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Recommendations on off-label use of intravenous azithromycin in children

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Abstract

Objective: Intravenous azithromycin (AZM) has been widely used in children worldwide, but there still remains much concern regarding its off-label use, which urgently needs to be regulated. Therefore, we developed a rapid advice guideline in China to give recommendations of rational use of intravenous AZM in children.

Methods: This guideline focuses on antimicrobial therapy with intravenous AZM in children. The Delphi research method was used to select questions. A systematic literature review was also conducted. Data were pooled and ranked according to the GRADE system. Recommendations were developed based on expert clinical experience, patients' values and preferences, and evidence availability. After an external review, the recommendations were revised and approved.

Results: This guideline included eighteen recommendations that covered four domains: (a) Indications: the treatment of pneumonia caused by atypical but common pathogens, such as *Mycoplasma pneumoniae*, *Chlamydia trachomatis* or *Chlamydophila pneumoniae* and *Legionella pneumophila*, more typical bacteria as well as the treatment of bronchitis of presumed bacterial aetiologies; (b) Usage and dosage: administration route, infusion concentrations, treatment duration, course of sequential treatment, and dosage stratified by age; (c) Adverse reactions and treatment: the management of gastrointestinal reactions, arrhythmias, pain or phlebitis at the infusion site, and anaphylaxis; and (d) Special population: children with renal or liver dysfunction, congenital heart disease, and obesity. This guideline will hopefully help promote a rational use of intravenous AZM in children worldwide.

Conclusion: This guideline has summarised the evidence and has developed recommendations on the use of intravenous AZM in children worldwide. Further attention and well-designed researches should be conducted on the off-label use of intravenous AZM in children.

1 | INTRODUCTION

Azithromycin (AZM) is a macrolide antibacterial drug with the following advantages: short-course therapy, good tolerance, compliance, and few serious contraindications or adverse reactions. It has unique pharmacokinetic characteristics and strong antibacterial activity against atypical pathogenic bacteria, along with a good postantibiotic effect, a high concentration in the tissues, and a long half-life.[1]

Intravenous AZM has been widely used globally in children with moderate or severe infections caused by susceptible bacteria, especially atypical pathogens.[2] However, its rational use, safety, and effectiveness have not been established in children under 16 years of age.[3] Consequently, the widespread off-label use of intravenous AZM in children has aroused broad concerns amongst the public and health professionals, which can lead to therapeutic uncertainty. Therefore, guidelines for the appropriate use of intravenous AZM in the paediatric population need to be urgently developed.

Clinical practice guidelines are statements that include recommendations intended to optimise patient care. These recommendations are based on results from systematic reviews of the available evidence and on assessments of the benefits and harm associated with alternative options.[4] Although a few guidelines in the field of paediatric infectious disease have mentioned AZM, there is still a lack of comprehensive guidelines for the use of intravenous AZM in the overall management of paediatric patients globally. Therefore, the aim of this guideline is to provide recommendations for off-label use of intravenous AZM based on extensive investigations, a comprehensive review of quality-controlled literatures, and expert consensus.

What's known

- The questions in this guideline were collected and evaluated by frontline medical stuff through a questionnaire survey.
- Systematic reviews and meta-analyses of literatures from main databases were conducted referring to the Cochrane handbook and PRISMA checklist.
- Expert opinions and recommendations of this guideline were collected by a three-round Delphi method survey in panel meetings.
- The values and references of patients were collected through a questionnaire survey.

What's new

- The widespread off-label use of intravenous AZM in children has aroused broad concerns amongst the public and health professionals and there are few consensuses on this critical issue.
- 18 recommendations were developed based on expert clinical experience, patients' values and preferences, and evidence availability, including indications, dosage and usage, management of adverse reactions and management in the special paediatric population.

2 | METHODS

According to the *WHO handbook for guideline development* and methodology guidance, the guideline review committee (GRC), guideline development group (GDG), secretary group, and external review group were established (Table S1).[5,6] The GDG consisted of 27 authoritative experts from 18 hospitals or universities from 11 regions in China, including 13 paediatricians, 9 pharmacists, 1 antimicrobial expert, 1 microbiologists, 1 pharmacologist, 1 guideline methodologist, and 1 nurse, and we also invited a representative of patients' family. Since the guideline was required to be developed urgently, we only invited experts from China, and the selection of GDG members took into account regional differences, the level of authority of participating members, and the presence of multidisciplinary cooperation.[7]

We chose the rapid advice guideline because, even though the recommendations were mainly based on secondary evidence rather than original studies, the risks associated with off-label use of intravenous AZM in children needed to be addressed urgently.[8-11] Systematic reviews (SRs) and/or meta-analyses were conducted if there was the lack of available secondary evidence to answer important clinical questions. The intended readers of our guideline are paediatric clinicians, pharmacists, and nursing staff. The guideline had been registered on the International Practice Guidelines Registry Platform (IPGRP-2016CN013),[12] and the protocol has been published.

Important and pressing questions to be included in our guideline were selected as follows. First, potential intervention research questions with components and outcomes based on PICO (P: participants; I: intervention; C: comparison; O: outcomes) were drafted after a comprehensive review of the literature and interviews with

experts in paediatric infectious disease. Then, frontline clinicians were surveyed to quantitatively evaluate the importance of alternative questions and outcomes.[13] Finally, these questions and outcomes were selected by the GDG using a three-round Delphi method with the online questionnaire software Wenjuanxing (WJX). In the first round, experts were asked to evaluate the importance of each question (score 1 to 5) and outcome (score 1 to 9), with higher scores representing greater importance. Questions were included (if the mean score was ≥4 and the coefficient of variation (CV) was ≤15%) or excluded (if the mean score was ≤3 and the CV was ≥15%). The remaining questions were carried over into the next round for further evaluation. Outcomes were included if the CV was ≤30%, otherwise, they would be moved to the next round. In the second-round, experts whose scores were outside the quartile were asked to share their opinions anonymously using PowerPoint slides. In the third round, all experts graded the questions that had yet to be selected again and included those with a mean score ≥4, while excluding those with a mean score ≤3, regardless of the CV. Questions that failed to reach a consensus were selected according to the quality of the evidence and expert consensus. Outcomes were divided into "key outcomes" (score 7 to 9), "important outcomes" (score 4 to 6), and "general outcomes" (score 1 to 3). The details of the procedure and consensus rules are shown in Figure 1.[14]

A comprehensive review of the literature was conducted after the questions were selected. The databases PubMed, EMBASE, The Cochrane Library, clinicaltrials.gov, SinoMed, CNKI and WanFang Data were systematically searched from inception to 12th July 2017. The search strategy is presented in Table S2. The following study types that reported the effects or cost-effectiveness of intravenous AZM for infection-related outcomes in children were included: SR-based clinical practice guideline, health technology assessment (HTA), SR or meta-analysis, network meta-analysis and randomised controlled trials (RCTs). Articles were excluded if 1) the study population or formulation of AZM was unclear; 2) data related to AZM were unavailable; or 3) they were conference abstracts. There were no limitations on language.

