



SPECIAL ARTICLE

Beta-lactam antibiotics and *viridans* group streptococci



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Received 14 February 2022; accepted 24 June 2022

Available online 17 October 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 ≥ 4 μg/ml).

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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 $\geq 4 \mu\text{g/ml}$).

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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 subspecies².

The multilocus sequence analysis (MLSA), employing seven house-keeping gene sequences, has demonstrated its ability to identify VGS at the species level⁷. 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 genes¹⁹.

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

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

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

tract. However, they are the causative microorganisms of up to 40–60% of cases of native-valve endocarditis²⁷, and also of 16% of cases of prosthetic-valve endocarditis²⁶. 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 screening¹¹.

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 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 group⁴¹.

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 strains¹.

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 alone³⁴. However, VGS isolates with enzymatic resistance to streptomycin and gentamicin have been described, in which the synergistic effect was nullified³⁰.

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 MIC⁴³.

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 VGS²⁴.

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 described¹⁸. Two and three decades after, several authors published the occurrence of PNS VGS⁸, especially in the gingival microbiota of patients receiving prophylaxis with PEN¹⁷. 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 patients⁴².

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	$\leq 0.12 \mu\text{g/ml}$	$0.25\text{--}2 \mu\text{g/ml}$	$\geq 4 \mu\text{g/ml}$	2021 guidelines for <i>in vitro</i> interpretation
EUCAST	≤ 0.25	$0.5\text{--}2 \mu\text{g/ml}$	$\geq 4 \mu\text{g/ml}$	2021 guidelines for <i>in vitro</i> interpretation Medium is supplemented with 20 mg/l β -NAD
AHA	$\leq 0.12 \mu\text{g/ml}$	$0.25\text{--}0.5 \mu\text{g/ml}$	$\geq 1 \mu\text{g/ml}$	2015 guidelines for endocarditis
ESC	$\leq 0.12 \mu\text{g/ml}$	$0.25\text{--}2 \mu\text{g/ml}$	$\geq 4 \mu\text{g/ml}$	2009 guidelines for endocarditis
BSAC	$\leq 0.12 \mu\text{g/ml}$	$0.25\text{--}0.5 \mu\text{g/ml}$	$\geq 1 \mu\text{g/ml}$	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
$\leq 0.12 \mu\text{g/ml}$	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 plus GEN	2 g/24 h iv/im in one dose	2 w
	VAN	3 mg/kg/24 h iv/im in one dose	2 w
$0.25\text{--}0.5 \mu\text{g/ml}$	VAN	30 mg/kg/24 h iv in 2 doses	4 w
	PEN	24 MU/24 continuously or in 4–6 doses	4 w
	or		
	CRO plus GEN	2 g/24 h iv/im in 1 dose	4 w
	VAN	3 mg/kg/24 h iv/im in 1 dose	2 w
$\geq 1 \mu\text{g/ml}$	VAN	30 mg/kg/24 h iv in 2 doses	4 w
	PEN	18/30 MU/24 continuously or in 6 doses	4–6 w
	or		
	AMP plus GEN	12 g/24 h iv in 6 doses	4–6 w
	VAN	3 mg/kg/24 h iv/im in 3 doses	4–6 w
	VAN plus GEN	30 mg/kg/24 h iv in 2 doses	6 w
		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		
>0.12 µg/ml	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
	PEN	24 MU/24 continuously or in 4–6 doses	6 w
	or		
>0.12 µg/ml	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/ml³⁵.

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* group³³.

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 outcome³⁶.

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 onset³⁵.

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
Nandakumar 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 Pericàs et al.²⁹ The use of VAN when the MIC is ≥4 was recommended, but there is no evidence of superiority¹³.

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

Ref.	Category	<i>S. mitis</i>	<i>S. salivarius</i>	<i>S. anginosus</i>	<i>S. bovis</i>	<i>S. mutans</i>
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%) groups¹⁶.

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 cephalosporins³².

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 $\geq 4 \mu\text{g/ml}$, 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.

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