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Original Article

Vancomycin-resistant *Enterococcus faecium* in Algeria: phenotypic and genotypic characterization of clinical isolates

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Abstract

Introduction: vancomycin-resistant *Enterococcus faecium* (VREfm) is a major public health problem worldwide. The aim of our study was to determine the microbiological, epidemiological and molecular characteristics of VREfm isolated in north-central, eastern and western Algeria.
Methodology: a collection of 48 VREfm isolated from September 2010 to April 2017 in several Algerian hospitals were studied. Minimum inhibitory concentrations (MICs) were determined by E-test method according to CLSI guidelines. the detection of *van* genotype of all strains was performed by PCR. Clonal relationship of five VREfm targeted by region were characterized using multilocus sequence typing (MLST).
Results: All isolates have multidrug-resistance (MDR) and were resistant to at least five classes of antibiotics; however, all were susceptible to tigecycline and daptomycin with MIC_{50} at 0.094 µg/mL and 2 µg/mL respectively. All strains belonged to *vanA* genotype and have high level of resistance to vancomycin and teicoplanin. MLST revealed two sequence types (STs): ST80 (from the four regions of Algeria) and ST789, both belonging to the former hospital-adapted clonal complex CC17.
Conclusion: the alarming dissemination of MDR *E. faecium vanA* and the ST80 in several regions of Algeria suggest a clonal spread of VREfm strains, which urgently require implementation of adequate infection control measures.

Key words: Vancomycin-resistant *E. faecium;* antimicrobial susceptibility*; vanA;* MLST; Algeria.

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Introduction

Enterococcus faecium has become an important nosocomial pathogen, involved in healthcare-associated infections (HAIs), especially among severely ill and/or immunocompromised patients and causes multiples infections (e.g. urinary tract infections, surgical site infections, bacteremia and endocarditis) [1-3]. *E. faecium* characterized by its remarkable survival abilities in harsh conditions and by its capacity to colonize and persist in gastrointestinal tract of healthy carriers and patients, leading to rapid spread and outbreaks [2-4]. *E. faecium*, naturally resistant to many antimicrobial agents, has acquired resistance to almost all drugs, including the glycopeptides [2-4]. Therefore, multidrug-resistant (MDR) *E. faecium* has significantly limited therapeutic options for treating serious and sometimes deadly infections due to these pathogens. In this context, the World Health Organization recognized VREfm as a high priority in its list of 12 resistant-bacteria that pose the greatest threat to human health [5]. Moreover, VREfm can serve as a reservoir of resistance genes and can also transfer to other strains of bacteria such as *Staphylococcus aureus* [2,4,6]. Over last 30 years, VREfm has increased worldwide and becomes a cause of concern [2-4, 7]. The European Antimicrobial hold Surveillance Network (EARS-Net) showed that the detection rate of VREfm from 2015 to 2018 increased from 10.5 to 17.3% [8]. In 2014, the detection rate of VRE in the United States was 8.1% [9]. Furthermore, according to the Korean Antimicrobial hold state Monitoring System (KARMS) from 2013 to 2015, the detection rate of VREfm grew from 29 to 31% [10]. The Algerian Antimicrobial Resistance Network (AARN) indicated that the VREfm rate from 2014 to 2017 similarly rose from 7.1 to 16% [11,12]. Vancomycin-resistant

Enterococci (VRE) strains have emerged during the 1980s and have gradually increasingly reported worldwide as an important cause of nosocomial infection, due mainly to *E. faecium* [2-4]. The glycopeptide resistance genotypes include *vanA*-*vanE*, *vanG* and *vanL*-*vanN*) [3, 4]. The *vanA* genotype is the most prevalent in VRE and confers high level resistance to both vancomycin and teicoplanin [3, 4]. This species is characterized by its genome plasticity, which allows it to generate subpopulations highly adapted to the hospital environment such as the clonal complex CC17, which is highly virulent and has epidemic potential. In addition, the strains belonging to this clonal complex are highly resistant to ampicillin and fluoroquinolones [2,4,13]. In Algeria, the first VREfm was isolated in 2010. Since then, these MDR strains have spread in Algerian hospitals. The main objectives of this study was to determine the microbiological, epidemiological and molecular characteristics of VREfm isolated in north-central, eastern and western regions of Algeria.

