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Comparative Clinical Efficacy of Doxycycline versus Levofloxacin in the Treatment of Drug-Resistant Mycoplasma Pneumoniae Infections: A Thematic Report

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Abstract

Background: In 2024, a nationwide pandemic of drug-resistant Mycoplasma pneumoniae emerged, increasing treatment challenges. Children were treated with medications contraindicated or used with caution in pediatric patients, such as intravenous levofloxacin and oral doxycycline, leading to prolonged treatment duration, high costs, significant antibiotic side effects, and insufficient research on long-term impacts. In the second half of 2024, the number of drug-resistant Mycoplasma pneumoniae cases surged in our hospital, prompting the clinical implementation of nucleic acid testing for Mycoplasma resistance, targeting the 23S rRNA gene locus.

Objective: Based on clinical data of Mycoplasma pneumoniae infections in our hospital, this retrospective case-control study compares oral doxycycline and intravenous levofloxacin treatment groups for drug-resistant Mycoplasma pneumoniae infections to enhance diagnostic and treatment standards, reduce drug side effects, and decrease the risk of pathogen resistance.

Methods: A retrospective case-control study design was employed, comparing the oral doxycycline treatment group with the intravenous levofloxacin treatment group.

Results: Using t-tests and chi-square tests for statistical analysis, the conclusions are as follows: 1. There was a statistically significant difference in the average time to drug efficacy between oral doxycycline and intravenous levofloxacin. Oral doxycycline showed a significantly faster onset of action in this patient population compared to intravenous levofloxacin. 2. The difference in the proportion of "off-label drug use" between the oral doxycycline group and the intravenous levofloxacin group was extremely statistically significant. These findings indicate that oral doxycycline offers greater advantages and should be the preferred choice for treating drug-resistant Mycoplasma infections in older children (over 8 years old).

Clinical trial number: not applicable.

Introduction

Epidemiological data on Mycoplasma pneumoniae (MP) infection:

The pathogenic mechanisms of MP in respiratory tract infections primarily include cell adhesion, tissue damage, immune injury, and apoptosis. However, some children infected with MP may remain asymptomatic. It has been reported that approximately 21.2% of children are asymptomatic MP carriers, who may serve as potential sources of infection [1].

Mycoplasma pneumoniae pneumonia (MPP) is a common type of pneumonia among pediatric inpatients in our hospital. It predominantly affects school-age children, though infants and young children are also frequently affected. The pathogen is Mycoplasma pneumoniae (MP), a microorganism intermediate between bacteria and viruses, lacking a cell wall.

In clinical practice, pediatric patients with MP infection in our hospital who receive macrolide antibiotics for 5–7 days or longer but show no significant improvement in clinical symptoms—or even experience worsening symptoms such as persistent fever or radiological deterioration (on chest X-ray or CT)—are considered to have refractory MPP. Although MPP is generally regarded as a mild, self-limiting disease responsive to macrolides, it can progress to severe, fulminant illness.

Notably, the prevalence of macrolide-resistant MPP (MRMP) has increased rapidly in recent years, particularly in Asian countries. Macrolide-resistant Mycoplasma pneumoniae (MRMP) carries a point mutation in the V region of the 23S rRNA gene, primarily at positions 2063 and 2064. Overuse of macrolide antibiotics may promote such mutations. MRMP can lead to clinically refractory pneumonia with no clinical or radiological response to macrolides, potentially progressing to severe and complicated pneumonia [2].

Latest literature reports on current resistance rates:

Overall resistance rate: According to recent studies and surveillance data, the resistance rate of Mycoplasma pneumoniae (MP) to macrolide antibiotics (e.g., azithromycin, erythromycin) in China is extremely high. Due to the overuse and unnecessary administration of macrolides over the years, macrolide-resistant MP (MRMP) has become widely prevalent, presenting a severe resistance crisis—particularly in Asian regions, with China, South Korea, and Japan being the most affected. Notably, the detection rate of macrolide-resistant MP has even reached 100% in some areas of China.

Antibiotic resistance rate in children:

The resistance situation in the pediatric population is equally concerning, with a resistance rate exceeding 50%. Data from the Shanghai region in 2023 showed that the resistance rate in children ranged from approximately 70% to 80%.

