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Review article

Molecular mechanisms, epidemiology, and clinical implications of macrolide resistance in group A *Streptococcus*: a narrative review

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Abstract

Group A *Streptococcus* (GAS), or *Streptococcus pyogenes*, remains predictably susceptible to penicillin, whereas resistance to macrolides has become an important therapeutic and epidemiological concern. This narrative review summarizes the molecular mechanisms, epidemiology, clonal dissemination, and clinical implications of macrolide resistance in GAS. Macrolide resistance is mediated mainly by active efflux, commonly associated with *mef* genes and the M phenotype, and by ribosomal target-site methylation mediated by *erm* genes, which produces constitutive or inducible macrolide-lincosamide-streptogramin B resistance. Reported resistance rates vary markedly across geographic regions and study settings, from < 5% in some surveillance populations to > 90% in selected East Asian cohorts. However, direct comparisons are limited by differences in study period, patient population, infection type, and susceptibility testing methods. Molecular epidemiological and whole-genome sequencing studies indicate that both clonal expansion of successful *emm* lineages and horizontal transfer of resistance determinants carried by mobile genetic elements contribute to dissemination. Clinically, macrolide resistance may compromise treatment in patients requiring non-β-lactam therapy, while *erm*-mediated cross-resistance can limit the activity of clindamycin in invasive infections. Particular attention is required for inducible clindamycin resistance, which may be missed by routine susceptibility testing. GAS has not developed widespread clinically established penicillin resistance, although isolates with reduced *in vitro* β-lactam susceptibility associated with penicillin-binding protein alterations have been reported. Fluoroquinolone and tetracycline resistance remain less prominent but warrant continued surveillance. Integrated phenotypic and genomic surveillance, antimicrobial stewardship, and development of effective preventive strategies, including vaccines, are essential to monitor emerging resistant lineages and preserve therapeutic options.

Keywords: *Streptococcus pyogenes*; Drug resistance, bacterial; Macrolides; Molecular epidemiology; Anti-bacterial agents

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Introduction

Group A *Streptococcus* (GAS), or *Streptococcus pyogenes*, is a major human pathogen responsible for a wide spectrum of diseases ranging from mild infections, such as pharyngitis and impetigo, to severe invasive conditions, including necrotizing fasciitis and streptococcal toxic shock syndrome [1,2]. GAS infections continue to pose a substantial public health concern, particularly in low- and middle-income countries [3]. Annually, more than 500,000 deaths are attributed to GAS infections and their complications, including

rheumatic heart disease and post-streptococcal glomerulonephritis [3].

Despite extensive antibiotic use over several decades, GAS remains predictably susceptible to β-lactam antibiotics, particularly penicillin, according to current clinical susceptibility criteria, and penicillin continues to be the first-line treatment [4]. Macrolides, including erythromycin, azithromycin, and clarithromycin, are commonly used as alternative drugs, particularly in patients with β-lactam allergies [4]. Over the past two decades, the emergence and global spread of macrolide-resistant GAS strains have raised significant concerns [5–11]. Resistance rates vary widely by geographic region and over time, reflecting differences in antibiotic consumption and clonal dissemination [7–11]. Recent genomic studies have further demonstrated that both clonal expansion of successful lineages and horizontal transfer of resistance determinants carried by mobile genetic elements contribute to the dissemination of macrolide-resistant GAS, emphasizing the importance of molecular epidemiology in understanding resistance mechanisms [8–11].

This review aimed to provide a comprehensive overview of macrolide resistance in GAS, focusing on its molecular mechanisms, epidemiology, and clinical implications. In addition, the biological basis for the persistent susceptibility of GAS to penicillin is discussed, and resistance to quinolones and tetracyclines is briefly reviewed.

Mechanisms of macrolide resistance

Macrolide resistance in GAS is primarily mediated by two distinct mechanisms: active drug efflux and ribosomal target site modification (Fig. 1).