Methodology

Patients and bacterial strains

Between September 2010 and April 2017, 48 non-repetitive VREfm clinical isolates from several Algerian hospitals were collected at the Medical Bacteriology Laboratory, Institut Pasteur of Algeria. VREfm strains, recovered from ill and colonized patients, were from north-central (Algiers, Boumerdes, Blida and Tipaza), eastern (Constantine, Setif and Batna) and western (Oran) Algeria. Patients' demographic characteristics, medical conditions and clinical outcome were recorded. All the VREfm isolates collected were stored at – 80 °C until analysis.

Species identification and antimicrobial susceptibility

This study was carried out between January 2012 and December 2017. Clinical isolates were identified by the strep API32 system (bioMérieux, Marcy l'Etoile, France). A PCR assay based on the amplification of specific gene encoding D-alanine-D-alanine ligase (*ddl*) was used to confirm the identification of *E. faecium* as previously described [14].

The minimum inhibitory concentrations (MICs) to ampicillin, high-level gentamicin, high-level streptomycin, erythromycin, quinupristin-dalfopristin, levofloxacin, rifampicin, tetracycline, nitrofurantoin, fosfomycin, chloramphenicol, vancomycin, teicoplanin, tigecycline and daptomycin were determined by the E-test (bioMérieux, Marcy l'Etoile, France) method on Mueller-Hinton agar following the CLSI recommendations [15]. CLSI interpretive criteria were used for all antibiotics [15], excluding tigecycline for which EUCAST breakpoints were used for interpretative criteria [16]. MIC_{50} and MIC_{90} of all antibiotics studied were also determined. Cefinase test (bioMérieux, Marcy l'Etoile, France) was used to detect β-lactamase. Multidrug resistance (MDR) definition was adopted as reported [17]. *E. faecalis* ATCC 29212 strain was used for quality control.

Genotyping of vancomycin-resistance genes

Genotyping for the detection of *vanA*, *vanB* and *vanC-1/2* resistance genes was performed for 21 strains by PCR reverse hybridization using the GenoType *Enterococcus* assay (Hain Lifescience, Nehren, Bade-Wurtemberg, Germany) as recommended by the manufacturer. For the remaining 27 strains, this research was carried out by the van multiplex PCR assay as previously described [14]. Quality control strains used were: *E. faecium* BM4107 (susceptible), *E. faecium* BM4147 (*vanA*), *E. faecalis* V583 (*vanB*) and *E. gallinarum* BM4174 (*vanC1*).

Multilocus sequence typing

Molecular typing of five clinical isolates targeted on the basis of one strain by region (north-central: Algiers and Tipaza, eastern: Constantine and Batna, and western: Oran was determined by multilocus sequence typing (MLST) using internal fragments from seven housekeeping genes (*atpA*, *ddl*, *gdh*, *purK*, *gyd*, *pstS* and *adk*) [18].

The allelic profiles and sequence type (ST) designations were identified in the online PubMLST database (http://pubmlst.org/efaecium/). Global eBURST implemented by PHYLOViZ was used to analyze the genetic relationship of the six studied strains and those of all the CC17 referenced strains deposited in the *E. faecium* PubMLST database on December 31, 2019.

Results

Description of patients' characteristics

From September 2010 to April 2017, 48 non-repetitive VREfm strains were isolated from inpatients in several Algerian hospitals. Thirty seven (77.1%) patients were infected and 11 (22.9%) were colonized with VREfm strains. The median age was 40 years and the gender ratio (male/female) was 1.2.

VREfm strains were more frequently recovered from intensive care units (ICUs) (n = 24; 50.0%) and haematology ward (n = 15; 31.2%), and were isolated mostly from blood (n = 15; 33.3%) and urinary tract (n = 10; 20.8%) and abscesses (n = 7; 14.6%).