A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) and Preferred Reporting Items for Systematic Review and Meta-analysis protocols (PRISMA) were used to evaluate the quality of included SRs.[15,16] When there was a high-quality SR and no new RCT was published in 2 years, the existing SR would be adopted. If there was a high-quality SR but new RCT was published in 2 years, we would update the SR. In addition, if there was low-quality SR or no secondary evidence available, a SR or meta-analysis based on RCTs was conducted.

The data were screened, evaluated, extracted, and reviewed by pairs of reviewers from the secretary group with rich experience in conducting systematic reviews independently using predesigned forms according to the inclusion and exclusion criteria. Reviewers resolved any disagreement by discussion or if possible, by consultation with a third reviewer. The Cochrane Risk of Bias Tool was used to evaluate the quality of the included RCTs. Relative risks (RRs) or the mean difference (MD) was calculated, and meta-analysis was performed using Review Manager 5.3 software. The data was considered homogeneous for $I^2 \leq 50\%$, and the fixed-effect model was used; otherwise, the random-effect model was employed. A $P < .05$ was considered statistically significant.

The overall quality of evidence for each research question was evaluated using the GRADE system (Table 1),[17] and the evaluation was conducted by two researchers independently. We summarised the sample size and treatment measures of each outcome and evaluated quality by assessing factors such as limitations, inconsistency,

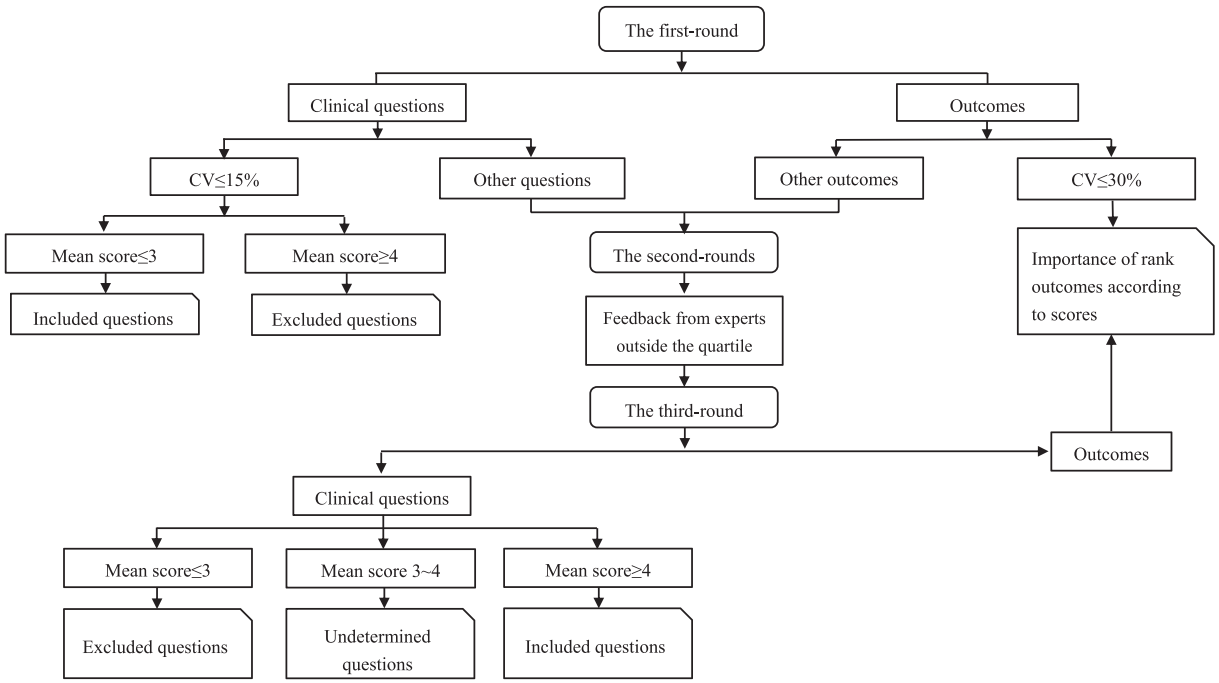

FIGURE 1 Procedure and consensus rules for the three-round Delphi research method for developing questions and outcomes

indirectness, imprecision, and publication bias. Any disagreement was resolved by consulting a third researcher. If the GRADE results of the outcomes were different, we chose the GRADE quality of the more important outcome to represent the overall quality of the evidence pertaining to a certain question.

Patients' values and preferences were surveyed after reviewing and evaluating the evidence. Paper questionnaires were administered to the parents of patients in the Respiratory Department of Beijing Children's Hospital to evaluate issues such as their preference for sequential antimicrobial therapy (SAT) in nonsevere or severe pneumonia, their views regarding the maximum acceptable course of AZM SAT treatment, their opinions regarding the continuation vs a change in the therapeutic regimen if AZM was ineffective, and their perceptions about the importance of adverse events (AEs) related to AZM.

Based on factors such the patients' values and preferences, clinical experience, an economic analysis, the quality of available evidence, the magnitude of intravenous AZM, the balance between benefits and risk, and the potential impact on the equity, acceptability, and feasibility of the implementation, the GDG developed recommendations with the three-round Delphi method using WJX.[18,19] The process employed with the Delphi method was similar to that used with the question development (Figure 2), except for the use of different scoring criteria, which was in accordance with the GRADE grid and included an assessment of strength and quality (Table 2).[20] In the first round, experts evaluated the strength of each drafted recommendation, with the score of "2" (strongly agreement) to "-2" (strongly disagreement). The final strength of recommendations was defined as "strong recommendations" (if the proportion of "2" was ≥50% and "2" + "1" was ≥70%) or "weak recommendations" (if the proportion of "2" + "1" was ≥50% and "-1" + "-2" was ≤20%). The remaining recommendations were carried over into the second-round and third-round. The details of the procedure and consensus rules are shown in Figure 2.

Experts and the parents of patients from an external review group were invited to evaluate the four aspects of the recommendations, which included appreciations, clarity, feasibility, and subjective opinions. The recommendations were excluded if the appreciations and feasibility ratings were below 60%, and the main body was not revised if the appreciations and feasibility ratings were greater than 80%. When the appreciations and feasibility ratings were between 60% and 80%, the expression and main body of recommendation should be revised cautiously by GRC and then be reviewed by the external review group (approved only if the ratings after revision are greater than 80%, otherwise excluded). The mode of expression was revised if the clarity rating was below 60%.[21] The opinions of the patients' parents were carefully considered. The recommendations were finally revised by the GDG and approved by the GRC.

