Revista Argentina de Microbiología xxx (xxxx) xxx–xxx

asociación argentina de microbiología

REVISTA ARGENTINA DE MICROBIOLOGÍA

www.elsevier.es/ram

SPECIAL ARTICLE

Beta-lactam antibiotics and viridans group streptococci

Horacio A. Lopardo[a,b,*], **Laura Vigliarolo**[a,b], **Laura Bonofiglio**[a,c,d], **Paula Gagetti**[a,e], **Gabriela García Gabarrot**[a,f], **Sara Kaufman**[a,g], **Marta Mollerach**[a,c,d], **Inés Toresani**[a,h], **Martha von Specht**[a,i,j]

[a] *Grupo STREP de la Sociedad Argentina de Bacteriología, Micología y Parasitología Clínicas (SADEBAC), División de la Asociación Argentina de Microbiología, Argentina*
[b] *Cátedra de Microbiología Clínica, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, La Plata, Provincia de Buenos Aires, Argentina*
[c] *Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Departamento de Microbiología, Inmunología y Biotecnología, Cátedra de Microbiología, Ciudad Autónoma de Buenos Aires, Argentina*
[d] *CONICET, Argentina*
[e] *Servicio Antimicrobianos, Departamento de Bacteriología, Instituto Nacional de Enfermedades Infecciosas (INEI), ANLIS «Dr. Carlos G. Malbrán», Ciudad Autónoma de Buenos Aires, Argentina*
[f] *Programa de Desarrollo de las Ciencias Básicas (PEDECIBA), Universidad de la República, Montevideo, Uruguay*
[g] *Sección Microbiología Clínica, División Laboratorio, Hospital Juan A. Fernández, Ciudad Autónoma de Buenos Aires, Argentina*
[h] *Cátedra de Bacteriología, Facultad de Ciencias Bioquímicas, Universidad Nacional de Rosario, Rosario, Provincia de Santa Fe, Argentina*
[i] *Laboratorio de Bacteriología, Hospital Provincial de Pediatría «Dr. F. Barreyro», Posadas, Misiones, Argentina*
[j] *Departamento de Microbiología, Facultad de Ciencias Exactas Químicas y Naturales, Universidad Nacional de Misiones, Posadas, Misiones, Argentina*

Received 14 February 2022; accepted 24 June 2022

KEYWORDS
Viridans group streptococci;
β-Lactams;
Resistance;
Penicillin-binding proteins;
Endocarditis

Abstract The aim of this review is to present an update on the susceptibility of viridans group streptococci (VGS) to β-lactam antimicrobials, with emphasis on the Argentinean scenario. VGS are a heterogeneous group including five groups of species, each one exhibiting peculiar susceptibility patterns to penicillin (PEN). Species of the *Streptococcus mitis* group are frequently nonsusceptible to PEN. PEN resistance is associated with changes in PEN-binding proteins. In Argentina, one to two thirds of VGS are nonsusceptible to PEN. Third generation cephalosporins and carbapenems are currently more effective *in vitro* than PEN against VGS. Mortality was associated to nonsusceptibility to PEN in at least two studies involving patients with bacteremia caused by VGS. Treatment of endocarditis due to VGS should be adjusted/to the PEN susceptibility of the isolates. Vancomycin may be an alternative choice for treating endocarditis caused by PEN-resistant isolates (MIC $\geq 4\,\mu g/ml$).

* Corresponding author.
E-mail address: hlopar25@gmail.com (H.A. Lopardo).

https://doi.org/10.1016/j.ram.2022.06.004

Please cite this article as: H.A. Lopardo, L. Vigliarolo, L. Bonofiglio et al., Beta-lactam antibiotics and viridans group streptococci, Revista Argentina de Microbiología, https://doi.org/10.1016/j.ram.2022.06.004

PALABRAS CLAVE
Estreptococos del grupo *viridans*;
β-Lactámicos;
Resistencia;
Proteínas ligadoras de penicilina;
Endocarditis

Antibióticos beta-lactámicos y estreptococos grupo *viridans*

Resumen El objetivo de esta revisión es presentar una actualización sobre la sensibilidad de los estreptococos del grupo *viridans* (EGV) a los antimicrobianos β-lactámicos, con énfasis en el escenario argentino. Los EGV son un grupo heterogéneo que incluye cinco grupos de especies, y cada una presenta su patrón especial de sensibilidad a la penicilina (PEN). Las especies del grupo *Streptococcus mitis*, con mayor frecuencia, no son sensibles a la PEN. La resistencia a la PEN se asocia con cambios de las proteínas ligadoras de PEN. En la Argentina, de uno a dos tercios de los EGV no son sensibles a la PEN. Las cefalosporinas de tercera generación y los carbapenemes son actualmente más eficaces *in vitro* que la PEN contra los EGV. La mortalidad se asoció con la no sensibilidad a la PEN en al menos dos estudios de pacientes con bacteriemia por EGV. El tratamiento de las endocarditis por EGV debe ajustarse según la sensibilidad a la PEN de los aislados. La vancomicina podría ser una elección alternativa para el tratamiento de las endocarditis por cepas resistentes a PEN (CIM $\geq 4\,\mu g/ml$).