Analysis of underlying diseases showed serious illnesses, mostly haematological malignancy (n = 15; 31.2%), digestive diseases, immunosuppressive chemotherapy and polytrauma (n = 5; 10.4% for each one of these illnesses).

Prior antibiotic therapy was mainly glycopeptides (n = 16; 33.3%), third generation cephalosporins (n = 14; 29.2%), aminoglycosides and carbapenems (n = 13; 27.1% for each one of these antibiotic families). Deaths were recorded among 14 (29.2%) patients. Detailed characteristics of patients infected with VREfm strains are presented in Table 1.

Antimicrobial susceptibility and genotyping of vancomycin-resistance genes

All the 48 strains belonged to the *vanA* genotype and showed high level of resistance to vancomycin (MICs 32-256 µg/ml) and teicoplanin (MICs 16-256 µg/ml). The *vanB* and *vanC1/2* genotypes have not been detected in any strain. In addition, all the strains were resistant to ampicillin without production of β-lactamase. All the strains were MDR and were resistant to at least five classes of antimicrobial agents, in addition to glycopeptides. High levels of resistance (rates higher than 80%) was recorded to erythromycin, quinupristin-dalfopristin, rifampicin, levofloxacin, high-level gentamicin and high-level streptomycin. Resistance to tetracycline and fosfomycin was 66.6% and 77.1% respectively. However, tigecycline, daptomycin and chloramphenicol exhibited good activity against VREfm strains with MICs ≤ 0.25 µg/ml, ≤ 3 µg/ml and ≤ 8 µg/ml respectively. Nitrofurantoin showed moderate activity with MIC_{50} at 32 µg/mL. The antimicrobial resistance rates with MIC_{50} and MIC_{90} are shown in Table 2.

Multilocus sequence typing

Of the five isolates studied, four isolates (from Algiers, Tipaza, Constantine and Oran) were assigned to ST80 and one isolate, from Batna, belonged to ST789. Moreover, the comparative eBURST analysis with the all CC17 referenced strains deposited in the *E. faecium* PubMLST database showed that ST80 and ST789 derived from ST117 and ST17 respectively, both originated from the former hospital-adapted clonal complex CC17 (Table 3).

Discussion

The widespread of VRE is a serious issue in healthcare settings of various countries around the world. In Algeria, the first VRE strain was isolated since 2010. To date, only two papers have reported the emergence of this highly resistant pathogen, one case from Algiers and four cases from Batna [19, 20]. To the

Table 1. Demographic data and medical conditions of patients infected with VREfm.

Characteristics	VREfm (n=48)
Demographic data	
Age (y), mean (range)	40 (< 1-86)
Male/Female, sex ratio	26/22, 1.2
Underlying diseases, n (%)	
Haematological malignancy	15 (31.2)
Medullar aplasia	4 (8.3)
Immunosuppressive chemotherapy	5 (10.4)
Digestive diseases	5 (10.4)
Neurological diseases	3 (6.2)
Immune deficiency	1 (2.1)
Diabetes	2 (4.2)
Renal failure	1 (2.1)
Respiratory diseases	3 (6.2)
Cerebrovascular accident	1 (2.1)
Extensive burns	2 (4.2)
Bone diseases	3 (6.2)
Polytrauma	5 (10.4)
Cardiovascular diseases	2 (4.2)
Other serious diseases	6 (12.5)
Not available	6 (12.5)
Clinical outcome, n (%)	
Mortality rate	14 (29.2)
Not available	19 (39.6)
Prior antibiotic therapy, n (%)	
Third generation cephalosporins	14 (29.2)
Fluoroquinolones	5 (10.4)
Aminoglycosides	13 (27.1)
Carbapenems	13 (27.1)
Glycopeptides	16 (33.3)
Metronidazole	8 (16.7)
Not available	18 (37.5)
Isolation site, n (%)	
Blood	16 (33.3)
Wound	6 (12.5)
Urinary tract	10 (20.8)
Abscesses	7 (14.6)
Redon	1 (2.1)
Stools	5 (10.4)
Rectal swab	3 (6.2)
Clinical interpretation, n (%)	
Infection	37 (77.1)
Colonization	11 (22.9)
Clinical wards, n (%)	
Intensive care unit	24 (50)
Haematology	15 (31.2)
Nephrology	1 (2.1)
Internal medicine	2 (4.2)
Orthopedics	3 (6.2)
Cardiology	1 (2.1)
Surgery	1 (2.1)
Oncology	1 (2.1)

Table 2. MIC_{50}, MIC_{90}, MIC range and antimicrobial resistance of VREfm isolates.

