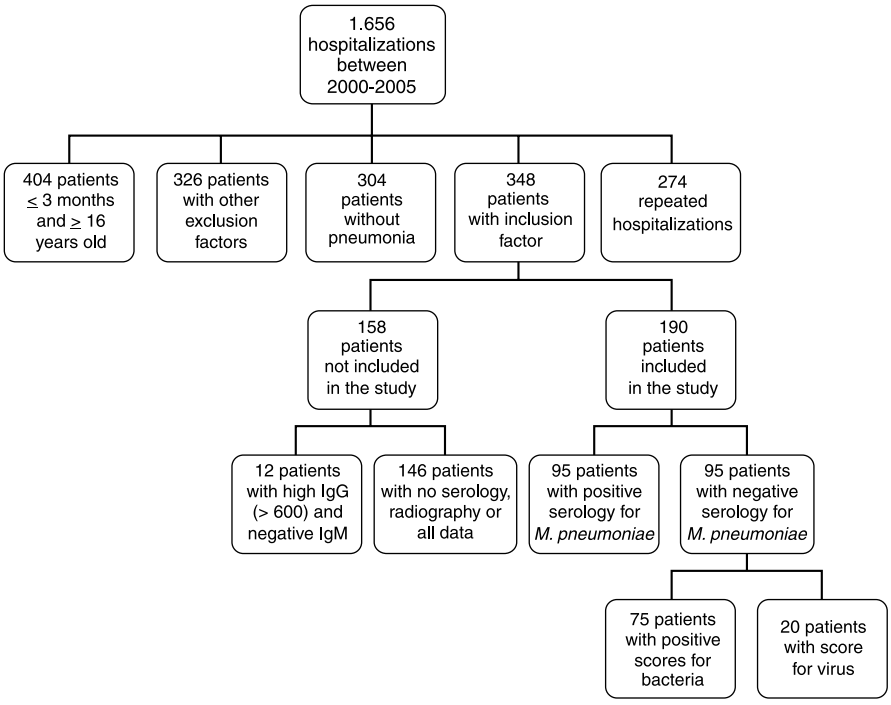

Figure 1 - Flowchart of inclusion, losses and exclusion of study population. Comparative study of patients suffering from *Mycoplasma pneumoniae* pneumonia and other etiologic agents

presence of positive IgM according to the enzyme-linked immunosorbent assay (ELISA) method.

The study used the GenBio ImmunoWELL® (Gen Bio, USA) kit, based on the identification of IgG and IgM for MP. The product has 90% specificity and 92% sensitivity during the acute stage when compared to PCR for MP.[10] All laboratory exams were done at the hospital's regular lab, performed by a technician unaware of the clinical, hematological and radiographic characteristics of the patients in the study.

The score described by Moreno et al.[8] was used to analyze the characteristics of the pneumonia. The score is a clinical, radiographic and hematological scale, originally conceived to make presumptive assessments of whether a pneumonic status had viral or bacterial etiology, but which, for the sake of analysis, was applied to the two groups described above.

The score consists of age, axillary temperature, absolute neutrophil count, and percent bands, and radiographic aspect. The score ranges from -3 to 15; values equal to or greater than 4 indicate bacterial etiology, while viral status can be suspected when the score is equal to 3 points or less. Therefore, axillary temperature ≥ of 39 ºC equals 3 points; age ≥ 9 months equal 2 points; absolute neutrophil count ≥ 8,000 cells/mm^3 equals 2 points; and 1 point for bands ≥ 5%.

Radiographic aspects can be divided into infiltrate type (Well-defined, lobular, segmental, subsegmental (rounded) = 2; poorly defined, patchy = 1; interstitial, peribronchial = -1), location (single lobe or multiple lobes in one or both lungs, but well-defined as in infiltrates = 1; multiple lobes, perihilar, poorly defined = -1), fluid in pleural space (minimal = 1; obvious fluid = 2), abscess, bullae, or pneumatocele (equivocal = 1; evident = 2), and presence of atelectases (subsegmental, usually multiple = -1; lobar, involving right midium lobe or right upper lobe = -1; lobar in other lobes = 0). The cutoff point of 4 is 100% sensitive and 93.8% specific, with positive predictive value of 75.8% and negative of 100% for bacterial etiology. Beware, however, that the score was developed using only the etiological survey of typical viruses and germs, which did not include MP.[8]

Chest X-rays were analyzed by a radiologist with more 25 years of experience in pediatric radiology and who had no knowledge of clinical and hematological characteristics or of ELISA results for MP.