Introduction

Viridans group streptococci (VGS) are a heterogeneous group that includes five groups of species: *Streptococcus mitis* group, *Streptococcus salivarius* group, *Streptococcus anginosus* group (sometimes still referred to as ''*Streptococcus milleri*'', which is not a validly published denomination), *Streptococcus mutans* group, and *Streptococcus bovis* group (frequently referred to as group D streptococci)[23].

Despite belonging to the *S. mitis* group because of its molecular similarity, *S. pneumoniae* is usually described separately due to its distinguishing clinical and epidemiological impact, and will not be covered in the present review.

Identifying them at the species or subspecies level is very difficult using current biochemical methods, including API 20 Strep, Vitek 2, Phoenix and similar automated methods. Moreover, mass spectrometry and some sequencing methods may also misidentify some VGS species or subspecies[2].

The multilocus sequence analysis (MLSA), employing seven house-keeping gene sequences, has demonstrated its ability to identify VGS at the species level[7]. However, there are still problems to identify some species such as *S. mitis* and *S. oralis*, and also to differentiate them from *S. pneumoniae* due to their frequent intra- and interspecies gene transfer of mosaic genes[19].

The aim of this review was to present an update of β-lactam resistance among VGS, emphasizing the Argentinean experience. It is not a systematic review but a report on information obtained from selected studies and guidelines.

Human diseases associated with viridans group streptococci

VGS are an important part of the commensal microbiota of the human oropharyngeal cavity, vagina and gastrointestinal tract. However, they are the causative microorganisms of up to 40–60% of cases of native-valve endocarditis[27], and also of 16% of cases of prosthetic-valve endocarditis[26]. Their role in the bacteremia of neutropenic patients, especially those with hematologic malignancies, is a matter of growing concern[28,31].

An association of *S. bovis* group with colorectal carcinoma has been largely reported since the 50s. Despite being especially related to *Streptococcus gallolyticus* subsp. *gallolyticus*, when isolated from clinical samples, it is advisable to report *S. bovis* at group level in order to promote colorectal cancer screening[11].

S. anginosus group is associated with different types of purulent collections, including brain, liver and pulmonary abscesses[5,6]. These and other associated pathologies are shown in Table 1.

Table 1 VGS Species groups and their most frequently associated pathologies.

Species group	Most frequently associated pathologies
S. mutans	Caries, endocarditis
S. mitis	Endocarditis, bacteremia in neutropenic patients
S. salivarius	Transient bacteremia, endocarditis, iatrogenic meningitis, poor association with bowel malignancies
S. bovis	Bacteremia, sepsis, endocarditis (*S. gallolyticus* subsp. *gallolyticus* = colorectal cancer). (*S. gallolyticus* subsp. *pasteurianus* = meningitis, urinary tract infections)
S. anginosus	Abscess and empyema, rarely endocarditis

Table 2 Non-susceptibility to penicillin of viridans group streptococci, with special focus on isolates from Argentina.

Year[a]	Country	Observations	PNS%	Reference
1979	USA	10% of VGS with MICs >0.06 μg/ml	10	8
1989	Italy	No isolates with MICs >4 μg/ml	22	42
1996	USA	Some isolates with MICs >32 μg/ml	66.3	12
1998	Taiwan	11% of isolates with MICs ≥4 μg/ml	25.0	39
2000	Argentina	33.3% MICs >2 μg/ml	66.0	22
2007	Argentina	Argentinean Multicenter Study, 6.5% MICs >2 μg/ml	27.5	21
2016	Turkey	MIC90 0.5 μg/ml	61.2	38
2018	Taiwan	VGS from bacteremia cases	12.5	37
2019	Argentina	0.8% MICs >2 μg/ml	25.8	1

PNS: penicillin nonsusceptible viridans group streptococci.
[a] Year of publication.

Mechanisms of beta-lactam resistance in viridans group streptococci and synergy of β-lactams with aminoglycosides

The antibacterial efficacy of penicillin (PEN) against VGS depends on the affinity to bind penicillin-binding proteins (PBPs) and its decreased affinity leads to decreased sensitivity or resistance to PEN.

These PBPs are often called mosaic proteins because they are the result of successive point mutations and genetic material transfer to and from related species.

PEN-susceptible VGS species contain particular *pbp2x* alleles distinct from those of other species of the group and *S. pneumoniae*. However, PBP2x genes in resistant *Streptococcus pseudopneumoniae* (species belonging to the *S. mitis* group) display complex mosaic structures that are typical for resistant strains of *S. pneumoniae* and other members of the group[41].