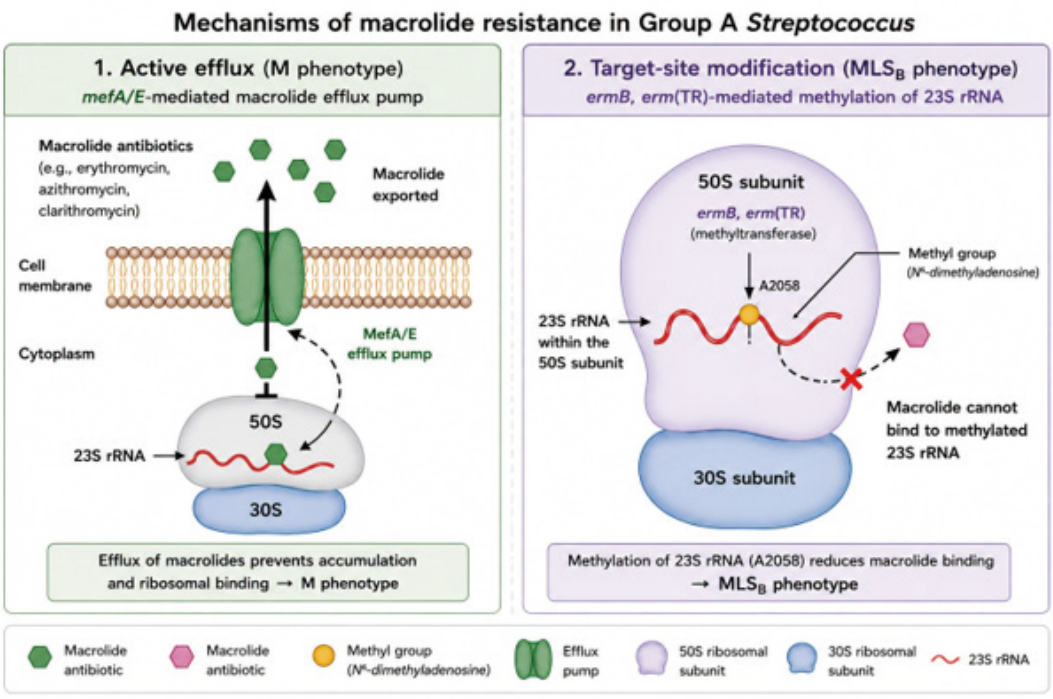

Fig. 1. Two major mechanisms of macrolide resistance in group A *Streptococcus*: active drug efflux mediated by *mef* genes (left) and target-site modification mediated by *erm* genes through methylation of 23S rRNA within the 50S ribosomal subunit (right). MLS_B, macrolide-lincosamide-streptogramin B resistance phenotype.

The efflux mechanism is encoded by *mef* genes, particularly *mefA* and *mefE*, which confer the M phenotype. This mechanism results in low- to moderate-level resistance and primarily affects 14- and 15-membered macrolides, such as erythromycin and azithromycin, whereas susceptibility to lincosamides is generally preserved. In contrast, target site modifications are mediated by *erm* genes, including *ermB*, *erm(T)*, and *erm(TR)*. These genes encode methyltransferases that modify the 23S rRNA component of the 50S ribosomal subunit, leading to a reduced binding affinity for macrolides. This results in the macrolide-lincosamide-streptogramin B (MLS_B) resistance phenotype, which confers cross-resistance to macrolides, lincosamides (e.g., clindamycin), and streptogramin B antibiotics [12,13].

Expression of *erm(B)* may be constitutive or inducible and is often associated with high-level MLS_B resistance. In contrast, *erm(TR)* is more commonly associated with inducible MLS_B resistance, in which clindamycin resistance may be induced during treatment. This inducible phenotype is readily detected by the disk diffusion method using the D-test, in which erythromycin and clindamycin disks are placed in close proximity. Importantly, both *mef* and *erm* genes are often located on mobile genetic elements such as transposons and prophages, facilitating horizontal gene transfer and rapid dissemination among GAS strains [5,12].

