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PHARMACOKINETIC AND PHARMACODYNAMIC CHARACTERISTICS OF ANTIBIOTICS USED IN THE TREATMENT OF PERTUSSIS

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Abstract: Pertussis, caused by Bordetella pertussis, remains a significant public health concern despite widespread vaccination. Antibiotic therapy plays a crucial role in eradicating bacterial carriage, reducing transmission, and mitigating disease severity when administered early. The present review analyzes the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of antibiotics recommended for pertussis treatment, including macrolides (azithromycin, clarithromycin, erythromycin) and trimethoprim-sulfamethoxazole (TMP-SMX). Data were synthesized from peer-reviewed publications, clinical guidelines, and pharmacological references. Macrolides demonstrate high intracellular penetration, prolonged half-lives (notably azithromycin), and concentration-dependent activity against B. pertussis. TMP-SMX exhibits time-dependent bacteriostatic effects by sequential inhibition of folate synthesis. Understanding PK/PD parameters such as minimum inhibitory concentration (MIC), area under the concentration–time curve (AUC), peak plasma concentration (Cmax), and time above MIC (T>MIC) is essential for optimizing dosing regimens and minimizing resistance.

Keywords: pertussis, Bordetella pertussis, macrolides, azithromycin, clarithromycin, erythromycin, trimethoprim-sulfamethoxazole, pharmacokinetics, pharmacodynamics, MIC

Introduction

Pertussis (whooping cough) is an acute respiratory infection caused by Bordetella pertussis, a Gram-negative coccobacillus [1, p. 965]. Despite vaccination efforts, outbreaks continue worldwide. According to the World Health Organization (WHO), approximately 24 million cases and 160,000 deaths occurred globally in 2014, predominantly among infants [2].

Antibiotic therapy aims primarily to eliminate nasopharyngeal carriage of B. pertussis, thereby reducing transmission [3, p. 1546]. Early administration during the catarrhal phase may reduce symptom severity, but once the paroxysmal stage begins, antibiotics mainly limit contagion rather than clinical progression [4, p. 314]. Current guidelines recommend macrolides as first-line agents and TMP-SMX as an alternative [3, p. 1548].

Methodology

A structured literature review was conducted using PubMed, WHO reports, CDC guidelines, and pharmacology textbooks published between 2000 and 2023. Inclusion criteria comprised randomized clinical trials, pharmacokinetic studies, in vitro susceptibility analyses, and official treatment recommendations. Data regarding absorption, distribution, metabolism, elimination, MIC values, AUC/MIC ratios, and clinical outcomes were extracted and analyzed.

Results

Macrolides

Azithromycin demonstrates rapid absorption with oral bioavailability approximately 37% and extensive tissue distribution, achieving intracellular concentrations exceeding plasma levels [5, p. 502]. Its elimination half-life ranges from 48 to 68 hours, permitting once-daily dosing [5, p. 504]. Azithromycin exhibits concentration-dependent bacteriostatic activity and a prolonged post-antibiotic effect (PAE) against susceptible organisms [6, p. 112].

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Clarithromycin has an oral bioavailability of about 55%, undergoes hepatic metabolism via CYP3A4 to an active metabolite (14-hydroxyclarithromycin), and has a half-life of 3–7 hours depending on dose [5, p. 498]. It achieves high epithelial lining fluid concentrations and demonstrates time-dependent activity [6, p. 114].

Erythromycin, historically the standard therapy, has variable bioavailability (30–65%) and a short half-life (1.5–2 hours), requiring four daily doses [5, p. 493]. Gastrointestinal adverse effects are common due to motilin receptor stimulation [7, p. 276].

MIC values for B. pertussis isolates are typically ≤0.12 µg/mL for azithromycin and clarithromycin, indicating high susceptibility [8, p. 887].

Trimethoprim-Sulfamethoxazole (TMP-SMX)

TMP-SMX inhibits sequential steps in folate synthesis, exerting bacteriostatic activity [9, p. 105]. Oral bioavailability exceeds 85%, and both components distribute widely into respiratory tissues [5, p. 517]. The half-life of trimethoprim is approximately 8–10 hours, and sulfamethoxazole 10 hours [5, p. 518].

In vitro studies show susceptibility of B. pertussis to TMP-SMX, with MIC values generally below 1 µg/mL [8, p. 889].

