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Comprehensive Analysis of Therapeutic Strategies for *Mycoplasma pneumoniae* Infections: A Global and European Review of Current Antibiotic Treatment Standards in Paediatric and Adult Populations in an Era of Increasing Antimicrobial Resistance

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Abstract

Background.
Mycoplasma pneumoniae infections remain a significant clinical challenge, particularly in the paediatric population, where they constitute a common cause of community-acquired pneumonia (CAP). The absence of a cell wall results in intrinsic resistance to beta-lactam antibiotics, necessitating the use of antimicrobials targeting intracellular processes. In the post-pandemic period, a resurgence of *M. pneumoniae* infections has been observed, partly attributed to an "immunity gap" following non-pharmaceutical interventions. At the same time, macrolide-resistant *M. pneumoniae* (MRMP) has become an increasing concern, especially in Asia and increasingly in Europe, significantly influencing therapeutic strategies.

Aim.
To review current antibiotic treatment standards for *Mycoplasma pneumoniae* infections in children and adults, with particular emphasis on macrolide resistance, regional epidemiology, and practical clinical management of CAP of suspected mycoplasmal aetiology.

Material and methods.
This narrative review analysed contemporary literature published primarily between 2010 and 2025. Data sources included clinical guidelines for CAP in adults and children, systematic reviews and meta-analyses on MRMP, primary studies on resistance mechanisms (23S rRNA mutations, L4/L22 alterations, resistance emergence during therapy), and studies evaluating doxycycline safety in children. Peer-reviewed articles indexed in PubMed and PubMed Central were included. The synthesis was structured according to patient age, disease severity, geographical region, and therapeutic decision pathways.

Results.
Available evidence indicates increasing global prevalence of MRMP, with marked regional differences. Macrolides remain first-line therapy in many settings; however, treatment failure rates are higher in regions with elevated resistance. Doxycycline and fluoroquinolones represent effective alternatives, with growing evidence supporting doxycycline safety in paediatric populations. Escalation of therapy after 48–72 hours of non-response is a key component of effective management, particularly in severe or refractory cases.

Conclusions.
Mycoplasma pneumoniae remains a major cause of CAP in both children and adults. Rising macrolide resistance necessitates region-specific treatment strategies, careful clinical reassessment, and judicious antibiotic selection. Updated management algorithms incorporating resistance patterns and timely therapy escalation are essential to optimise outcomes and support antibiotic stewardship.

Key words: Mycoplasma pneumoniae, MRMP, community-acquired pneumonia, macrolides, doxycycline, levofloxacin, paediatrics, antibiotic stewardship, immunity gap.

Abbreviations and Definitions

CAP – community-acquired pneumonia

MRMP – macrolide-resistant *Mycoplasma pneumoniae*

PK/PD – pharmacokinetics/pharmacodynamics

SMPP – severe *Mycoplasma pneumoniae* pneumonia

RMPP – refractory *Mycoplasma pneumoniae* pneumonia

SmPC – Summary of Product Characteristics

Antibiotic stewardship – clinical and systemic interventions to limit inappropriate antibiotic use in order to curtail the development of resistance.

1. Introduction:

Mycoplasma pneumoniae infections remain a significant clinical challenge, particularly in the paediatric population, where M. pneumoniae represents a common cause of community-acquired pneumonia (CAP) and presents specific diagnostic and therapeutic challenges. A key characteristic of this pathogen is the absence of a cell wall, which confers intrinsic resistance to beta-lactam antibiotics and necessitates the use of agents targeting intracellular processes (macrolides, tetracyclines, fluoroquinolones).
In the post-pandemic era, there has been a resurgence in M. pneumoniae infections, attributed in part to an ‘immunity gap’ resulting from non-pharmaceutical interventions implemented during 2020–2023. Concurrently, the significance of macrolide resistance (MRMP) has grown, particularly in Asia and increasingly in Europe, influencing the selection of both empirical and targeted therapy.
This article provides a review of current antibiotic treatment standards for M. pneumoniae infection in children and adults, discusses regional differences in MRMP epidemiology, and presents practical management algorithms for CAP of suspected mycoplasmal aetiology, including strategies for therapy escalation in cases of non-response after 48–72 hours. [1–6]

