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SHORT REPORT

Molecular Basis of Antimicrobial Resistance in Group B *Streptococcus* Clinical Isolates from Saudi Arabia

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Abstract: Published data on the molecular mechanisms underlying antimicrobial resistance in Group B *Streptococcus* (GBS) isolates from Saudi Arabia are lacking. Here, we aimed to determine the genetic basis of resistance to relevant antibiotics in a collection of GBS clinical isolates (n = 204) recovered from colonized adults or infected patients and expressing serotypes Ia, Ib, II, III, V, and VI. Initial susceptibility testing revealed resistance to tetracycline (76.47%, n = 156/204), erythromycin (36.76%, n = 75/204), clindamycin (25.49%, n = 52/204), levofloxacin (6.37%, n = 13/204), and gentamicin (2.45%, n = 5/204). Primers designed for the detection of known resistance determinants in GBS identified the presence of *erm(A), erm(B), mef(A)*, and/or *lsa(C)* genes at the origin of resistance to macrolides and/or clindamycin. Of these, *erm(B)* and *erm(A)* were associated with the $cMLS_B$ (n = 46) and $iMLS_B$ (n = 28) phenotypes, respectively, while *mef(A)* was linked to the M phenotype (n = 1) and *lsa(C)* was present in isolates with the L phenotype (n = 8). Resistance to tetracycline was mainly mediated by *tet(M)* alone (n = 112) or in combination with *tet(O)* (n = 10); the remaining isolates carried *tet(O)* (n = 29), *tet(L)* (n = 2), or both (n = 3). Isolates resistant to gentamicin (n = 5) carried *aac(6')-Ie-aph(2')-Ia*, and those exhibiting resistance to levofloxacin (n = 13) had alterations in GyrA and/or ParC. Most isolates with the *erm* gene (93.24%, n = 69/74) also had the *tet* gene and were therefore resistant to erythromycin, clindamycin, and tetracycline. Overall, there were no clear associations between serotypes and resistance genotypes except for the presence of *erm(B)* in serotype Ib isolates. Dissemination of antibiotic resistance genes across different serotypes represents a public health concern that requires further surveillance and appropriate antibiotic use in clinical practice.

Keywords: antibiotic resistance, gene resistance, macrolides, levofloxacin, gentamicin, Group B *Streptococcus* (GBS)

Introduction

The Lancefield group B β-hemolytic *Streptococcus* or GBS has long been recognized as the leading cause of life-threatening infections in newborns, with maternal colonization being the principal route of transmission.[1] GBS is part of the human microbiota that colonizes the gastrointestinal and genitourinary tracts of up to one-third of healthy individuals but is becoming increasingly associated with severe infections in non-pregnant adults, particularly the elderly and those with underlying conditions.[2,3]

The emergence of antimicrobial-resistant bacteria through the acquisition of mutations or genetic elements carrying resistant genes poses a significant challenge to the long-term effectiveness of therapies against GBS infections.[4] GBS is universally regarded as susceptible to beta-lactam antibiotics; however, reports of reduced susceptibility to these agents, in particular penicillin, have been documented in several countries.[5,6] The use of macrolides and related drugs, such as erythromycin and clindamycin provided useful alternative treatment options for individuals who are allergic to penicillin. However, there has been a steady increase of reported resistance to macrolides and lincosamides in the species.[4,7] In

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GBS, resistance to macrolides and lincosamides often arise through target-site modification by methylation, giving rise to the macrolide–lincosamide–streptogramin B (MLS_B) resistance phenotype. MLSB phenotypes, which can manifest as inducible ($iMLS_B$) or constitutive ($cMLS_B$), are predominantly associated with the acquisition of methyltransferases encoded by *erm(A)* and *erm(B)*, respectively.[8] Resistance to macrolides only, referred to as the M phenotype, involves drug efflux and has been largely linked to the acquisition of efflux pumps encoded by the *mef* gene family.[8] Otherwise, exclusive resistance to lincosamides, also called the L phenotype, is commonly mediated by active efflux encoded by the *lsa* genes.[4,8] On the other hand, resistance to tetracycline in GBS involves ribosomal protection proteins encoded by *tet(M)* or *tet(O)*, or active efflux pumps encoded by the *tet(K)* or *tet(L)* genes.[9,10] Similar to other clinically important Gram-positive bacteria, high levels of resistance to gentamicin in GBS have been, in most cases, linked to the acquisition of the gene encoding the bifunctional aminoglycoside-modifying enzyme AAC(6′)-Ie-APH(2″)-Ia. Furthermore, alterations in the quinolone resistance determinant regions of DNA gyrase GyrA and topoisomerase IV ParC are associated with fluoroquinolone resistance.[4,9]