The decrease in affinity is evidenced when the entirety of genetic alterations leads protein to change one or more aminoacids in the site or close to the penicillin-binding site. Similarly to *S. pneumoniae*, decreased PEN susceptibility in VGS involves alterations in several PBPs, mainly PBPs 2x, 2b, and 1a[15,44], while all high molecular-mass PBPs are modified among the fully resistant strains[1].

The combinations of PEN with aminoglycosides as treatment of infective endocarditis due to VGS demonstrated synergistic behavior and doubled the rate of bacterial killing compared to the use of PEN alone[34]. However, VGS isolates with enzymatic resistance to streptomycin and gentamicin have been described, in which the synergistic effect was nullified[30].

When the minimal inhibitory concentration (MIC) of PEN is higher than 0.125 μg/ml, and if the patient has bacterial endocarditis caused by VGS, gentamicin or streptomycin should be added to the β-lactam, trying to achieve a synergistic effect[3,14].

As was demonstrated for enterococci, synergy between penicillin and aminoglycosides is achieved when penicillin concentration in the infection site is equal or higher than the respective MIC[43].

Enhanced aminoglycoside uptake by the action of PEN would explain the increased rate of killing of PEN when an aminoglycoside is added. However, other authors suggested that another mechanism, not yet elucidated, may be the cause of this phenomenon in VGS[24].

Evolution of beta-lactam resistance

β-Lactams are still the antibiotics of choice for treating severe infections due to VGS. Before the 80s, VGS was considered to be uniformly susceptible to PEN, but it was not noted that as early as during the 40s, PEN-non-susceptible (PNS) VGS had already been described[18]. Two and three decades after, several authors published the occurrence of PNS VGS[8], especially in the gingival microbiota of patients receiving prophylaxis with PEN[17]. After 1980, higher levels of PEN MICs and higher rates of antimicrobial resistance among VGS were observed[12,22].

Endocarditis due to resistant strains remains rare but a high rate of PEN nonsusceptibility was found among VGS isolated from blood samples of febrile neutropenic patients[42].

More than 60% of PNS VGS, some of them with MICs of PEN as high as 32 μg/ml were described in the USA and also in Argentina during the 90s. These series included large numbers of *S. mitis* isolated from neutropenic patients[12,22]. When other species were prevalent, less PNS VGS were found[16,21].

According to CLSI breakpoints, about one to two thirds of VGS would be included in the resistant or intermediate categories in Argentina[16,21,22]. Percentages of PNS VGS of various studies are shown in Table 2.

Beta-lactam antibiotics (other than penicillin)

Currently VGS are more susceptible to carbapenems and cephalosporins than to PEN. Significant differences (I + R = 0 and 3.1% vs. 25.8%, respectively)[16] were found in an Argentinean study.

In another study, all VGS strains with a MIC of PEN = 1 μg/ml were fully susceptible to cefepime (FEP), meropenem (MEM) and piperacillin-tazobactam (PTZ). VGS isolates with a MIC of PEN = 2 μg/ml were generally susceptible to the tested β-lactams, with the exception of MEM, while VGS isolates considered PEN-resistant by CLSI and EUCAST guidelines (MIC ≥ 4 μg/ml)[10,40] were generally non-susceptible to FEP and MEM but, not necessarily to PTZ. Thus, VGS isolates with *in vitro* non-susceptibility to FEP,

Table 3 Penicillin susceptibility categories in viridans group streptococci according to the different guidelines for *in vitro* testing or for treating patients with endocarditis.

Guidelines	Susceptible	Intermediate	Resistant	Comments
CLSI	≤0.12 μg/ml	0.25–2 μg/ml	≥4 μg/ml	2021 guidelines for *in vitro* interpretation
EUCAST	≤0.25	0.5–2 μg/ml	≥4 μg/ml	2021 guidelines for *in vitro* interpretation Medium is supplemented with 20 mg/l β-NAD
AHA	≤0.12 μg/ml	0.25–0.5 μg/ml	≥1 μg/ml	2015 guidelines for endocarditis
ESC	≤0.12 μg/ml	0.25–2 μg/ml	≥4 μg/ml	2009 guidelines for endocarditis
BSAC	≤0.12 μg/ml	0.25–0.5 μg/ml	≥1 μg/ml	2011 guidelines for endocarditis

AHA: American Heart Association; ESC: European Society for Cardiology; BSAC: British Society for Antimicrobial Chemotherapy; CLSI: Clinical and Laboratory Standards Institute; EUCAST: European Committee on Antimicrobial Susceptibility Testing.