2. Research materials and methods.

This narrative review focuses on contemporary pharmacotherapy standards for M. pneumoniae infections in children and adults, with particular attention to the epidemiological context of 2023–2025 and increasing macrolide resistance.
The synthesis incorporated: (I) clinical guidelines for CAP in adults and children; (II) systematic reviews and meta-analyses concerning MRMP; (III) primary studies describing resistance mechanisms (23S

rRNA mutations, L4/L22 alterations, emergence of resistance during therapy); and (IV) studies and reviews addressing doxycycline safety in children with respect to dental discolouration. [4–6, 10–18]
Data sources (typical of a narrative review): peer-reviewed publications indexed in PubMed and articles available through PubMed Central.

Timeframe: primarily 2010–2025; older publications were included as foundational sources for resistance mechanisms and pharmacology. [14–16]
Synthesis approach: material was organised along clinically relevant axes: (a) age (children vs adults), (b) disease severity (uncomplicated CAP vs SMPP/RMPP), (c) geographical region (Asia vs Europe), and (d) decision pathway (first-line → assessment at 48–72 h → escalation). [1–6, 10–13]

3. Introduction: Biological and Epidemiological Context in the Post-Pandemic Era

Infections caused by *Mycoplasma pneumoniae* represent one of the most significant challenges in contemporary clinical microbiology and pulmonology, particularly in the paediatric population. This atypical pathogen, characterised by unique biology—most notably the absence of a cell wall—evades standard therapeutic algorithms for community-acquired pneumonia, which traditionally rely on beta-lactam antibiotics. [1,5,6]

For decades, macrolides constituted the gold standard for treating these infections, offering a favourable safety profile and high efficacy. However, the rapidly evolving epidemiological landscape, marked by a dramatic increase in macrolide resistance (MRMP)—especially in Asia and increasingly in Europe—necessitates revision of established treatment paradigms. [7–11]

The situation was further complicated by the COVID-19 pandemic. Global implementation of non-pharmaceutical interventions to limit SARS-CoV-2 transmission (face masks, social distancing, lockdowns) led to a historic, near-complete suppression of *M. pneumoniae* circulation during 2020–2023, followed by a marked re-emergence in Europe and beyond. [2,3,12,13]

While this phenomenon was beneficial in the short term, it resulted in the development of a so-called "immunity gap" (immunity debt). The population of children born during the pandemic, as well as those who under normal circumstances would have acquired immunity through natural exposure, remained immunologically naïve. The consequence has been a resurgence of mycoplasmal infections observed since mid-2023, intensifying through 2024 and 2025, in some countries exceeding the scale of previous epidemic waves. [2,3,12,13]

This review examines current treatment approaches for *M. pneumoniae* infections, with particular emphasis on antibiotic therapy in at-risk groups. The analysis encompasses both established guideline-based management standards and approaches necessitated by increasing antimicrobial resistance, including the renewed role of tetracyclines in paediatrics and the role of immunomodulatory treatment in severe disease. [4–6,8,9,20]

Special attention is given to the European perspective, including that of Poland, where drug availability and local resistance patterns shape clinical practice.

3.1 Unique Pathogen Biology and Pharmacotherapeutic Limitations

Understanding the fundamentals of *M. pneumoniae* infection therapy requires reference to the biology

of the class Mollicutes. These bacteria—among the smallest free-living prokaryotic organisms—have lost the genes responsible for peptidoglycan synthesis, a loss that confers intrinsic resistance to beta-lactam antibiotics and glycopeptides. [1,6]

In clinical practice, this means that empirical use of amoxicillin—the first-line agent for typical bacterial pneumonia in children—will be ineffective in cases of mycoplasmal aetiology. [5,6]

Targeted therapy must therefore rely on agents that inhibit intracellular processes: protein synthesis (macrolides, tetracyclines, ketolides), DNA replication via topoisomerase inhibition (fluoroquinolones). The choice of a specific drug class depends on patient age, safety profile, local resistance epidemiology, and clinical severity. [1,6,10]

