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REVIEW

Doxycycline for Macrolide-Resistant *Mycoplasma pneumoniae* Pneumonia in Children: Clinical Updates and Therapeutic Insights Post-COVID-19

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Abstract: Mycoplasma pneumoniae (MP) is a leading cause of community-acquired pneumonia (CAP) in children. Macrolides have long been first-line therapy due to favorable safety profiles and low minimum inhibitory concentrations (MICs) in pediatric populations. However, the global surge in macrolide-resistant MP (MRMP) has compromised conventional treatments, creating an urgent need for alternative agents. Mounting evidence supports doxycycline, a second-generation tetracycline, as an effective therapy for pediatric MRMP, particularly post-COVID-19. Compared to azithromycin, doxycycline shortens disease duration, accelerates the resolution of fever and cough, promotes pulmonary infiltrate absorption, and yields robust outcomes in children ≥8 years old. It also reduces corticosteroid use and exhibits a favorable safety profile. For refractory MP pneumonia (RMPP), combination therapy with doxycycline and corticosteroids (eg, methylprednisolone) enhances therapeutic effects. Ongoing research explores innovative combinations and personalized dosing to mitigate resistance. This narrative overview synthesizes recent advances in doxycycline use for pediatric MRMP since the COVID-19 pandemic, aiming to inform evidence-based practice. It also highlights the need for large-scale, well-designed trials to confirm long-term safety and efficacy, supporting standardized clinical implementation.

Keywords: doxycycline, *Pediatric mycoplasma pneumoniae* pneumonia, macrolide resistance, clinical management, post-COVID-19

Introduction

Mycoplasma pneumoniae pneumonia (MPP) is a major cause of acute respiratory tract infections in children, particularly among those aged 2–12 years.[1,2] As an atypical, cell wall-deficient intracellular pathogen, MP is inherently resistant to cell wall-targeting antibiotics (eg, β-lactams, glycopeptides).[3] Macrolides have remained first-line therapy for decades, but rising MRMP prevalence—driven primarily by 23S rRNA gene mutations—has rendered them ineffective in many cases.[4,5] Post-COVID-19, MP infections have rebounded sharply in Europe and Asia, with more severe clinical manifestations and higher pneumonia incidence in children.[6,7] In China (Wuhan City, Hubei Province), the dominant P1-1 genotype of MP exhibits a macrolide resistance rate of up to 96% in 2020–2022,[8] posing a critical threat to pediatric health. Doxycycline has emerged as a promising alternative, leveraging broad-spectrum activity, high bioavailability, and favorable safety profiles. This narrative overview synthesizes recent clinical evidence on doxycycline for pediatric MRMP, focusing on epidemiological trends, resistance mechanisms, therapeutic advantages, and clinical recommendations to guide frontline practice.[9]

Key terms used in this study are uniformly defined as follows:

MRMP (Macrolide-Resistant *Mycoplasma pneumoniae*): Defined by molecular mutation (23S rRNA gene A2063G/A2064G) and phenotypic MIC (minimum inhibitory concentration for erythromycin ≥16 μg/mL);[10]

Macrolide-refractory MPP: Clinical failure of macrolide monotherapy (azithromycin/clarithromycin) for 72 hours with persistent fever (>38.5°C) and no improvement in respiratory symptoms[11](not identical to MRMP, as refractoriness may be due to inflammation rather than resistance);

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RMPP (Refractory *Mycoplasma pneumoniae* Pneumonia): Defined by persistent fever >7 days despite appropriate antibiotic therapy, radiologic progression of pulmonary lesions, and elevated inflammatory markers (CRP >80 mg/L).[11,12]

Epidemiological Trends of Pediatric MP Infections Post-COVID-19 and the Macrolide Resistance Crisis

Pediatric MP infections exhibit distinct epidemiological patterns: seasonal peaks occur in winter (northern China) and summer-autumn (southern China), with a slight female predominance.[13] During the COVID-19 pandemic, non-pharmacological interventions (eg, mask-wearing, social distancing) temporarily reduced MP transmission.[14–16] However, relaxation of these measures triggered a marked resurgence in 2023–2025 (post-COVID-19 period, defined as the stage after the relaxation of global non-pharmacological interventions in late 2022), with MP becoming the leading pathogen of pediatric respiratory infections in China.[16,17] The first rebound wave occurred in China and East Asia in 2023 Q2-Q4, and the second wave in Europe and Southeast Asia in 2024 Q1-Q3.[18,19] This rebound is attributed to cyclical MP epidemiology, pre-existing high macrolide resistance, and potential post-pandemic immune dysregulation.[20]