Clinical, hematological and radiographic differences, as well as the score for both groups (MP pneumonia and pneumonia from other etiologic agents) were analyzed using the chi-square test, Fisher's exact test, Student's *t* test, and Mann-Whitney test. Significance, i.e., probability at which the null hypothesis is rejected, was set at 0.05 or 5% ($\alpha < 0.05$).

The study was approved by the research ethics committee of the hospital (protocol number 34/04) and of Universidade Federal de Minas Gerais (protocol ETIC 0421/06).

Results

Table 1 contains descriptive characteristics from both groups. Age was below 5 years old for 75.8% of patients with MP pneumonia and 86.3% for patients with pneumonia caused by other etiologic agents; the difference in mean age was statistically significant ($p < 0.01$). Female gender was more common for the group positive for MP ($p < 0.01$). There was no statistically significant difference in disease course ($p = 0.53$), hospitalization time ($p = 0.25$), use of mechanical ventilation ($p = 0.36$), and number of deaths ($p = 0.62$). Among the signs and symptoms present upon admission, only dry cough, present predominantly in the positive group, was statistically significant ($p < 0.01$) (Table 1).

Table 2 compares the frequency of extrapulmonary manifestations in both groups with statistically significant differences ($p < 0.01$), especially in terms of cardiac alterations ($p = 0.02$).

Comparison between groups with MP pneumonia and pneumonia caused by other etiologic agents with score suggestive of bacterial condition

There was no statistically significant difference between the presence of children younger than 9 months old in the group positive for MP (n = 95) and the group with scores suggestive of bacteria (n = 75). The presence of fever with temperatures ≥ 39 ºC was more frequent in the group with scores suggestive of bacterial pneumonia ($p = 0.02$). Regarding presence of anemia (defined as hemoglobin ≤ 11 g/dL), leukocytes ≥ 12,000 cells/mm^3 and neutrophils ≥ 8,000 cells/mm^3, there was no statistically significant difference. However, the presence of immature neutrophils above 5% was highest in the group suggestive of bacterial pneumonia ($p < 0.01$) (Table 3).

Comparison of radiographic aspects shows that MP had higher frequency of poorly defined or diffuse and interstitial infiltrate; and the other group had greater lobar and lobular aspect at a statistically significant rate ($p = 0.03$). Pleural effusion was present in both groups, but the group with score suggestive of bacterial pneumonia had it at higher rates ($p = 0.03$) and also more apparent ($p < 0.01$) (Table 3).

The difference between the scores of the two groups was statistically significant ($p < 0.01$). The group with MP pneumonia had a score ranging from 0 to 15 points, with mean and standard deviation of 6.95±3.13 and a median of 7; the group with pneumonia caused by other etiologic agents had bacterial scores ranging from 4 to 15 points, with mean and standard deviation of 8.27±2.79 and a median of 8 (Table 3).

Table 1 - Comparison between patients with *Mycoplasma pneumoniae* pneumonia and those with pneumonia from other etiologic agents

Variables	*M. pneumoniae* pneumonia n = 95 (%)	Pneumonia from other etiologic agents n = 95 (%)	p
Age	44.39±39.83 (27; 5-167)	29.98±37.41 (14; 4-183)	< 0.01
< 5 years	72 (75.8)	82 (86.3)	0.06
< 9 months	8 (8.4)	26 (27.4)	< 0.01
Female	59 (62.1)	38 (40.0)	< 0.01
Disease course	10.66±16.86 (6; 1-120)	8.76±7.82 (6; 1-45)	0.53
Signs/symptoms			
Dyspnea	82 (86.3)	79 (83.1)	0.54
Dry cough	58 (79.4)	37 (49.3)	< 0.01
Wheezing	48 (50.5)	45 (47.3)	0.66
Nausea/vomiting	22 (23.1)	29 (30.5)	0.25
Coryza	21 (22.1)	30 (31.5)	0.14
Temperature ≥ 39 ºC	17 (17.9)	25 (26.3)	0.16
Chest pain	18 (18.9)	11 (11.5)	0.15
Diarrhea	14 (14.7)	9 (9.4)	0.26
Abdominal pain	12 (12.6)	10 (10.5)	0.65
Hospitalization time	17.73±13.08 (14; 2-88)	15.97±12.42 (12; 3-74)	0.25
Mechanical ventilation	22 (23.1)	17 (17.9)	0.36
Death	1 (1.0)	3 (3.1)	0.62

Comparison between groups with MP pneumonia and pneumonia caused by other etiologic agents with score suggestive of viral condition

The presence of children younger than 9 months old was equal to 8.4% in the group with positive serology for MP (n = 95) and 80% in the group with negative serology for MP, but with scores suggestive of viral pneumonia (n = 20) (p < 0.01). Axillary temperature ≥ 39 ºC was found in 17.9% of patients with MP pneumonia, but absent in the group with scores suggestive of viral pneumonia (p = 0.04) (Table 3).