Although the prevalence of antimicrobial resistance among GBS isolates has been documented in a limited number of reports in Saudi Arabia, no data are available on the genetic mechanisms underlying these resistances. The current study aimed to investigate these mechanisms and examine their associations with GBS serotypes in a representative collection of GBS clinical isolates.

Materials and Methods

The molecular mechanisms underlying resistance to clinically important antibiotics in a previously characterized collection of GBS isolates were further investigated in this study.[11] Isolates of this recent collection (n = 204) were recovered between February and September 2022 from colonized adults (n = 109) and infected (n = 95) patients from three different hospital settings in Saudi Arabia. The studied isolates were recovered from various clinical specimen, including urine (n = 108), rectovaginal swabs (n = 73), wound swabs (n = 12), soft tissues (n = 5), blood (n = 5), and bone (n = 1). Isolates were considered colonizing if they were recovered from non-sterile site without signs of infections. Initial susceptibility testing, performed according to the Clinical and Laboratory Standards Institute (CLSI) guidelines, detected resistance to tetracycline, erythromycin, clindamycin, and levofloxacin in 76.47%, 36.76%, 25.49%, and 6.37% of the isolates, respectively, while all remained susceptible to penicillin, ceftriaxone and vancomycin.[11] Phenotypic resistance to gentamicin was further investigated in this study for all the isolates by disk diffusion according to CLSI standards.[12] Capsular serotyping, carried out using multiplex PCR assays targeting nine *cps* genes as previously described, identified serotypes Ia (13.24%, n = 27/204), Ib (8.82%, n = 18/204), II (16.18%, n = 33/204), III (25%, n = 51/204), V (25%, n = 51/204), VI (9.31%, n = 19/204) and few non-typeable (2.45%, n = 5/204).[11] To investigate the molecular mechanisms of resistance to antibiotics, primers were designed to simultaneously detect three macrolide [*erm(A), erm(B)*, and *mef(A)*] and three tetracycline [t*et(M), tet(O)*, and *tet(L)*] resistance determinants that are commonly reported in the species (Table 1). In addition, primers for the detection of the lincosamide resistance genes *lsa(C)* and *lnu(B)* or the high-level gentamicin resistance gene *aac(6')-Ie-aph(2')-Ia* were also designed as detailed in Table 1. Moreover, the quinolone resistance determinant regions of *gyrA* and *parC* were amplified and Sanger sequenced according to a previously published method.[13] Sequence analysis was performed using the QIAGEN CLC Genomics Workbench v.7.9.1 (CLC, Aarhus, Denmark) software. The associations between the resistance determinants and serotypes were statistically checked by the chi-square ($\chi 2$) test using the Statistical Package for the Social Sciences software IBM SPSS Statistics for Windows, v.25.0. (IBM Corp., Armonk, NY) with a *P*-value of < 0.05 considered statistically significant.

Results

Molecular Basis of Resistance to Macrolide-Lincosamide-Streptogramin B

Phenotypic susceptibility testing showed that a large proportion of the studied isolates were resistant to erythromycin (36.76%, n = 75/204) and clindamycin (25.49%, n = 52/204), of which 40.69% (n = 83/204) were resistant to either erythromycin or clindamycin. The majority of resistant isolates exhibited the $cMLS_B$ (55.42%, n = 46/83) or $iMLS_B$ (33.74%, n = 28/83) phenotypes, whereas eight showed the L phenotype (9.64%, n = 8/83), and one had the M phenotype (1.2%, n = 1/83). PCR screening detected *erm(B)* in all isolates exhibiting the $cMLS_B$ phenotype and *erm(A)* in those

