



# Challenges in the treatment of pediatric *Mycoplasma pneumoniae* pneumonia

Guodong Ding<sup>1</sup> · Xiaobo Zhang<sup>2</sup> · Angela Vinturache<sup>3</sup> · Annemarie M. C. van Rossum<sup>4</sup> · Yong Yin<sup>5</sup> · Yongjun Zhang<sup>1</sup>

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## Abstract

*Mycoplasma pneumoniae* (MP) is an important cause of community-acquired pneumonia in children and young adolescents. Despite macrolide antibiotics effectiveness as a first-line therapy, persistence of fever and/or clinical deterioration sometimes may complicate treatment and may even lead to severe systemic disease. To date, there is no consensus on alternative treatment options, optimal dosage, and duration for treating severe, progressive, and systemic MP pneumonia after macrolide treatment failure. Macrolide-resistant MP pneumonia and refractory MP pneumonia are the two major complex conditions that are clinically encountered. Currently, the vast majority of MP isolates are resistant to macrolides in East Asia, especially China, whereas in Europe and North America, whereas in Europe and North America prevalence is substantially lower than in Asia, varying across countries. The severity of pneumonia and extrapulmonary presentations may reflect the intensity of the host's immune reaction or the dissemination of bacterial infection. Children infected with macrolide-resistant MP strains who receive macrolide treatment experience persistent fever with extended antibiotic therapy and minimal decrease in MP-DNA load. Alternative second-line agents such as tetracyclines (doxycycline or minocycline) and fluoroquinolones (ciprofloxacin or levofloxacin) may lead to clinical improvement after macrolide treatment failure in children. Refractory MP pneumonia reflects a deterioration of clinical and radiological findings due to excessive immune response against the infection. Immunomodulators such as corticosteroids and intravenous immunoglobulin (IVIG) have shown promising results in treatment of refractory MP pneumonia, particularly when combined with appropriate antimicrobials. Corticosteroid-resistant hyperinflammatory MP pneumonia represents a persistent or recrudescing fever despite corticosteroid therapy with intravenous methylprednisolone at standard dosage.

**Conclusion:** This report summarizes the clinical significance of macrolide-resistant and refractory MP pneumonia and discusses the efficacy and safety of alternative drugs, with a stepwise approach to the management of MP pneumonia recommended from the viewpoint of clinical practice.

## What is Known:

- Although MP pneumonia is usually a benign self-limited infection with response macrolides as first line therapy, severe life-threatening cases may develop if additional treatment strategies are not effectively implemented.
- Macrolide-resistant and refractory MP pneumonia are two conditions that may complicate the clinical course of MP pneumonia, increasing the risk for exacerbation and even death.

## What is New:

- This report summarizes the clinical relevance of macrolide-resistant and refractory MP pneumonia and discusses the efficacy and safety of alternative drug therapies.
- A practical stepwise approach to the management of MP pneumonia is developed based on a comprehensive analysis of existing evidence and expert opinion.

**Keywords** *Mycoplasma pneumoniae* · Pneumonia · Macrolide · Community-acquired pneumonia · Macrolide-resistant · Refractory · Children

Guodong Ding and Xiaobo Zhang contributed equally to this work.

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Extended author information available on the last page of the article

## Introduction

*Mycoplasma pneumoniae* (MP), a cell-wall-deficient prokaryote, is one of the most common infectious pathogens, accounting for up to 40% of cases of community-acquired pneumonia in children, especially in school-aged children and adolescents. MP infections tend to be endemic, interspersed by epidemics at 4–7-year intervals. The estimated annual incidence of sporadic MP pneumonia in children aged 5–14 years ranges from 3/1000 to 4/1000 which may increase several folds during epidemics [1, 2]. Younger children appear to have milder or subclinical infections, whereas older children, over 5 years of age, are more likely to develop pneumonia. Although pneumonia due to MP is usually characterized by a benign self-limited infection generally associated with a favorable prognosis, severe life-threatening cases of pneumonia with extrapulmonary manifestations involving almost every organ system may develop if early and accurate diagnosis and appropriate treatment strategies are not implemented [3, 4]. The severity of pneumonia and extrapulmonary presentations may represent the intensity of the host's immune reaction or the spread of bacterial infection [5]. Macrolide-resistant MP infection and refractory MP pneumonia are the two conditions frequently proposed, especially in East Asia, which may complicate the clinical management of MP pneumonia, increasing the risk for exacerbation and even death. There has been no consensus on alternative treatment options and optimal dosage and duration for treating severe, progressive, and systemic MP pneumonia after macrolide treatment failure. Therefore, this report summarizes the clinical relevance of macrolide-resistant and refractory MP pneumonia and discusses the efficacy and safety of alternative drug therapies. Ultimately, we propose a practical stepwise approach to the management of MP pneumonia developed on a comprehensive analysis of existing evidence and expert opinion.