This guideline followed the Appraisal of Guidelines for Research and Evaluation Reporting Checklist and A Reporting Tool for Practice Guidelines in Health Care.[22,23]

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TABLE 1 Quality of evidence and strength of recommendation in GRADE

Quality rating	Description	Underlying methodology
High (A)	Very confident that the real effect value is close to the effect estimate	Randomised trials
		Double-upgraded observational studies
Moderate (B)	Moderate confidence in the effect estimate : the real effect value may significantly different from the estimate	Downgraded randomised trials
		Upgraded observational studies
Low (C)	Limited confidence in the effect estimate: the real effect value may significantly differ from the estimate	Double-downgraded randomised trials
		Observational studies
Very low (D)	Almost no confidence in the effect estimate: the true value is likely to be significantly differ from the estimate	Triple-downgraded randomised trials
		Downgraded observational studies
		Case series
		Case reports
Recommendation strength		
Strong (1)	Desirable effects clearly outweigh undesirable effects or vice versa	
Weak (2)	Uncertainty in the estimates of desirable effects, harms, and burden; desirable effects, harms, and burden may be closely balanced	

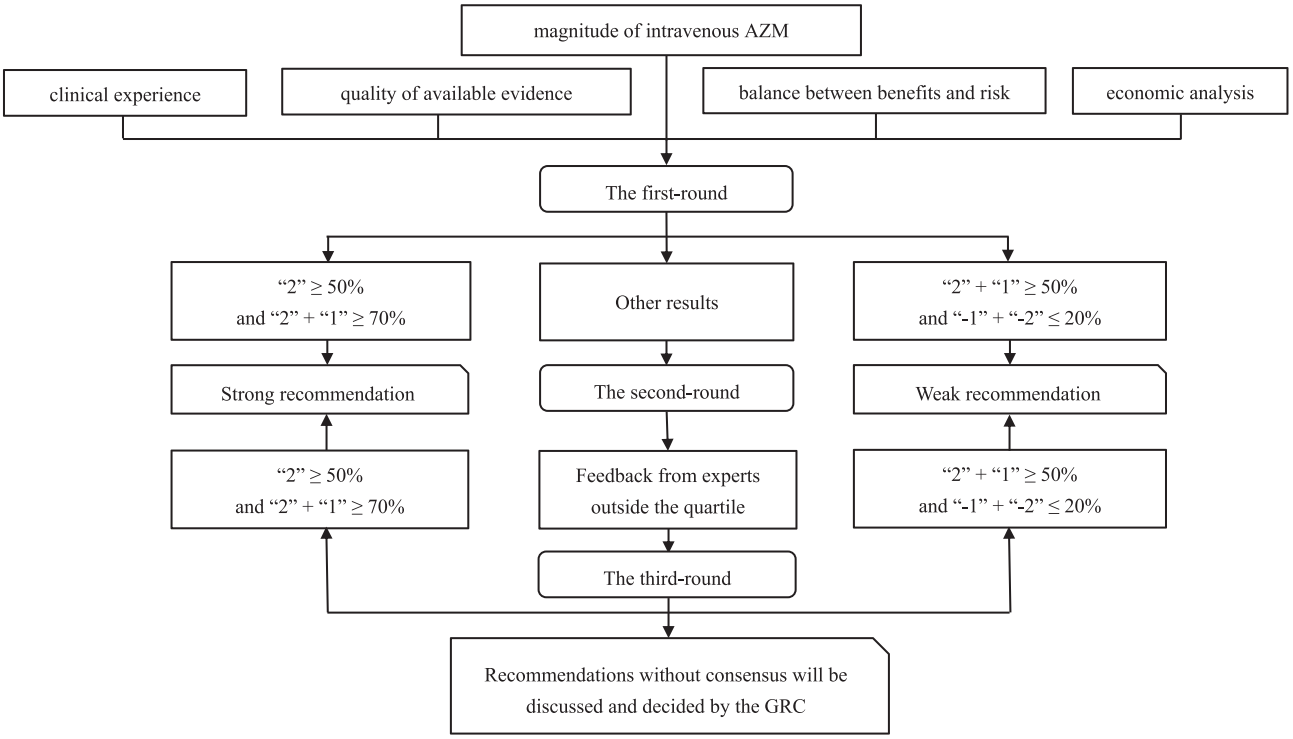

FIGURE 2 Procedure and consensus rules for the three-rounds Delphi research method for developing recommendations

3 | RESULTS

Twenty-seven questions and twelve outcomes were drafted and subsequently evaluated by 155 clinicians (Table S3). Finally, twenty-two questions and twelve outcomes were selected to be included using the Delphi research method (Table S4). A total of 15,844 records were initially retrieved, and the results of the literature search are shown in Figure 3. Overall, six clinical practice guidelines, four SRs (AMSTAR-2 evaluation results: Table S5A-D; PRISMA checklist result: Table S6) and six RCTs were included. Eighteen recommendations (Table 3) were ultimately developed after a review and evaluation of the evidence combined with expert consensus obtained using the Delphi research method (Table S7A-C) and an external review group comprising sixty-three experts and two patients (Table S8). The results of the GRADE evaluation are summarised in Table S9. Additional details regarding the results can be found in related published articles.[7,13,14,19,21]

3.1 | Indications

Question 1: Is intravenous AZM effective and safe for the treatment of *Mycoplasma pneumoniae* (*M pneumoniae)* pneumonia in children?

Recommendation 1: Intravenous AZM is strongly recommended for the treatment of *M pneumoniae* pneumonia in children. (1B).