Global MRMP prevalence varies substantially by region, with clear distinctions between resistance prevalence (chronic regional stable data) and outbreak reports (acute localized incidence increase).[10] Europe reports localized MPP outbreaks (eg, Italy, Scotland, Czech Republic) with a resistance prevalence of 20–30%,[21–23] while Asia bears the highest burden—central China has a resistance rate of 90–96%,[10,24] followed by Japan with 60–70%.[25] Such global heterogeneity is associated with differences in antibiotic use patterns, diagnostic ascertainment (molecular vs. culture-based testing), and regional epidemiological characteristics.[24] Culture-based testing may underestimate resistance rates due to the fastidious growth of *Mycoplasma pneumoniae*, while molecular testing (PCR for 23S rRNA mutations) is more sensitive but less widely available in low-resource regions.[26–28]

Resistance is primarily mediated by point mutations in the V domain of the 23S rRNA gene (A2063G or A2064G),[29,30] which reduce macrolide binding to ribosomal targets. A study on influenza-like illness cases in China found that among *Mycoplasma pneumoniae* positive samples in children, the mutation rate of A2063G was 48.00%, A2064G was 8.00%, and 8.00% were double mutations of both A2063G and A2064G.[31]

Epidemiological data from Ningbo, China, during the 2022–2023 season showed that the mutation rate of A2063G/A2064G exceeded 70%, reaching 100% in some months.[32] A systematic review and meta-analysis showed that in Asia, the prevalence of the A2063G mutation ranges from approximately 91% to 100%, while the prevalence of the A2064G mutation ranges from approximately 2% to 100%.[33] This widespread resistance has necessitated a shift to alternative antibiotic classes, including tetracyclines and fluoroquinolones.[29]

Pathophysiology of MP and RMPP

MP's lack of a cell wall enhances environmental adaptability and immune evasion.[34,35] Pathogenesis involves high-affinity adhesion to respiratory epithelial cells via membrane proteins, leading to direct cellular injury and a robust inflammatory cascade driven by proinflammatory cytokine release.[36] Most MP infections present as self-limiting upper respiratory tract disease, but a subset of children progresses to RMPP—characterized by dysregulated inflammation, extensive airway damage (eg, bronchial mucosal necrosis), and pulmonary consolidation.[37,38] MP may also induce extrapulmonary complications (eg, cutaneous rashes, neurological sequelae) via molecular mimicry or immune complex deposition.[37,39] Recent transcriptomic studies have identified distinct circular RNA (circRNA) profiles in RMPP versus non-refractory MPP, implicating circRNAs in regulating inflammatory pathways and offering potential diagnostic biomarkers and therapeutic targets.[40]

Mechanisms of Macrolide Resistance in MP

Macrolide resistance in MP is multifactorial, with point mutations in the 23S rRNA gene as the primary driver.[29,41] The A2063G mutation is the most prevalent, followed by A2064G, both reducing macrolide-ribosome binding affinity and diminishing antimicrobial efficacy.[42] Secondary mechanisms include plasmid-mediated horizontal transfer of resistance determinants, target gene mutations altering protein structure/function, and adaptive strategies (eg, cell membrane modifications, biofilm formation) that enhance MP's ability to withstand antibiotic pressure.[43–45] These mechanisms collectively contribute to the global spread of MRMP and highlight the need for antibiotics with distinct modes of action, such as doxycycline.[46,47]

Therapeutic Advantages and Safety of Doxycycline for Pediatric MRMP

Doxycycline vs. Conventional Alternatives

Fluoroquinolones and tetracyclines are the main alternatives for MRMP, but fluoroquinolones are contraindicated in children due to musculoskeletal risks (eg, joint pain, tendon disorders).[47,48] Doxycycline demonstrates a more acceptable safety profile in clinical application: adverse effects are mild and transient, primarily gastrointestinal disturbances (eg, nausea, diarrhea), esophagitis, and photosensitivity.[49,50] Unlike earlier tetracyclines, doxycycline has a lower calcium-binding affinity, which may reduce the risk of tooth discoloration in children during tooth development with short-term use (≤21 days);[49,50] however, potential tooth discoloration remains a minor concern in clinical practice, and rigorous risk-benefit assessment is still recommended for children <8 years old.[49,50] The American Academy of Pediatrics (AAP) Red Book removed the warning on doxycycline-induced tooth discoloration in 2018, endorsing its short-term use in children of all ages when clinically indicated.[51]