Discussion and Analysis

The clinical effectiveness of antibiotic therapy in pertussis is determined not only by the intrinsic antimicrobial activity of the selected agent but also by its pharmacokinetic (PK) and pharmacodynamic (PD) profile in relation to the biological characteristics of Bordetella pertussis. Because B. pertussis is a fastidious, exclusively human respiratory pathogen that colonizes ciliated epithelial cells of the nasopharynx and tracheobronchial tree, optimal therapy requires adequate antibiotic penetration into respiratory mucosa and epithelial lining fluid, as well as sufficient intracellular concentrations in phagocytic cells. These pharmacologic considerations directly influence bacterial eradication, duration of carriage, and public health control of transmission [3, pp. 1546–1550].

Macrolides remain first-line therapy primarily because of their favorable PK properties in respiratory tissues. Azithromycin, in particular, demonstrates extensive tissue distribution and high intracellular accumulation, reaching concentrations in phagocytes and respiratory epithelium that significantly exceed plasma levels [5, pp. 502–504]. This property is highly relevant in pertussis, where bacterial adherence to epithelial cells and toxin production are central to pathogenesis. High intracellular concentrations enhance the exposure of colonizing organisms to the drug and may prolong antibacterial activity even when plasma concentrations decline.

The prolonged elimination half-life of azithromycin (48–68 hours) permits once-daily dosing and short-course regimens (5 days), which contrasts with erythromycin's shorter half-life (1.5–2 hours) requiring four daily doses for 14 days [5, pp. 493–504; 3, p. 1549]. From a PK perspective, the extended half-life ensures sustained tissue concentrations above the minimum inhibitory concentration (MIC) for B. pertussis, typically ≤0.12 µg/mL for susceptible isolates [8, p. 887]. Clinically, this translates into improved adherence, particularly in pediatric populations, where prolonged multi-dose regimens are associated with decreased compliance. Treatment adherence is crucial because incomplete courses may result in persistent carriage and ongoing transmission.

Pharmacodynamically, macrolides are traditionally classified as bacteriostatic agents that inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit [7, p. 274]. However, the distinction between bacteriostatic and bactericidal activity is concentration- and organism-dependent. For macrolides, antibacterial efficacy correlates more closely with the ratio of the

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area under the concentration–time curve to MIC (AUC/MIC) rather than solely with peak concentration (Cmax) or time above MIC (T>MIC) [6, pp. 112–116]. This AUC/MIC-dependent behavior explains why azithromycin's prolonged exposure profile contributes substantially to clinical success in respiratory infections.

Higher AUC/MIC ratios have been associated with enhanced bacterial eradication and reduced relapse rates in respiratory pathogens [6, p. 116]. Although specific PK/PD target thresholds for B. pertussis are not universally established, extrapolation from respiratory infection models suggests that maximizing AUC relative to MIC is advantageous. Because azithromycin achieves sustained tissue levels even after cessation of dosing, the effective AUC in target tissues remains elevated, supporting shorter therapeutic courses without compromising microbiological clearance.

Clarithromycin presents a somewhat different PK profile. With an oral bioavailability of approximately 55% and a shorter half-life (3–7 hours), clarithromycin requires twice-daily dosing [5, pp. 498–500]. However, its active metabolite, 14-hydroxyclarithromycin, contributes additional antimicrobial activity, effectively increasing total antibacterial exposure [5, p. 500]. This metabolite's presence may enhance the composite AUC/MIC ratio, supporting therapeutic efficacy comparable to azithromycin when adherence is maintained. Nevertheless, the requirement for longer treatment durations relative to azithromycin may affect compliance in outpatient settings.

Erythromycin, historically the standard therapy for pertussis, demonstrates variable oral bioavailability (30–65%) and frequent gastrointestinal adverse effects due to motilin receptor stimulation [5, p. 493; 7, p. 276]. These adverse effects can limit adherence, particularly in infants and children. From a PK standpoint, the short half-life necessitates frequent dosing to maintain concentrations above MIC. Because erythromycin's PD activity is also AUC/MIC-dependent, suboptimal adherence or missed doses can reduce effective exposure and potentially compromise bacterial eradication.

Another important pharmacodynamic consideration in pertussis therapy is the timing of antibiotic initiation. Antibiotics are most effective in reducing symptom severity when administered during the catarrhal phase, when bacterial replication and colonization are active [4, p. 314]. Once the paroxysmal phase is established, clinical manifestations are largely toxin-mediated, and antibiotics primarily reduce transmission rather than alter disease course [3, p. 1548]. Thus, even optimal PK/PD properties cannot fully reverse toxin-induced pathophysiology once it has progressed. This highlights the necessity of early diagnosis and treatment initiation to maximize therapeutic benefit.