Evidence: The results of a moderate quality SR (1,785 children, Table S5A) demonstrated that when compared with intravenous erythromycin (ERY), intravenous AZM had advantages in terms of the treatment success rate (RR = 1.13, 95% confidence interval (CI): 1.06 to 1.20), length of hospital stay (mean difference (MD) = −2.72, 95% CI: −3.50 to −1.94), rate of gastrointestinal AEs (RR = 0.36, 95% CI: 0.28 to 0.47), liver toxicity (RR = 0.55, 95% CI: 0.34 to 0.89), and pain at the injection site (RR = 0.31, 95% CI: 0.20 to 0.48) in the target population.[24] The data also showed that AZM SAT, administered at a dosage of 10 mg/kg on the first and second day of intravenous therapy followed by a transition to oral therapy if possible, was the preferred choice of regimen for school-age children and adolescents with *M pneumoniae* pneumonia (MPP). For hospitalised children with suspected MPP, empirical treatment with AZM (oral or parenteral) in combination with β-lactam antibiotics should be started empirically, while awaiting the results from rapidly performed diagnostic tests to determine aetiology. Intravenous AZM was preferred for children diagnosed with MPP.[25]

Statement: MPP accounts for 10% to 40% of community-acquired pneumonias (CAPs) in hospitalised children. These percentages may be higher in children older than 5 years of age , whether they are outpatients or inpatients (5-9 years: 40%, 10-14 years: 67%[26]), with no discernible difference in seasonal prevalence. Macrolide antibiotics should be considered as alternative therapy if there is no response to the frontline empirical therapy and may be added if MPP is suspected, especially for children who are hospitalised with a severe infection.[27-29]

Question 2: Is intravenous AZM effective and safe for the treatment of *Chlamydia trachomatis* (*C trachomatis)* or *Chlamydophila pneumoniae* (*C pneumoniae*) infections in children?

Recommendation 2: Intravenous AZM can be used for the treatment of *C pneumoniae* pneumonia or *C*. trachomatis infections in children. (2C).

TABLE 2 GRADE grid and consensus rules

	GRADE score				
	2	1	0	−1	−2
Balance between desirable and undesirable consequences of intervention	Desirable clearly outweigh undesirable	Desirable probably outweigh undesirable	Trade-offs equally balanced or uncertain	Undesirable probably outweigh desirable	Undesirable clearly outweigh desirable
Recommendation	Strong: "definitely do it"	Weak: "probably do it"	No specific recommendation	Weak: "probably don't do it"	Strong: "definitely don't do it"
Rules					
Strong recommendation	"2" ≥ 50% and "2" + "1" ≥ 70%				
Weak recommendation	"2" + "1" ≥ 50% and "-1" + "-2" ≤ 20%				
No consensus	Other results				

Evidence: Regarding *C pneumoniae* pneumonia, three RCTs (176 children) met the preplanned study selection criteria, and a meta-analysis was performed.[30-32] The results demonstrated that, when compared with intravenous ERY, intravenous AZM had a better treatment success rate (RR = 1.23, 95% CI: 1.02 to 1.48) in the target population. The data also showed that AZM SAT was the preferred treatment of choice for school-age children and adolescents with *C trachomatis* or *C pneumonia* infections.[30-32]

Statement: Macrolide antibiotics should be used for the treatment of *C pneumoniae* pneumonia in children.[27,29] There was a consensus that adolescents should receive AZM at a dose equivalent to that given to adults for the treatment of uncomplicated *C trachomatis* infection, based on limited recent data but extensive clinical experience presented in a guideline.[33] The GDG believed that the treatment strategies were similar for *C pneumoniae*, *C trachomatis*, and *M pneumoniae* infections in children.

Question 3: Is intravenous AZM an effective and safe treatment for *Legionella pneumophila (L pneumophila)* pneumonia in children?

Recommendation 3: Intravenous AZM can be used as the treatment for *L pneumophila* pneumonia in children. (2C).

Evidence: We performed a meta-analysis based on two RCTs (124 children). Compared with intravenous ERY, intravenous AZM showed an advantage in terms of treatment success rate (RR = 1.18, 95% CI: 1.03 to 1.35).[34,35] Intravenous macrolide antibiotics were the preferred treatment for hospitalised children with severe *L pneumophila* pneumonia.[27] The incidence of *Legionnaires* pneumonia (LP) in children is relatively low in China, and the direct evidence was limited.

Statement: LP is caused by *Legionella* pneumophila, which exists in unpurified water and may be one of the independent or mixed pathogens associated with cases of severe CAP.[36] AZM is the effective treatment for LP; however, no comparative clinical studies have ever been performed.[37] It was suggested that hospitalised children with severe LP disease should be treated with AZM SAT.

Question 4: Is intravenous AZM an effective and safe treatment for CAP caused by bacterial pathogens in children?

Recommendation 4: Intravenous AZM can be one of the treatment choices for severe CAP caused by bacterial pathogens in children. (2D).

Evidence: The guideline showed that AZM can be used initially or added when first-line empirical therapy fails.[37] No available SRs were identified to answer this question.

Statement: The most common bacterial pathogens responsible for CAP in children older than 4 months include *Streptococcus pneumoniae (S pneumoniae)*, *Haemophilus influenzae (H influenzae)*, and *Staphylococcus aureus (S aureus)*. In addition, the infection is usually mixed with *M pneumoniae* or other atypical pathogens.[38] Although AZM may be effective and safe, it should be used as the treatment of choice rather than as a preferred alternative, especially when a mixed infection is suspected. However, some studies have also shown that AZM cannot be used as monotherapy because of the increasing resistance of *S pneumoniae* and *M pneumoniae* to macrolides in many countries.[39] Nevertheless, for

