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Review

Atypical pneumonia: Pathophysiology, diagnosis, and treatment

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ABSTRACT

Atypical pneumonia is caused by atypical pathogens that are not detectable with Gram stain and cannot be cultured using standard methods. The most common causative organisms of atypical pneumonia are *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species. The therapeutic approach for atypical pneumonias is different than that for typical pneumonia. Typical bacterial pathogens classically respond to β-lactam antimicrobial therapy because they have a cell wall amenable to β-lactam disruption. On the contrary, most atypical pathogens do not have a bacterial cell wall, some are intracellular (e.g., *Legionella*), and some are paracellular (e.g., *M. pneumoniae*). To prevent an increase in the number of antimicrobial-resistant strains, the Japanese pneumonia guidelines have proposed a differential diagnosis for typical bacterial pneumonia and atypical pneumonia to select an appropriate antibiotic for the management of mild-to-moderate pneumonia. The guidelines have set up six parameters and criteria based on the clinical symptoms, physical signs, and laboratory data. However, in the elderly individuals and patients with underlying diseases, the differential diagnosis may be difficult or a mixed infection may be latent. Therefore, in these individuals, the administration of a β-lactam drug plus a macrolide or tetracycline, or only fluoroquinolone should be considered from the beginning to cover bacterial and atypical pneumonia.

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1. Introduction

The term "atypical pneumonia" was first used to describe viral community-acquired pneumonias (CAPs) that were clinically and radiologically distinct from bacterial CAPs. The most common causative organisms of atypical pneumonia are *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species. Other possible pathogens include *Chlamydia psittaci* (psittacosis), *Coxiella burnetii* (Q fever), and respiratory viruses such as the novel severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019).

Atypical pneumonias differ fundamentally from bacterial CAPs. However, the major feature differentiating atypical CAP from typical CAP is the presence or absence of extrapulmonary findings. All atypical pulmonary pathogens cause systemic infectious diseases with a pulmonary component (i.e., pneumonia) [1–5]. Pneumonias caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis* are typical CAPs with clinical and laboratory findings limited to the lungs.

In this mini-review, I have summarized the results of atypical pneumonia obtained from a series of experiments performed over the last 30 years.

2. Epidemiology

Atypical CAPs represent >15% of all CAPs; however, their incidence varies with location [6–13]. Atypical pathogens causing pneumonia may also cause outbreaks of nursing and healthcare associated pneumonia (NHCAP) and hospital-acquired pneumonia (HAP) [14]. However, the occurrence of atypical pneumonia pathogens causing NHCAP or HAP is rare [15–17].

Atypical CAP pathogens, particularly *M. pneumoniae* and *C. pneumoniae*, cause the majority of CAPs in young adults in the ambulatory or outpatient setting [18]. An outpatient setting is the area where atypical pathogens are quantitatively more important than their typical CAP counterparts. Atypical pathogens, particularly *Legionell*a, are an important cause of severe CAP.

Sero-epidemiological studies have demonstrated that 50%–70% of adults have antibody against *C. pneumoniae*; hence, it is estimated that nearly everyone acquires at least one *C. pneumoniae* infection during their lifetime [19]. *M. pneumoniae* and *C. pneumoniae* can cause asymptomatic prolonged or chronic infections lasting for months or years [20,21] and persistent MUC5AC production may contribute to airway inflammation [22]. Thus, persistent *M. pneumoniae* and *C. pneumoniae* infections may induce transient wheezing or precede the onset of asthma in individuals with no history of asthma. In patients with asthma and those with chronic obstructive pulmonary disease (COPD), *M. pneumoniae* and *C. pneumoniae* can precipitate an asthma and COPD exacerbation or make disease control more difficult [23–26].

3. Morphological analysis of *C. pneumoniae*

Chlamydiae, obligate intracellular parasites, depend on the biosynthetic machinery of the host cells for several metabolic functions. All chlamydiae multiply through a common, unique developmental cycle involving two morphologically and functionally distinct forms: one is the infectious elementary body (EB) and the other is the reproductive reticulate body (RB). Morphologically, EBs have a high density and are small in size (diameter: 0.3–0.35 μm), whereas RBs consist of rather homogeneous internal material and are large in size (diameter: 0.5–2.0 μm). RBs are metabolically active and reproductive, but noninfectious. On the contrary, EBs are infectious but metabolically inactive, suggesting their adaptation to an extracellular environment. This unique developmental cycle occurs in a membrane-bound cytoplasmic vacuole, termed inclusion. These morphological characteristics of *C. pneumoniae* are based on the findings of transmission and scanning electron microscopy studies.