### Classical treatment of MP pneumonia: macrolides

Owing to the lack of a cell wall, MP is inherently resistant to beta-lactams and to all antimicrobials targeting the cell wall, leaving relatively few therapeutic alternatives for this organism. Macrolides are the most potent and first-line agents against macrolide-susceptible MP infections, probably owing to both the antimicrobial activities and the anti-inflammatory properties mediated through cytokine inhibition, with minimal inhibitory concentrations (MIC<sub>50s</sub>) typically being  $\leq 0.001$   $\mu\text{g/mL}$  [6]. In addition, macrolides have a favorable toxicity profile and are easy to administer in a short (3 days) once daily dosing schedule. However,

plasma concentration of ordinary dosage of macrolide treatment often cannot reach the effective MIC for macrolide-resistant MP infections. For example, mutations at positions A2063G and A2064G confer high-level resistance to macrolides, and MIC<sub>50</sub> of erythromycin for those strains is 16  $\mu\text{g/mL}$ , which is almost 10,000 times higher than that for susceptible strains [7]. Despite the fact that modern molecular methods capable of highlighting mutations in identified MP-DNA are available, these tests are not routinely used in clinical practice due to costs and feasibility [8]. Comparative clinical studies on macrolide-resistant and macrolide-susceptible patients have shown that 71–88% of patients with sensitive MP pneumonia experienced abatement of fever within 48 h after initiation of macrolide treatment. In resistant MP pneumonia patients, fever persisted in 52–73% more than 48 h and in 30% of patients for 72 h after initiation of macrolide treatment [9–11]. Thus, the clinical response of MP infections either susceptible or resistant to macrolides can be promptly assessed through the defervescence within 48–72 h after treatment is started [12, 13] (Table 1).

Overt macrolide treatment failure has also been reported, highlighting a need for alternative antibiotic treatment options for infections caused by resistant strains. Two main classes of second-line agents including tetracyclines and fluoroquinolones have been proposed and shown clinical improvement after macrolide treatment failure in children [14–17]. Drugs in the fluoroquinolone and tetracycline classes are not routinely used in pediatric populations because of their toxicity profile, but they continue to be prescribed for selected cases with difficult-to-treat infections where the benefit of therapy may outweigh the risk of toxicity. To date, naturally occurring acquired resistance to tetracyclines or fluoroquinolones in MP clinical isolates have not been reported in the literature.

### Macrolide-resistant MP pneumonia

Since macrolide-resistant MP was first reported in Japan in the early 2000s, it has subsequently spread through Asia and eventually to Europe and North America, attributable, at least in part, to the widespread usage of macrolides globally. Almost 90% of MP isolates are now resistant to macrolides in East Asia including China and Japan, followed by Europe (approximately 1–30%) and North America (12 to 13%) [18]. Macrolides block protein synthesis by binding to specific nucleotides in domains II and/or V of 23S rRNA in the 50S bacterial ribosomal subunit, and mutations at the positions 2063 (A2063G/C), 2064 (A2064G/C), and 2617 (C2617G/A) in the V domain of the 23S rRNA of MP are the primary mechanisms of macrolide resistance [19]. To date, no plasmids or genes that mediate ribosomal modifica-

**Table 1** Clinical features and management of *M. pneumoniae* pneumonia in children**Childhood *M. pneumoniae* pneumonia**

- *M. pneumoniae* accounts for up to 40% of cases of community-acquired pneumonia in children, especially in school-aged children and adolescents
- Macrolides are the most potent and first-line agents against macrolide-susceptible *M. pneumoniae* infections
- Routine dosage of macrolide treatment cannot reach their effective minimal inhibitory concentrations for macrolide-resistant *M. pneumoniae* strains
- Clinical response of *M. pneumoniae* infections either susceptible or resistant to macrolides can be assessed through the symptoms defervescence within 48–72 h after starting treatment