Table 4 Antimicrobial therapy recommended for adult patients with native valve endocarditis caused by viridans group streptococci, according to penicillin minimal inhibitory concentrations of the isolates (American Heart Association)[3]

MIC of PEN	Antibiotics	Dosage and route	Duration
≤0.12 μg/ml	CRO	2 g/24 h iv/im in one dose	4 w
	PEN	12/18 MU/24 h continuously or in 4–6 doses	4 w
	PEN	12/18 MU/24 h continuously or in 6 doses	2 w
	or		
	CRO	2 g/24 h iv/im in one dose	2 w
	plus		
	GEN	3 mg/kg/24 h iv/im in one dose	2 w
	VAN	30 mg/kg/24 h iv in 2 doses	4 w
0.25–0.5 μg/ml	PEN	24 MU/24 continuously or in 4–6 doses	4 w
	or		
	CRO	2 g/24 h iv/im in 1 dose	4 w
	plus		
	GEN	3 mg/kg/24 h iv/im in 1 dose	2 w
	VAN	30 mg/kg/24 h iv in 2 doses	4 w
≥1 μg/ml	PEN	18/30 MU/24 continuously or in 6 doses	4–6 w
	or		
	AMP	12 g/24 h iv in 6 doses	4–6 w
	plus		
	GEN	3 mg/kg/24 h iv/im in 3 doses	4–6 w
	VAN	30 mg/kg/24 h iv in 2 doses	6 w
	plus		
	GEN	3 mg/kg/24 h iv/im in 3 doses	6 w

MIC: minimal inhibitory concentration; CRO: ceftriaxone sodium; PEN: aqueous crystalline penicillin G sodium; GEN: gentamicin sulfate; VAN: vancomycin hydrochloride; AMP: ampicillin sodium; iv/im: intravenous/intramuscular; w: weeks; MU: millions of units.

Table 5 Antimicrobial therapy recommended for adult patients with endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci, according to penicillin minimal inhibitory concentrations of the isolates (American Heart Association)[3]

MIC of PEN	Antibiotics	Dosage and route	Duration
≤0.12 μg/ml	PEN	24 MU/24 h continuously or in 6 doses	6 w
	or		
	CRO	2 g/24 h iv/im in one dose	6 w
	plus		
	GEN	3 mg/kg/24 h iv/im in one dose	2 w
	VAN	30 mg/kg/24 h iv in 2 doses	6 w
>0.12 μg/ml	PEN	24 MU/24 continuously or in 4–6 doses	6 w
	or		
	CRO	2 g/24 h iv/im in 1 dose	6 w
	plus		
	GEN	3 mg/kg/24 h iv/im in 1 dose	6 w
	VAN	30 mg/kg/24 h iv in 2 doses	6 w

MIC: minimal inhibitory concentration; CRO: ceftriaxone sodium; PEN: aqueous crystalline penicillin G sodium; GEN: gentamicin sulfate; VAN: vancomycin hydrochloride; iv/im: intravenous/intramuscular; w: weeks; MU: million of units.

MEM, and PTZ were restricted to strains with a MIC of PEN ≥2 μg/ml[35].

In the USA, the new cephalosporin, ceftaroline, was *in vitro* active against 840 VGS with a MIC90 of 0.06 μg/ml (100% susceptibility). The highest ceftaroline MIC values (0.5 μg/ml) were observed in the *S. mitis* group[33].

In the same study, higher MICs of MEM (MIC90 = 0.125 μg/ml) and CRO (MIC90 = 0.5 μg/ml; 2% nonsusceptibility, with one isolate having a MIC of 8 μg/ml) were found. MIC90 of PEN was 0.25 μg/ml, but the percentage of PNS was 15.1%.

Clinical impact of β-lactam resistant viridans group streptococci

Bacteremia in patients with cancer

Clinical significance of PNS has been historically described in *S. pneumoniae*[20]. However, its influence in mortality of VGS bacteremic patients was only demonstrated in two studies conducted by the same Slovakian group.

In one of those studies, including 60 patients with cancer and bacteremia due to VGS, a multiple logistic regression analysis showed that only acute leukemia and PEN-resistance were significant independent predictors of inferior outcome[36].

In another of those studies, including 127 cases of bacteremia due to VGS, a significant difference was found between the evolution of patients infected with PEN-susceptible isolates and those infected with PEN-resistant isolates (mortality: 22.5% vs. 71%, respectively)[25]. In the latter case, only 32 patients had cancer as underlying disease.

Concern for serious infection due to β-lactam-resistant VGS is a major factor driving the empiric use of an anti-gram positive antimicrobial in febrile neutropenic patients. Patients infected by VGS with a MIC of PEN ≥2 μg/ml had at least one of the following risk factors: current use of a β-lactam as antimicrobial prophylaxis, having used a β-lactam in the previous 30 days, or nosocomial VGS bacteremia onset[35].

Infectious endocarditis

The American Heart Association (AHA)[3], the European Society for Cardiology (ESC)[14] and the British Society for Antimicrobial Chemotherapy (BSAC)[13] published guidelines for the treatment of VGS endocarditis according to type (native or prosthetic valve endocarditis) and their MIC of PEN. PEN susceptibility categories of the AHA and the BSAC did not coincide with those established by the ESC, the Clinical and Laboratory Standards Institute (CLSI)[10] or the European Committee on Antimicrobial Susceptibility Testing (EUCAST)[40] (Table 3).