3.1. *Surface projections and related structures*

Each EB of *C. pneumoniae* has a dense nucleus located eccentrically and a cytoplasm containing ribosomes, moderately dense particles, and amorphous material. These components are tightly enclosed with a cytoplasmic membrane and therefore, the cytoplasm appears to be round in EBs of *C. pneumoniae*. This results in the formation of a "cytoplasmic body" and a wide, less dense periplasmic space (Fig. 1A) [27–29]. Interestingly, the cytoplasmic body tends to be

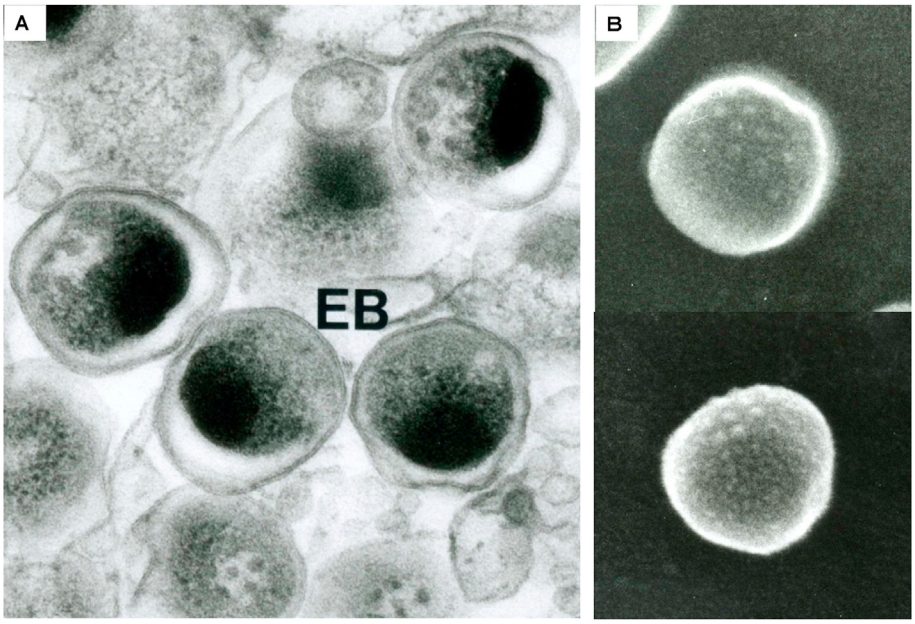

Fig. 1 – A. Thin sections of *Chlamydia pneumoniae* strain in HeLa 229 cells at 60 h after infection. EBs have a narrow periplasmic space and are round in shape. B. Scanning electron micrographs of EBs of *Chlamydia pneumoniae*. Micrograph show hexagonally arrayed projections in a limited area of the surface.

closely associated with the outer membrane at a site far from the nucleus. This strongly suggests that the association of the cytoplasmic body with the outer membrane is mediated by surface projections; however, these projections have not been visualized because of inadequate opacity in thin sections prepared by ordinary procedures. This supposition is supported by evidence that the projections are located in a group on a limited surface area (Fig. 1B) and that one end of each projection is anchored in the cytoplasmic membrane, whereas the other end protrudes beyond the outer membrane.

In situ inclusion at the late stage of multiplication are visualized as convex and concave faces using the freeze-replica technique (Fig. 2). Button structures or craters have been noted in some concave faces (Fig. 2B, ars) [27–29]. A direct correlation between the craters and projections has been confirmed.

Several groups of fine particles arranged hexagonally with a spacing of approximately 50 nm are observed when the inclusion membrane is exposed using the freeze-replica technique (Fig. 3A, ars). The *C. pneumoniae* RB frequently makes contact with the inclusion membrane, where a comb-like structure is evident (Fig. 3). Therefore, it is likely that the fine particles observed on the surface of the inclusion membrane are RB projections that penetrate into the inclusion membrane, resulting in a direct connection with the host cytoplasm.

In isolated chlamydial inclusions (Fig. 3B), RBs close to the inclusion membrane are closely connected to the inside surface of the inclusion membrane by the means of projections, which appear to penetrate into the inclusion membrane (Fig. 4). This evidence evokes a subject of deep interest in the function of the projections in reference with the host–parasite relationship during chlamydial multiplication.

These projections may function in the secretion of proteins from developing RBs, possibly through a type III secretion mechanism. It is likely that the chlamydiae use an alternate secretory pathway, a type III secretion pathway (Fig. 4). The surface projections are, therefore, possible candidates for that function. Although their actual function remains to be elucidated, it is reasonable to propose that the surface projections are involved in some aspect of the interaction between the intracellular environment and the infecting EBs and/or developing RBs.