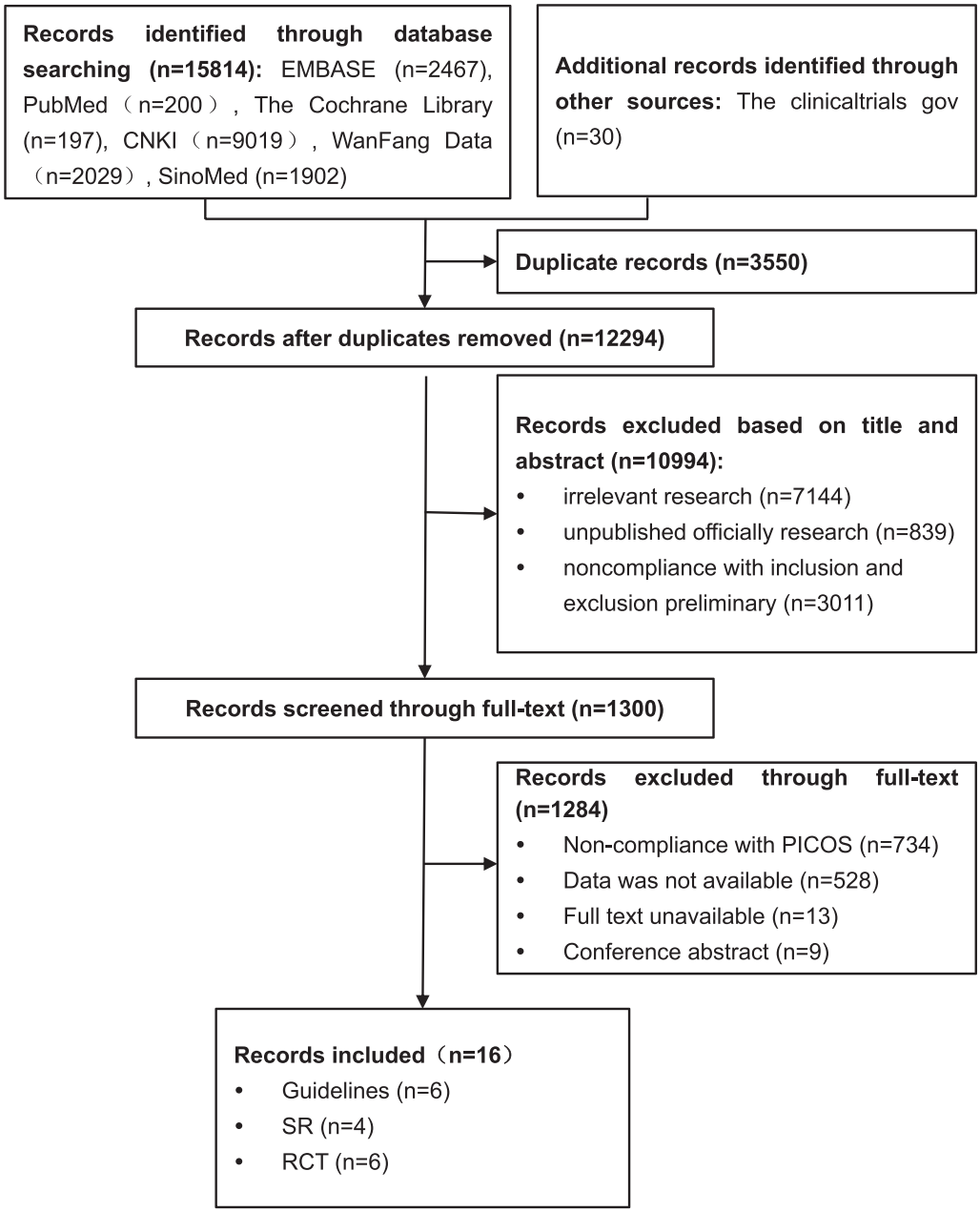

FIGURE 3 Literature screening and process

children hospitalised with severe *H influenzae* or *Moraxella catarrhalis (M catarrhalis)* infection, intravenous AZM can be used as an alternative treatment when β-lactam antibiotics are ineffective.[27] Intravenous AZM can also be used to treat children with severe pertussis infection.[40,41]

Question 5: Can intravenous AZM be used for the treatment of bronchitis in children?

Recommendation 5: Intravenous AZM should not be routinely used for the treatment of bronchitis in children. (1B).

Evidence: A moderate-quality SR (Table S5B) including three RCTs (350 children) showed no significant difference between oral AZM and placebo in terms of the duration of oxygen requirement (MD = −0.20; 95% CI: −0.72 to 0.33) and length of hospital stay (MD = −0.58, 95 CI%: −1.18 to 0.02) in children with bronchitis.[42]

Statement: A SR enrolling adults and children indicated that AZM offered no significant advantage in the treatment of bronchitis.[43] The most common pathogens causing bronchitis in children are viruses, and the GDG did not recommend intravenous AZM for routine treatment.

3.2 | Usage and dosage

Question 6: Does treatment with AZM SAT or oral therapy lead to better patient outcomes in children with nonsevere pneumonia?

TABLE 3 Recommendations, strength, and quality of evidence developed in the guideline

Recommendations	Strength	Quality of evidence
1. Intravenous AZM is strongly recommended for the treatment of *M pneumoniae* pneumonia in children.	1	B
2. Intravenous AZM can be used for the treatment of *C pneumoniae* pneumonia or *C*. trachomatis infections in children.	2	C
3. Intravenous AZM can be used as the treatment for *L pneumophila* pneumonia in children.	2	C
4. Intravenous AZM can be one of the treatment choices for severe CAP caused by bacterial pathogens in children.	2	D
5. Intravenous AZM should not be routinely used for the treatment of bronchitis in children.	1	B
6. Oral AZM should be used in children in whom antimicrobial therapy is indicated for the treatment of nonsevere MPP.	1	C
7. If children with severe MPP have an indication for antimicrobial therapy, AZM should be used intravenously first, then the patient should be transitioned to oral therapy when the signs of clinical infection have improved and are stable.	1	B
8. The concentration of AZM infusion may be 1 to 2 mg/mL, and the duration of administration should not be less than 1 h in children with CAP.	2	C
9. Less than 10 d may be recommended as the treatment course of AZM SAT for children with CAP. The transition time from intravenous to oral therapy is based on whether signs of infection are significantly improved and are relatively stable.	2	D
10. For neonates, if oral administration is not appropriate, intravenous therapy may be used with caution at a dosage of 10 mg/kg per day. For children older than 28 d, AZM may be administered at a dosage of 10 mg/kg per day.	2	D
11. When intravenous AZM causes mild gastrointestinal AEs, if possible, the treatment regimen should not be adjusted. Another option is to relieve symptoms by decreasing the infusion rate or extending the infusion time.	1	D
12. During the administration of intravenous AZM, physicians should pay attention to the development of cardiac arrhythmias, and this therapy should be used with caution in high-risk groups. If arrhythmias develop, intravenous AZM should be discontinued and appropriate treatment implemented if necessary.	1	D
13. When infusion site pain or phlebitis resulting from intravenous AZM cannot be tolerated by the children, treatment may be terminated.	2	D
14. When children are being treated with intravenous AZM, attention should be paid to signs of anaphylaxis and, if present, AZM should be immediately discontinued and epinephrine administered. Careful attention should be paid to any signs of relapse.	1	D
15. Intravenous AZM should be used with caution in children with liver dysfunction and abnormal liver function tests (such as serum ALT, AST, and bilirubin), and the children should be closely monitored.	1	D
16. Intravenous AZM should be used to treat children with mild to moderate kidney dysfunction, but caution should be exercised when treating children with severe kidney dysfunction.	1	D
17. Intravenous AZM should be used with caution in children with congenital heart disease, and changes in the electrocardiogram (ECG) should be monitored carefully and regularly.	2	D
18. When intravenous AZM is administered to children with obesity, the dosage calculated by body weight should not exceed the adult dosage.	2	D

Recommendation 6: Oral AZM should be used in children in whom antimicrobial therapy is indicated for the treatment of nonsevere MPP. (1C).