Epidemiology of macrolide resistance

The prevalence of macrolide-resistant GAS varies substantially across geographic regions and over time, largely reflecting differences in antimicrobial consumption, clonal dissemination, and regional epidemiological characteristics [5–11] (Table 1). Macrolide resistance rates in Asia are among the highest reported worldwide. Several studies from China have reported very high macrolide resistance rates, particularly among selected pediatric and outbreak-associated populations [9,10]. Recent population-based surveillance in the United States has documented a substantial increase in macrolide and clindamycin nonsusceptibility among invasive GAS isolates, from 12.7% in 2013 to 33.1% in 2022 [11]. However, these estimates apply specifically to invasive GAS populations and should not be generalized to all GAS infections. Recent population-based genomic surveillance from Norway demonstrated relatively low erythromycin resistance among invasive GAS isolates, highlighting substantial geographic heterogeneity even among contemporary invasive-disease populations [14].

These geographic differences are influenced not only by patterns of macrolide consumption, but also by the circulation of successful resistant clones carrying mobile genetic elements. Therefore, continuous molecular surveillance is essential to monitor regional epidemiological trends and establish antimicrobial stewardship strategies.

Table 1. Selected studies reporting macrolide resistance and molecular epidemiology of group A *Streptococcus* in different geographic settings

Country/region	Study period	Population/infection type	No. of isolates	Susceptibility method/breakpoint	Reported resistance/ nonsusceptibility (%)	Major resistance determinants/*emm* types	Representative reference (first author, year)
China (Beijing)	2016–2017	Children with scarlet fever; throat isolates	297	Disk diffusion; CLSI	98.3 (erythromycin)	*ermB* 97.6%; predominantly *emm12* and *emm1*	Li, 2020 [9]
China (Shanghai)	2011–2024	Children with scarlet fever	3,370	MIC-based susceptibility testing; CLSI	95.3 (erythromycin)	Predominantly *emm12* and *emm1*; resistance higher among *emm12* isolates	Cai, 2025 [10]
South Korea	2017	Children with acute pharyngitis	190	Disk diffusion	3.2 (erythromycin)	*emm4* 53.2%, *emm89* 12.6%, *emm28* 11.6%, *emm1* 10.0%	Kim, 2019 [15]
Japan	2010–2012	Invasive GAS	283	MIC-based susceptibility testing	54.4 (macrolide resistance)	*mef(A)* predominant; 92.2% of *emm1* isolates showed *mef(A)*-mediated resistance; *erm(A)*/*erm(B)* frequent in *emm12*/*emm28*	Wajima, 2013 [16]
Norway	2017–2023	Population-based surveillance of invasive GAS	1,163	Phenotypic AST with WGS characterization	6.7 (erythromycin), 4.0 (clindamycin)	*emm1* 30.9%, *emm12* 13.8%, *emm89* 9.3%, *emm28* 8.3%; 62.3% of *emm1* were $M1_{UK}$	Brynildsrud, 2026 [14]
United States (10 states)	2013–2022	Population-based surveillance of invasive GAS	18,358	Conventional AST (2013–2014); WGS-based characterization from 2015	12.7 → 33.1 (macrolide and clindamycin nonsusceptibility, 2013 → 2022)	Changing *emm*-type distribution; resistance increasingly associated with contemporary invasive GAS populations	Gregory, 2025 [11]

Resistance estimates are study-specific and should not be interpreted as directly comparable national prevalence estimates because study periods, patient populations, infection types, isolate-selection criteria, and antimicrobial susceptibility testing methods differed across studies.
Abbreviations: AST, antimicrobial susceptibility testing; CLSI, Clinical and Laboratory Standards Institute; GAS, group A *Streptococcus*; MIC, minimum inhibitory concentration; WGS, whole-genome sequencing.