Table 1 Primers Used for PCR Amplification of Antimicrobial Resistant Genes

Antibiotic Agent	Gene	Primer	Sequence (5′–3′)	Expected Amplicon Size (bp)*	Reference
Erythromycin and clindamycin	*erm(A)*	*erm(A)_F*	GGAACTTGTGGAAATGAGTCAAC	297	This study PCR I
		erm(A)_R	AGCAAACCTAAAGCTCGTTGG		
	erm(B)	*erm(B)_F*	GAAACCGATACCGTTTACGAA	525	
		erm(B)_R	GACGATATTCTCGATTGACCC		
	mef(A)	*mef(A)_F*	TAGTGGATCGTCATGATAGGAA	810	
		mef(A)_R	CTCCTGAAAAAGAGCTGTTTGC		
Tetracycline	*tet(M)*	*tet(M)_F*	TCATAGACACGCCAGGACATA	405	
		tet(M)_R	CTTATGCTTTCCTCTTGTTCGAG		
	tet(O)	*tet(O)_F*	GAATCACTATCCAGACAGCAGTG	633	
		tet(O)_R	GATTGACCTTCAGGCGTTGAT		
	tet(L)	*Tet(L)_R*	TTTGGAATATAGCGCGCAAC	208	
		tet(L)_F	GAACAGCTSTATATGGAAAGCT		
Clindamycin	*lsa(C)*	*lsa(C)_F*	GGCTATGTAAAACCTGTATTTG	429	This study PCR II
		lsa(C)_R	ACTGACAATTTTTCTTCCGT		
	lnu(B)	*lnu(B)_F*	GTCAGATGAACGAATTACAGC	692	
		lnu(B)_R	TCAATAAGGTGACTTTGCAAA		
Gentamicin	*aac(6′)-aph(2″)*	*aac(6′)-aph(2″)_F*	GAGCAATAAGGGCATACCAAAAATC	348	This study PCR III
		aac(6′)-aph(2″)_R	CCGTGCATTTGTCTTAAAAAACTGG		
Levofloxacin	*gyrA*	*gyrA_F*	GGTTTAAAACCTGTTCATCGTCGT	407	[13]
		gyrA_R	GCAATACCAGTTGCACCATTGACT		
	parC	*parC_F*	CCGGATATTCGTGATGGCTT	403	
		parC_R	TGACTAAAAGATTGGGAAAGGC		

Notes: *PCR amplifications of all targeted genes were performed by annealing at 58 °C.

showing the iMLS$_B$ phenotype, whereas the detection of *mef(A)* or *lsa(C)* explained the M and L phenotypes in the remaining isolates, respectively (Table 2). Of note, six of the isolates carrying *erm(A)* had also *mef(A)* (n = 5) or *erm(B)* with *lsa(C)* (n = 1). Otherwise, the presence of *lnu(B)* gene was not observed in any of the isolates (Table 2).

Molecular Basis of Resistance to Other Relevant Antibiotics

More than three-quarters (76.5%, n = 156/204) of the isolates exhibited resistance to tetracycline. PCR amplifications showed that the majority (78.21%, n = 122/156) of these isolates carried the *tet(M)* gene alone (n = 112) or in combination with *tet(O)* (n = 10). Of the remaining (n = 34), 29 carried *tet(O)*, two had *tet(L)*, and three isolates had both (Table 2). On the other hand, sequence analysis showed that all isolates that were phenotypically resistant to levofloxacin (n = 13) had alterations in ParC (S79A/F/Y) (n = 2) alone or in combination with GyrA (S81L) (n = 11) (Table 2). Only five isolates showed reduced susceptibility to gentamicin, and all carried the *aac(6′)-Ie-aph(2″)-Ia* aminoglycoside resistance gene.