Briefly, for the AHA, the treatment of native valve endocarditis of adult patients due to PEN-susceptible VGS (MIC ≤ 0.12 μg/ml) is based on the use of intravenous (iv) PEN or iv/intramuscular (im) ceftriaxone (CRO) for 4 weeks, shortened treatment of 2 weeks with the use of iv/im gentamicin (GEN) or iv vancomycin (VAN) for patients allergic to β-lactams. For endocarditis caused by PNS VGS (MICs of 0.25 or 0.5 μg/ml), the addition of GEN for 2 weeks is mandatory, and higher doses of PEN should be used. For endocarditis caused by VGS with MIC of PEN ≥1 μg/ml and for prosthetic valve endocarditis duration of treatment may last for 6 weeks, including the use of GEN (Table 4)[3].

In Tables 5 and 6, guidelines of the AHA for treatment of prosthetic valve endocarditis of adult patients and native valve endocarditis of pediatric patients, are respectively shown.

However, the appropriate treatment for cases in which the MIC of PEN is equal to or higher than 4 μg/ml is not yet established. As can be seen in Table 7, different antibiotics or antibiotic combinations have been used with similar results in specific cases.

Table 6 Antimicrobial therapy recommended for pediatric patients presenting native valve endocarditis caused by viridans group streptococci, according to penicillin minimal inhibitory concentrations of the isolates (American Heart Association)[3]

MIC of PEN	Antibiotics	Dosage and route	Duration
≤0.12 μg/ml	CRO	100 mg/kg per 24 h iv/im in one dose	4 w
	PEN	200 000 U/kg per 24 h in 4–6 doses	4 w
	PEN	200 000 U/kg per 24 h in 4–6 doses	2 w
	or		
	CRO	100 mg/kg per 24 h iv/im in one dose	2 w
	plus		
	GEN	3 mg/kg/24 h iv/im in 1 or 3 doses	2 w
	VAN	40 mg/kg/24 h iv in 2–3 doses	4 w
0.25–0.5 μg/ml	PEN	300 000 U/kg per 24 h in 4–6 doses	4 w
	or		
	CRO	100 mg/kg per 24 h iv/im in one dose	4 w
	plus		
	GEN	3 mg/kg/24 h iv/im in 1 or 3 doses	2 w
	VAN	40 mg/kg/24 h iv in 2–3 doses	4 w
≥1 μg/ml	PEN	300 000 U/kg per 24 h in 4–6 doses	4–6 w
	or		
	AMP	300 mg/kg per 24 h iv in 4–6 doses	4–6 w
	plus		
	GEN	3 mg/kg/24 h iv/im in 3 doses	4–6 w
	VAN	40 mg/kg/24 h iv in 2–3 doses	6 w
	plus		
	GEN	3 mg/kg/24 h iv/im in 3 doses	6 w

MIC: minimal inhibitory concentration; CRO: ceftriaxone sodium; PEN: aqueous crystalline penicillin G sodium; GEN: gentamicin sulfate; VAN: vancomycin hydrochloride; AMP: ampicillin sodium: iv/im: intravenous/intramuscular; w: weeks; MU: million of units.

Table 7 Cases of infective endocarditis caused by viridans group streptococci resistant to more than 2 μg/ml penicillin (modified from Pericàs et al.)[29]

Reference[a]	Year	Type of valve	MIC of PEN	Treatment	Outcome
Garrod and Waterworth	1962	N	8	PEN + STR 6 w	Cured
Garrod and Waterworth	1962	N	4	PEN + STR 10 d	Cured
Doyle et al.	1967	N	10	PEN + STR 3 w	Cured
Knoll et al.	1978	N	4	PEN (3 w) + STR (2 w)	†
Knoll et al.	1987	P	4	PEN + GEN 4 w	Cured
Knoll et al.	1987	P	4	GEN 4 w	Cured
Levitz	1999	P	>4	VAN 4 w	Cured
Levy et al.	2001	N	>4	VAN + GEN 16 d	†
Sabella et al.	2001	N	4	VAN + GEN 4 w, VAN + CRO 2 w	Cured
Nandakhumar et al. (7 cases)	2008	N	4–16	PEN or AMP + CRO or AMP + CIP or CRO + GEN 4 w	Cured
Fujitani et al.	2008	N	4	VAN + GEN 10 d, CRO + GEN 7 d, VAN 6 w	Cured but died 4 m later
Pericàs et al.	2001	P	8	VAN + GEN 4 w, VAN 2 w	Cured but died 10 m later
Pericàs et al.	2016	P	4	VAN + CRO 4 d, VAN 6 w	Cured

MIC: minimal inhibitory concentration; PEN: penicillin; STR: streptomycin; w: weeks; d: days; GEN: gentamicin; VAN: vancomycin; CRO: ceftriaxone; CIP: ciprofloxacin; m: months.

[a] References have been taken from Pericás et al.[29] The use of VAN when the MIC is ≥4 was recommended, but there is no evidence of superiority[13].