**Macrolide-resistant *M. pneumoniae* pneumonia**

- Mutations at positions 2063, 2064, and 2617 in the V domain of the 23S rRNA of *M. pneumoniae* are the primary mechanisms of macrolide resistance
- Acquisition of resistance does not make the pathogen more virulent, but it leads to more difficult treatment and complications with ineffective antimicrobial therapy
- Two main classes of second-line agents, including tetracyclines and fluoroquinolones, have shown clinical improvement after macrolide treatment failure in children
- Although tetracyclines or fluoroquinolones pose potential toxicity to children, it is unlikely that children with macrolide-resistant MP pneumonia would receive a total dosage that would result in significant side effects

**Refractory *M. pneumoniae* pneumonia**

- Refractory *M. pneumoniae* pneumonia is diagnosed when prolonged fever and/or deterioration of clinical and radiological findings have occurred despite administration of appropriate antibiotics for 7 days or more
- Macrolide-resistant strains are not associated with development of refractory *M. pneumoniae* pneumonia because acquisition of resistance does not render increased virulence of the pathogen or severity of pneumonia
- A hyperactive immune-mediated inflammatory response to infection has been considered to be the primary pathological mechanism of refractory *M. pneumoniae* pneumonia
- Immunomodulators such as corticosteroid and IVIG have shown a beneficial effect by reducing the pulmonary injuries and extrapulmonary complications in refractory *M. pneumoniae* pneumonia

**Corticosteroid-resistant hyperinflammatory *M. pneumoniae* pneumonia**

- Corticosteroid-resistant hyperinflammatory *M. pneumoniae* pneumonia is characterized by persistent or recrudescing fever for more than 3 days despite intravenous methylprednisolone therapy at standard dosage
- In this condition, the increase of methylprednisolone dosage or pulse therapy and/or IVIG may be considered
- There have been no serious adverse events reported during or after corticosteroid and/or IVIG administration

tion, or any enzymes that break down macrolides, have been described for MP [20]. Mutations at position 2617 tend to produce lower levels of resistance, while those at positions 2063 and 2064 lead to high-level macrolide resistance. In some regions of China, the transition mutation A2063G has been reported to be the most common one, accounting for almost 90% of point mutations [21–23]. Although the presence of macrolide-resistant MP renders a longer febrile period and extended antibiotic therapy, its clinical relevance has been debated because whether resistant strains can cause more severe disease remains controversial and macrolides appear clinically effective in some patients infected by macrolide-resistant strains [9, 15, 17]. This phenomenon is probably attributable to the fact that MP infections are often self-limited diseases and that the anti-inflammatory effects of macrolides may improve clinical symptoms. Several studies have reported no differences in the clinical or radiographic presentation of pneumonia between macrolide-resistant and macrolide-susceptible MP in children [9, 24]. However, others reported that children infected with macrolide-resistant MP treated with azithromycin experienced more serious radiological findings and significantly more extrapulmonary complications than those infected with macrolide-susceptible

strains [25]. These authors suggested that ineffective treatment of resistant MP pneumonia led to a stronger host reaction with increased cytokine-mediated inflammation, particularly interleukin-8 (IL-8) and IL-18, which may be associated with severity of illness in children. However, Matsuda et al. observed no differences in IL-8 and IL-18 in children with resistant MP infection but did observe higher levels of IL-10, interferon gamma (IFN- $\gamma$ ), and interferon gamma-induced protein 10 (IP-10) [26]. The consensus is that the acquisition of resistance does not render increased pathogen virulence but leads to more difficult treatment and complications with ineffective antimicrobial therapy [18].

**Tetracyclines**

Doxycycline and minocycline are broad-spectrum, second-generation semisynthetic bacteriostatic antibiotics belonging to the tetracycline family, which block protein synthesis by binding to the bacterial ribosome at high- (30S) and low-affinity (50S) sites and by inhibiting the attachment of transfer RNA to an acceptor site on the messenger RNA ribosomal complex. Doxycycline and minocycline each have good activity against both macrolide-susceptible