Evidence: The analysis of an RCT (260 children) showed that, when compared with continuous oral administration for the treatment of MPP, AZM SAT had similar results in terms of the treatment success rate (RR = 0.95, 95 CI%: 0.89 to 1.02) and the rate of gastrointestinal AEs (RR = 1.33, 95 CI%: 0.48 to 3.74).[44] According to the patients' views and preferences, 90.63% of patients preferred oral therapy when the child had nonsevere pneumonia.[45]

Statement: Antibiotics administered orally are safe and effective for children presenting with even severe CAP.[29] Parenteral administration of antibiotics does not improve outcomes in cases of uncomplicated pneumonia.[46] Furthermore, it is traumatic for children and is not associated with better compliance or less cost. Therefore, oral AZM is the preferred treatment for children with severe diseases or gastrointestinal disturbances. Although the direct evidence supporting this recommendation was of low-quality, the GDG believed that it was strong enough to support prioritising oral therapy.

Question 7: Does treatment with AZM SAT or intravenous therapy lead to better patient outcomes in children with severe pneumonia?

Recommendation 7: If children with severe MPP have an indication for antimicrobial therapy, AZM should be used intravenously

first, then the patient should be transitioned to oral therapy when the signs of clinical infection have improved and are stable. (1B).

Evidence: A moderate-quality SR (1,216 children, Table S5C) showed that, when compared with continuous intravenous administration for the treatment of MPP, AZM SAT had similar results in terms of the treatment success rate (RR = 0.99, 95 CI%: 0.95 to 1.02), the rate of gastrointestinal AEs (RR = 0.67, 95 CI%: 0.38 to 1.17), phlebitis (RR = 0.17, 95 CI%: 0.02 to 1.33), a lower incidence in infusion site pain (RR = 0.35, 95 CI%: 0.17 to 0.76), and was also associated with lower cost.[47] According to the patients' views and preferences, 62.50% of patients preferred SAT and 25.00% preferred continuous intravenous therapy when their children were severely ill.[45]

Statement: SAT in children yielded clinical outcomes comparable to those of intravenous therapy and reduced the healthcare costs.[48] SAT also has been used to support discharge from an inpatient setting, thus decreasing the risks associated with intravenous therapy and reducing exposure to nosocomial pathogens.[25] When a child receives intravenous therapy, oral therapy should be considered when there is clinical improvement, and the child is able to tolerate oral intake.[29,46]

Question 8: What is the concentration and duration of AZM infusion in children with CAP?

Recommendation 8: The concentration of AZM infusion may be 1 to 2 mg/mL, and the duration of administration should not be less than 1 hour in children with CAP. (2C).

Evidence: An RCT (120 children) showed that extending infusion time was associated with increased efficacy ($P = .005$), but the rate of AEs was simultaneously increased ($P < .05$). Shortening infusion time was associated with improved patient compliance ($P < .05$).[49]

Statement: If the infusion rate is too fast, it may lead to a rapid increase in blood volume over a short period of time and increase cardiac workload. Moreover, shortening the infusion time can improve compliance and reduce the risk of pain or phlebitis at the infusion site.

Question 9: What is the appropriate duration of AZM SAT treatment for children with CAP?

Recommendation 9: Less than 10 days may be recommended as the treatment course of AZM SAT for children with CAP. The transition time from intravenous to oral therapy is based on whether signs of infection are significantly improved and are relatively stable. (2D).

Evidence: The guideline revealed that there is no set recommendation about when the transition to oral therapy should occur because of a lack of RCTs.[29,46] No evidence has been found evaluating the duration of treatment with AZM SAT.

Statement: AZM prescribing information recommends 7 to 10 days of intravenous or oral AZM therapy.[3] Treatment courses of 10 days have been best studied for the treatment of CAP in children. In addition, antibacterial therapy should be used for an additional 3 to 5 days after there is a clinical improvement in systemic symptoms, especially those related to lung function.[25,27] Although published guidelines recommend 3 or 5 days of AZM because of its distinctly different pharmacokinetics, the GDG reached a consensus that, since the treatment varied amongst children, the treatment duration should depend on the pattern of clinical improvement but should not exceed 10 days in the absence of strong evidence.[25,29]

Question 10: What is the dose recommendation for intravenous AZM for children of different ages?

Recommendation 10: For neonates, if oral administration is not appropriate, intravenous therapy may be used with caution at a dosage of 10 mg/kg per day. For children older than 28 days, AZM may be administered at a dosage of 10 mg/kg per day. (2D).

Evidence: A moderate-quality SR (Table S5D) demonstrated the efficacy of intravenous AZM in the prevention of bronchopulmonary dysplasia in preterm neonates and concluded that the majority of the AEs reported were related to prematurity rather than to AZM.[50] This study reviewed the efficacy and safety of AZM use in neonates. Apart from the recommended regimens listed in authoritative reference books, no relevant high-quality studies were found.

Statement: Owing to a paucity of efficacy and safety studies, the specific dosage of intravenous AZM for children of various ages was not clearly identified. Still, there are dosage recommendations designed to meet clinical demand: for neonates, intravenous therapy may be used cautiously at a general intravenous dose of 10 mg/kg per day only when oral therapy is inappropriate.[41,51] For children older than 28 days, intravenous AZM can be administered at a dose of 10 mg/kg per day.[52] In addition, the guideline recommended that children older than 3 months of age should receive intravenous AZM at a dose of 10 mg/kg per day on the first or second day of therapy, followed by a transition to oral therapy at a dose of 5 mg/kg per day for the remainder of the course of treatment.[25]

3.3 | Adverse reactions and management

Question 11: What is the management of gastrointestinal AEs associated with intravenous AZM?

Recommendation 11: When intravenous AZM causes mild gastrointestinal AEs, if possible, the treatment regimen should not to be adjusted. Another option is to relieve symptoms by decreasing the infusion rate or extending the infusion time. (1D).

Evidence: Studies of oral AZM conducted worldwide and a trial of intravenous AZM revealed that the most common gastrointestinal AEs in the paediatric population were of mild to moderate severity. The absence of high-quality research has made it difficult to determine whether any intervention designed to alleviate the gastrointestinal symptoms is needed.

Statement: The incidence of gastrointestinal AEs associated with AZM (9.6%) was significantly lower than that associated with ERY (28.5%).[1] The incidence of gastrointestinal AEs associated with macrolide antibiotics may be reduced by increasing the infusion time

a rapid infusion rate may aggravate the symptoms.[53] The GDG did not recommend routine interventions to mitigate the occurrence of these AEs. If the infusion is not tolerable, physicians should reduce the infusion speed, increase infusion time, or change medication after careful consideration of the advantages and disadvantages of each course of action.

Question 12: What is the management of arrhythmias caused by intravenous AZM?

Recommendation 12: During the administration of intravenous AZM, physicians should pay attention to the development of cardiac arrhythmias, and this therapy should be used with caution in high-risk groups. If arrhythmias develop, intravenous AZM should be discontinued and appropriate treatment implemented if necessary. (1D).