Molecular epidemiology and clonal spread

The molecular epidemiology of macrolide-resistant GAS is closely associated with the distribution of specific *emm* types and horizontal transfer of resistance determinants carried by mobile genetic elements [5]. *emm* typing, which is based on sequence variations in the *emm* gene encoding the M protein, has become an essential tool for investigating the epidemiology and transmission of GAS. Several *emm* types, including *emm4*, *emm11*, *emm12*, *emm77*, and *emm92*, are associated with macrolide resistance in various geographic regions [5,6,9,10,15–18]. However, associations between *emm* types and macrolide resistance determinants are strongly influenced by geography, study period, and clonal background [19–21] (Table 2).

Recent whole-genome sequencing (WGS) studies have further improved the understanding of GAS molecular epidemiology. In particular, the emergence of the hypervirulent $M1_{UK}$ lineage has attracted considerable attention because of its enhanced production of streptococcal pyrogenic exotoxin A, increased transmissibility, clonal expansion, and association with the resurgence of invasive GAS infections in several countries in Europe and United States [22–24]. Recent population-based WGS studies have further

demonstrated the dynamic nature of GAS clonal epidemiology. Genomic surveillance in the United States identified frequent transmission clusters among invasive GAS isolates, with the extent of clustering varying across *emm* types [25]. During the post-pandemic upsurge in the United Kingdom, $M1_{UK}$ underwent rapid clonal expansion and international dissemination [22,24]. In contrast, recent longitudinal genomic surveillance in China identified distinct *emm1* and *emm12* evolutionary lineages, including the China-specific $M1_{China}$ lineage, and demonstrated associations between expanding sublineages and mobile genetic elements carrying antimicrobial resistance determinants [26].

The $M1_{UK}$ lineage provides an important example of successful clonal expansion and enhanced virulence in GAS; however, its epidemiological success should not be equated with macrolide resistance, because antimicrobial resistance varies among $M1_{UK}$ populations. Accordingly, genomic surveillance should evaluate virulence lineage dynamics and antimicrobial resistance determinants as related but distinct epidemiological features. These findings highlight the value of genomic surveillance for monitoring the evolution and international dissemination of clinically virulent GAS clones.

Horizontal gene transfer mediated by transposons, integrative conjugative elements, and prophages plays a critical role in the dissemination of macrolide resistance genes among GAS strains [12,13]. These mobile genetic elements facilitate the spread of *erm* and *mef* genes and contribute to the rapid emergence of resistant clones under antimicrobial selective pressure [9]. Understanding the molecular epidemiology of resistant GAS is increasingly important for identifying emerging clones, monitoring the dissemination of resistance determinants, and supporting antimicrobial stewardship and future vaccine development [27–29].

Table 2. Representative associations between *emm* types and macrolide resistance determinants in group A *Streptococcus*

emm type	Geographic setting	Reported resistance determinant(s)	Typical phenotype	Representative epidemiological association	Representative reference (first author, year)
emm4	Europe, North America	*mefA*	M phenotype	*emm4*/ST39 lineage associated with *mefA*-mediated macrolide resistance	Berbel, 2022 [5]; Silva-Costa, 2015 [6]
emm11	Europe, North America	*ermB*, often with *tet(M)*	$cMLS_B$	*emm11*/ST403 lineage associated with *ermB*-mediated macrolide resistance	Chochua, 2017 [18]; Silva-Costa, 2015 [6]
emm12	East Asia, Europe, North America	*ermB*, *erm(TR)*, or *mefA* depending on lineage and region	$cMLS_B$, $iMLS_B$, or M phenotype	Multiple resistance genotypes reported; *ermB*-associated resistant *emm12* lineages have been prominent in China	Li, 2020 [9]; Cai, 2025 [10]; Chochua, 2017 [18]
emm77	Europe, North America	*erm(TR)*; *erm(T)* reported in some lineages	Predominantly $iMLS_B$	Resistance genotype varies by clonal background; *erm(TR)* has been associated with *emm77*/ST63	Silva-Costa, 2015 [6]; Chochua, 2017 [18]
emm92	North America	*erm(T)*, often with *tet(M)*	Predominantly $iMLS_B$	Strong association of *emm92*/ST82 with *erm(T)* in US invasive GAS surveillance	Chochua, 2017 [18]

Associations between *emm* types and resistance determinants are epidemiological rather than invariant biological characteristics and may differ substantially across geographic regions, study periods, and clonal backgrounds.