Clinical Efficacy

Clinical studies and meta-analyses confirm doxycycline's efficacy in pediatric MRMP.[52] In children ≥8 years old with mild-to-moderate MRMP, compared to azithromycin, it can shorten the time to fever resolution by approximately 2–3 days, reduce the time to cough resolution by approximately 3–5 days, accelerate the absorption of pulmonary lesions, and lower levels of inflammatory markers (such as C-reactive protein).[53,54] A retrospective study of pediatric lobar pneumonia caused by MRMP found doxycycline reduced hospitalization length by 30% compared to extended-release azithromycin.[53,54] Meta-analyses further confirm that doxycycline yields better clinical cure rates and symptom resolution outcomes than macrolide-based regimens in pediatric MRMP patients.[52] In refractory MRMP (RMPP), doxycycline combined with methylprednisolone can reduce hospitalization time by approximately 30%, which is superior to monotherapy with macrolides.[52–54]

Combination Therapy

For RMPP, doxycycline combined with methylprednisolone modulates excessive inflammation and improves outcomes.[55–58] Other synergistic combinations include doxycycline plus compound furazolidone (reducing inflammation and hospitalization duration) and doxycycline plus hydroxychloroquine (showing better safety and clinical effects than hydroxychloroquine-azithromycin combinations during COVID-19).[59,60] Bronchoalveolar lavage combined with doxycycline also enhances clinical response rates in severe MRMP cases.[50,57,58]

Innovative Perspectives on Resistance Management

Doxycycline addresses antimicrobial resistance through three key mechanisms, with its immunomodulatory effects supported by in vitro and clinical evidence:

Dual therapeutic action: It inhibits bacterial protein synthesis and exerts immunomodulatory effects by inhibiting the release of proinflammatory cytokines (eg, IL-6, TNF-α) and reducing neutrophil infiltration in the lung tissue,[61,62] which differentiates it from macrolides and contributes to its efficacy in severe MRMP with excessive inflammation. Recent real-world studies on children with MRMP pneumonia support the efficacy of doxycycline. These studies indicate that doxycycline remains highly sensitive to macrolide-resistant strains, making it an effective alternative treatment option, with its effects possibly partly attributed to antibacterial and potential immunomodulatory effects.[50,53] By inhibiting bacterial metalloproteases, it also disrupts resistance mechanisms in severe infections (eg, ventilator-associated pneumonia).[59]

Novel therapeutic strategies: Synergistic combinations (eg, doxycycline + polymyxin B)[63] and advanced delivery systems (eg, microfluidic lipid-based nanocarriers)[64] enhance bioavailability and reduce systemic adverse effects, further improving the clinical application value of doxycycline.

Personalized medicine integration: Genotype profiling and antimicrobial susceptibility testing guide tailored dosing, duration, and combinations, mitigating resistance at the individual level.[50,53]

Clinical Recommendations and Future Directions

Clinical Practice Guidelines

Indications: Doxycycline is recommended as a first-line alternative for MRMP in children ≥8 years, particularly in macrolide-refractory cases or with confirmed 23S rRNA mutations.[54,65] For children <8 years, it may be considered in severe MRMP (eg, RMPP, respiratory failure) after rigorous risk-benefit assessment.[65]

Administration: Short-term courses (≤21 days) are preferred to minimize adverse effects. Oral doxycycline has high bioavailability and pulmonary tissue penetration, suitable for both outpatient and inpatient use.[54]

Safety monitoring: Patients should avoid direct sunlight (to prevent photosensitivity) and take the drug with food (to reduce gastrointestinal irritation).[10,53] Routine laboratory monitoring is unnecessary for courses ≤21 days.[53]

Antimicrobial stewardship: Doxycycline use should be guided by susceptibility testing or molecular diagnostics to reduce unnecessary exposure and delay resistance.[50]

Future Research Priorities

Systematic evaluation of doxycycline's safety and efficacy in children <8 years, including long-term effects on growth and development.[51,66] Development of precision treatment protocols integrating genotypic analysis (eg, 23S rRNA mutation status) to optimize dosing and combinations.[50,66,67] Investigation of innovative formulations (eg, nanocarriers) to enhance bioavailability, stability, and tissue targeting.[68] Large-scale, multicenter prospective trials involving multi-ethnic populations to confirm comprehensive efficacy in complex infections (eg, RMPP).[69]

Methodological Considerations and Limitations

This narrative overview synthesizes peer-reviewed clinical studies, meta-analyses, and clinical guidelines on doxycycline for pediatric MRMP published between 2019 and 2025, retrieved from PubMed, CNKI, and Web of Science. Unlike systematic reviews, this study does not include a standardized search strategy, inclusion/exclusion criteria, study selection process, risk of bias assessment, or PRISMA flow diagram, which is a typical characteristic of narrative overviews.