3.2. *Persistent infection and aberrant forms*

Persistent chlamydial infections can be established in vitro using several methods such as gamma interferon (IFN-γ), antibiotics, and deprivation of certain nutrients. However, despite differences in treatment, chlamydiae respond to form inclusions containing atypical RBs, which occasionally have been shown to be pleomorphic forms, termed aberrant bodies (ABs). The ABs are generally larger in diameter than typical RBs and have a sparse densinometric appearance (Fig. 5). No evidence of redifferentiation into EBs has been documented. However, ABs can be transformed back to RB that differentiate back to infectious EBs by removal of growth inhibitory factors.

In addition, aberrant chlamydial development is concomitant with decreased levels of the major outer membrane protein, 60-KDa outer membrane protein, and lipopolysaccharide [30–34]. Moreover, *C. pneumoniae* up-regulates the transcription of specific genes such as ompA, ompB, pyk, nlpD, and Cpn0585 in response to IFN-γ treatment. Thus, an altered host cell environment, a condition of nutritional stress, is created that makes the *C. pneumoniae* organisms enter into a persistent state.

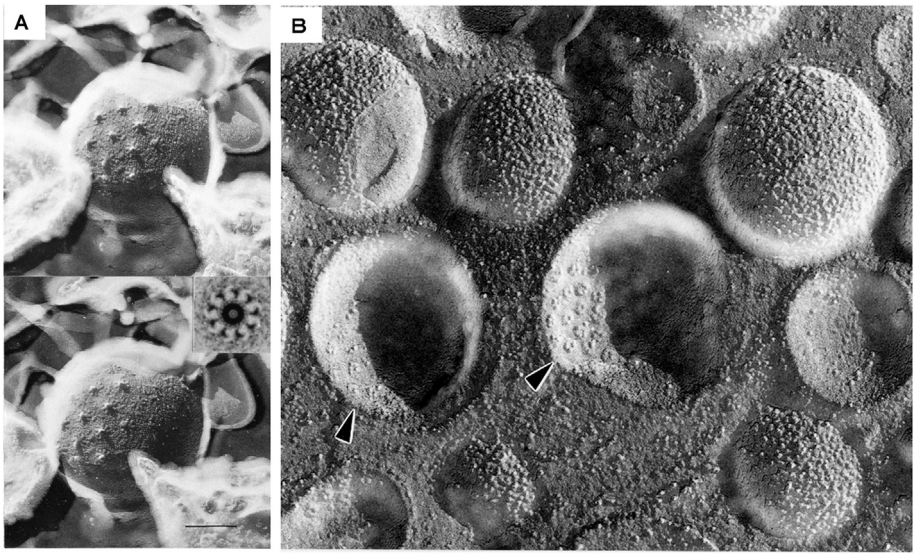

Fig. 2 – Freeze-replica images: A. in situ chlamydial bodies and B. inclusion membrane of the *Chlamydia pneumoniae* strain at 60 h after infection. Chlamydial bodies are cleaved into convex or concave faces. Many EB structures are observed (ars). The bar indicates 1 μm.

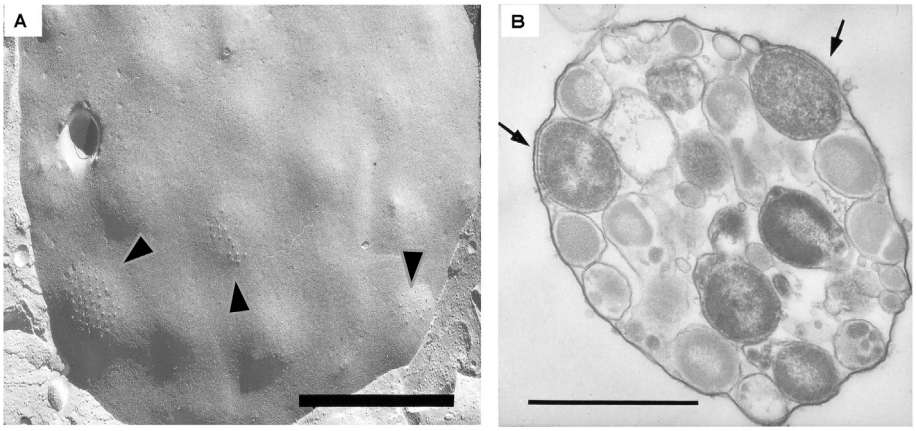

Fig. 3 – Freeze-replica images of an in situ chlamydial inclusion membrane containing the *Chlamydia pneumoniae* strain at 60 h after infection. A. Fine particles in groups are indicated by ars. The face is rugged over the RB outline. B. All projections are penetrating the inclusion membrane. The bar indicates 1 μm.