Abbreviations: $cMLS_B$, constitutive macrolide-lincosamide-streptogramin B resistance; $iMLS_B$, inducible macrolide-lincosamide-streptogramin B resistance; M phenotype, macrolide efflux phenotype; ST, sequence type.

Clinical implications

In severe invasive GAS infections, particularly toxin-mediated syndromes such as necrotizing fasciitis and streptococcal toxic shock syndrome, β-lactam therapy has traditionally been combined with a protein-synthesis inhibitor, most commonly clindamycin, to suppress toxin production [30]. Macrolides, by contrast, are primarily used as alternative agents for selected patients with β-lactam allergy [4,30]. Therefore, increased clindamycin or macrolide resistance may have important clinical implications. More recently, linezolid has emerged as a potential alternative adjunctive protein-synthesis inhibitor for invasive GAS infection. In a large retrospective cohort study using target trial emulation, adjunctive linezolid showed clinical outcomes consistent with non-inferiority to clindamycin in β-lactam-treated patients with invasive GAS infection, although prospective comparative studies are still needed [31].

Macrolide resistance may lead to microbiological treatment failure when a macrolide is used against a resistant isolate and may contribute to persistent carriage and onward transmission [30]. Furthermore, resistance mediated by *erm* genes frequently confers cross-resistance to clindamycin (the MLS_B phenotype), potentially limiting its therapeutic value in severe invasive GAS infections. The inducible MLS_B phenotype, primarily mediated by *erm(TR)*, deserves particular clinical attention since isolates may appear susceptible to clindamycin in routine antimicrobial susceptibility testing, but become resistant during therapy. Therefore, the D-test should be routinely performed for erythromycin-resistant, clindamycin-susceptible isolates to identify inducible clindamycin resistance and guide appropriate antimicrobial therapy. Given the continuing emergence of resistant GAS clones, ongoing antimicrobial resistance surveillance and antimicrobial stewardship are essential to preserve the effectiveness of currently available therapeutic agents.

Persistent susceptibility to penicillin

Despite more than 80 years of clinical use, GAS remains predictably susceptible to penicillin according to current clinical susceptibility criteria, and clinically established penicillin resistance has not become widespread. Nevertheless, isolates with penicillin-binding protein (PBP)2X-associated reductions in β-lactam susceptibility *in vitro* have been reported, warranting continued surveillance [32,33]. In contrast, other streptococcal species, particularly *Streptococcus pneumoniae*, have developed widespread β-lactam resistance through alterations in PBPs [5,33].

Several biological and genetic factors have been proposed to explain the sustained susceptibility of GAS to penicillin, including constraints on PBP-mediated resistance and horizontal acquisition of β-lactam resistance determinants [32–34] (Table 3). Although sporadic isolates with reduced β-lactam susceptibility have been reported, clinically established penicillin resistance in GAS remains exceedingly rare, and penicillin continues to be recommended as first-line therapy [4,35]. Continued microbiological and genomic surveillance are warranted to detect any potential emergence of reduced β-lactam susceptibility.

Table 3. Proposed biological constraints associated with sustained β-lactam susceptibility in group A *Streptococcus*