Antimicrobial agent	MIC_{50}	MIC_{90}	MIC range	Resistant strains Number (%)
Vancomycin	256	256	32-256	48 (100)
Teicoplanin	32	256	12-256	48 (100)
Ampicillin	128	256	24-256	48 (100)
High-level gentamicin	1024	1024	1.5-1024	41 (85.4)
High-level streptomycin	1024	1024	0.19-1024	45 (93.7)
Erythromycin	256	256	0.25-256	47 (97.9)
Quinupristin-dalfopristin	6	16	1-32	40 (83.3)
Levofloxacin	32	32	2-32	45 (93.7)
Tetracycline	32	96	0.016-256	32 (66.6)
Rifampicin	32	32	0.006-32	46 (95.8)
Nitrofurantoin	32	128	8-512	23 (47.9)
Fosfomycin	128	1024	24-1024	37 (77.1)
Chloramphenicol	3	8	1-12	4 (8.3)
Tigecycline	0.094	0.125	0.016-0.25	0 (0.0)
Daptomycin	2	3	1-3	0 (0.0)

best of our knowledge, we describe for the first time the microbiological, epidemiological and molecular characteristics of VREfm involved in HAIs from several regions of Algeria.

Description of patients' characteristics

In total, 48 VREfm clinical isolates, collected from September 2010 to April 2017, were confirmed as VRE. Virtually most of them were from adults hospitalized in ICUs and haematology ward, and were isolated from blood and urinary tract specimens as also noted globally [3, 21-23]. Simirarly to several reports [3, 21-24], most VREfm strains were isolated in patients with co-morbidities or immunosupression, including haematological malignancy, digestive diseases, polytrauma and immunosupressive chemotherapy.

Nearly 23% (n = 11) of patients were colonized with VREfm strains. The most common clinical impact of VRE strains is intestinal colonization that can persist for long periods. Colonized patients are potential reservoirs for transmission of VRE strains [1]. Epidemic potential recognized for VRE strains explains their rapid diffusion [1, 2]. The lack of rapid and accurate screening of patients infected or colonized with VRE strains in admission to the hospital in our country contributes to this dissemination.

Colonization or infection due to VRE strains is recognized to be associated with therapeutic use of glycopeptides, broad-spectrum cephalosporins, anti-anaerobes and quinolones [2,4,13]. In Algeria, vancomycin was introduced for therapeutic use since 1998; a study on the antibiotics consumption carried out in several hospitals of the Central and Eastern Algeria in 2009 showed a high vancomycin use in ICUs (66.9%) and haematology ward (28.1%) [25]. Likewise, our results showed that glycopeptides and third generation cephalosporins were the main prior antimicrobial agents used. The mortality rate was high (29.2%) as reported by other studies [3,13].

Antimicrobial susceptibility and genotyping of vancomycin-resistance genes

Simirarly to numerous studies, that reported the prevalence of *vanA* genotype [2-4,13], all strains in our study harbored the *vanA* gene and showed high-level resistance to vancomycin (MICs 256 µg/mL) and teicoplanin (MICs 16-256 µg/mL) which are characteristic of VanA phenotype [4,10,13].

All strains showed high level of resistance to ampicillin (CMI_{50} at 128µg/mL) with no production of β-lactamase. It has been shown in several reports that an increase in the detection of ampicillin-resistant *E. faecium* precedes the emergence of VREfm and is most frequently due to the over production of penicillin binding protein 5 [2, 4, 13]. In fact, high resistance rate to ampicillin (95%) among vancomycin-susceptible *E.*

Table 3. Sequence type and clonal complex of the five VREfm isolates.