In general, it is likely that this aberrant developmental step leads to the persistence of viable but nonculturable chlamydiae within infected cells for long periods. Removal of several aforementioned stress factors results in the condensation of nuclei, appearance of late proteins, and production of viable infectious EBs. Most of the major sequelae of chlamydial disease are thought to arise from either repeated or persistent chlamydial infection of an individual. The persistence would allow constant presentation of these potentially deleterious immune targets to the individual's immune systemI. Repeated infection can certainly be documented in many clinical settings and therefore, persistence is also thought to play a role.

4. Clinical presentation

Although pneumonia caused by *M. pneumoniae*, *C. pneumoniae*, and SARS-CoV-2 is usually a benign, self-limited disease, some cases are known to develop into refractory or severe, life-threatening pneumonia [35–37]. On the contrary, pneumonia caused by *Legionella* often presents as a rapidly progressive, severe pneumonia. *Legionella* CAP has a high mortality rate of approximately 10%, which may increase up to 27% in patients who do not receive adequate antibiotics as a part of their empiric treatment on admission.

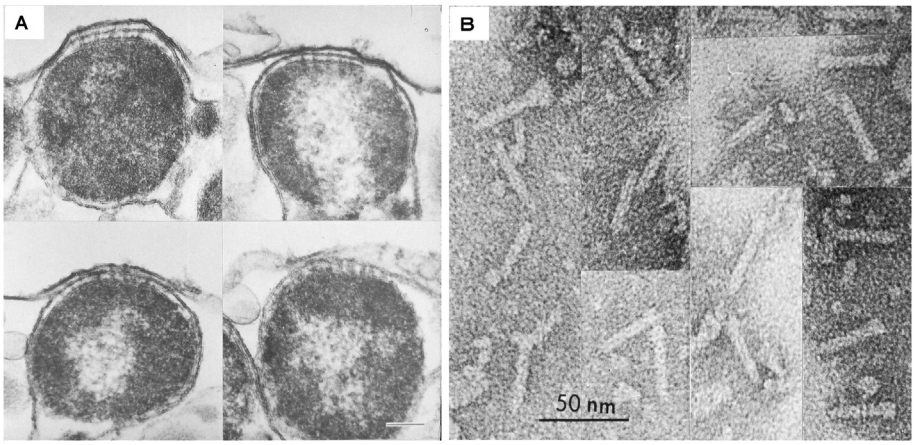

Fig. 4 – A. Freeze-replica images of higher magnification obtained from the micrograph shown in Fig. 3B. B. Negatively stained purified surface projections.

Respiratory tract infection is one of the most common causes of persistent cough, and postinfectious cough is often persistent. Among respiratory pathogens, *Bordetella pertussis*, *M. pneumoniae*, and *C. pneumoniae* are well known causes of persistent cough in both children and adults [38–40]. Cough caused by *B. pertussis* and *M. pneumoniae* is frequently stubborn or paroxysmal [41,42].

The mean age of the patients with *Legionella* pneumonia is significantly lower than that of those with *S. pneumoniae* pneumonia and significantly higher than those with *M. pneumoniae* pneumonia [43–47]. The frequency of patients with *Legionella* pneumonia who are current smokers is significantly higher than that of patients with pneumonia caused by other causative pathogens. Body temperature of patients with *Legionella* pneumonia is significantly higher than that of patients with *S. pneumoniae* pneumonia and similar to that of patients with *M. pneumoniae* pneumonia. The mean white blood cell (WBC) count is significantly lower in patients with *M. pneumoniae* pneumonia and those with *C. pneumoniae* pneumonia. The C-reactive protein (CRP), aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase (LDH), and creatinine levels are significantly higher in patients with *Legionella* pneumonia. Hyponatremia is more frequent in patients with *Legionella* pneumonia compared with patients with other types of pneumonia [43–47].

5. Diagnosis

5.1. *Particle counting method*

I established a method to purify the EBs of all chlamydial species (Fig. 6) [48]. Additionally, they established a method for counting the number of EBs under a scanning electron microscope after sedimentation of EBs on a coverslip by centrifugation. A series of purified EBs are prepared by 2- or 10-fold serial dilution based on the number of EBs. Thereafter, EBs are assayed with antigen or gene detection assay to