Resistance patterns must also be evaluated in the context of PK/PD optimization. Although macrolide-resistant B. pertussis strains remain relatively uncommon globally, reports from China have documented resistance associated with mutations in the 23S rRNA gene [10, p. 1185]. Resistance mechanisms typically increase MIC values, thereby reducing the AUC/MIC ratio for standard dosing regimens. If MIC rises beyond achievable tissue concentrations, clinical efficacy may decline. Consequently, surveillance of susceptibility patterns is essential to ensure that current dosing regimens remain pharmacodynamically adequate.

Subtherapeutic antibiotic exposure, whether due to inappropriate dosing, poor adherence, or altered pharmacokinetics in specific populations (e.g., neonates or patients with hepatic dysfunction), may contribute to selective pressure favoring resistant strains. Macrolides undergo hepatic metabolism and biliary excretion to varying extents; therefore, hepatic impairment could alter drug exposure [5, pp. 498–504]. Adjustments in dosing or careful monitoring may be required to maintain optimal AUC/MIC ratios in such patients.

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Trimethoprim-sulfamethoxazole (TMP-SMX) serves as an alternative for patients who cannot tolerate macrolides or in whom macrolide resistance is documented [3, p. 1550]. Its mechanism involves sequential inhibition of folate synthesis, resulting in bacteriostatic activity [9, p. 105]. Unlike macrolides, TMP-SMX exhibits predominantly time-dependent killing, with efficacy correlated to the duration that free drug concentrations exceed MIC (T>MIC) [9, p. 108]. Therefore, dosing regimens must ensure sustained plasma levels above the susceptibility threshold.

TMP-SMX demonstrates high oral bioavailability (>85%) and adequate distribution into respiratory tissues [5, pp. 517–518]. However, because its PD activity depends on maintaining concentrations above MIC for a sufficient proportion of the dosing interval, missed doses can have a greater impact on therapeutic success compared with concentration-dependent agents. The requirement for consistent dosing underscores the importance of patient education and adherence monitoring.

Safety considerations are integral to PK/PD evaluation, particularly in vulnerable populations such as neonates. Erythromycin has been associated with an increased risk of infantile hypertrophic pyloric stenosis when administered during early infancy [11, p. 903]. This association influences antibiotic selection, favoring azithromycin in neonates due to its improved tolerability profile [12, p. 1122]. From a pharmacologic perspective, minimizing adverse effects supports adherence and reduces treatment discontinuation, thereby preserving effective drug exposure.

In neonates younger than two months, TMP-SMX is contraindicated because sulfamethoxazole may displace bilirubin from plasma proteins, increasing the risk of kernicterus [3, p. 1550]. This pharmacodynamic risk is unrelated to antibacterial activity but reflects drug–host interactions affecting safety. Consequently, therapeutic decision-making must integrate both antimicrobial efficacy and developmental pharmacology.

The relationship between PK/PD parameters and public health impact in pertussis deserves particular attention. Because the primary goal of antibiotic therapy in many cases is to reduce transmission rather than shorten symptoms, eradication of nasopharyngeal carriage is the critical endpoint. Macrolides have demonstrated rapid clearance of B. pertussis from the nasopharynx, often within 5 days of therapy initiation [3, pp. 1548–1549]. Sustained tissue concentrations above MIC facilitate this microbiological clearance. Therefore, ensuring that dosing regimens achieve adequate tissue exposure is essential for outbreak control.

The concept of post-antibiotic effect (PAE) further supports the use of azithromycin. Macrolides demonstrate a measurable PAE against susceptible respiratory pathogens, meaning that bacterial growth remains suppressed even after drug concentrations fall below MIC [6, p. 113]. Although specific PAE data for B. pertussis are limited, the general pharmacodynamic behavior of macrolides suggests that prolonged suppression of bacterial replication contributes to therapeutic efficacy and justifies once-daily dosing.

Conclusion

Antibiotics remain central to pertussis management by eliminating B. pertussis carriage and preventing transmission. Macrolides—particularly azithromycin—possess favorable pharmacokinetic characteristics, including extensive tissue penetration and prolonged half-life, supporting short-course therapy and high adherence. PK/PD parameters such as AUC/MIC and T>MIC are crucial for optimizing therapeutic outcomes. TMP-SMX is an effective alternative when macrolides are contraindicated. Continuous surveillance of susceptibility patterns and resistance mechanisms is essential to preserve treatment efficacy.

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