Table 2 - Comparison between primary extrapulmonary manifestations of patients with *Mycoplasma pneumoniae* pneumonia and those with pneumonia from other etiologic agents

Extrapulmonary manifestations	MP pneumonia (n = 95)	Pneumonia from other agents					
		Total (n = 95)	p*	Bacteria (n = 75)	p†	Virus (n = 20)	p‡
Alterations present	49 (51.58)	21 (22.11)	< 0.01	16 (21.3)	< 0.01	5 (25.0)	0.03
Cardiac	14 (14.74)	5 (5.26)	0.02	4 (5.3)	0.04	1 (5.0)	0.21
Upper airways	8 (8.42)	3 (3.16)	0.12	2 (2.7)	0.10	1 (5.0)	0.51
Digestive	7 (7.37)	5 (5.26)	0.55	3 (4.0)	0.27	2 (10.0)	0.48
Neurological	6 (6.32)	3 (3.16)	0.49	2 (2.7)	0.22	1 (5.0)	0.64
Renal	6 (6.32)	2 (2.11)	0.27	2 (2.7)	0.22	0 (0.0)	0.30
Dermatological	4 (4.21)	1 (1.05)	0.36	1 (1.3)	0.26	0 (0.0)	0.46
Hematologic	3 (3.16)	1 (1.05)	0.62	1 (1.3)	0.40	0 (0.0)	0.56
Articular	1 (1.05)	1 (1.05)	1.00	1 (1.3)	1.00	0 (0.0)	0.82

MP = *Mycoplasma pneumoniae.*
* Comparison between group with MP pneumonia and without MP.
† Comparison between group with MP pneumonia and score for bacteria.
‡ Comparison between group with MP pneumonia and score for virus.

The presence of leukocytes ≥ 12,000 cells/mm^3 and neutrophils ≥ 8,000 cells/mm^3 was larger in the group positive for MP (both with $p < 0.01$), as well as the presence of bands ≥ 5% ($p = 0.02$) (Table 3).

Comparison of radiographic aspects shows that the group with scores suggestive of viral pneumonia had more diffuse, interstitial and peribronchial infiltrate, located in multiple lobes, perihilar, poorly defined, and with absence of apparent pleural effusion (all $p < 0.01$) (Table 3).

The difference between the scores of the two groups was statistically significant ($p < 0.01$). The group with MP pneumonia had a score ranging from 0 to 15 points, with mean and standard deviation of 6.95±3.13 and a median of 7; the group with viral scores ranged from -2 to -3 points, with mean and standard deviation of 0.90±1.65 and a median of 1 (Table 3).

Discussion

In terms of clinical variables, mean age was highest in the group suffering from MP pneumonia. Age is an important predictor of etiologic agent in pneumonia.[11,12] According to the British Thoracic Society,[2] bacterial pneumonia is most frequent in children 3 years old and older; viral ones, in younger infants; and MP in school-age children. In Finland,

Table 3 - Comparison between patients positive for *Mycoplasma pneumoniae* and patients negative for *Mycoplasma pneumoniae* with score suggestive of bacterial and viral conditions