4. Global and European Epidemiology: Evidence from 2023–2024

4.1 The Immunity Gap Phenomenon and Infection Resurgence

Traditionally, *M. pneumoniae* epidemics occur cyclically every 3 to 7 years. However, the COVID-19 pandemic disrupted this pattern; current data indicate a delayed but intense re-emergence in many countries. [2,3,12,13]

In the United States, the proportion of patients hospitalised for CAP of *M. pneumoniae* aetiology increased from below 5% during 2021–2023 to as high as 53.8% at the peak in 2024. [2]

Similar trends have been observed in Europe, including Scandinavian countries and Germany, where a sharp rise in detection rates has been documented since late 2023. [3,12,13]

Analysis of 2024 demographic data reveals a shift in patient age distribution. Although *M. pneumoniae* has historically been a pathogen of school-aged children (5–15 years), the current wave of illness also significantly affects younger children (<5 years). This finding is consistent with the immunity gap hypothesis, whereby younger cohorts are entering pre-school age without prior exposure. [2,3,12]

4.2 Macrolide Resistance Map (MRMP): The East–West Divide

The key factor determining antibiotic selection is the local macrolide resistance rate. In this respect, the world remains clearly divided. [8–11]

4.2.1 Asia: The Epicentre of Resistance

East Asian countries (China, Japan, South Korea) report the highest resistance rates, associated with historically widespread and often excessive macrolide use. [8–11]

China: the proportion of MRMP strains is very high (frequently >90% in the paediatric population), necessitating early initiation of second-line agents. [8–10,28]

Japan: resistance rates have fluctuated in recent years, with data indicating significant clonal shifts in the pathogen; clinically, this translates into more frequent use of tetracyclines in children ≥8 years with MRMP. [26,28]

4.2.2 Europe: Heterogeneity and Growing Threat

In Europe, resistance rates are generally lower than in Asia, although they show an upward trend and periodic variability depending on season and region. [7,8,11]

Overall picture: the average resistance level in Europe is estimated as low but non-zero, with individual outbreaks and local increases well documented. [7,17]

Germany: low but real MRMP presence has been demonstrated in PCR/sequencing-based studies, with a need for ongoing surveillance. [3,17]

Poland: according to NPOA data and regional trends, there is no evidence of "widespread" resistance, but increased outpatient macrolide consumption justifies vigilance and stewardship.

4.3 Mechanisms of Antibiotic Resistance (with Emphasis on MRMP)

M. pneumoniae resistance mechanisms have fundamental practical significance because they (i) explain macrolide treatment failure in MRMP, (ii) justify the selection of tetracycline or fluoroquinolone as escalation therapy, and (iii) enable development of molecular tests detecting resistance directly from clinical specimens. [10,14–16]

4.3.1 Macrolide Resistance: Domain V of 23S rRNA and L4/L22 Proteins

The best-characterised MRMP mechanism involves point mutations in domain V of the 23S rRNA gene, classically A2063G and A2064G (*M. pneumoniae* numbering; corresponding to A2058/A2059 in *E. coli* nomenclature). These changes reduce macrolide affinity for the ribosome and result in high MIC, particularly for 14- and 15-membered macrolides. [14–16]

Mutations in genes encoding ribosomal proteins L4 and L22 have also been implicated, although they occur less frequently and may modulate the resistance phenotype. [10,16]

A clinically important phenomenon is the potential for resistance development during therapy—described, for instance, in cases where A2063G/A2064G mutants emerged after short courses of azithromycin, underscoring the importance of rational antibiotic use and clinical response monitoring. [18]

4.3.2 Molecular Detection of MRMP

Macrolide resistance can be identified by molecular methods (PCR, HRM, sequencing) without the need for culture. A classic example is the development of real-time assays detecting A2063G/A2064G mutations, enabling prompt selection of alternative therapy. [16]