Table 8 Occurrence of penicillin resistance (in percentages) among different species groups of viridans group streptococci.

Ref.	Category	*S. mitis*	*S. salivarius*	*S. anginosus*	*S. bovis*	*S. mutans*
16	R%	0.7	0	0	0	0
	R + I%	18.2	2.3	4.5	0	0.7
21	R%	32	6	0	0	0
	R + I%	46	12	6	22	0
9	R%	17.2	7.3	3.1	0	28.6
	R + I%	55.3	61.8	5.2	0	42.9
33	R%	1.1	0	0	0	0
	R + I%	28.8	37.7	1	0	0
38	R%	NA	NA	NA	NA	NA
	R + I%	58.3	100	54.2	NA	66.7
39	R%	20.0	8	0	NA	0
	R + I%	36.4	50	10.8	NA	0
37	R%	NA	NA	NA	NA	NA
	R + I%	17.0	29.4	9.1	0	0

R: resistant; I: intermediate; NA: not applicable.

Species-specific difference in antimicrobial susceptibility among viridans group streptococci

Species belonging to the *S. mitis* group are the most resistant to PEN (7.6% for *S. sanguinis* group and 10.6% for *S. mitis* group) vs. *S. anginosus* (4.5%) and *S. salivarius* (2.3%) groups[16].

Except for a few cases, β-lactam susceptibility data for the *S. bovis* and *S. anginosus* groups have remained relatively stable, with MICs in the susceptibility range not only to PEN, but also to AMP, AMX, CRO, OXA, and MEM[4,11].

Rarely, it is possible to find isolates of the *S. anginosus* group susceptible to PEN but resistant to third generation cephalosporins[32].

With less accurate methods to identify species, other authors arrived at different conclusions, most of them observing higher percentages of PEN resistance mainly within the *S. mitis* group streptococci[12,21,22], and others reporting also high percentages of PNS isolates of *S. salivarius* and *S. mutans* groups. In the latter group, Chun et al. found isolates with MICs $\geq$4 μg/ml, but it was the result of only 7 isolates (Table 8)[9].

Conclusions

The viridans group is a heterogeneous species group, each one with its characteristic susceptibility to β-lactams. PEN nonsusceptibility is due to modifications of the PBPs, especially those of higher molecular mass. Reduced susceptibility to PEN is more frequent among isolates of *S. mitis* and to a lesser extent *S. salivarius*, than among isolates of *S. anginosus* or *S. bovis* groups. According to their relative frequency, PNS ranges from 20 to 60%. Third generation cephalosporins and carbapenems are currently more effective *in vitro* than PEN against VGS. The main clinical impact of PEN resistance occurs in endocarditis, where it seems to play an important role in relation to mortality.

Ethical responsibilities

Not applicable.

Funding

None declared.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgment

Authors are grateful to Sociedad Argentina de Bacteriología, Micología y Parasitología Clínicas (SADEBAC), a division of Asociación Argentina de Microbiología for its permanent encouragement and support.

References

1. Amoroso A, Demares D, Mollerach M, Gutkind G, Coyette J. All detectable high molecular-mass penicillin-binding proteins are modified in high-level beta-lactam resistant clinical isolate of *Streptococcus mitis*. Antimicrob Agents Chemother. 2001;45:2075–81.
2. Angeletti S, Dicuonzo G, Avola A, Crea F, Dedej E, Vailati F, Farina C, De Florio L. Viridans group streptococci clinical isolates: MALDI-TOF mass spectrometry versus gene sequence-based identification. PLOS ONE. 2015;10:e0120502.
3. Baddour LM, Wilson WR, Bayer AS, Fowler VG Jr, Tleyjeh IM, Rybak MJ, Barsic B, Lockhart PB, Gewitz MH, Levison ME, Bolger AF, Steckelberg JM, Baltimore RS, Fink AM, O'Gara P, Taubert KA, American Heart Association Committee on Rheumatic Fever,

Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, Stroke Council. Infective endocarditis in adults: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. Circulation. 2015;132:1435–86.
4. Berardinelli E, Lopardo H. Estreptococos del grupo *Streptococcus anginosus*. Parte II. Patogenia y sensibilidad a los antibióticos. Acta Bioquím Clín Latinoam. 2021;55:61–77.
5. Berardinelli E, Rosanova MT, Lopardo HA. Estreptococos del grupo *Streptococcus anginosus*. Parte III.a. Epidemiología e infecciones de cabeza y cuello. Acta Bioquím Clín Latinoam. 2021;55:177–89.
6. Berardinelli E, Rosanova MT, Lopardo HA. Estreptococos del grupo *Streptococcus anginosus*. Parte III.b. Infecciones en localizaciones diferentes de las de cabeza y cuello. Acta Bioquím Clín Latinoam. 2021;55:31–74.
7. Bishop CJ, Aanensen DM, Jordan GE, Kilian M, Hanage WP, Spratt BG. Assigning strains to bacterial species via the internet. BMC Biol. 2009;7:3.
8. Bourgault AM, Wilson WR, Washington JA 2nd. Antimicrobial susceptibilities of species of viridans streptococci. J Infect Dis. 1979;140:316–21.
9. Chun S, Huh HJ, Lee NY. Species-specific difference in antimicrobial susceptibility among viridans group streptococci. Ann Lab Med. 2015;35:205–11.
10. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing, CLSI supplement M100. 31st ed. Wayne, PA, USA: CLSI; 2021.
11. Dekker JP, Lau AF. An update on the *Streptococcus bovis* group: classification, identification, and disease associations. J Clin Microbiol. 2016;54:1694–9.
12. Doern GV, Ferraro MJ, Brueggemann AB, Ruoff KL. Emergence of high rates of antimicrobial resistance among viridans group streptococci in the United States. Antimicrob Agents Chemother. 1996;40:891–4.
13. Gould FK, Denning DW, Elliott TSJ, Foweraker J, Perry JD, Prendergast BD, Sandoe JAT, Spry MJ, Watkin RW, Working Party of the British Society for Antimicrobial Chemotherapy. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the Working Party of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother. 2012;67:269–89.
14. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, Antunes MJ, Thilen U, Lekakis J, Lengyel M, Müller L, Naber CK, Nihoyannopoulos P, Moritz A, Zamorano JL, ESC Committee for Practice Guidelines. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J. 2009;30:2369–413.
15. Hakenbeck R, Brückner R, Denapaite D, Maurer P. Molecular mechanism of beta-lactam resistance in *Streptococcus pneumoniae*. Future Microbiol. 2012;7:395–410.
16. Heine AC, García S, Barberis C, Vay C, Mollerach M, Bonofiglio L, Famiglietti A. Identificación y sensibilidad a los antimicrobianos de aislados de estreptococos del grupo viridans provenientes de pacientes internados en un hospital universitario de la ciudad de Buenos Aires. Rev Argent Microbiol. 2019;51:26–31.
17. Hess J, Holloway Y, Dankert J. Penicillin prophylaxis in children with cardiac disease: postextraction bacteremia and penicillin-resistant strains of viridans streptococci. J Infect Dis. 1983;147:133–6.
18. Kaye D, Mc Cormack RC, Hook EW. Bacterial endocarditis: the changing pattern since the introduction of penicillin therapy. Antimicrob Agents Chemother. 1962;1:37–46.
19. Kilian M, Riley DR, Jensen A, Bruggemann H, Tettelin H. Parallel evolution of *Streptococcus pneumoniae* and *Streptococcus mitis* to pathogenic and mutualistic lifestyles. mBio. 2014;5:e01490–1514.
20. Klugman KP. Pneumococcal resistance to antibiotics. Clin Microbiol Rev. 1990;3:171–96.
21. Lopardo H, Blanco A, Vigliarolo L, Gagetti P, Corso A, grupo colaborativo de la Red WHONET. Estudio multicéntrico nacional de resistencia a los antibióticos en estreptococos del grupo viridans. In: XIII Jornadas Argentinas de Microbiología. 2008.
22. Lopardo H, Vidal P, Bottero D, Moviglia AM, Gobet LM. Is the diffusion method appropriate to determine the susceptibility to penicillin of viridans group streptococci? Resumen T-287. 3rd. European Congress of Chemotherapy, Madrid, May 7–10, 2000. Rev Esp Quimioter. 2000;13 Suppl. 2:104.
23. Lopardo H. Estreptococos del grupo viridans. In: Lopardo H, Predari SC, Vay C, editors. Manual de Microbiología Clínica de la Asociación Argentina de Microbiología. Volumen I. Bacterias de importancia clínica. Parte II.a.2. Cocos gram positivos catalasa negativos. 2016. p. 132–74. www.aam.org.ar [publicación on-line].
24. Miller MH, El-Sokkary MA, Feinstein SA, Lowy FD. Penicillin-induced effects on streptomycin uptake and early bactericidal activity differ in viridans group and enterococcal streptococci. Antimicrob Agents Chemother. 1986;30:763–8.
25. Mrazova M, Docze A, Buckova E, Bucko L, Kacmarikova M, Grey E, Korcova J, Koprnova J, Saboova Z, Beno P, Karvaj M, Svetlansky I, Ondrus A, Benca J, Taziarova M, Rudinsky B, Krcmery V Jr. Prospective national survey of viridans streptococcal bacteraemia risk factors, antibacterial susceptibility and outcome of 120 episodes. Scand J Infect Dis. 2005;37:637–41.
26. Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG Jr, Bayer AS, Karchmer AW, Olaison L, Pappas PA, Moreillon P, Chambers ST, Chu VH, Falcó V, Holland DJ, Jones P, Klein JL, Raymond NJ, Read KM, Tripodi MF, Utili R, Wang A, Woods CW, Cabell CH, International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med. 2009;169:463–73.
27. Mylonakis E, Calderwood SB. Infective endocarditis in adults. N Engl J Med. 2001;345:1318–30.
28. Paganini H, Staffolani V, Zubizarreta P, Casimir L, Lopardo H, Luppino V. Viridans streptococci bacteremia in children with fever and neutropenia: a case–control study of predisposing factors. Eur J Cancer. 2003;39:1284–9.
29. Pericàs JM, Nathavitharana R, Garcia-de-la-Mària C, Falces C, Ambrosioni J, Almela M, García-González J, Quintana E, Marco F, Moreno A, Bayer AS, Miró JM, Karchmer AW, Hospital Clínic Endocarditis Study Group. Endocarditis caused by highly penicillin-resistant viridans group streptococci: still room for vancomycin-based regimens. Antimicrob Agents Chemother. 2019;63:e00516–519.
30. Potgieter E, Carmichael M, Koornhof HJ, Chalkey LJ. *In vitro* antimicrobial susceptibility of viridans streptococci isolated from blood cultures. Eur Clin Microbiol Infect Dis. 1992;11:543–6.
31. Radocha J, Paterová P, Zavřelová A, Víšek B, Gabalec F, Žemličková H, Žák P. Viridans group streptococci bloodstream infections in neutropenic adult patients with hematologic malignancy: single center experience. Folia Microbiol (Praha). 2018;63:141–6.