Variables	MP pneumonia (n = 95)	Pneumonia from other agents			
		Bacteria (n = 75)	p*	Virus (n = 20)	p†
Clinical and laboratory					
Age	44.39±39.83	34.52±38.89	0.01	12.95±25.39	< 0.01
≥ 9 months	87 (91.6)	65 (86.7)	0.30	4 (20.0)	< 0.01
Temperature ≥ 39 ºC	17 (17.9)	25 (33.3)	0.02	0 (0.0)	0.02
Leukocytes ≥ 12,000 cells/mm^3	64 (67.4)	43 (57.3)	0.17	7 (35.0)	< 0.01
Neutrophils ≥ 8,000 cells/mm^3	59 (62.1)	45 (60.0)	0.77	2 (10.0)	< 0.01
Immature neutrophils ≥ 5 (%)	45 (47.4)	53 (70.7)	< 0.01	4 (20.0)	0.02
Radiographic aspect					
Infiltrate			0.03		< 0.01
Lobar, lobular	48 (50.5)	53 (70.7)		4 (20.0)	
Poorly defined	35 (36.9)	15 (20.0)		5 (25.0)	
Diffuse, interstitial peribronchial	10 (10.5)	4 (5.3)		11 (55.0)	
Undefined	2 (2.11)	3 (3.16)		0 (0.0)	
Location			0.16		< 0.01
Single or multiple lobes, well defined	80 (84.2)	68 (90.6)		9 (45.0)	
Multiple perihilar lobes, poorly defined	13 (13.7)	4 (5.3)		10 (50.0)	
Undefined	2 (2.11)	3 (3.16)		1 (5.0)	
Pleural effusion					
Present	39 (41.05)	43 (57.33)	0.03		< 0.01
Minimal	9 (9.5)	0 (0.0)	< 0.01	1 (5.0)	< 0.01
Apparent	30 (31.6)	43 (57.3)		0 (0.0)	
Abscesses, pneumatoceles and bullae					
Present	11 (11.57)	6 (8.0)	0.43		0.20
Doubtful	1 (1.1)	0 (0.0)	0.56	0 (0.0)	0.27
Evident	10 (10.5)	6 (8.0)		0 (0.0)	
Atelectases					
Present	13 (13.7)	3 (4.0)	0.03	0 (0.0)	0.12
Subsegmental (usually multiple) or lobar (upper and right-middle lobe)	7 (7.4)	2 (2.7)	0.09	0 (0.0)	0.21
Lobar (other lobes)	6 (6.3)	1 (1.3)		0 (0.0)	
Score, mean and standard deviation	6.95±3.13	8.27±2.79	< 0.01	0.90±1.65	< 0.01

MP = *Mycoplasma pneumoniae*.
* Comparison between group with MP pneumonia and score for bacteria.
† Comparison between group with MP pneumonia and score for virus.

hospitalized children had mean ages of 29.5 months for typical bacterial, 60.2 months for MP, and 18.5 months for viruses.[13]

In the MP group, 75.8% of cases were of patients younger than 5 years old. According to the literature, MP can strike patients regardless of age. Waris et al.[14] found that 21% of patients with MP pneumonia among children younger than 5 years old. Esposito et al.,[15] in a survey of 196 children younger than 5 years old, found *Streptococcus pneumoniae* in 24.5% and MP in 15.3% of children. Though frequency is lower in that age range, this is also the group for which hospitalization is most frequent. In Finland, in 2004, Korppi et al.[13] found hospitalization rates of 67% for children younger than 4 years old, 5% for children 5 to 9 years old, and 9% for children 10 to 14 years old. The present study assessed only hospitalized children, which explains its large share of subjects younger than 5 years old.

In this study, female patients were more common in the MP positive group. This matches the work by Heiskanen-Kosma et al.,[16] who describe higher rates of incidence for female (2.1 cases/1,000 children/year) rather than male (1.3 cases/1,000 children/year) patients.

In MP pneumonia, symptoms usually appear gradually and can persist for weeks or months.[17] Disease course was longest in the positive serology group (120 days), compared to the 45 days of the negative serology group. Dry cough was most frequent in the positive serology group. According to the literature, when the MP infection is located in the trachea, bronchi and bronchioles, the result is constant, uncontrollable, nonproductive coughing, awakening the patient in the middle of the night and preventing them from going back to sleep.[17] We should stress that the absence of this symptom does not rule out MP infection, and that absence of coughing was greater for the positive serology group (22.11%) than for negative cases (13.68%).

Fever above 39 °C suggests bacterial infection, while low intensity fever is usually associated with viral infections.[18] In this study, fever in MP pneumonia was lower than in bacterial infections and higher than in viral ones.

Increased bands immature neutrophil count in patients without MP is caused by more acute statuses. In MP pneumonia, symptoms usually have a more insidious onset, a fact reflected in blood tests.[17] Leukocytes ≥ 12,000 cells/mm^3 are not statistically different among groups, but the variable is not part of the score.[8]

The presence of extrapulmonary manifestations in MP infections is well documented in the literature. Practically any organ can suffer from MP infections, though the respiratory tract is their primary target. According to the literature, approximately 25% of patients hospitalized for MP infections can have extrapulmonary complications at some point of the disease course. The pathogeny of those complications is unknown and can occur before, during or after pulmonary manifestations and even in complete absence of respiratory symptoms.[17] In this study, 51.58% of MP pneumonia cases had extrapulmonary manifestations, a number above descriptions in the literature, probably due to the severity of patient conditions and the characteristics of the hospital to which patients were admitted. In non-MP cases, only 22.11% of patients had extrapulmonary alterations (21.3% of patients with bacterial scores, 25% of those with viral scores). The most important manifestations were cardiac alterations, found predominantly in the positive group (14 cases, 14.75%, vs. 5 cases and 5.26% in the negative group).