4.3.3 Resistance to Tetracyclines and Fluoroquinolones

M. pneumoniae typically remains susceptible to tetracyclines and fluoroquinolones; however, the literature describes the emergence of mutants with reduced susceptibility under *in vitro* selection pressure. [10,14]

Clinically, resistance to tetracyclines and fluoroquinolones is reported rarely, but it may potentially increase with their growing use as alternatives in MRMP, providing an argument for stewardship and

trend monitoring. [10,14]

5. Clinical Pharmacology: Drug Classes and Their Application

Selection of the appropriate antibiotic requires understanding the pharmacokinetics (PK) and pharmacodynamics (PD) of available agents, as well as the epidemiological context of MRMP. [4–6,10]

5.1 Macrolides: The Gold Standard with Caveats

Macrolides remain the cornerstone of *M. pneumoniae* therapy in Europe and North America, particularly in children. Their mechanism of action involves reversible binding to the bacterial ribosomal 50S subunit, inhibiting protein synthesis. [1,6,10]

5.1.1 Azithromycin (Azalides)

Azithromycin is the most commonly prescribed macrolide for *M. pneumoniae* infections owing to its unique pharmacokinetic profile.

Pharmacokinetics: long half-life and intracellular accumulation (including in phagocytes), favouring maintenance of therapeutic concentrations in lung tissue after completion of the course. [1]

Paediatric dosing: 10 mg/kg once daily for 3 days or a 5-day regimen (10 mg/kg on day 1, then 5 mg/kg on days 2–5). [6]

Safety: generally well tolerated; rare risk of QT prolongation. [1]

5.1.2 Clarithromycin

Pharmacokinetics: requires twice-daily administration. [1]

Paediatric dosing: typically 7.5 mg/kg twice daily. [6]

Interactions: CYP3A4 inhibitor with potential for clinically significant interactions. [1]

5.2 Tetracyclines: The Renaissance of Doxycycline

Tetracyclines bind to the 30S ribosomal subunit. They are active against MRMP strains because mutations in domain V of 23S rRNA do not affect their binding site. [10,14]

5.2.1 Doxycycline Safety in Children <8 Years (Risk of Dental Staining)

Historically, tetracyclines were restricted in children under 8 years of age owing to concerns about dental discolouration and enamel defects. For doxycycline, which differs from "classical" tetracyclines in its physicochemical properties, the evidence base is now substantially stronger and includes both clinical studies and systematic reviews.

An observational study published in The Journal of Pediatrics (Todd et al., 2015) found no cosmetically significant dental staining, enamel hypoplasia, or differences in tooth colour in children <8 years who received short courses of doxycycline. [21]

A randomised clinical trial in children aged 2–8 years (Volovitz et al., 2007) similarly found no dental staining following doxycycline exposure. [22]

A study assessing dental status after doxycycline exposure in children <8 years (Pöyhönen et al., 2017) indicated that treatment in this age group does not appear to cause permanent discolouration. [23]

A narrative review with systematic elements (Stultz et al., 2019) summarised data from several studies (≥338 children exposed to doxycycline before age 8), indicating that although isolated cases of potential changes were described, overall results consistently showed no differences in dental staining between exposed and control groups. [24]

Clinical implications: doxycycline is gaining status as the preferred second-line agent in MRMP (particularly when there is no improvement after 48–72 h of macrolide therapy), with the caveat that data primarily concern short courses and that the decision in children <8 years should remain based on a risk–benefit assessment. [10,21–24]

5.3 Fluoroquinolones: Rescue Therapy

Fluoroquinolones (levofloxacin, moxifloxacin) are the only discussed class with bactericidal activity against *M. pneumoniae*. [10]

Place in therapy: in paediatrics, these are considered third-line agents owing to concerns about cartilage toxicity (preclinical data) and signals of musculoskeletal adverse effects. [25–30]

Actual risk: meta-analyses and large safety analyses indicate that the risk of musculoskeletal events is typically low and often reversible, but requires monitoring, especially when used outside licensed indications. [26–30]

In severe MRMP, clinical benefits may outweigh risks, justifying "rescue" use in carefully selected situations. [10,25–30]

