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MINIREVIEWS

Origin of *de novo* daptomycin non susceptible enterococci

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Abstract

The emergence of daptomycin non-susceptible enterococci (DNSE) poses both treatment and infection control challenges. Clinicians should be vigilant that DNSE may be isolated from patients with or without (*de novo* DNSE) prior use of daptomycin. Recent epidemiological data suggest the presence of a community reservoir for DNSE which may be associated with environmental, foodborne and agricultural exposures. The mechanisms of nonsusceptibility to daptomycin have not been well characterized and may not parallel those for *Staphylococcus aureus*. The identification of daptomycin resistance genes in anaerobes, in farm animals and in an ecosystem that has been isolated for million years, suggest that the environmental reservoir for *de novo* DNSE may be larger than previously thought. Herein, the limited available scientific evidence regarding the possible origin of *de novo* DNSE is discussed. The current existing evidence is not sufficient to draw firm conclusions on the origin of DNSE. Further studies to determine the mechanisms of *de novo* daptomycin nonsusceptibility among enterococci are needed.

Key words: Daptomycin non-susceptible enterococci; Antimicrobial resistance; Environmental reservoir

Core tip: Daptomycin non-susceptible enterococci (DNSE) is an emerging clinical problem and may be isolated from patients with or without (*de novo* DNSE) prior exposure to daptomycin. Recent epidemiological data suggest the presence of a community reservoir for DNSE which may be associated with environmental, foodborne and agricultural exposures and may be larger than previously thought. Herein, the limited available scientific evidence regarding the possible origin of *de novo* DNSE is discussed. Further studies to determine the mechanisms of *de novo* daptomycin nonsusceptibility among enterococci are needed.

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INTRODUCTION

Antibiotic resistance is a major threat to human health[1]. Multidrug-resistant organisms such as vancomycin-resistant enterococci (VRE) may increase morbidity and mortality[1]. Daptomycin has bactericidal activity against VRE. However, daptomycin non-susceptible enterococci

(DNSE) are difficult to treat and clinicians often have limited treatment options[2]. Enterococci with daptomycin MIC > 4 μg/mL are non-susceptible, according to the Clinical Laboratory Standards Institute[3] and the Food and Drug Administration[4]. Although most DNSE isolates develop after daptomycin therapy they have also emerged in subjects with no prior use of daptomycin[5]. Elucidating the origin of *de novo* DNSE infections may help us understand mechanisms of daptomycin non-susceptibility. Herein, the available scientific evidence regarding the possible origin of *de novo* DNSE is reviewed.

OVERALL PREVALENCE OF DNSE IS LOW

Despite initial *in vitro* studies that emergence of DNSE is rare[3,6-10], recent studies suggest that DNSE is an emerging infection[2]. In large surveys of clinical isolates less than 0.6% of *Enterococcus faecalis* (*E. faecalis)* or *E. faecium* isolates were DNSE[11-15]. However, there is lack of data on daptomycin non-susceptible enterococcus isolates from international and national programs[2]. In a recent literature review, DNSE were present in 0.6% of all enterococci isolates (range 0%-19.1%)[2] and out of 150 DNSE isolates, 93.3% were vancomycin resistant enterococci (VRE), 6.0% were vancomycin susceptible enterococci (VSE), 88% were *E. faecium* and 8.7% were *E. faecalis*[2]. Most DNSE isolates were reported in Asia (40.3%) and in Europe (34%) while 26% of isolates were reported in North America[2]. Reporting bias, use of different susceptibility testing method among clinical microbiology laboratories such as MicroScan and presence of clones may overestimate the detection of DNSE[16-21]. Thus, the overall prevalence of DNSE was low.

MECHANISMS OF EMERGENCE OF DAPTOMYCIN RESISTANCE IN ENTEROCOCCI ARE COMPLEX

The mechanisms for daptomycin nonsusceptibility in enterococci are different than in staphylococci and are poorly-understood[22-30]. Whole-genome sequencing of DNSE[30-34] suggest that few genetic mutations may be adequate to induce daptomycin non-susceptibility. Compared to their susceptible counterparts DNSE isolates have mutations in stress response regulators (such as the LiaFSR, yycG and YybT regulatory systems)[29-39], phospholipid composition regulators [such as cardiolipin synthase (Cls), glycerophosphoryl diester phosphodiesterase (GdpD), cyclopropane fatty acid synthase (Cfa)][27-33,40], and phenotypic changes such as reduced cell membrane fluidity[28,30,31,41] and increased septation (*via* Ezr A)[30,31].

DNSE may develop without prior use of daptomycin

Spontaneous emergence of daptomycin non susceptibility *in vitro* is rare[24]. Although DNSE usually emerge in the setting of daptomycin therapy[2] DNSE have also been identified in subjects without prior use of daptomycin[5] and daptomycin use may not be a risk factor for DNSE in a case control study[42]. The risk factors related to emergence of *de novo* DNSE remain unclear.