Number of isolates	Clonal complex	Sequence type	Allelic profile*	Van type	Ward	Source	Geographical origin
4	CC17	ST80	9-1-1-1-12-1-1	*vanA*	ICU, surgery	Blood, urine, wound	Algiers, Tipaza, Constantine, Oran
1	CC17	ST789	1-1-1-1-12-1-1	*vanA*	Haematology	Blood	Batna

*In the order: *atpA, ddl, gdh, purK, gyd, pstS, adk*; ICU: intensive care unit.

faecium strains isolated in 2010 have reported in a hospital of eastern Algeria [24].

Almost all strains were resistant to erythromycin, quinupristin-dalphopristin, high-level gentamicin, high-level streptomycin, levofloxacin, tetracycline, rifampicin and fosfomycin. In addition to their natural resistance to cephalosporins and low concentrations of aminoglycosides, the ability of *enterococci* to acquire resistance to other antibiotics is recognized, which is often supported by the same mobile genetic element harboring multiple resistance genes [2, 4, 13]. The multidrug-resistance of VREfm strains is prevalent as reported in several parts of the world [2-4, 7-10, 13] and recently in North Africa (including Tunisia and Egypt) [26-29].

The MDR *E. faecium* is a major concern, as it substantially limited the therapeutic options and poses a great challenges for treatment. Treatment options for VRE include tigecycline, linezolid, daptomycin, quinupristin-dalphopristin, nitrofurantoin and fosfomycin [2, 3, 10, 21, 30, 31]. Interestingly, our results showed good antibacterial activity of tigecycline and daptomycin against VREfm strains. A good activity against VREfm was also noted for chloramphenicol, which can represent a potential therapeutic option [1, 32]. However, high resistance rates to quinupristin/dalphopristin (83%) and fosfomycin (77%) were recorded among VREfm strains. In addition, linezolid and daptomycin are not yet approved in Algeria, leading to more difficulties in the management of patients infected with VREfm.

Multilocus sequence typing

The two STs (ST80 and ST789) found in the five VREfm strains belonged to the widespread adapted-hospital clonal complex CC17. Furthermore, this clonal complex was mostly reported among vancomycin-susceptible *E. faecium* strains isolated in 2012 and 2016 in north-eastern regions of Algeria [24,33].

The four VREfm strains from several regions (Algiers, Tipaza, Constantine and Oran) belonged to ST80, suggesting the spread of this subgroup in Algerian hospitals. The ST80, previousely reported in some European countries (including Germany and Danemark) [34, 35] and in Tunisia [27, 28] was also reported in 2012 among vancomycin-susceptible *E. faecium* strains from Annaba hospital [24] and recently in 2018 among three VREfm isolated in Batna hospital [20].

One strain from Batna belonged to ST789, which first identified in South Korea (https://pubmlst.org/efaecium/). Interestingly, this sequence type was also reported in 2018 in Batna [20].

Conclusions

In conclusion, on the basis of our findings, the dissemination of MDR *E. faecium vanA* and the presence of ST80/CC17 in several regions of Algeria is alarming and suggest a clonal spread of the strains. Rational use of vancomycin and broad-spectrum antibiotics, systematically rapid and accurate screening of patients at the admission to hospital and implementation of early adequate infection control measures are urgently required to restrict the spread of this highly resistant species. Further molecular investigations are needed to better understand the epidemiology of circulating VREfm strains in Algeria and to improve infection control policies.