6. Treatment Strategies in Children

Treatment of children poses the greatest challenge owing to high incidence, diagnostic difficulties, and regulatory restrictions on drugs. [1,6,10]

6.1 First-Line Therapy: Are Macrolides Always Indicated?

According to paediatric guidelines, macrolides remain the drugs of first choice for targeted treatment of confirmed *M. pneumoniae* infections, particularly in school-age children and adolescents. [5,6]

The "Myth vs. Maxim" dilemma: experts emphasise that many mild pneumonias are self-limiting, and routine addition of a macrolide to beta-lactam in every CAP case is not justified and may drive resistance. [1,5]

Recommendation: a macrolide should be initiated after confirmation of aetiology or with very high clinical suspicion (older child, school outbreak) and when there is no response to beta-lactams after 48 h. [5,6]

Dosing regimens (per SmPC and guidelines):

Azithromycin: Option 1: 10 mg/kg once daily for 3 days. Option 2: 10 mg/kg on day 1, then 5 mg/kg on days 2–5. Maximum dose: 500 mg per day.

Clarithromycin: 7.5 mg/kg every 12 hours for 7–10 days (maximum 500 mg per dose).

6.2 Management of Non-Response (Suspected MRMP)

Failure of temperature normalisation and symptom resolution after 48–72 hours of appropriately administered macrolide therapy suggests infection with a resistant strain (MRMP) or a refractory course. [10,20]

6.2.1 Switching to Second-Line Agents

In this clinical situation, available data and expert guidelines support antibiotic change. [6,10,28]

Doxycycline – preferred choice: Drug of choice for suspected MRMP. [10,26,28]

Paediatric dosing: 2–4 mg/kg/day in 1 or 2 divided doses (usually 2 mg/kg every 12 h). In children >45 kg, adult dose (100 mg every 12 h).

Efficacy: studies from high-resistance regions indicate that switching to tetracycline shortens fever duration compared with continuing macrolide in MRMP. [26]

Levofloxacin – alternative: In cases of tetracycline intolerance or when doxycycline administration is not possible; typically off-label use. [25–30]

Dosing (per international MRMP regimens): Children 6 months – 5 years: 8–10 mg/kg twice daily. Children >5 years: 10 mg/kg once daily (max 750 mg).

7. Treatment Strategies in Adults

The clinical picture in adults is often less characteristic, and *M. pneumoniae* may coexist with other pathogens typical of this age group. [4,10]

7.1 European and American Guidelines

Recommendations for adults vary according to treatment setting and comorbidities; in practice, the key is coverage of both typical and atypical pathogens in outpatients and appropriate combination therapy in patients with comorbidities. [4]

7.1.1 Outpatient Treatment (Mild/Moderate CAP)

In patients without significant risk factors, standard options include doxycycline or a macrolide depending on local epidemiological considerations and patient profile. [4]

Doxycycline: 100 mg twice daily (often with a loading dose of 200 mg on day 1). [4]

Macrolides: azithromycin (500 mg on day 1, then 250 mg for 4 days) or clarithromycin (500 mg twice daily). [4]

7.1.2 Treatment of Patients with Comorbidities

In patients with COPD, diabetes, heart disease, or the elderly, macrolide monotherapy may be insufficient.

Combination therapy: beta-lactam (e.g. amoxicillin-clavulanate) + macrolide or beta-lactam + doxycycline. [4]

Respiratory fluoroquinolone monotherapy: levofloxacin (500–750 mg once daily) or moxifloxacin (400 mg once daily) – an effective option, but reserved owing to safety concerns and the potential for selecting resistant strains. [4]

7.2 Resistance in Adults

In adults, the proportion of MRMP infections may be lower than in children, but in cases of macrolide non-response (48–72 h), switching to doxycycline or a fluoroquinolone represents a standard management approach with high efficacy. [4,10,20]

8. Severe and Refractory Pneumonia (SMPP and RMPP)

A distinct group comprises patients with severe *Mycoplasma pneumoniae* pneumonia (SMPP) and refractory *Mycoplasma pneumoniae* pneumonia (RMPP). [10,20]

8.1 Immunopathogenesis and Cytokine Storm

Pulmonary damage in SMPP is largely attributable to excessive host immune responses (T lymphocyte activation, cytokine release). The clinical picture may resemble a cytokine storm, leading to extensive consolidation and respiratory failure. [10,31]

8.2 Role of Corticosteroids

Owing to the immunological basis of tissue injury, antibiotic therapy alone may be insufficient to halt progression in SMPP.