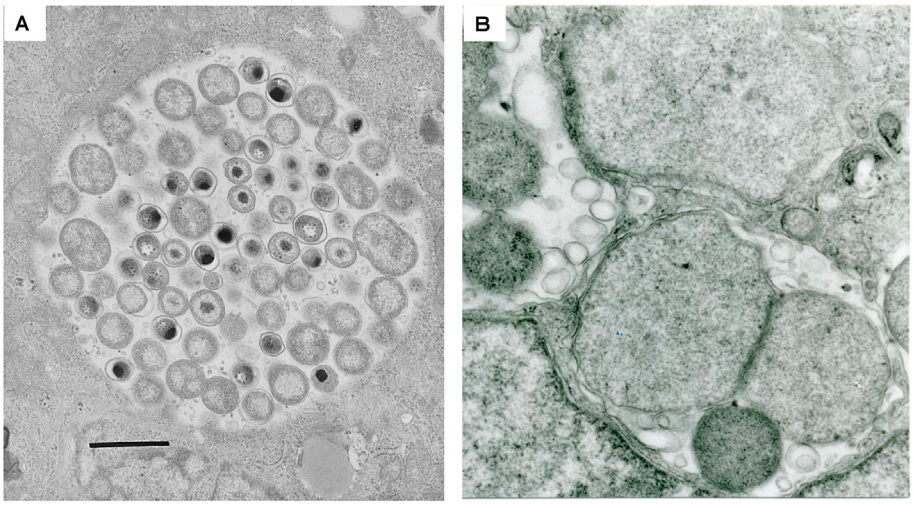

Fig. 5 – Aberrant RB forms produced during culture of the *Chlamydia pneumoniae* strain in the presence of ampicillin. A. A thin section of normal and B. ampicillin-treated infected cells fixed at 60 h after infection. Large and abnormal RBs are seen in inclusions. The bar indicates 1 μm.

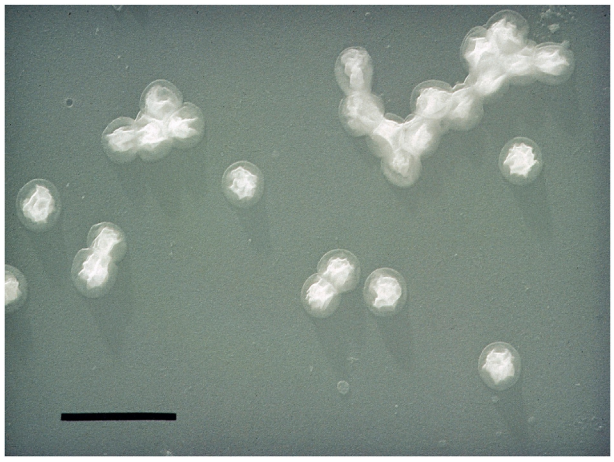

Fig. 6 – Shadowcast of purified EBs of the *Chlamydia pneumoniae* strain. The EBs were air-dried on a smooth-surfaced agar plate, transferred to a specimen grid using the pseudoreplica method with collodion, and thereafter, shadowcast with Pt-palladium alloy. Bars indicate 1 μm.

compare the number of EBs at the detection limit (cutoff level) of each test kit. The nucleic acid amplification techniques can detect 2–4 EBs/assay, indicating that their sensitivity is extremely higher than those of the other assays [49–51].

5.2. *Laboratory testing*

Culture is considered the "gold standard" for the diagnosis of causative agents. However, cultures of atypical pathogens are not widely available because the isolation of atypical pathogens is time-consuming and technically complex and they cannot be cultured using standard methods. Atypical pathogens are not detectable with Gram stain [52]. Although direct fluorescent antibody techniques are simple and rapid diagnostic tests, they are technically complex [53]. Another rapid and simple diagnostic tool is the urinary antigen test; however, it is available only for the detection of *L. pneumophila* and *S. pneumoniae* [54].

To diagnose *C. pneumoniae* infections, antigen detection assays and molecular techniques are not routinely used because these tests require specialized laboratories and/or are expensive, time-consuming, and labor-intensive [55–57]. Thus, currently, serological analysis is the routinely used method for the diagnosis of *C. pneumoniae* infections. Why is the diagnosis of *C. pneumoniae* pneumonia difficult? There are several reasons. First, the appearance of anti-*C. pneumoniae* immunoglobulin M (IgM) antibodies is late, and positive-IgM results may be detected after the resolution of pneumonia [58,59]. The IgG antibody response might be missed if convalescent sera are obtained too early (i.e., earlier than 3 weeks after the onset of illness) because a significant increase in IgG antibodies requires 4–8 weeks [58]. Second, most clinicians and researchers are used to using the enzyme-linked immunosorbent assay (ELISA) kit (e.g., Hitazyme) for the diagnosis of *C. pneumoniae* infection in Japan. It is well known that ELISA IgM antibody frequently shows false-positive findings in both healthy subjects and patients with respiratory tract infections [60–64]. Third, studies have demonstrated that *C. pneumoniae* is a low-frequency etiologic pathogen in both CAP and NHCAP. The severity of *C. pneumoniae* pneumonia is very mild. Asymptomatic or mildly symptomatic *C. pneumoniae* infections are common [18–20], and pneumonia shadows may be quite difficult to detect on routine chest radiographs [58]. Thus, many *C. pneumoniae* pneumonia cases may be missed.