Evidence: A study (56 children) found that chronic AZM therapy did not prolong the QTc interval in paediatric patients with cystic fibrosis, and only adolescent males demonstrated an increase in QTc interval.[54] A study of adults suggested that AZM-related QTc prolongation might be transient.[55] Another study (44 children) indicated that in all cases, the QTc was less than 440 msec, and no arrhythmias were detected during AZM AST therapy of between 2 and 72 months duration.[56] Therefore, the relationship between the development of arrhythmias and AZM treatment in paediatric patients is unclear, and no high-quality evidence has been identified.

Statement: Patients with the following conditions should be considered at high risk of arrhythmias: heart disease, prolonged QTc interval, hypokalaemia, hyponatremia, bradycardia, or use of certain antiarrhythmic medications. Prescription drug instructions and FDA warnings indicate that AZM may be associated with abnormal changes in cardiac electrical activity leading to arrhythmias with fatal consequences. Although there are case reports of arrhythmias in children treated with intravenous AZM,[57,58] the GDG believed these to be rare cardiac adverse events and that greater attention should be paid to high-risk children by careful evaluation of the patient's history, physical examination, and electrocardiogram (ECG) results.

Question 13: What is the management of intravenous AZM-related infusion site pain or phlebitis?

Recommendation 13: When infusion site pain or phlebitis resulting from intravenous AZM cannot be tolerated by the children, treatment may be terminated. (2D).

Evidence: Some interventions, such as local analgesics used in clinical practice, may relieve severe pain or phlebitis. However, there was no study identified that evaluated the methods used to alleviate symptoms.

Statement: Considering clinical experience, the GDG agreed that the interventions used to alleviate pain or phlebitis at the infusion site were not very beneficial. Clinically, therefore, if the symptoms could not be tolerated, discontinuation of the drug should be considered.

Question 14: What is the management of intravenous AZM-related anaphylaxis?

Recommendation 14: When children are being treated with intravenous AZM, attention should be paid to signs of anaphylaxis and, if present, AZM should be immediately discontinued and epinephrine administered. Careful attention should be paid to any signs of relapse. (1D).

Evidence: Steven–Johnson syndrome has been rarely reported in adults and children receiving either oral or intravenous AZM therapy.[59,60] No related study was identified that determined the association between a severe allergic reaction and AZM and that would clarify the uncertainty.

Statement: Though allergic reactions caused by azithromycin are rare, anaphylaxis can cause serious consequences. FDA drug warnings state that severe allergic reactions have been reported in patients treated with AZM.[3] However, in one study, most urticarial reactions associated with AZM treatment appeared to be because of the underlying infection and did not occur following re-exposure to AZM.[61] In other patients, the allergic symptoms recurred soon after symptomatic therapy was discontinued without further AZM exposure. Because the course of anaphylaxis is unpredictable, anaphylaxis should be treated immediately. The guideline recommended that epinephrine should be administered as soon as possible and injected in the medial side of the thigh in children who have an anaphylactic reaction. The concentration of epinephrine should be 1:1000, and the dose should be 0.01 mg/kg with a maximum dose of 0.3 mg (0.3 mg/0.3 mL). If the symptoms are not alleviated after 5 to 15 minutes, the above doses can be repeated.[62,63]

3.4 | Special people medication

Question 15: How should treatment with intravenous AZM be managed in children with liver dysfunction?

Recommendation 15: Intravenous AZM should be used with caution in children with liver dysfunction and abnormal liver function tests (such as serum ALT, AST, and bilirubin), and the children should be closely monitored. (1D).

Evidence: No available study in accordance with the inclusion criteria has indicated what adjustments of intravenous AZM should be made when treating children with liver dysfunction.

Statement: The precise pharmacokinetics of AZM in patients with hepatic insufficiency is well described, and there are no recommendations for adjusting the dosage to date. The potential hepatotoxicity of macrolide antibiotics may be related to the formation of nitroalkanes. However, AZM rarely if ever forms nitroalkanes, so the hepatotoxicity is low.[53] A study showed that different macrolide antibiotics exhibited different hepatotoxicity in children, and the risk of liver injury associated with AZM was not significant.[64] However, another study reported that AZM may be the offending agent in a higher proportion of patients with pre-existing liver disease. Therefore, caution must be exercised when faced with these conditions.[65]

Question 16: How should treatment with intravenous AZM be managed in children with kidney dysfunction?

Recommendation 16: Intravenous AZM should be used to treat children with mild to moderate kidney dysfunction, but caution should be exercised when treating children with severe kidney dysfunction. (1D).

Evidence: A pharmacokinetic study showed that the pharmacokinetic parameters of oral AZM in adult patients with mild to moderate kidney dysfunction were similar to those in normal patients.[66] No available study was identified to answer this question.

Statement: AZM is mainly eliminated via biliary excretion and intestinal secretion. Twelve percent of the intravenous dose is excreted unchanged through the kidney. The pharmacokinetic parameters of AZM are not significantly altered in patients with mild to moderate renal insufficiency.[67] While renal clearance is significantly reduced, nonrenal clearance is not affected. Therefore, AZM should be used with caution in patients with severe renal impairment (glomerular filtration rate <10 mL/min). No dose adjustment is required in patients with mild to moderate kidney dysfunction.

Question 17: How should treatment with intravenous AZM be managed in children with congenital heart disease?

Recommendation 17: Intravenous AZM should be used with caution in children with congenital heart disease, and changes in the electrocardiogram (ECG) should be monitored carefully and regularly. (2D).

Evidence: No study has been conducted evaluating adjustments in intravenous the AZM treatment regimen in children with congenital heart disease.

Statement: The FDA warned that AZM may increase the risk of lethal cardiac arrhythmias in a certain group of high-risk patients, such as patients with congenital long QTc syndrome, torsades de pointes, and bradyarrhythmias.[3,68] However, because of the limitations of the current study, the GDG came to a consensus that intravenous AZM can be administered to children with congenital heart disease along with ECG monitoring. Although abnormal QTc-interval morphology might predict an increased risk of torsade de pointes, analytic methods for assessing this correlation remain to be validated.[69] In the absence of data, measuring the peak plasma concentration of a QTc-prolonging medication manually with heart rate monitoring represents a reasonable alternative in a clinical setting.[70] Some risk factors for torsades de pointes include hypokalaemia, hypomagnesemia, drug-drug interactions, and bradycardia. The ECG and serum electrolytes should also be regularly and carefully monitored.[71]

Question 18: How should intravenous AZM be managed in children with obesity?

Recommendation 18: When intravenous AZM is administered to children with obesity, the dosage calculated by body weight should not exceed the adult dosage. (2D).