Sequential azithromycin therapy is safe and effective for treating MP infections in children and does not induce drug-resistant strains. However, irregular use of azithromycin can induce resistant strains, and the resistance rate is positively correlated with the number of irregular administrations [3].

Global and regional differences:

The resistance of M. pneumoniae continues to increase worldwide, particularly in China and Japan [4]. Statistical data from relevant literature indicates that the countries publishing the most mycoplasma-related studies are China and the United States.

Causes of high drug resistance:

The persistently high resistance rate of Mycoplasma pneumoniae (MP) to macrolide antibiotics is attributed to the following key factors:

2.1. Antibiotic selective pressure: Due to their high oral bioavailability and once-daily dosing, macrolides have been widely used in outpatient settings. However, the emergence of resistant strains in recent years has become a global concern. Overuse and unnecessary administration of macrolides (especially azithromycin) in clinical practice and home settings have selected for resistant strains, making them dominant. In China, the grim situation of macrolide-resistant MP (MRMP) prevalence is likely linked to its high usage frequency [5].

2.2. Mechanisms of bacterial resistance to macrolides: There are three main mechanisms:

- Target site mutations/modifications: Base mutations in the 23S rRNA gene (e.g., MP's 2063/2064 loci, corresponding to E. coli's 2058/2059 loci) or methylation of 23S rRNA by methyltransferases, reducing drug binding or causing "off-target" effects.

- Efflux pumps/membrane permeability changes: Mediated drug efflux or altered membrane permeability lowers effective intracellular drug concentrations.

- Enzymatic inactivation: Bacterial enzymes (e.g., esterases, hydrolases, transferases, phosphorylases) hydrolyze or modify drug molecules, inactivating their efficacy.

To date, studies indicate MP resistance to macrolides primarily stems from single-point mutations in the 23S rRNA V region [6].

2.3.Impact of the COVID-19 pandemic: Research suggests non-pharmaceutical interventions during the COVID-19 pandemic (e.g., mask-wearing, prolonged home isolation) may have caused a general decline in population immunity to MP (referred to as "immunity debt"). Reduced exposure to infectious pathogens due to pandemic-era hygiene measures likely decreased immune training in children, making them more susceptible to infections [7]. After the relaxation of pandemic controls, increased pathogen exposure combined with the transmission advantage of resistant strains collectively led to a resurgence of infections and high resistance rates. In the autumn of 2024, Chinese children developed respiratory illnesses earlier and more frequently than usual [8]. Globally, MP causes regional outbreaks every 3–7 years, each lasting 1–2 years [9].

Treatment options for drug-resistant infections:

In the face of high resistance rates, appropriate alternative treatment regimens are selected based on factors such as patient age and disease severity:

- Macrolides: Azithromycin and erythromycin remain first-line choices but require efficacy evaluation. Due to high resistance rates, switching medications should be considered if no improvement is seen within 72 hours of administration. Notably, macrolides have immunomodulatory effects: compared to untreated patients or those receiving ineffective antibiotics (e.g., β-lactams), patients with MRMP

infections treated with macrolides have shorter fever resolution times. Thus, they may still be effective for some resistant strain infections [10].

- Tetracyclines: Doxycycline and minocycline are suitable for children aged ≥8 years and adults. For children <8 years, potential side effects include tooth discoloration (low risk with short-term use) and hepatotoxicity.

- Fluoroquinolones: Levofloxacin and moxifloxacin are approved for adults aged ≥18 years. In children, they may cause cartilage development issues or Q-T interval prolongation and require off-label use with parental consent.

For pediatric patients:

- Macrolides are still recommended as first-line therapy in domestic and international guidelines.

- If no improvement (e.g., persistent high fever) is observed 72 hours after macrolide initiation, clinicians should consider resistance and adjust treatment accordingly.

- For children ≥8 years, doxycycline or minocycline may be considered. Short-term use in children <8 years carries a low risk of tooth discoloration but requires physician assessment and parental informed consent. Long-term use (≥8 weeks) of doxycycline is generally safe with potential mild side effects; further research is needed on its long-term metabolic impacts [11].

- Fluoroquinolones (e.g., levofloxacin) are typically contraindicated in minors <18 years due to potential cartilage development risks, though data from our hospital in 2024 showed a high usage rate of levofloxacin injection.