Serological testing has been the most common tool for the diagnosis of *M. pneumoniae* infection for long time. Further, a rapid serological test kit (ImmunoCard STAT! HpSA, Meridian Diagnosis Inc, Cincinnati, Ohio, USA) was developed for the detection of IgM antibodies. However, analysis of only the acute-phase sera resulted in IgM-positive reactions in 35% of the adult patients with serologically and/or culture confirmed *M. pneumoniae* pneumonia using the ImmunoCard [65]. In addition, this kit showed many false-positive reactions in healthy adults and that IgM antibodies persisted for several weeks and months [65,66]. Since 2013, several immunochromatography-based rapid antigen tests for the detection of *M. pneumoniae* have been developed. A study showed that the diagnostic sensitivity and specificity of the immunochromatography-based rapid antigen detection test (Ribotest, Asahi kasei Pharma Co., Tokyo, Japan) in CAP patients with PCR as the control test were 62.5% and 88.3%, respectively [67]. Although the diagnostic accuracy for *M. pneumoniae* has dramatically improved, the disadvantages of such rapid antigen detection assays include a lower diagnostic sensitivity than genetic diagnostic methods. However, the silver amplification assay has overcome this disadvantage [68].

5.3. *Auxiliary diagnosis*

Radiographic findings with chest computed tomography (CT) may distinguish *M. pneumoniae* pneumonia from *S. pneumoniae* pneumonia [69–71]. The sensitivity, specificity, and area under the receiver operating characteristic (ROC) curves for distinguishing *M. pneumoniae* pneumonia from other bacterial pneumonia have been found to be 73%, 85%, and 0.858, respectively [69]. Although several cases of other bacterial pneumonias were judged as *M. pneumoniae* pneumonia using CT findings, all of these cases were judged as non-*M. pneumoniae* pneumonia using the Japanese Respiratory Society (JRS) scoring system (these cases met less than one parameter) and improved with β-lactam antibiotics [69]. The data indicated that the JRS scoring system and radiographic features on CT are useful tools for the presumptive diagnosis of *M. pneumoniae* pneumonia. However, these distinctive radiographic features are not observed in progressed *M. pneumoniae* pneumonia, suggesting that the timing of CT performance is important.

5.4. *Presumptive clinical diagnosis*

The patterns of extrapulmonary organ involvement of *Legionella* pneumonia and *M. pneumoniae* pneumonia is very different and distinct from that of bacterial CAP and provides the basis for a presumptive clinical diagnosis [45–47]. If the

Table 1 – Logistic regression analysis for *Legionella* diagnosis in the development cohort.

	Odds ratio (95% CI)	P value	sprc
Age (10 year)	1.02 (1.00–1.04)	0.075	0.37
Male sex	3.79 (1.84–7.77)	<0.001	0.64
Current smoker	3.04 (1.56–5.93)	0.001	0.49
Ex-smoker	1.32 (0.63–2.77)	0.467	0.11
Body temperature (Celsius)	1.34 (0.91–1.98)	0.134	0.24
Cough	0.21 (0.09–0.47)	<0.001	−0.54
Sputum	0.62 (0.33–1.18)	0.145	−0.23
Dyspnea	6.41 (3.52–11.67)	<0.001	0.90
Chest pain	0.72 (0.26–1.96)	0.518	−0.10
Psychosis	1.30 (0.64–2.64)	0.473	0.10
Headache	0.96 (0.41–2.24)	0.926	−0.01
Gastrointestinal symptom	1.03 (0.38–2.79)	0.950	0.01
White blood cell (1000/μL)	1.03 (0.98–1.08)	0.291	0.15
Platelets (10,000/μL)	1.00 (0.96–1.04)	0.878	−0.02
C-reactive protein (mg/dL)	1.08 (1.05–1.12)	<0.001	0.93
Aspartate transaminase (10 U/L)	0.98 (0.93–1.02)	0.313	−0.22
Lactate dehydrogenase (10 U/L)	1.05 (1.02–1.08)	<0.001	0.94
Creatinine (mg/dL)	0.81 (0.56–1.18)	0.280	−0.14
Sodium (mmol/L)	0.85 (0.80–0.91)	<0.001	−0.69
Creatine kinase (100 U/L)	1.03 (1.00–1.07)	0.069	0.46

CI, confidence interval; sprc, standardized partial regression coefficient.

distinctive patterns of extrapulmonary organ involvement associated with each atypical pathogen are recognized, a presumptive clinical diagnosis is usually straightforward and accurate. Although presumptive clinical diagnosis is not definitive, it should be prompt and specific that confirms or rules out specific pathogens.