Mechanism	Explanation	Clinical significance	Representative reference (first author, year)
Lack of alterations in PBPs	GAS rarely develops mutations in PBPs, the primary targets of β-lactam antibiotics, unlike *Streptococcus pneumoniae*	Prevents emergence of intrinsic β-lactam resistance	Musser, 2020 [32]
Absence of β-lactamase production	GAS does not produce β-lactamase enzymes capable of degrading penicillin	Ensures continued efficacy of penicillin therapy	Yu, 2023 [34]
Limited horizontal gene transfer	GAS has a relatively low capacity to acquire β-lactam resistance genes from other bacteria	Restricts dissemination of resistance determinants	Horn, 1998 [33]
Potential fitness constraints associated with some PBP alterations	The fitness effects appear mutation- and genetic-background-dependent, and reduced β-lactam susceptibility does not invariably impose a prohibitive fitness cost.	May limit persistence or dissemination of some variants, depending on mutation and genetic background	Musser, 2020 [32]
Lack of documented clinical resistance	No confirmed penicillin-resistant GAS strains have been widely established in clinical practice	Supports penicillin as first-line therapy	Musser, 2020 [32]
Treatment failures unrelated to true resistance	Failures are associated with intracellular persistence, biofilm formation, or poor adherence rather than resistance	Reinforces continued clinical reliability of penicillin	Brook, 2017 [35]

Despite more than 80 years of clinical use, GAS remains predictably susceptible to penicillin according to current clinical susceptibility criteria; several biological and evolutionary mechanisms have been proposed to explain this sustained susceptibility.
Abbreviations: GAS, group A *Streptococcus*; PBP, penicillin-binding protein.

Quinolone and tetracycline resistance

Although macrolide resistance remains a major concern in GAS, resistance to other antimicrobial classes has also been reported.

Fluoroquinolone resistance remains uncommon, but has occasionally been identified, particularly in countries where fluoroquinolone use is widespread. Resistance is primarily associated with mutations in the quinolone resistance-determining regions of *gyrA* and *parC* genes [16]. These mutations reduce the affinity of DNA gyrase and topoisomerase IV for fluoroquinolones. However, the overall prevalence of fluoroquinolone resistance in GAS remains low [16,18].

Tetracycline resistance is more frequently observed and is mainly mediated by the acquisition of ribosomal protection proteins encoded by *tet(M)* and *tet(O)* or less commonly by efflux pumps encoded by *tet(K)* and *tet(L)* [18,36]. These resistance determinants are frequently carried by conjugative transposons, facilitating horizontal dissemination among GAS strains.

Although resistance to quinolones and tetracyclines is currently less clinically important than macrolide resistance, continued surveillance remains important because multidrug-resistant GAS strains carrying multiple resistance determinants have occasionally been reported [37,38].

Future directions

Future efforts to combat macrolide-resistant GAS should focus on continuous surveillance, antimicrobial stewardship, and development of effective preventive strategies.

Advances in molecular epidemiology, particularly WGS, have greatly improved the ability to monitor the emergence and dissemination of resistant GAS clones. The integration of genomic surveillance into national and international surveillance programs will facilitate early detection of emerging resistant lineages and improve our understanding of the evolution of GAS.

Antimicrobial stewardship programs are essential to reduce unnecessary antibiotic use and minimize the selective pressure that promotes the emergence and spread of resistant strains. Continued research on GAS vaccines offers the most promising long-term strategy for reducing the global burden of GAS infections and their sequelae. Future multidisciplinary collaborations between clinicians, microbiologists, epidemiologists, and public health authorities are needed to monitor the emergence and spread of invasive GAS lineages, improve surveillance, optimize antimicrobial use, and support vaccine implementation.

Conclusion

Macrolide resistance in GAS is highly heterogeneous across geographic regions, time periods, clinical populations, and circulating lineages. Both mobile resistance determinants and clonal expansion contribute to its dissemination, but reported resistance rates should be interpreted in the context of study design and infection type. β-Lactams remain the cornerstone of GAS treatment, whereas increasing macrolide and clindamycin resistance may limit alternative and adjunctive therapeutic options. Continued phenotypic and genomic surveillance using standardized methods is therefore essential for monitoring emerging resistant lineages and informing antimicrobial therapy and stewardship.

Ethics statement

This narrative review is based solely on previously published literature and does not involve human participants, human-derived materials, or identifiable personal data. Therefore, approval from the Institutional Review Board was not required.

Conflicts of interest

No potential conflicts of interest relevant to this article were reported.

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Data availability

This review article did not generate or analyze new datasets.

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