Evidence: There is no direct evidence from high-quality studies to suggest that the dosage of intravenous AZM requires adjustments in children with obesity.

Statement: Antibiotic drug dosing extrapolated by total body weight may be unreasonable nowadays with the increasing incidence of obesity or overweight in children. Reduction of the dose to the maximum recommended adult dose was common practice, when the dose calculated by total body weight (ie, mg/kg) exceeded this maximum.[72] Therefore, the GDG stated that the single intravenous dosage of AZM should not exceed 500 mg per day, which is based on the adult treatment regimen.

4 | DISCUSSION

This rapid advise guideline provides 18 recommendations regarding off-label use of intravenous AZM in children, based on available evidence and a consensus of clinical opinions when evidence was not found. The recommendations regarding the treatment of children with intravenous AZM from published guidelines have been fragmented and are far from meeting the demand considering the drug's wide use. To fill this gap, our guideline focuses on indications, dosage and usage, management of adverse reactions, and management in special paediatric populations, largely in line with the common situations encountered in clinical practice as possible. During the development process, a poorly controlled selection process and consensus bias from evidence and experts were reduced through the use of extensive presurveys of frontline clinicians as well as the use of external surveys, systematic literature reviews, GRADE quality evaluations, and the Delphi research method.

According to the literature review, off-label use of antibiotics are frequent in both adult (19%-43%) and paediatric patients (1%-97%), and the wide range may be because of the differences between countries, age groups or the severity of disease.[38] Possible reasons for the use of off-label prescription in children include lack of paediatric dosage information, lack of appropriate paediatric formulations and lack of safety and effectiveness in clinical trials, in addition to ethical issues that require special consideration.[73] AZM is a broad-spectrum macrolide antibiotic and is frequently prescribed for the treatment of infections caused by gram-negative, gram-positive bacteria, and atypical pathogens. However, in light of the inconsistent results reported with beta-lactam antibiotic skin testing, restricted use of fluoroquinolones, and mixed infections with multiple pathogenic bacteria, intravenous AZM may be the only therapeutic regimen for the treatment of moderate to severe bacterial infections in children. Therefore, the off-label use of intravenous AZM plays an important role in the clinical arena and cannot be avoided.

The off-label use of a drug should be based on sound scientific evidence, expert medical judgement, or reliable evidence from the published literature.[74] According to this principle, this guideline provides applicable recommendations to fill the gap. We further clarify the available evidence regarding intravenous AZM use in children, which is mainly primarily based on published guidelines, quality-evaluated systematic reviews, and a standardised consensus amongst experts. This rapid advice guideline will be decided to be updated or expanded to the standard guideline around 2022 according to new evidence available. Before that, we will popularise the recommendations by publishing the Chinese version through journals and media, and reporting the guideline on nationwide or nosocomial academic

conference. Furthermore, We plan to investigate the applicability, satisfaction, and patients feedback to evaluate the clinical application of the guideline.

The novelty and the advantages of the current guideline are: (a) The protocol was registered online, ensuring the transparency of the guideline formulation and the avoidance of duplicated work and waste of resources.[75] (b) All of the questions were formulated from the investigation of frontline medical workers, indicating the urgency of the questions as they pertain to AZM use. (c) The three-round Delphi research method was used, which is a formal method of obtaining expert consensus, and software was used for online feedback to improve the efficiency of the process of reaching a consensus. (d) Each recommendation lists the question, recommendations, evidence summary, and statement and clearly defines the GRADE classification so that the reader can follow the process of moving from evidence to recommendation.

The limitations of this guideline are: (a) The GDG members were only consisted of Chinese experts, since the guideline was required to be developed urgently. Nevertheless, the off-label use of paediatric intravenous AZM was universal worldwide and the evidence were searched in global databases without any language restriction. Additionally, the experts had rich experience and international perspective in paediatric infectious diseases and antimicrobial medication, which could improve the generalisability of our recommendations. Therefore, this limitation could be minimised. (b) Because of the lack of research data on children, some direct and high-quality evidence was not available. Using indirect evidence based on AZM use in adults could lead to bias; however, if the questions were not related to the drug's mechanism of action in relation to the patient's age or drug formulation, this bias might be reduced. (c) Some clinical problems might not be answered in this guideline. The guideline mainly focuses on the use of intravenous AZM for the treatment of respiratory infections in children, rather than its use in the treatment of other diseases.

AZM has played a very important role in antimicrobial therapy, and there are still many unsolved issues. Therefore, we should actively undertake a series of studies evaluating the AZM use in children. For instance, what is the incidence of *M pneumoniae* resistance to AZM in children, and what are the alternative options? Is interval AZM therapy necessary considering the long elimination half-life, post-antibiotic effect, and tissue concentration? What is the negative impact of long-term treatment with AZM on liver function? What is the mechanism underlying AZM-related gastrointestinal AEs? Moreover, several warnings and precautions have been added to AZM prescription drug instructions that reflect the growing concern voiced by paediatricians about infantile hypertrophic pyloric stenosis (IHPS). Current evidence reveals that the use of macrolides, especially ERY, increases the risk of IHPS (OR = 2.01 (95% CI = 1.13 to 3.58), $P = .018$).[76] Although the mechanism underlying this risk with AZM is similar to that of ERY, there is insufficient evidence to clarify the correlation between AZM and IHPS, with only a few studies and case reports currently published.[77,78]

China has about 250 million children, which accounts for 15% of the paediatric population worldwide. The paediatric guidelines are particularly important for paediatric healthcare and for improvements in medical equality throughout China.[79] This guideline not only develops recommendations, but also faithfully reflects the current evidence regarding intravenous AZM use in children, which will help to improve clinical practice and encourage more well-designed and high-quality studies in the future.

STATEMENTS

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We invited one patient's parent to join in the development of questions and outcomes in this guideline and considered opinions cautiously. In addition, 33 patients were surveyed after reviewing and evaluating the evidence to reflect the values and preferences of children's families. All patients' families attended to this guideline declared that they had no conflict of interest.

AUTHORS' CONTRIBUTIONS

All of the authors are core members and involved in the whole work of the guideline and the manuscript. Pengxiang Zhou (secretary) was responsible for the management and organisation of the work and this manuscript. Kunling Shen and Suodi Zhai designed the study and were chairmen of the guideline review committee. Xiaoling Wang (paediatric pharmacy expert), Xianglin Zhang (pharmacologist), Baoping Xu (paediatrician), Xiaomei Tong (paediatrician), and Wei Zhou (paediatrician) participated in the development of PICO questions and recommendations. All authors reviewed and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

All data that support the findings of this study are available from articles in the *References* and *Supplementary Materials*, except that the unpublished values and preferences investigation data of patients' families are available from the corresponding authors upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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