This review is limited by the lack of a systematic search strategy and risk of bias assessment; the evidence is dominated by retrospective studies, and large-scale prospective trials in children <8 years old are lacking. In addition, the included clinical data are mainly from Asian and European regions, and the applicability of the conclusions to other regions needs to be further verified.

Conclusion

Doxycycline is increasingly recognized as a viable and generally safe treatment option for pediatric macrolide-resistant *Mycoplasma pneumoniae* pneumonia, particularly in the wake of the COVID-19 pandemic.[70] Its dual mechanisms—bacterial protein synthesis inhibition and anti-inflammatory activity—enable effective control of MRMP and modulation of excessive inflammation in severe cases.[71] Compared to fluoroquinolones, it exhibits a more favorable safety profile in short-term use, with mild, transient adverse effects and a reduced risk of tooth discoloration in pediatric patients.[10,72,73] Combination therapy with corticosteroids or other agents further enhances clinical efficacy in refractory cases.[10] Clinical practice should prioritize antimicrobial stewardship, with doxycycline use guided by susceptibility testing or molecular diagnostics.[50,53] Future research focusing on younger children, precision medicine, and novel formulations will strengthen the evidence base, addressing the global challenge of antimicrobial resistance and improving pediatric respiratory health outcomes. At the same time, multi-center, cross-regional prospective studies are needed to further verify the long-term safety and clinical efficacy of doxycycline in pediatric MRMP treatment.

Data Sharing Statement

This review is based on previously published clinical and epidemiological data.

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Disclosure

The authors declare no potential conflicts of interest in this work.