MP strains ( $MIC_{90}$  0.125–0.5  $\mu\text{g/mL}$  and 0.125–2  $\mu\text{g/mL}$ , respectively) and resistant strains ( $MIC_{90}$  0.5 and 2  $\mu\text{g/mL}$ , respectively) with comparable concentrations [27]. Several studies have shown that in children with macrolide-resistant MP pneumonia, tetracyclines (doxycycline, minocycline) exhibited excellent clinical and microbial efficacy on achieving defervescence and decreasing MP-DNA load after macrolide treatment failure [28–30] or compared with macrolide treatment [14, 30]. The remarkable side effect of tetracyclines is incorporation into mineralizing tissues such as teeth, cartilage, and bone that are calcifying at the time of their administration, resulting in discoloration of both the primary and permanent dentitions [31]. Consequently, the application of tetracyclines in pregnant women and children less than 8 years of age was discouraged. However, recent studies on doxycycline use have reported no or only negligible teeth staining even in young children aged 2–8 years, possibly attributed to a low affinity for calcium binding [32, 33]. The development of teeth discoloration by tetracyclines appears to be dependent on the dose and the duration of treatment. Short cycles with limited courses (less than six courses, approximately 6 days per course) were reported to cause negligible tooth discoloration in children in the first 5 years of life [34]. Although adverse reactions are more commonly reported for minocycline, both doxycycline and minocycline are generally well tolerated. It is unlikely that children with macrolide-resistant MP pneumonia would receive a total dosage of tetracyclines that would result in cosmetically significant staining of the teeth. Considering the above, we recommend doxycycline as first alternative antibiotic for macrolide-resistant MP pneumonia at a dose of 4 mg/kg/day orally administered twice daily (Table 2).

## Fluoroquinolones

Fluoroquinolones act against topoisomerases, thus inhibiting DNA synthesis and replication, with high effectiveness against MP in vitro [35]. In vitro activity against macrolide-resistant PM isolates has been reported for some fluoroquinolones, with  $MIC_{90s}$  being 0.0008–0.125 mg/mL for moxifloxacin, 0.25–0.5 mg/mL for levofloxacin and tosufloxacin, and 0.5–4.0 mg/mL for ciprofloxacin [27]. Levofloxacin is known as a respiratory fluoroquinolone due to strong activity against many of the respiratory pathogens, such as *Streptococcus pneumoniae* and MP, while retaining activity against many of the Gram-negative pathogens. A newer fluoroquinolone, tosufloxacin, developed by Toyama Chemical Co. Ltd. (Tokyo, Japan), has been approved only in Japan for pediatric pneumonia when a resistant bacterial infection is suspected, and ordinary antimicrobial agents are expected to be ineffective [36]. Despite not being as effective as other fluoroquinolones, ciprofloxacin is the only fluoroquinolone to be included on the list of “Essential Medicines for Chil-

dren” prepared by the WHO, probably due to its lowest cartilage toxicity [37]. Various case reports have shown that replacing macrolides with fluoroquinolones in children with resistant MP infections (levofloxacin, ciprofloxacin, and tosufloxacin) resulted in clinical improvement with prompt resolution of fever and cough [10, 15, 38]. Although early observations of fluoroquinolone-associated joint/cartilage toxicity in juvenile animals led to contraindication of use in pediatric population, fluoroquinolones have been generally considered to be well tolerated, and they continue to be prescribed for selected pediatric patients with difficult-to-treat infections [39, 40]. Among children included in randomized, prospective, comparative studies treated with levofloxacin or a comparator, safety monitoring focused on musculoskeletal disorders including arthralgia, arthritis, tendinopathy, and gait abnormality. Higher incidences of disorders involving weight-bearing joints were reported at 2 months (2.1% vs. 0.9%) and 12 months (3.4% vs. 1.8%) after starting levofloxacin versus nonfluoroquinolone antibiotics, but no clinically detectable differences were observed between levofloxacin- and comparator-treated children for 1–5 years posttreatment assessment [41, 42]. These findings suggest that if long-term injury occurs with levofloxacin, the rate of these events is low; if injury occurs, it appears to be reversible within 1–5 years.