Table 2 Distribution of Antibiotic Resistance Patterns and Associated Genes Among GBS Serotypes (n = 204)

Serotype (n)	Antibiotic Resistance Profile	Macrolide Resistant Phenotype (n)	Acquired Resistance Genes (n)	Chromosomal Alteration (n)
Ia (27)	ERY^r, CLI^r, TET^r	$cMLS_B$ (2)	*erm(B), tet(M)* (1)	
			erm(B), tet(O) (1)	
	ERY^r, TET^r	$iMLS_B$ (2)	*erm(A), tet(O)* (2)	
	CLI^r	L (1)	*lsa(C)* (1)	
	CLI^r, TET^r	L (1)	*lsa(C), tet(M)* (1)	
	ERY^r, CLI^r, TET^r	M (1)	*mef(A), tet(M)* (1)	
	TET^r	none (13)	*tet(M)* (13)	
	–	none (7)		
Ib (18)	ERY^r, CLI^r, TET^r	$cMLS_B$ (11)	*erm(B), tet(M)* (7)	
			erm(B), tet(O) (2)	
			erm(B), tet(M), tet(O) (1)	
			erm(B), tet(O), tet(L) (1)	
	ERY^r, CLI^r	$cMLS_B$ (1)	*erm(B)* (1)	
	ERY^r, CLI^r, LVX^r	$cMLS_B$ (2)	*erm(B)* (2)	GyrA (S81L), ParC (S79F) (2)
	CLI^r, TET^r	L (1)	*lsa(C), tet(O)* (1)	
	TET^r	none (3)	*tet(M)* (2)	
			tet(O) (1)	
II (33)	ERY^r, CLI^r, TET^r, LVX^r	$cMLS_B$ (1)	*erm(B), tet(M)* (1)	ParC (S79A) (1)
	ERY^r, CLI^r, TET^r	$cMLS_B$ (4)	*erm(B), tet(M), tet(O)* (1)	
			erm(B), tet(O) (2)	
			erm(B), tet(M) (1)	
	ERY^r, TET^r	$iMLS_B$ (4)	*erm(A), tet(M)* (3)	
			erm(A), mef(A), tet(M) (1)	
	ERY^r	$iMLS_B$ (2)	*erm(A)* (2)	
	CLI^r, TET^r	L (2)	*lsa(C), tet(M)* (1)	
			lsa(C), tet(O) (1)	
	TET^r	none (11)	*tet(M)* (9)	
			tet(L) (1)	
			tet(O) (1)	
	LVX^r	none (1)		ParC (S79F) (1)
	–	none (8)		

(*Continued*)

Table 2 (Continued).

Serotype (n)	Antibiotic Resistance Profile	Macrolide Resistant Phenotype (n)	Acquired Resistance Genes (n)	Chromosomal Alteration (n)
III (51)	ERY^r, CLI^r, TET^r	$cMLS_B$ (12)	*erm(B), tet(M)* (1)	
			erm(B), tet(O) (4)	
			erm(B), tet(M), tet(O) (6)	
			erm(B), lsa(C), tet(O) (1)	
	ERY^r, TET^r, LVX^r	$iMLS_B$ (1)	*erm(A), mef(A), tet(M)* (1)	GyrA (S81L), ParC (S79F) (1)
	ERY^r, TET^r	$iMLS_B$ (8)	*erm(A), tet(M)* (4)	
			erm(A), tet(O) (3)	
			erm(A), mef(A), tet(O) (1)	
	CLI^r, TET^r	L (3)	*lsa(C), tet(M)* (1)	
			lsa(C), tet(O) (2)	
	TET^r	none (18)	*tet(M)* (15)	
			tet(O) (2)	
			tet(L) (1)	
	TET^r, GEN^r	none (1)	*tet(O), aac(6')-Ie-aph(2")-Ia* (1)	
	TET^r, LVX^r, GEN^r	none (1)	*tet(O), tet(L), aac(6')-Ie-aph(2")-Ia* (1)	GyrA (S81L), ParC (S79Y) (1)
	–	none (7)		
V (51)	ERY^r, CLI^r, TET^r	$cMLS_B$ (11)	*erm(B), tet(M)* (7)	
			erm(B), tet(O) (1)	
			erm(B), tet(M), tet(O) (2)	
			erm(B), tet(O), tet(L) (1)	
	ERY^r, TET^r, GEN^r, LVX^r	$iMLS_B$ (3)	*erm(A), tet(M), aac(6')-Ie-aph(2")-Ia* (3)	GyrA (S81L), ParC (S79F) (3)
	ERY^r, TET^r, LVX^r	$iMLS_B$ (2)	*erm(A), tet(M)* (1)	GyrA (S81L), ParC (S79F) (1)
			erm(A), mef(A), tet(M) (1)	GyrA (S81L), ParC (S79F) (1)
	ERY^r, TET^r	$iMLS_B$ (4)	*erm(A), tet(M)* (4)	
		$iMLS_B$ (1)	*erm(A), tet(O)* (1)	
		$iMLS_B$ (1)	*erm(A), mef(A), tet(M)* (1)	
	TET^r	none (24)	*tet(M)* (23)	
			tet(O) (1)	
	TET^r, LVX^r	none (2)	*tet(M)* (2)	GyrA (S81L), ParC (S79F) (2)
	–	none (3)		