References

1. Phongsamart W, Imwattana K, Siriboriruk J, Kiratisin P, Chokephaibulkit K. Prevalence of macrolide-resistant *Mycoplasma pneumoniae* in children and adolescents with community-acquired pneumonia: a prospective study in Thailand. *Pediatr Infect Dis J*. 2026. doi:10.1097/INF.0000000000005147
2. Lv W, Guo C, Lv G, Xi X. Epidemiological characteristics and related risk factors of mixed infection in children with *Mycoplasma pneumoniae* pneumonia. *New Microbiol*. 2024;47(3):251–257.
3. Saikku P. Atypical respiratory pathogens. *Clin Microbiol Infect*. 1997;3(6):599–604. doi:10.1111/j.1469-0691.1997.tb00464.x
4. Wang N, Xu X, Xiao L, Liu Y. Novel mechanisms of macrolide resistance revealed by in vitro selection and genome analysis in *Mycoplasma pneumoniae*. *Front Cell Infect Microbiol*. 2023;13:1186017. doi:10.3389/fcimb.2023.1186017
5. Esposito S, Argentiero A, Gramegna A, Principi N. *Mycoplasma pneumoniae*: a pathogen with unsolved therapeutic problems. *Expert Opin Pharmacother*. 2021;22(9):1193–1202. doi:10.1080/14656566.2021.1882420
6. Bača L, Slováková L, Vočková J, Doležalová K. Rising incidence of *Mycoplasma pneumoniae* pneumonias in a tertiary paediatric centre: implications for antibiotic therapy. *Cent Eur J Public Health*. 2025;33(1):77–79. doi:10.21101/cejph.a8434
7. Bianchi M, Pisani M, Ricotta L, et al. Epidemiology and clinical impact of *Mycoplasma pneumoniae* in an italian pediatric center: an observational study from 2017 to 2024. *Pediatr Infect Dis J*. 2026;45(2):132–139. doi:10.1097/INF.0000000000004993
8. Xu M, Li Y, Shi Y, et al. Molecular epidemiology of *Mycoplasma pneumoniae* pneumonia in children, Wuhan, 2020–2022. *BMC Microbiol*. 2024;24(1):23. doi:10.1186/s12866-024-03180-0
9. de Groot RCA, Streng BMM, Bont LJ, Meyer Sauteur PM, van Rossum AMC. Resurgence of *Mycoplasma pneumoniae* infections in children: emerging challenges and opportunities. *Curr Opin Infect Dis*. 2025;38(5):468–476. doi:10.1097/QCO.0000000000001126
10. Wang YS, Zhou YL, Bai GN, et al. Expert consensus on the diagnosis and treatment of macrolide-resistant *Mycoplasma pneumoniae* pneumonia in children. *World J Pediatr*. 2024;20(9):901–914. doi:10.1007/s12519-024-00831-0
11. National Health Commission of the People's Republic of China. Clinical practice guidelines for *Mycoplasma pneumoniae* pneumonia in children (2023 Edition). *Exploration of Rational Drug Use in China*. 2023;20(3):16–24. doi:10.3969/j.issn.2096-3327.2023.03.003
12. Liu JR, Lu J, Dong F, et al. Low bacterial co-infection invalidates the early use of non-anti-*Mycoplasma pneumoniae* antibiotics in pediatric refractory *Mycoplasma pneumoniae* pneumonia patients. *Front Pediatr*. 2018;6:296. doi:10.3389/fped.2018.00296
13. Hongfei D, Mengchuan Z, Xiaoshuang Z, et al. Epidemiological characteristics of *Mycoplasma pneumoniae* infection in hospitalized children with respiratory tract infections at Hebei Children's Hospital from 2016 to 2024. *J PLA Med Sci*. 2025;50(9):1097–1102. doi:10.11855/j.issn.0577-7402.1935.2025.0623
14. Fu C, Zhou C, Zheng C, et al. Etiological analysis of acute respiratory infections in hospitalized children after the relaxation of COVID-19 non-pharmacological interventions in Quzhou, China. *BMC Infect Dis*. 2024;24(1):1362. doi:10.1186/s12879-024-10257-8
15. Raghuram A, Furmanek S, Chandler T, Rashid S, Mattingly W, Ramirez J. Description of a current outbreak of *Mycoplasma pneumoniae* in the United States. *Pathogens*. 2025;14(1):60. doi:10.3390/pathogens14010060
16. Xu X, Pan Z, Dong H, et al. Inhibition, transition, and surge: dynamic evolution of pediatric respiratory pathogen trends amid COVID-19 pandemic policy adjustments. *Front Public Health*. 2024;12:1420929. doi:10.3389/fpubh.2024.1420929
17. Li H, Li S, Yang H, Chen Z, Zhou Z. Resurgence of mycoplasma pneumonia by macrolide-resistant epidemic clones in China. *Lancet Microbe*. 2024;5(6):e515. doi:10.1016/S2666-5247(23)00405-6
18. Merișescu MM, Jugulete G, Dijmărescu I, Dragomirescu AO, Răduț LM. The clinical profile of pediatric *M. pneumoniae*infections in the context of a new post-pandemic wave. *Microorganisms*. 2025;13(5):1152. doi:10.3390/microorganisms13051152
19. Chen Y, Jia X, Gao Y, et al. Increased macrolide resistance rate of *Mycoplasma pneumoniae* correlated with epidemic in Beijing, China in 2023. *Front Microbiol*. 2024;15:1449511. doi:10.3389/fmicb.2024.1449511
20. Jiang C, Bao S, Shen W, Wang C. Predictive value of immune-related parameters in severe *Mycoplasma pneumoniae* pneumonia in children. *Transl Pediatr*. 2024;13(9):1521–1528. doi:10.21037/tp-24-172
21. Loconsole D, De Robertis AL, Sallustio A, et al. Update on the epidemiology of macrolide-resistant *Mycoplasma pneumoniae* in Europe: a systematic review. *Infect Dis Rep*. 2021;13(3):811–820. doi:10.3390/idr13030073
22. Eschenauer GA, Xiao L, Waites KB, et al. Macrolide-resistant *Mycoplasma pneumoniae* pneumonia in transplantation: increasingly typical? *Transpl Infect Dis*. 2020;22(5):e13318. doi:10.1111/tid.13318
23. Chironna M, Loconsole D, De Robertis AL, et al. Clonal spread of a unique strain of macrolide-resistant *Mycoplasma pneumoniae* within a single family in Italy. *Medicine*. 2016;95(11):e3160. doi:10.1097/MD.0000000000003160
24. Pereyre S, Goret J, Bébéar C. *Mycoplasma pneumoniae*: current knowledge on macrolide resistance and treatment. *Front Microbiol*. 2016;7:974. doi:10.3389/fmicb.2016.00974
25. Akashi Y, Hayashi D, Suzuki H, et al. Clinical features and seasonal variations in the prevalence of macrolide-resistant *Mycoplasma pneumoniae*. *J Gen Fam Med*. 2018;19(6):191–197. doi:10.1002/jgf2.201
26. Guo D, Hu W, Xu B, et al. Allele-specific real-time PCR testing for minor macrolide-resistant *Mycoplasma pneumoniae*. *BMC Infect Dis*. 2019;19(1):616. doi:10.1186/s12879-019-4228-4