32. Rose L, Chasanov W, Fraimow H. Tricuspid valve endocarditis partly due to a penicillin susceptible, ceftriaxone-resistant *Streptococcus anginosus* isolate. Am J Ther. 2017;24:e501–3.
33. Sader HS, Rhomberg PR, Castanheira M, Farrell DJ, Flamm RK, Mendes RE, Jones RN. Ceftaroline activity tested against viridans group streptococci from US hospitals. Diagn Microbiol Infect Dis. 2016;84:232–5.
34. Sande MA, Irvin RG. Penicillin-aminoglycoside synergy in experimental *Streptococcus viridans* endocarditis. J Infect Dis. 1974;129:572–6.
35. Shelburne SA III, Lasky R, Sahasrabhojane P, Tarrand JT, Rolston KVI. Development and validation of a clinical model to predict the presence of β-lactam resistance in viridans group streptococci causing bacteremia in neutropenic cancer patients. Clin Infect Dis. 2014;54:223–30.
36. Spanik S, Trupl J, Kunova A, Botek R, Sorkovska D, Grey E, Studena M, Lacka J, Oravcova E, Krchnakova A, Rusnakova V, Svec J, Krupova I, Grausova S, Stopkova K, Koren P, Krcmery V Jr. Viridans streptococcal bacteraemia due to penicillin-resistant and penicillin-sensitive streptococci: analysis of risk factors and outcome in 60 patients from a single cancer centre before and after penicillin is used for prophylaxis. Scand J Infect Dis. 1997;29:245–9.
37. Su T-Y, Lee M-H, Huang C-T, Liu T-P, Lu J-J. The clinical impact of patients with bloodstream infection with different groups of viridans group streptococci by using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS). Medicine (Baltimore). 2018;97:e13607.
38. Süzük S, Kaşkatepe B, Çetin M. Antimicrobial susceptibility against penicillin, ampicillin and vancomycin of viridans group *Streptococcus* in oral microbiota of patients at risk of infective endocarditis. Infez Med. 2016;24:190–3.
39. Teng LJ, Hsueh PR, Chen YC, Ho SW, Luh KT. Antimicrobial susceptibility of viridans group streptococci in Taiwan with an emphasis on the high rates of resistance to penicillin and macrolides in *Streptococcus oralis*. J Antimicrob Chemother. 1998;41:621–7.
40. The EUCAST Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 11.0; 2021. http://www.eucast.org
41. van der Linden M, Otten J, Bergmann C, Latorre C, Liñares J, Hakenbeck R. Insight into the diversity of penicillin-binding protein 2x alleles and mutations in viridans streptococci. Antimicrob Agents Chemother. 2017;61:e02646–2716.
42. Venditti M, Baiocchi P, Santini C, Braandimarte C, Serra P, Gentile G, Girmenia C, Martino P. Antimicrobial susceptibility of *Streptococcus* species that cause septicemia in neutropenic patients. Antimicrob Agents Chemother. 1989;33:580–2.
43. Vigliarolo L, Ramírez MS, Centrón D, Lopardo H. Influencia de la concentración inhibitoria mínima de penicilina en la acción sinérgica de su combinación con gentamicina frente a estreptococos del grupo viridans. Rev Argent Microbiol. 2007;39:107–12.
44. von Specht M, García Gabarrot G, Mollerach M, Bonofiglio L, Gagetti P, Kaufman S, Vigliarolo L, Toresani I, Lopardo HA. Resistance to β-lactams in *Streptococcus pneumoniae*. Rev Argent Microbiol. 2021. S0325-7541(21)00041-9.