The JRS proposed a differential diagnosis between bacterial pneumonia and atypical pneumonia mainly caused by *M. pneumoniae* for the selection of an appropriate antibiotic for the management of mild-to-moderate CAP [12,13]. The JRS identified six parameters for the diagnosis of *M. pneumoniae* pneumonia through multiple regression analysis of the data of patients with *M. pneumoniae* pneumonia [72]. The parameters are: 1) age <60 years, 2) no or minor comorbid illness, 3) presence of stubborn cough, 4) absence of chest adventitious sounds, 5) no sputum or no identified etiological agent by rapid diagnostic tests (Gram staining, urinary antigen tests, and nasopharyngeal antigen test), and 6) a peripheral WBC count of <10,000/μL. The sensitivity and specificity rates for presumptive diagnosis of *M. pneumoniae* based on four or more parameters of the criteria are 86.3% and 93.0%, respectively [12,13]. Several studies have supported the usefulness of the JRS scoring system to distinguish between bacterial pneumonia and *M. pneumoniae* pneumonia [45,73,74]. However, distinguishing between atypical pneumonia and bacterial pneumonia in elderly individuals using the JRS scoring system is difficult [45,46].Hence, physicians should select fluoroquinolones or β-lactams plus macrolides as empirical first-choice drugs, a potential antibiotic cover for atypical pathogens, when treating patients aged ≥60 years.

The Legionella Score has been developed to distinguish patients with *Legionella* pneumonia from patients with non-*Legionella* pneumonia based on the clinical information at diagnosis [75,76]. The Legionella Score is based on the following parameters: male sex, absence of cough, dyspnea, elevated CRP and LDH levels, and low Na level (Table 1). Based on the Youden's index, the best cutoffs values for the Legionella Score parameters are as follows: CRP, ≥17.5 mg/dL; LDH, ≥259 U/L; and Na, <134 mmol/L (Fig. 7). The scoring system has demonstrated good diagnostic ability exception of mild severity pneumonia with A-DROP 0 point. The cutoff, a Legionella Score of ≥3, provided sensitivity of 93%, specificity of 75%, positive likelihood of 3.7, and negative likelihood of 0.10 [75,76].

6. Treatment

6.1. *In vitro and in vivo activity*

A different therapeutic approach is required for atypical pneumonias require compared with typical CAPs. Typical bacterial pathogens classical respond to β-lactam antimicrobial therapy because they have a cell wall amenable to β-lactam disruption. On the contrary, most of the atypical pathogens do not have a bacterial cell wall, some are intracellular, (e.g., Legionella), and others are paracellular (e.g., M. pneumoniae).

Antimicrobials that inhibit or eradicate microorganisms by interfering with intracellular protein synthesis enzymes are effective against atypical pathogens. Macrolides, tetracyclines, and ketolides interfere with intracellular bacterial protein synthesis [77–81]. Quinolones have been found to be the most highly effective antimicrobials against atypical pathogens, particularly Legionella [82–88]. Because some of the atypical pathogens are intracellular (e.g., *Legionella*), intracellular antibiotic penetration into alveolar macrophages

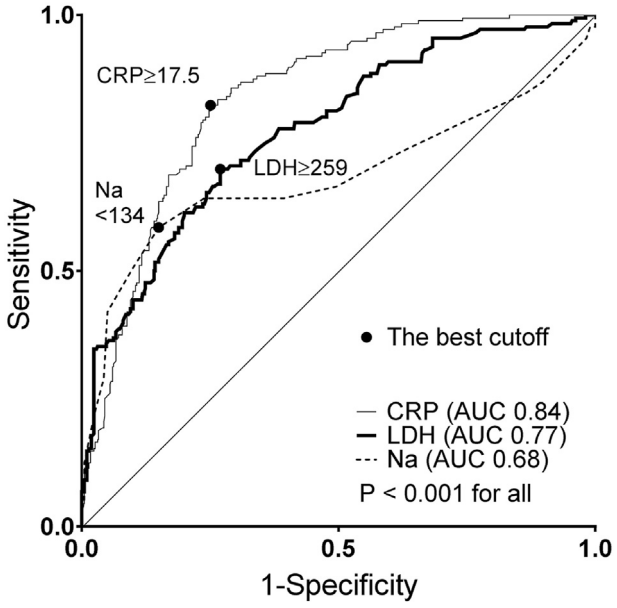

Fig. 7 – Receiver operating characteristics curve. The cut-off values of C-reactive protein (CRP), lactate dehydrogenase (LDH), and sodium (Na). AUC: area under the receiver operating characteristics curve.

(AM) is important. Macrolides, tetracyclines, quinolones, and ketolides concentrate in AMs. Excellent therapeutic efficacy of quinolones has been observed in patients with atypical pneumonia [47,89,90].