27. Chen B, Gao L-Y, Chu Q-J, et al. The epidemic characteristics of *Mycoplasma pneumoniae* infection among children in Anhui, China, 2015–2023. *Microbiol Spectr*. 2024;12(10):e0065124. doi:10.1128/spectrum.00651-24
28. Li P, Wang W, Zhang X, Pan J, Gong L. Observational retrospective clinical study on clinical features of macrolide-resistant *Mycoplasma pneumoniae* pneumonia in Chinese pediatric cases. *Sci Rep*. 2024;14(1):5632. doi:10.1038/s41598-024-55311-2
29. Ning J, Qiao L, Yu Z, Chen Z. Clinical score for early escalation in pediatric A2063G *Mycoplasma pneumoniae* pneumonia: a retrospective cohort study. *BMC Infect Dis*. 2025;25(1):1198. doi:10.1186/s12879-025-11634-7
30. Xu C, Deng H, Zhang J, et al. Mutations in domain V of *Mycoplasma pneumoniae* 23S rRNA and clinical characteristics of pediatric *M. pneumoniae* pneumonia in Nanjing, China. *J Int Med Res*. 2021;49(6):3000605211016376. doi:10.1177/03000605211016376
31. Tu P, Dou H, Shi D, et al. Study on *Mycoplasma pneumoniae* infection and drug resistance in patients with influenza-like illness. *Chin Gen Pract*. 2022;25(2):145–148,158. doi:10.12114/j.issn.1007-9572.2021.01.112
32. Fei X, Yefang K, Fei L, Wenbo L, Junhua W, Liu W. Epidemiological characteristics of *Mycoplasma pneumoniae* epidemic among children in Ningbo, China, 2022–2023. *J Pediatr Infect Dis*. 2025;20(3):Article5.
33. Wang G, Wu P, Tang R, Zhang W. Global prevalence of resistance to macrolides in *Mycoplasma pneumoniae*: a systematic review and meta-analysis. *J Antimicrob Chemother*. 2022;77(9):2353–2363. doi:10.1093/jac/dkac170
34. Wang J, Liang K, Chen L, et al. Unveiling the stealthy tactics: mycoplasma's immune evasion strategies. *Front Cell Infect Microbiol*. 2023;13:1247182. doi:10.3389/fcimb.2023.1247182
35. Xinyu L, Liu X. Progress in immune research of *Mycoplasma pneumoniae* infection. *J Clin Med Res*. 2022;3(2):61–63.
36. Sun B, Ling Y, Li J, et al. Advances in adhesion-related pathogenesis in *Mycoplasma pneumoniae* infection. *Front Microbiol*. 2025;16:1613760. doi:10.3389/fmicb.2025.1613760
37. Georgakopoulou VE, Lempesis IG, Sklapani P, Trakas N, Spandidos DA. Exploring the pathogenetic mechanisms of mycoplasmapneumoniae (Review). *Exp Ther Med*. 2024;28(1):271. doi:10.3892/etm.2024.12559
38. Zhang Y, Zhou Y, Li S, Yang D, Wu X, Chen Z. The clinical characteristics and predictors of refractory *Mycoplasma pneumoniae* pneumonia in children. *PLoS One*. 2016;11(5):e0156465. doi:10.1371/journal.pone.0156465
39. Narita M. Classification of extrapulmonary manifestations due to *Mycoplasma pneumoniae* infection on the basis of possible pathogenesis. *Front Microbiol*. 2016;7:23. doi:10.3389/fmicb.2016.00023
40. Huang F, Fan H, Yang D, et al. Ribosomal RNA-depleted RNA sequencing reveals the pathogenesis of refractory *Mycoplasma pneumoniae* pneumonia in children. *Mol Med Rep*. 2021;24(5):761. doi:10.3892/mmr.2021.12401
41. Eun BW, Go U, Chun G, et al. *Mycoplasma pneumoniae* infections among children and adolescents in Korea, 2014–2024. *J Korean Med Sci*. 2025;40(40):e253. doi:10.3346/jkms.2025.40.e253
42. Zhang Z, Dou H, Yuan Q, et al. Proteomic and phenotypic studies of *Mycoplasma pneumoniae* revealed macrolide-resistant mutation (A2063G) associated changes in protein composition and pathogenicity of type i strains. *Microbiol Spectr*. 2023;11(4):e0461322. doi:10.1128/spectrum.04613-22
43. Xie P, Zhang Y, Qin Y, et al. Macrolide resistance in *Mycoplasma pneumoniae* in adult patients. *Front Cell Infect Microbiol*. 2025;15:1496521. doi:10.3389/fcimb.2025.1496521