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References

1. Murray BE (2000) Vancomycin-resistant enterococcal infections. N Engl J Med 342: 710-721.
2. Cattoir V, Leclercq R (2013) Twenty-five years of shared life with vancomycin-resistant Enterococci: is it time to divorce? J Antimicrob Chemother 68: 731–742.
3. Raza T, Ullah SR, Mehmood K, Andleeb S (2018) Vancomycin resistant eterococci: A brief review J Pak Med Assoc 68: 768-772.
4. Ahmed MO, Baptiste KE (2018) Vancomycin-resistant eterococci: A review of antimicrobial resistance mechanisms and perspectives of human and animal health. Microb Drug Resist 24: 590-606.
5. World Health Organizaion (WHO) (2017) Global priority list of antibiotic-resistant bacteria to guide research, discovery, and

development of new antibiotics. 27 February. Available: https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf. https://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/. Accessed 19 December 2019.
6. Hiramatsu K, Kayayama Y, Matsuo M, Aiba Y, Saito M, Hishinuma T, Iwamoto A (2014) Vancomycin-intermediate resistance in *Staphylococcus aureus*. J Glob Antimicrob Resist 2: 213-224.
7. Arias CA, Murray BE (2012) The rise of the *Enterococcus*: beyond vancomycin resistance. Nat Rev Microbiol 10: 266–278.
8. European Centre for Disease Prevention and Control (ECDC) (2019) Surveillance of antimicrobial resistance in Europe 2018. Stockholm. Available at https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2018. Accessed 19 December 2019.
9. Monteserina N, Larson E (2016) Temporal trends and risk factors for healthcare-associated vancomycin-resistant enterococci in adults. J Hosp Infect. 94(3): 236–241.
10. Yang J, Yuan Y, Tanga M, Liu L, Yang K, Liu J (2019) Phenotypic and genetic characteristics of vancomycin-resistant *Enterococcus faecium*. Microb Pathog 128: 131-135.
11. Algerian Antimicrobial Resistance Network (AARN) (2016) 15th evaluation report. ANDS Editions 150 p. [Report in French]
12. Algerian Antimicrobial Resistance Network (AARN) (2018) 18th evaluation report. ANDS Editions 157 p. [Report in French].
13. Terence L, Pang S, Abrahama S, Coombs GW (2019) Antimicrobial-resistant CC17 *Enterococcus faecium*: The past, the present and the future. J Glob Antimicrob Resist. 16: 36–47.
14. Depardieu F, Perichon B, Courvalin P (2004) Detection of the *van* Alphabet and Identification of Enterococci and Staphylococci at the Species Level by Multiplex PCR. J Clin Microbiol. 42: 5857-5860.
15. Clinical and Laboratory Standards Institute (CLSI) (2019) Performance Standards for Antimicrobial Susceptibility Testing. 29th ed. CLSI supplement M100. Wayne, PA.
16. European Committee on Antimicrobial Susceptibility Testing (EUCAST) (2020) Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0. Available at http://www.eucast.org. Accessed 19 December 2019.
17. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL (2012) Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 18: 268–281.
18. Homan WL, Tribe D, Poznanski S, Li M, Hogg G, Spalburg E, Van Embden JD, Willems RJ (2002) Multilocus Sequence Typing Scheme for *Enterococcus faecium*. J Clin Microbiol 40: 1963-1971.
19. Hamidi M, Ammari H, Ghaffor M, Benamrouche N, Tali Maamar H, Tala-Khir F, Younsi M, Rahal K (2013) Emergence of glycopeptide resistant *Enterococcus faecium* in Algeria: a case report. Ann Biol Clin 71: 104-106. [Available in French].
20. Benammar S, Pantel A, Aujoulat F, Benmehidi M, Courcol R, Lavigne JP, Romano-Bertrand S, Marchandin H (2018) First molecular characterization of related cases of healthcare-associated infections involving multidrug-resistant *Enterococcus faecium vanA* in Algeria. Infect Drug Resist 11: 1483–1490.