(*Continued*)

Table 2 (Continued).

Serotype (n)	Antibiotic Resistance Profile	Macrolide Resistant Phenotype (n)	Acquired Resistance Genes (n)	Chromosomal Alteration (n)
VI (19)	TET^r	none (4)	*tet(M)* (3)	
			tet(O) (1)	
	–	none (15)		
NT (5)	ERY^r, CLI^r, TET^r	$cMLS_B$ (2)	*erm(B), tet(M)* (2)	
	TET^r	none (2)	*tet(M)* (2)	
	–	none (1)		

Abbreviations: ERY^r, erythromycin-resistance; CLI^r, clindamycin-resistance; TET^r, tetracycline-resistance; LVX^r, levofloxacin-resistance; GEN^r, gentamicin-resistance; NT, non-typable.

Gene Combinations and Associations with Serotypes

Phenotypic resistance to macrolides and lincosamides was variably distributed across different capsular serotypes, and molecular characterization did not show statistically significant associations between these serotypes and resistance genotypes, except for the presence of *erm(B)* in serotype Ib ($P < 0.05$) (Figure 1, Table 2). In addition, no significant association was observed between infected or colonized GBS isolates and the presence of *erm* genes. Almost all isolates (n = 69/74, 93.24%) carrying the *erm* gene also had the *tet* gene, and thus were phenotypically resistant to macrolides, lincosamides, and tetracycline. Similar to other resistance determinants, alterations in GyrA and ParC and acquisition of the AAC(6′)-Ie-APH(2″)-Ia encoding-gene were distributed across multiple serotypes (Table 2). Overall, multidrug resistance (ie, resistance to three or more antibiotic classes) was detected in only 3.9% (n = 8/204) of the isolates and these were also distributed across multiple serotypes. In addition, 20.1% (n = 41/204) of the studied isolates, including nearly all those belonging to serotype VI (78.95%, n = 15/19), lacked all the resistance determinants sought and thus remained fully susceptible to all tested antibiotics.