In the second half of 2024, the treatment of Mycoplasma pneumoniae pneumonia (MPP) became more challenging due to poor efficacy of azithromycin and erythromycin. Aligned with the national epidemiological trend of surging drug-resistant MP cases, our hospital implemented MP nucleic acid testing (with high positivity rates) and treated patients with either intravenous levofloxacin injection or oral doxycycline.

Study selection criteria:

- Participants: Pediatric patients aged 2–14 years with drug-resistant MPP.

- Exclusions: Cases with co-infections (e.g., adenovirus, Epstein-Barr virus).

- Groups: 25 patients in the oral doxycycline group and 25 in the intravenous levofloxacin group.

Objective: A retrospective comparative analysis of treatment efficacy between the two groups via statistical methods, aiming to guide future clinical practice.

This study was approved by the Ethics Committee of Zhangqiu District People's Hospital in Jinan.

Statistical Analysis

A summary of case data for the oral doxycycline group and intravenous levofloxacin group is presented in Table 1. Relevant statistical indicators calculated from these data are shown in Table 2. With complete data available for both groups, an independent-samples *t*-test was performed to compare the mean drug onset time (days) between the oral doxycycline group and the intravenous levofloxacin group. The final test results and conclusions are summarized in Table 3.

Data regarding off-label medication use in the two groups are summarized in Table 4. The results obtained by applying the chi-square test formula to these data are shown in Table 5.

Table 1: Baseline case data for the oral doxycycline group and intravenous levofloxacin group. Table 2: Calculated statistical indicators for mean drug onset time. Table 3: Independent-samples *t*-test results for mean drug onset time. Table 4: Summary of off-label medication use data Table 5: Chi-square test results for off-label medication use

At the $\alpha = 0.05$ significance level, $P < 0.05$, indicating that the difference in mean drug onset time between the oral doxycycline and intravenous levofloxacin groups was statistically significant. For off-label medication use, $P < 0.005$ (≈ 0.00092), far below 0.05, demonstrating that the between-group difference in the proportion of off-label drug use was highly statistically significant.

Result Interpretation: All cases in the intravenous levofloxacin group (100%) involved off-label medication use, while only some cases in the oral doxycycline group (36%) had this issue. The chi-square test result indicates that this difference between the two groups is highly unlikely to be due to chance.

This indicates that oral doxycycline offers greater advantages and should be the preferred choice for treating drug-resistant Mycoplasma infections in older children (over 8 years old).

Discussion

4.1. In clinical practice, various cases are encountered, requiring the development of individualized treatment plans. Based on a balance of benefits and risks, effective treatment methods are formulated for children, though they may not always be the most optimal. For instance, in this study, oral doxycycline demonstrated significant efficacy in practical application, with a portion of its use falling within the labeled indications, thus avoiding potential long-term risks to children from medication use. In this retrospective case study, neither the oral doxycycline group nor the intravenous levofloxacin group showed obvious drug side effects; however, long-term follow-up has not been conducted, and subsequent off-label medication cases will undergo special research.

4.2. The difference in mean time to symptom resolution between oral doxycycline and intravenous levofloxacin was statistically significant, with oral doxycycline demonstrating a significantly faster onset of action in this patient population. Historically, intravenous monotherapy was perceived to offer superior efficacy over oral medications. Consequently, for drug-resistant Mycoplasma pneumoniae infections or refractory mycoplasmal pneumonia, combination therapy with ceftriaxone is commonly used, or intravenous macrolides (azithromycin, erythromycin) are administered for 5–7 days initially. When switching antibiotics later in the course due to prolonged treatment duration and suboptimal response, clinicians often prefer intravenous levofloxacin. However, the statistical findings from this retrospective case analysis suggest that adding oral doxycycline confers greater advantages, which will have positive implications for future clinical practice.

4.3. The difference in the proportion of 'on-label medication use' between the oral doxycycline group and the intravenous levofloxacin group was statistically highly significant. This indicates that oral doxycycline offers greater advantages and should be the preferred choice for treating drug-resistant Mycoplasma infections in older children (over 8 years old). With its proven efficacy even when used within the labeled indications, there is no doubt that oral doxycycline is the first recommended option when combining antibiotics for refractory Mycoplasma pneumonia or drug-resistant Mycoplasma infections.

4.4. To date, there have been no reports of intrinsic resistance to tetracyclines in Mycoplasma pneumoniae [2]. While tetracyclines demonstrate strong efficacy and lack documented resistance, caution must still be exercised to prevent the emergence of new resistance patterns due to overuse.