There have been no prospective randomized controlled trials designed to directly compare the clinical efficacy between tetracyclines and fluoroquinolones in macrolide-resistant MP pneumonia. Data from several observational studies suggested that doxycycline or minocycline was more effective than tosufloxacin in achieving defervescence within 24–48 h and in decreasing the number of MP-DNA copies assessed by real-time PCR at 2–4 days compared with the number of DNA copies present at admission [14, 29]. Both doxycycline and minocycline showed a higher-peak serum concentration and longer half-life compared with tosufloxacin, which may explain these differences in clinical efficacy. For example, the advantage of minocycline was attributable to a relatively high blood concentration (2.3  $\mu\text{g/mL}$  after giving 4 mg/kg) and to a very long half-life of 10 h. However, when tosufloxacin was administered at 6 mg/kg, the maximum blood concentration was 1.0  $\mu\text{g/mL}$ , and the half-life was 3.8 h [14]. In a study comparing the killing kinetics of various antibiotics against macrolide-resistant MP strains, minocycline, doxycycline, and tosufloxacin showed excellent bactericidal activity. However, post-antibiotic effect on resistant strains was stronger for minocycline and doxycycline compared with tosufloxacin [43]. The findings should be interpreted with caution, and definitive conclusions cannot be drawn regarding the benefit of other fluoroquinolones. That is because most reports comparing the response of fluoroquinolones to tetracyclines are limited to tosufloxacin, and

**Table 2** Recommended antimicrobials and immunomodulators in the treatment of *M. pneumoniae* pneumonia in children

Drug	Route of administration	Dose (mg/kg/day)	Maximal tolerable daily dose (mg)	Duration of treatment (day)
<b>Macrolides</b>				
Azithromycin	Oral or IV	10, once daily; 10 on day 1, and followed by 5 on days 2–5	500	3 or 5
Clarithromycin	Oral	10–15, twice daily	1000	10
Erythromycin	Oral	25–50, four times daily	4000	14
Roxithromycin	Oral	5–8, twice daily	300	10
<b>Tetracyclines</b>				
Doxycycline	Oral	4, twice daily	200	10
Minocycline	Oral or IV	2–4, twice daily	400	7–14
<b>Fluoroquinolones</b>				
Ciprofloxacin	Oral or IV	20–40, twice daily	1500	7–14
Tosufloxacin*	Oral	12, twice daily	360	7–14
Levofloxacin	Oral or IV	<5 years: 16–20, twice daily; ≥5 years: 8–10, once daily	750	7–14
<b>Corticosteroids</b>				
Prednisolone	Oral	2, twice daily	/	3–7
Methylprednisolone	IV	2, twice daily; 30, once daily	/	3–7 for standard dosage; 3 for pulse therapy
Intravenous immunoglobulin	IV	500, 4 days; 1,000, 2 days; 2,000, 1 day	/	1–4
<i>IV</i> intravenous				

\*Tosufloxacin is approved for pediatric use in Japan

those reports were observational studies rather than prospective randomized controlled trials.

## Refractory MP pneumonia

In addition to macrolide-resistant MP pneumonia, refractory MP pneumonia is another condition that may complicate the clinical management of MP pneumonia. Refractory MP pneumonia is defined as prolonged fever and/or deterioration of clinical and radiological findings despite administration of appropriate antibiotics, including macrolides, for 7 days or more [44–46]. Children with refractory MP pneumonia not only have longer duration of fever and hospitalization than those with non-refractory MP pneumonia but also have more severe pneumonia and higher incidence of extrapulmonary complications [47, 48]. The clinical relevance of macrolide-resistant strains in refractory MP pneumonia has been debated due to lack of sufficient evidence. Macrolide-resistant strains are in general not associated with the development of refractory MP pneumonia because the acquisition of resistance does not render increased virulence of the pathogen or increased severity of pneumonia. Several studies have shown that resistance rates were comparable between refractory and non-refractory MP pneumonia groups [49, 50]. However, a possible relationship between the dramatic increase in macrolide-resistant MP strains and frequently reported refractory MP pneumonia in East Asia warrants further investigation.

The precise underlying pathological mechanisms of refractory PM pneumonia remains unclear. The immune-mediated inflammatory response has been considered to be the primary cause [49, 50]. MP infections could stimulate macrophages via toll-like receptors (TLR) to release immunomodulatory and inflammatory cytokines and chemokines, which in turn cause excessive immune responses, resulting in severe and life-threatening pneumonias and a variety of other extrapulmonary complications [51]. The critical importance of pulmonary macrophages in controlling MP infection and defining the extent of lung infection was demonstrated in several rodent models suggesting that macrophage depletion, but not neutrophils, impairs organism clearance [52]. Macrophage activation and subsequent clearance of MP are dependent on TLR, a mechanism further confirmed by studies in rodents deficient in the essential TLR signaling protein MyD88 [52]. Macrophage activation and cytokine production activate the antiviral/antibacterial immunity but can also trigger the so-called cytokine storm and normal tissue damage through immunological hypersensitivity [53]. For example, macrophage-derived proinflammatory cytokines such as IL-18 and IL-8 were closely associated with the