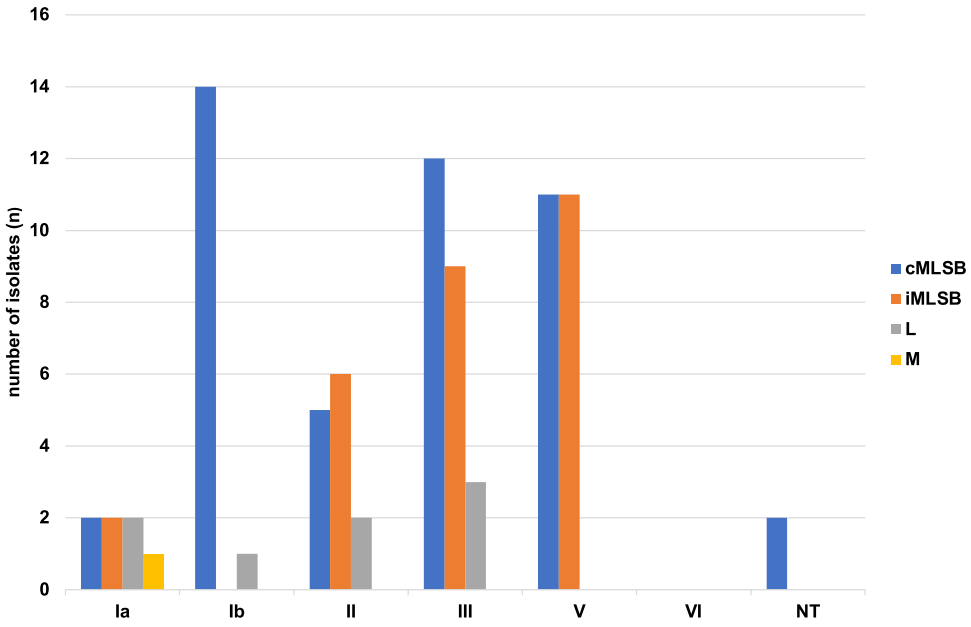

Figure 1 Distribution of macrolide and lincosamide resistance phenotypes among GBS serotypes.
Abbreviation: NT, non-typable.

Discussion

GBS infections can cause serious illnesses and sometimes death, especially in newborns, the elderly, and people with compromised immune systems. The emergence of antibiotic resistance in GBS poses a significant threat as it limits treatment options. Penicillin and other β-lactams are first-line drugs for the prevention and treatment of GBS infections, and decreased susceptibility to these agents remains uncommon.[14] The results of this study showed that all isolates remained fully susceptible to penicillin, ceftriaxone, and vancomycin; therefore, these agents remain an appropriate option for the prophylaxis and treatment of GBS disease. However, their use in patients at a high risk of anaphylaxis may present formidable challenges.[15] For patients allergic to penicillin, clindamycin and erythromycin can be alternative treatment options, but since they share similar binding sites, cross-resistance between them presents a therapeutic challenge.[8] Erythromycin is no longer considered an appropriate for intrapartum antibiotic prophylaxis in pregnant women with penicillin allergy, and clindamycin is currently the drug of choice, with vancomycin being considered an alternative to clindamycin-resistant isolates.[16] The increasing trend of clindamycin resistance has been observed over the past decades, which might lead to the discontinuation of clindamycin, like erythromycin, as a prophylactic option.[16] In this study, the acquisition of *erm(A), erm(B), mef(A)* or *lsa(C)* explained the high rates of resistance to erythromycin (36.76%) and clindamycin (25.49%) among the collected isolates, suggesting that laboratories should consider examining resistance to these drugs for appropriate treatment of GBS infections.[15] Although tetracycline is not recommended as an intrapartum prophylaxis, determining its susceptibility is useful for the treatment of GBS in other patient groups. The high rate of resistance to tetracycline (ie, 76.47%) in the collected isolates was mainly attributed to the acquisition of *tet(M)*, and less frequently to *tet(O)* and *tet(L)* genes. This was consistent with other published reports documenting the high prevalence of resistance to this agent in the species.[17–19] In this study, the tetracycline resistance determinant genes were highly linked to *erm(B) and erm(A)*, suggesting that dissemination is likely due to the acquisition of mobile elements carrying resistance to multiple classes of antibiotics, such as transposons (ie, Tn916-like elements) and integrative conjugative elements (ie, ICESag37) that were previously reported in GBS.[20,21] Presently, combination therapy with penicillin and gentamicin has been recommended for the treatment of invasive GBS infections.

Despite all preventative measures, the increasing burden of GBS remains a major problem for mothers and their newborns, adults, and the elderly with underlying conditions, substantiating the need for continued epidemiological surveillance and proper clinical antibiotic use for better prevention of GBS infections in all age groups. The acquisition of mobile elements that might contribute to the emergence of multidrug-resistant isolates highlights the necessity for monitoring antimicrobial susceptibility profiles.

Institutional Review Board Statement

This study was conducted in accordance with the ethical approval from the Institutional Review Board (IRB Log Number: 22-172E) of the centralized committee of King Fahad Medical City (KFMC). This retrospective study involved the collection of bacterial cultures, with no samples from humans or animals specifically collected for this research. Informed consent from patients was not required for this study as their data had been anonymized properly prior to access. In addition, the ethical committee of KFMC does not mandate patient consent to review medical records in such retrospective studies.

Disclosure

The authors report no conflicts of interest in this work.

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