44. Li SL, Sun HM, Zhu BL, Liu F, Zhao HQ. Whole genome analysis reveals new insights into macrolide resistance in *Mycoplasma pneumoniae*. *Biomed Environ Sci*. 2017;30(5):343–350. doi:10.3967/bes2017.045
45. Fahim RA, Rodriguez ZED, Oestreicher Z, et al. Eradication of *Mycoplasma pneumoniae* biofilm towers by treatment with hydrogen peroxide or antibiotic combinations acting synergistically. *PLoS One*. 2025;20(8):e0329571. doi:10.1371/journal.pone.0329571
46. Jiang Y, Dou H, Xu B, et al. Macrolide resistance of *Mycoplasma pneumoniae* in several regions of China from 2013 to 2019. *Epidemiol Infect*. 2024:152–e75. doi:10.1017/S0950268824000323
47. Hong KB, Choi EH, Lee HJ, et al. Macrolide resistance of *Mycoplasma pneumoniae*, South Korea, 2000–2011. *Emerg Infect Dis*. 2013;19(8):1281–1284. doi:10.3201/eid1908.121455
48. Binz J, Adler CK, So TY. The risk of musculoskeletal adverse events with fluoroquinolones in children: what is the verdict now? *Clin Pediatr*. 2016;55(2):107–110. doi:10.1177/0009922815599959
49. Stultz JS, Eiland LS. Doxycycline and tooth discoloration in children: changing of recommendations based on evidence of safety. *Ann Pharmacother*. 2019;53(11):1162–1166. doi:10.1177/1060028019863796
50. Chen Y, Zhang Y, Tang QN, Shi HB. Efficacy of doxycycline therapy for macrolide-resistant *Mycoplasma pneumoniae* pneumonia in children at different periods. *Ital J Pediatr*. 2024;50(1):38. doi:10.1186/s13052-024-01615-y
51. Qiao Y, Chen Y, Wang Q, et al. Safety profiles of doxycycline, minocycline, and tigecycline in pediatric patients: a real-world pharmacovigilance analysis based on the FAERS database. *Front Pharmacol*. 2024;15:1413944. doi:10.3389/fphar.2024.1413944
52. Bolormaa E, Park JY, Choe YJ, Kang CR, Choe SA, Mylonakis E. Treatment of macrolide-resistant *Mycoplasma pneumoniae* pneumonia in children: a meta-analysis of macrolides versus tetracyclines. *Pediatr Infect Dis J*. 2025;44(3):200–206. doi:10.1097/INF.0000000000004568
53. Yang R, Xu H, Zhang Z, et al. Doxycycline vs levofloxacin for macrolide-unresponsive *Mycoplasma pneumoniae* pneumonia in children: a real-world study from China. *Ital J Pediatr*. 2025;51(1):320. doi:10.1186/s13052-025-02156-8
54. Zheng K, Zhou SH, Han ZB. Clinical efficacy comparison of doxycycline versus azithromycin combined with methylprednisolone in the treatment of macrolide-unresponsive *Mycoplasma pneumoniae* pneumonia in children. *Eur J Clin Microbiol Infect Dis*. 2026. doi:10.1007/s10096-025-05393-1
55. Hui T, Yameng Z, Jing W. Observation on the effect of bronchoalveolar lavage with fiberoptic bronchoscope combined with methylprednisolone in the treatment of refractory pediatric mycoplasma pneumonia. *Chin J Pract Med*. 2022;49(24):57–60. doi:10.3760/cma.j.cn115689-20220914-04279
56. Yingqin Q, Yunbo M, Jie Y, et al. Efficacy and effect on pulmonary function of bronchoalveolar lavage combined with methylprednisolone sodium succinate in the adjuvant treatment of refractory *Mycoplasma pneumoniae* pneumonia. *J Pediatr Pharm*. 2024;30(5):44–47. doi:10.13407/j.cnki.jpp.1672-108X.2024.05.011
57. Nakashima T, Yanagihara T, Sanai R, et al. Diffuse alveolar hemorrhage due to macrolide-refractory *Mycoplasma pneumoniae* diagnosed by filmarray analysis of bronchoalveolar lavage fluid. *Cureus*. 2024;16(12):e75525. doi:10.7759/cureus.75525
58. Xiaoqian F, Hemin L. Successful rivaroxaban and doxycycline therapy for Mycoplasma pneumonia with pulmonary embolism in children: a case report. *Front Pediatr*. 2025;13:1449493. doi:10.3389/fped.2025.1449493