severity of MP pneumonia [54]. Therefore, the severity of pulmonary injuries and the extent of extrapulmonary complications appear to be related to the characteristics and the magnitude of host immune response to infection. In other words, the more vigorous the cytokine stimulation and cell-mediated response is, the more severe pulmonary injury becomes. In addition, the presence of MP in blood, cerebrospinal fluid, and pericardial fluid has been documented by PCR and/or culture, suggesting that direct invasion and damage may participate, at least in part, to an autoimmune process in the pathogenesis of extrapulmonary manifestations [55, 56]. Among various inflammatory biomarkers, lactate dehydrogenase (LDH) is substantially upregulated in this condition, being reported as the most reliable predictor for refractory pneumonia, with cut-off values ranging from 379 to 480 IU/L [49, 57, 58]. Immunosuppressive therapy has shown a beneficial effect by reducing the immune-mediated pulmonary injuries and extrapulmonary complications in refractory MP pneumonia with hyperactive immune-mediated response.

## Corticosteroids

Progression to severe MP pneumonia may occur despite appropriate antibiotic therapy. The potential pathogenesis of unresponsiveness and progressive condition is generally considered to be related to vigorous immunological responses. Corticosteroids have received considerable attention and have shown promising results in the treatment of refractory MP pneumonia, either macrolide susceptible or resistant, particularly when combined with appropriate antimicrobials. For example, children with refractory MP pneumonia who received prednisolone 2 mg/kg/day combined with azithromycin for 5 days had clinical, laboratory, and radiological improvement faster than children who received azithromycin [59] alone. A combination of intravenous methylprednisolone at 2 mg/kg/day and ciprofloxacin for 7–12 days improved clinical, laboratory, and radiological abnormalities of refractory MP pneumonia among children aged 4–12 years. These patients had initially received macrolide and third-generation cephalosporin treatment for more than 7 days, but they showed a persistent fever with aggravated respiratory symptoms and signs, while their radiographic findings had progressed to lobar consolidation and even pleural effusion [60]. Moreover, the elevated inflammatory biomarkers such as LDH were also down-regulated following corticosteroid treatment [44, 59, 60]. The rapid response to corticosteroids in children illustrates the importance of hyperactive immune responses of the host rather than direct invasion of the organism in the pathogenesis of refractory MP pneumonia.