Recommendations: some guidelines and expert opinions recommend initiation of systemic steroids in patients with RMPP (fever >7 days, radiological progression despite antibiotics). [10]

Dosing regimens: methylprednisolone 1–2 mg/kg/day intravenously for 3–5 days (typically max 60–80 mg/day in children, unless critically ill).

Benefits: a meta-analysis showed that adjunctive treatment (azithromycin + corticosteroid) may shorten fever duration and accelerate resolution of pulmonary findings. [20]

8.3 Thromboembolic Risk

M. pneumoniae infection may predispose to thrombotic complications. In patients with SMPP, particularly those with markedly elevated D-dimer levels, thromboprophylaxis (low-molecular-weight heparin) should be considered. [31]

9. Diagnostics and Therapeutic Decisions: PCR vs Serology

In an era of precision medicine and antibiotic stewardship, diagnostics play a crucial role, and interpretation of test results has direct implications for patient antibiotic exposure. [1,6,19]

9.1 Limitations of Serology

Serology (IgM/IgG) has limited utility in the acute phase (serological window, false-negative results early in infection). IgM may persist for months, yielding false-positive results. [1]

9.2 Advantages of Molecular Methods (PCR)

The gold standard is PCR from throat/nasopharyngeal swab. [1]

Advantages: speed and sensitivity in the early phase. [1]

Resistance detection: molecular tests can detect 23S rRNA mutations associated with MRMP, enabling targeted treatment (e.g. doxycycline instead of macrolide). [16]

Interpretation: PCR may detect carriage; a positive result should be correlated with the clinical picture. The phenomenon of asymptomatic carriage in children and limitations in distinguishing colonisation from infection are well documented. [19]

10. Summary and Conclusions: The Changing Treatment Paradigm

In the face of increasing infections during 2024–2025, the approach to *M. pneumoniae* treatment is evolving. [2,3,12]

Key conclusions:

- Rationalisation: macrolides should be reserved for cases where indicated. [5,6]
- Role of tetracyclines: doxycycline is highly effective in MRMP, and clinical data indicate that short courses in children <8 years are not associated with significant risk of permanent dental staining. [21–24]
- Vigilance: lack of improvement after 48–72 h of macrolide therapy should raise suspicion of MRMP and prompt a change in therapy rather than escalation "within the same class". [10,16,18]
- Comprehensive management: severe cases require a multi-pronged approach (second-line antibiotic + steroid + anticoagulation as indicated). [20,31]

Summary Table: Antibiotic Dosing Recommendations 2024/2025

Drug	Paediatric Dose	Adult Dose	Notes
Azithromycin	10 mg/kg/day × 3 days OR 10 mg/kg d1, then 5 mg/kg d2–5	500 mg d1, then 250 mg d2–5	First-line; max 500 mg/day paediatric
Clarithromycin	7.5 mg/kg q12h × 7–10 days	500 mg q12h × 7–10 days	First-line alternative; CYP3A4 interactions

Doxycycline	2–4 mg/kg/day in 1–2 doses; >45 kg: adult dose	100 mg q12h (loading 200 mg d1)	Second-line for MRMP; safe <8 years short course
Levofloxacin	6 mo–5 y: 8–10 mg/kg q12h; >5 y: 10 mg/kg qd	500–750 mg qd	Third-line/rescue; off-label paediatric
Methylprednisolone	1–2 mg/kg/day IV × 3–5 days (max 60–80 mg/d)	1–2 mg/kg/day IV × 3–5 days	Adjunctive for SMPP/RMPP

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