Physicians treating children with pneumonia still have trouble deciding if the etiology is viral, bacterial or of some atypical germ, such as MP, and defining if antibiotics should be administered or not. This is due to the need on the one hand to treat bacterial status with antibiotics to impact morbidity and mortality, and on the other to restrict indiscriminate use of antibiotics in viral statuses, which can lead to increased bacterial resistance. Another key point is choosing which antibiotic to prescribe. The availability of serology or other specific exams to diagnose MP pneumonia is poor in most practices; even when present, results may take too long. Therefore, knowledge of MP behavior can aid the choice of antibiotics, since its lack of cell wall means it does not respond to beta-lactams.[1]

Thoracic radiography is very useful, and should be requested whenever possible for differential diagnosis and to aid the assessment of the extension and level of complication of the pneumonia. However, interpretation of chest x-rays is highly dependent on the examiner.[19] Usually, an interstitial aspect suggests viral etiology, while an alveolar pattern indicates bacterial status. But in a Finnish study of 215 children, bacterial infection was present in only 71% of the 137 children with alveolar infiltrate evident in thoracic radiography and half of the 77 patients with interstitial infiltrate. The authors concluded that most children with alveolar pattern pneumonia, especially those with lobar infiltrate, had laboratory evidence of bacterial etiology; however, interstitial infiltrate is present in both viral and bacterial pneumonia.[20]

Scoring tables with radiographic characteristics provide parameters that help us differentiate between viral and bacterial pneumonia. In 2000, Swingler[21] performed a systematic review of the literature to assess the differentiation of bacterial and viral infections in pediatric chest x-rays. In that study, the Khamapirad & Glezen[22] score achieved the highest rates of sensitivity and specificity (89 and 84%, respectively). The score by Moreno et al.[8] was based on this pre-existing template; to the radiographic aspects were added other clinical and hematological variables, which increased accuracy, resulting in 100% sensitivity and 93.8% specificity, positive predictive value of 75.8% and negative of 100% for bacterial etiology.

When using the score[8] to differentiate between positive and negative serology for MP pneumonia, but with possible bacterial or viral etiology, clinical, laboratory and radiographic variables for MP pneumonia often have means somewhere between bacterial and viral processes, with more variables closer to those suggestive of bacteria than those suggestive of viruses. Mean scores[8] for MP pneumonia are lower than those for bacterial pneumonia, but higher than for viral ones; however, they are closer to bacterial pneumonia scores.

In the literature, viral infection is also associated to the interstitial peribronchial and perihilar infiltrate aspect, and is rarely concurrent with pleural effusion. Alveolar disease, consolidation, presence of aerial bronchogram, and pleural effusion are all characteristics of bacterial pneumonia.[18,20,23] According to the literature, the radiographic aspect of MP lies between the viral and bacterial aspects.[23] In the present study, radiographic comparison showed that infiltrate was more lobar, lobular and well defined in pneumonia with scores suggestive of bacteria, more poorly defined in MP pneumonia, and more diffuse, interstitial and peribronchial in cases of likely viral etiology.

Pleural effusion was apparent in bacterial pneumonia, almost absent in nonbacterial ones, and present, though often minimal, in MP pneumonia. The literature includes a study which evaluated 81 children with pleural effusion, which found *Streptococcus pneumoniae* in 20% of cases, followed by MP in 18%.[24]

A potential limitation of this study is its population, which consists of inpatients at a tertiary hospital, often referred to it by other practices. The score used in the study was developed based exclusively on a etiologic survey of viruses and typical bacteria, which did not include MP.

Results suggest some clinical, hematological and radiographic characteristics present in patients may contribute to the presumptive diagnosis of MP pneumonia and aid the process of differentiating it from cases cause by other etiologic agents.

In most cases, MP pneumonia scored between bacterial and viral pneumonia, though closer to the first. Therefore, if resources to confirm the diagnosis of MP pneumonia are unavailable, a score suggestive of bacterial etiology and lack of response to the antibiotics most commonly employed in the initial treatment for community-acquired pneumonia raise the possibility of MP pneumonia. In these cases, physicians should consider switching current antibiotics to macrolides.

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Correspondence:
Letícia Alves Vervloet
Rua Eugênio Netto, 488 - sala 712 - Praia do Canto
CEP 29055-270 – Vitória, ES – Brazil
Tel.: +55 (27) 3227.2825, +55 (27) 9234.0012
Fax: +55 (27) 3325.0489
E-mail: lvervloet@uol.com.br