## Corticosteroid-resistant hyperinflammatory MP pneumonia

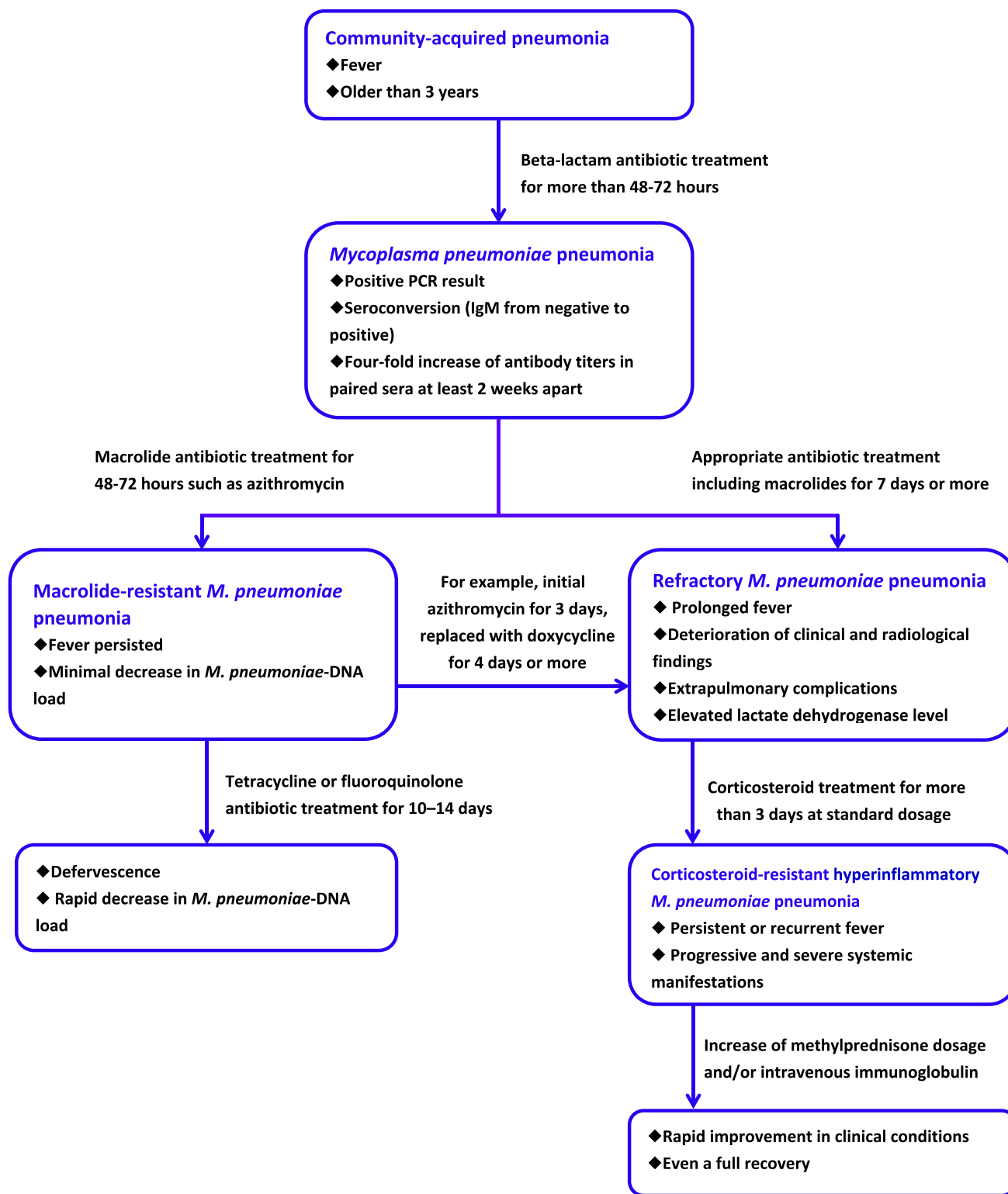
Most pediatric patients with refractory MP pneumonia achieve defervescence within 48 h after starting of conventional corticosteroid regimens at 2 mg/kg/day, but fever may persist for more than 3 days after treatment is initiated in about 20% of children [61, 62]. Corticosteroid-resistant hyperinflammatory MP pneumonia is defined as a persistent or relapsed fever for more than 3 days after intravenous methylprednisolone therapy at standard dosage [61, 62]. In this condition, an increase of corticosteroid dosage (4–6 mg/kg/day) and/or intravenous immunoglobulin (IVIG) may be considered [62]. Moreover, combination treatment of high-dose methylprednisolone pulse therapy at 30 mg/kg/day for 3 days, and appropriate antimicrobials led to improvement in clinical condition and even a full recovery in children with refractory MP pneumonia [44, 45]. Despite rapid clinical improvement of refractory MP pneumonia in children after systemic corticosteroid administration, the optimal dosage regimen is still undetermined. Systematic studies are warranted to determine the benefits of combinations of immunomodulators and antimicrobial agents in the treatment of refractory MP infections, as well as the appropriate dosage and course, including the timing of pulse corticosteroid treatment.

### Intravenous immunoglobulin (IVIG)

In addition to antimicrobials, IVIG therapy with a total dosage of 2 g/kg divided into 1 to 4 days has been reported to be another effective alternative approach in ameliorating symptoms of severe and systemic refractory MP infections, including fulminant MP pneumonia, pneumonia with neurological manifestations, and possibly the dermatological lesions associated with Stevens-Johnson syndrome [63–65]. Although IVIG has proved beneficial in a variety of autoimmune-mediated disorders, its effectiveness in MP-associated complications remains unclear. This rapid improvement may be related to the blockade of the immune-mediated response by the IVIG-induced provision of anti-idiotypic antibodies [65]. IVIG therapy has significant activity against MP, which could provide an additional protection against the disease, predominantly in those patients with suboptimal response to the current antibiotic therapy [66]. To date, there are no serious adverse events reported during or after corticosteroid and/or IVIG administration. Furthermore, clinical presentations and radiological findings did not deteriorate after discontinuation of corticosteroid treatment, and no patient has been reported with additional complications of MP infection.