4.5. Clinical Features and Resistance: No Direct Correlation Identified

Comparative analysis of drug-resistant vs. non-resistant cohorts revealed no statistically significant differences in key clinical parameters(age, weight, platelet counts, etc.), indicating a potential lack of direct association between resistance status and clinical presentation. As antimicrobial resistance continues to escalate, future management will face heightened challenges—clinicians must therefore prioritize timely resistance assessment and strategic treatment adjustments to optimize outcomes [12].

4.6.Numerous prospective, controlled investigations demonstrate that oral antibiotics are at least as effective, safer, and lead to shorter hospitalizations than IV-only therapy; no contrary data were identified. Treatment guidelines should be modified to indicate that oral therapy is appropriate for reasonably selected patients with osteomyelitis, bacteremia, and endocarditis[13].

This study has a limitation in its small sample size. I present this report as a starting point to spark discussion, and I urge fellow pediatricians to collectively focus on the rational treatment of drug-resistant Mycoplasma pneumoniae infections to safeguard children's healthy growth.

Declarations

Abbreviations

Not applicable.

Ethics approval and consent to participate

The Ethics Committee of Zhangqiu District People's Hospital, Jinan City has reviewed and approved this study, and this review was based on the Declaration of Helsinki. Ethics approval number: 2024087; Approval date: July 10, 2024. This study involves clinical data of children under 16 years of age, and all personal identifiable information of the pediatric participants has been completely de-identified and anonymized to protect patient privacy. Given the retrospective nature of the study and full data anonymization, the Ethics Committee waived the requirement for parental or legal guardian informed consent. All study procedures were conducted in accordance with relevant clinical research ethical regulations.

Consent for publication

Not applicable. This study does not contain any individual person's identifiable images, personal or clinical details that could compromise participant anonymity. Therefore, consent for publication is not required.

Availability of data and materials

All data generated and analyzed during this study are real clinical medical record data, which are fully provided in the supplementary materials of this article.

Competing interests

The authors declare that there are no competing interests.

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No funding was received for conducting this study.

Authors' contributions

Chonghua Wang made the greatest contribution to this study, responsible for the overall study design and manuscript writing. Zhijun Li was responsible for clinical data collection and sorting. Huazhen Wang undertook the overall design guidance, scheme optimization and revision of the manuscript. All authors have read and approved the final submitted manuscript.

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Tables

Table 1: Baseline case characteristics of oral doxycycline and intravenous levofloxacin groups

Metrics	Oral Doxycycline Group (n=25)	Intravenous Levofloxacin Group (n=25)
Total cases	25	25
Mean hospital stay (days)	11	10.96
Mean medication duration during hospitalization (days)	5.28	6.8

Note: n = number of subjects.

Table 2: Descriptive statistical indicators for mean drug onset time of the two groups

Indicator	Oral Doxycycline Group (n=25)	Intravenous Levofloxacin Group (n=25)
Mean (M)	5.28	6.8
Standard Deviation (SD)	2.65	2.13
Variance (S^2)	7.04	4.54

Note: SD = standard deviation; units for mean and SD are days.

Table 3: Independent-samples *t-test* results for mean drug onset time

Indicator	Oral Doxycycline Group (n=25)	Intravenous Levofloxacin Group (n=25)	Test Result
Sample size (n)	25	25	-
Mean (days)	5.28	6.8	Difference = −1.52 days
Standard Deviation (SD)	2.65	2.13	-
t-statistic	-	-	−2.235
Degrees of freedom (df)	-	-	48
P-value	-	-	0.030

Note: Independent-samples t-test was applied; significance level α = 0.05; SD = standard deviation; df = degrees of freedom.

Table 4: Off-label medication use in oral doxycycline and intravenous levofloxacin groups

	Oral Doxycycline	Intravenous Levofloxacin	Total
Total number of cases	25	25	50
Cases without off-label use	9	0	9
Cases with off-label use	16	25	41

Table 5: Chi-square test results for off-label medication use comparison

Indicator	Value
Chi-square statistic (χ^2)	10.976
Degrees of freedom (df)	1
P-value	0.00092

Note: χ^2 test was performed; significance level $\alpha = 0.05$; df = degrees of freedom.

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