59. Conforti C, Giuffrida R, Zalaudek I, Di Meo N. Doxycycline, a widely used antibiotic in dermatology with a possible anti-inflammatory action against IL-6 in COVID-19 outbreak. *Dermatol Ther*. 2020;33(4):e13437. doi:10.1111/dth.13437
60. Malek AJ, Robinson BD, Hitt AR, Shaver CN, Tharakan B, Isbell CL. Doxycycline improves traumatic brain injury outcomes in a murine survival model. *J Trauma Acute Care Surg*. 2020;89(3):435–440. doi:10.1097/TA.0000000000002801
61. Di Caprio R, Lembo S, Di Costanzo L, Balato A, Monfrecola G. Anti-inflammatory properties of low and high doxycycline doses: an in vitro study. *Mediators Inflamm*. 2015;2015:329418. doi:10.1155/2015/329418
62. Castro JE, Vado-Solis I, Perez-Osorio C, Fredeking TM. Modulation of cytokine and cytokine receptor/antagonist by treatment with doxycycline and tetracycline in patients with dengue fever. *Clin Dev Immunol*. 2011;2011:370872. doi:10.1155/2011/370872
63. Elemam A, Rahimian J, Doymaz M. In vitro evaluation of antibiotic synergy for polymyxin B-resistant carbapenemase-producing *Klebsiella pneumoniae*. *J Clin Microbiol*. 2010;48(10):3558–3562. doi:10.1128/JCM.01106-10
64. Zhang L, Chen Q, Ma Y, Sun J. Microfluidic methods for fabrication and engineering of nanoparticle drug delivery systems. *ACS Appl Bio Mater*. 2020;3(1):107–120. doi:10.1021/acsabm.9b00853
65. Zheng Y, Li G, Dai H, Zhu Y. Macrolide-resistant *Mycoplasma pneumoniae* pneumonia in Chinese children: a retrospective study of clinical features and prognosis. *Ital J Pediatr*. 2025;51(1):289. doi:10.1186/s13052-025-02137-x
66. Rajan AS, Gopal M, Periyathambi M, Kuttiatt VS. Dental safety of short-term doxycycline use in children under 8 years: a systematic review and meta-analysis. *Front Pharmacol*. 2025;16:1646638. doi:10.3389/fphar.2025.1646638
67. Li W, Gao W, Xiong X, Tang X, Li A. Association analysis of *Mycoplasma pneumoniae* 23S rRNA gene mutation with refractory *Mycoplasma pneumoniae* pneumonia in children. *PLoS One*. 2026;21(1):e0341580. doi:10.1371/journal.pone.0341580
68. Zaid Alkilani A, Sharaire Z, Hamed R, Basheer HA. Transdermal delivery system of doxycycline-loaded niosomal gels: toward enhancing doxycycline stability. *ACS Omega*. 2024;9(31):33542–33556. doi:10.1021/acsomega.4c01224
69. Wu X, Lu W, Liu W, et al. Predictive value of an early comprehensive assessment model for refractory *Mycoplasma pneumoniae* pneumonia and internal validation. *BMC Infect Dis*. 2025;25(1):744. doi:10.1186/s12879-025-11133-9
70. Lee H, Choi YY, Sohn YJ, et al. Clinical efficacy of doxycycline for treatment of macrolide-resistant *Mycoplasma pneumoniae* pneumonia in children. *Antibiotics*. 2021;10(2):192. doi:10.3390/antibiotics10020192
71. Deng YM. Research progress on azithromycin treatment for pediatric mycoplasma pneumonia. *Capital Food Med*. 2024;(2):20–22.
72. Tong L, Huang S, Zheng C, Zhang Y, Chen Z. Refractory *Mycoplasma pneumoniae* pneumonia in children: early recognition and management. *J Clin Med*. 2022;11(10):2824. doi:10.3390/jcm11102824
73. Varkey DA, Kochuparambil JJ. P-1964. tendon rupture and musculoskeletal events associated with fluoroquinolones: a longitudinal FAERS review. *Open Forum Infect Diseases*. 2026;13(Supplement_1):ofaf695.2131. doi:10.1093/ofid/ofaf695.2131