## Practical stepwise approach to the management of MP pneumonia

We propose a stepwise approach to the management of MP pneumonia which is summarized in Fig. 1. Although the diagnosis of MP infection based on clinical symptoms and signs alone is not reliable, there is a strong probability that MP infection occurs in children older than 3 years with community-acquired pneumonia who have fever and do not respond to beta-lactam antibiotics after more than 2–3 days of treatment [67, 68]. The diagnosis of acute MP respiratory infection is recommended by real-time PCR testing of sputum or nasopharyngeal specimens and/or paired serologic testing collected at least 2 weeks apart. Once MP infection is highly suspected or diagnosed, the class of macrolide antibiotics such as azithromycin (10 mg/kg/day, once daily for 3 consecutive days) should be prescribed as the first-line drug therapy, since some patients may benefit from macrolides even in the presence of resistance strains. Within 2–3 days after initiation of macrolides, almost all macrolide-susceptible patients show defervescence along with a rapid decrease in MP-DNA load, whereas the majority of macrolide-resistant patients exhibit persistent fever and a minimal decrease of DNA load [69]. The two main alternative second-line antibiotics in tetracycline and fluoroquinolone classes, doxycycline (4 mg/kg/day, twice daily for 10 days) and ciprofloxacin (20–40 mg/kg/day, twice daily for 7–14 days), are preferred as the main choice for the treatment of macrolide-resistant MP pneumonia. Refractory MP pneumonia is diagnosed when prolonged fever and/or deterioration of clinical and radiological findings have occurred despite administration of appropriate antibiotics for 7 days or more (e.g., initial azithromycin for 3 days, replaced with doxycycline for 4 days or more). Conventional corticosteroid therapy (2 mg/kg/day, twice daily for 3–7 days) combined with appropriate antibiotics would be prescribed for the treatment of refractory MP pneumonia. Corticosteroid-resistant hyperinflammatory MP pneumonia is characterized by persistent or recrudescing fever for more than 3 days despite intravenous methylprednisolone therapy at standard dosage. In this condition, initiation of methylprednisolone daily dose (4–6 mg/kg/day) or pulse therapy (30 mg/kg, once daily for 3 days), and/or IVIG (2 g/kg, divided into 1 to 4 days) may be considered. Finally, it is important that clinical benefit is evaluated at every stage of clinical decision-making and treatment regimen, and once significant clinical and/or radiological improvement is found, the next stage of treatment is not further required. The possibility of coinfection with other pathogens should be considered and included in the differential diagnosis at each stage of clinical decision-making. Fortunately, multiplexed PCR tests



**Fig. 1** A practical stepwise approach to the clinical management of *M. pneumoniae* pneumonia. Clinical benefit should be evaluated at every stage of clinical decision-making and treatment regimen, and

once significant clinical and/or radiological improvement is found, the next stage of treatment is not further required



for bacterial and viral pathogens of respiratory infections have been widely used, and can be helpful to rule out the possibility of co-infection.

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**Data availability** No datasets were generated or analyzed during the current study.

## Declarations

**Competing interests** The authors declare no competing interests.

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## Authors and Affiliations

Guodong Ding<sup>1</sup> · Xiaobo Zhang<sup>2</sup> · Angela Vinturache<sup>3</sup> · Annemarie M. C. van Rossum<sup>4</sup> · Yong Yin<sup>5</sup> · Yongjun Zhang<sup>1</sup>

✉ Yong Yin  
yinyong9999@163.com

✉ Yongjun Zhang  
zhangyongjun@sjtu.edu.cn

<sup>1</sup> Department of Pediatrics, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, 1665 Kongjiang Road, Shanghai 200092, China

<sup>2</sup> Department of Respiratory Medicine, Children's Hospital of Fudan University, National Children's Medical Center, Shanghai, China

<sup>3</sup> Department of Obstetrics & Gynecology, University of Alberta, Edmonton, AB, Canada

<sup>4</sup> Department of Pediatrics, Division of Pediatric Infectious Diseases and Immunology, Erasmus MC University Medical Center–Sophia Children's Hospital, Rotterdam, Netherlands

<sup>5</sup> Department of Respiratory Medicine, Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University, 1678 Dongfang Road, Shanghai 200127, China