6.2. Antimicrobial resistance

In 2000, *M. pneumoniae* showing resistance to macrolides was isolated from clinical samples obtained from Japanese pediatric patients with CAP. Since then, the prevalence of macrolide-resistant (MR) *M. pneumoniae* with mutations in the 23S rRNA gene has increased rapidly [91–95]. Most patients with MR *M. pneumoniae* infection had an A-to-G transition at position 2063 (A2063G) and some had an A-to-T transition at position 2063 (A2063T), an A-to-G transition at position 2064 (A2064G), an A-to-C transition at position 2063 (A2063C), and a C-to-G transition at position 2617 (C2617G). More than 60% of *M. pneumoniae* strains in pediatric patients showed high resistance to 14- and 15-membered ring macrolides with a minimum inhibitory concentration of ≥128 mg/L [96]. The clinical and bacteriological efficacy of macrolides for treating MR *M. pneumoniae* infections was lower than that for treating macrolide-sensitive *M. pneumoniae* infections [97–100].

6.3. Anti-inflammatory therapy against severe pneumonia

Although pneumonia caused by *M. pneumoniae* is usually a benign, self-limited disease, some cases are known to develop into refractory or severe, life-threatening pneumonia [36,101]. The pathogenesis of severe *M. pneumoniae* infections is closely related to an excessive immune response against the pathogen, such as highly activated cell-mediated immune responses and vigorous expression of cytokines. Thus, immunosuppressive therapy with corticosteroids downregulates the cell-mediated immune response and exhibits a profound beneficial effect by reducing the immune-mediated pulmonary injury observed in mycoplasmal infections [102–104].

Interleukin (IL)-18 is believed to be associated with the severity of pneumonia because its level increases particularly in the acute phase and it induces the expression of various cytokines. Thus, the serum IL-18 level is thought to be a useful predictor of refractory or severe *M. pneumoniae* pneumonia and is significantly correlated with of the serum LDH level [102,103]. A study suggested that the serum LDH cut-off level in patients with refractory and severe *M. pneumoniae* pneumonia at the initiation of steroid therapy is 364 IU/L and that at 1–3 days before the initiation of steroid therapy is 302 IU/L [103]. To prevent the progression of pneumonia severity, a serum LDH level of 302–364 IU/L appears to be an appropriate criterion for the initiation of steroid therapy. A stepwise algorithm to correlate diagnosis, serum markers, and initiation of steroid therapy is summarized in Fig. 8. However, further validation studies are warranted.

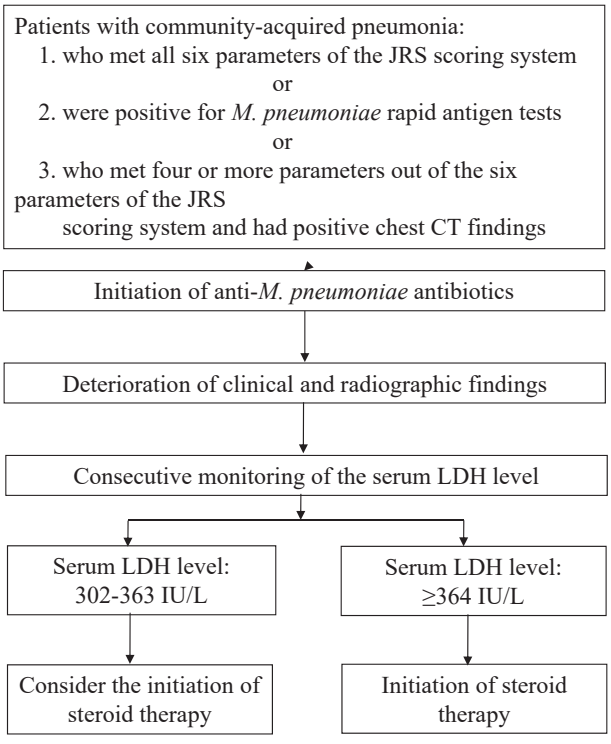

Fig. 8 – A stepwise algorithm to correlate diagnosis, serum markers, and initiation of steroid therapy in *Mycoplasma pneumoniae* pneumonia.

6.4. Guidelines for the management of pneumonia

Epidemiological studies have indicated that in the combined cause-of-death category, pneumonia (including, aspiration pneumonia) ranks fourth in Japan. Therefore, the JRS established guidelines for the management of pneumonia in adults in 2000. An update review highlighting important developments with respect to the evolving resistance of pathogens to antimicrobials and advances in the diagnostic methods, new treatment strategies [105–108], and prevention methods for pneumonia [109,110] should be published every several years to find answers to pressing questions".

Conflict of Interest

The author has no conflict of interest.

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