21. O'Driscoll T, Crank CW (2015) Vancomycin-resistant enterococcal infections: epidemiology, clinical manifestations, and optimal management. Infect Drug Resist 8: 217–230.
22. Fossi DL, Hodille E, Chomat-Jaboulay S, Coudrais S, De Santis N, Gardes S, Mauranne CC, Mourey N, Fredenucci I, Girard R (2017) Factors associated with vancomycin-resistant *Enterococcus* acquisition during a large outbreak. J Infect Public Health. 10: 185–190.
23. Kirdar S, Sener AG, Arslan U, Yurtsever SG (2010) Molecular epidemiology of vancomycin-resistant *Enterococcus faecium* strains isolated from haematological malignancy patients in a research hospital in Turkey. J Med Microbiol 59: 660-664.
24. Djahmi N, Boutet-Dubois A, Nedjai S, Dekhil M, Sotto A, Lavigne JP (2012) Molecular epidemiology of *Enterococcus* sp. isolated in a university hospital in Algeria. Scand J Infect Dis 44: 656–662.
25. Algerian Antimicrobial Resistance Network (AARN) (2010) 12th evaluation report. ANDS Editions 149 p. [Report in French].
26. Abbassi MS, Znazen A, Mahjoubi F, Hammami A, Ben Hassen A (2007) Emergence of vancomycin-resistant *Enterococcus faecium* in Sfax: clinical features and molecular typing. Med Mal Infect 37: 240–243.
27. Elhani D, Klibi N, Dziri R, Ben Hassan M, Asli MS, Ben Said L, Aouini M, Ben Slama K, Jemli B, Bellaj R, Barguellil F, Torres C (2014) *vanA*-containing *E. faecium* isolates of clonal complex CC17 in clinical and environmental samples in a Tunisian hospital. Diagn Microbiol. Infect Dis 79: 60–63.
28. Dziri R, El Kara F, Barguellil F, Ouzari HI, El Asli MS, Klibi N (2019) Vancomycin-Resistant *Enterococcus faecium* in Tunisia: Emergence of Novel Clones. Microb Drug Resist 25: 469-474.
29. Shehta H, Eman S, Abdelmegeed S (2019) Emergence of multidrug resistance and extensive drug resistance among enterococcal clinical isolates in egypt. Infect Drug Resist 12: 1113–1125.
30. Sadera HS, Moeta GJ, Farrella DJ, Jones RN (2011) Antimicrobial susceptibility of daptomycin and comparator agents tested against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: trend analysis of a 6-year period in US medical centers (2005–2010). Diag Microbiol Infect Dis 70: 412-416.
31. Bouchillon SK, Iredell JI, Barkham T, Leed K, Dowzickye MJ (2009) Comparative in vitro activity of tigecycline and other antimicrobials against Gram-negative and Gram-positive organisms collected from the Asia-Pacific Rim as part of the Tigecycline Evaluation and Surveillance Trial (TEST). Inter J Antimicrob Agents 33:130-136.
32. Ricaurtea, J.C., H.W. Boucherb, G.S. Turetta, R.C. Moelleringb, V.J. LaBombardia, J.W. Kislak (2001) Chloramphenicol treatment for vancomycin-resistant *Enterococcus faecium* bacteremia. Clin Microbiol Infect 7: 17-21.
33. Bourafa N, Abat C, Loucif L, Olaitan AO, Bentorki AA, Boutefnouchet N, Rolain JM (2016) Identification of vancomycin-susceptible major clones of clinical *Enterococcus* from Algeria. J Glob Antimicrob Resist 6: 78–83.

34. Liese J, Schüle L, Oberhettinger P, Tschörner L, Nguyen T, Dörfel D, Vogel W, Marschal M, Autenrieth I, Willmann M, Peter S (2019) Expansion of vancomycin-resistant *Enterococcus faecium* in an academic tertiary hospital in southwest Germany: a large-scale whole-genome-based outbreak investigation. Antimicrob Agents Chemother. 63: e01978-18.
35. Hammerum AM, Sharmin B, Kamel Y, Roer L, Pinholt M, Gumpert H, Holzknecht B, Røder B, Justesen US, Samulioniene J, Kjærsgaard M, Østergaard C, Holm A, Dzajic E, Søndergaard TS, Gaini S, Edquist P, Alm E, Lilje B, Westh H, Stegger M, Hasman H (2017) Emergence of *vanA Enterococcus faecium* in Denmark, 2005–15. J Antimicrob Chemother. 72: 2184–2190.

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