FACTORS THAT ARE ASSOCIATED WITH DEVELOPMENT OF DNSE

Host factors related to isolation of DNSE

In a review of DNSE isolates, the source patients were 54.6 years on an average and 62.5% of them were female[2]. Factors that may contribute to emergence of DNSE include a source of DNSE infection such as abscess[2], an intra-abdominal pathological process, recent surgery, a lengthy exposure to daptomycin[43,44], immunosuppression and pharmacokinetics[43] and suboptimal drug levels among patients with end stage renal disease[45-47]. Observations from a case report suggested that chronic severe hypocalcemia in one patient may have contributed to the even lower calcium levels at the nidus of DNSE infection (abscesses)[32], which may precipitate a loss of daptomycin activity[48]. Thus, DNSE may occur in the context of the above disorders and only few mutations may occur in DNSE[32].

Antimicrobial exposure may also be a risk factor for emergence of DNSE

Recent case controls studies with DNSE isolates have identified that many risk factors for emergence of VRE, including recent antimicrobial exposure, and increased hospitalization, were also present in the majority of DNSE cases[49]. Recent use of vancomycin, cephalosporins, or antibiotics active against anaerobes is associated with isolation of both VRE and DNSE[49]. VRE often causes colonize the colon[50,51] and vancomycin resistant[52] and daptomycin resistant gut anaerobes have been identified[53]. Resistance to vancomycin in gram-positive bacteria did not affect daptomycin activity[54]. Finally, multiple comorbidities, immunosuppression, and prior exposures to antimicrobials such as metronidazole and cephalosporins were independently associated with the isolation of DNSE (VRE) in a recent study[42].

Exposure to daptomycin has may contribute to emergence of DNSE especially in the setting of end stage renal disease

Although previous studies suggest that daptomycin resistance develops during treatment, MICs for daptomycin were often not reported[2]. In a review of DNSE isolates, the dose and duration of daptomycin that was administered prior to isolation of DNSE[2]. In one study, daptomycin-exposed DNSE patients received an

average of 44.9 d of daptomycin therapy[49]. Patients with end stage renal disease have lower C_{max} for daptomycin compared to healthy subjects[55] and the concentrations of daptomycin used in these patients may be relatively low[55-58]. Thus, more research should determine the optimal dosage and frequency of daptomycin administration in patients with end stage renal disease[43,44] since enterococci may become DNSE rapidly[32].

FACTORS RELATED TO ISOLATION OF *DE NOVO* DNSE

Limited data suggest that host factors are not known to be related to isolation of de novo DNSE

We found no significant differences in terms of age, sex and underlying immunosuppressive illnesses between patients with *de novo* DNSE infections and DNSE infections following exposure to daptomycin[49].

Environmental factors related to emergence of de novo DNSE

In our series, 45% of patients with DNSE had no prior use of daptomycin and clonally-related DNSE were isolated in patients with no prior hospitalization[49] suggesting an environmental reservoir of DNSE[5]. Shorter duration of hospitalization, less frequent exposure to antimicrobials associated with isolation of VRE, were associated with *de novo* DNSE infection[49] but since DNSE may persist for years[59], nosocomial acquisition of DNSE is possible. Factors that may contribute to formation of an environmental reservoir of DNSE include exchange of genetic material between enterococci, soil bacteria and bacteria of animal origin, foodborne origin of DNSE and agricultural exposures of humans to DNSE.

Transfer of genes that determine antimicrobial resistance between soil bacteria and DNSE may contribute to emergence of de novo DNSE

Daptomycin resistance genes were found in bacteria from an ancient ecosystem[60]. Soil actinomycetes may inactivate daptomycin[6,61] and we have also identified found mutations in DNSE isolates in genes that are also present in soil bacteria[31]. Soil bacteria and enterococci may exchange genetic material[62]. However in another study, mechanisms of inactivation of daptomycin found in soil bacteria were not identified in DNSE *E. faecium*[22]. Thus, it remained to be elucidated whether the interplay between soil bacteria and enterococci may contribute to emergence of DNSE.

Bacteria in animals may mediate acquired daptomycin resistance in enterococci

Humans and animals may exchange daptomycin resistance genes and this may lead to emergence of *de novo* DNSE[63]. The gut of humans and most animals harbors enterococci and VRE can spread from farm animals[64,65]. Enterococci of animal origin may transfer antimicrobial resistance genes to other enterococci[66]. Recombination between repetitive nucleotide sequences[30] that may encode resistance cassettes in enterococci[62,64,65] may contribute to emergence of DNSE. Finally, we also found similar nucleotide mutations in genes that are common between DNSE and bacteria found in poultry[31,67-69].

Limited data suggest that DNSE infections in humans may be foodborne

DNSE may have passed to humans *via* ingestion of meat[5]. Up to 25% of enterococci isolated from beef were DNSE[65]. Daptomycin resistant Enterococci were recently identified in cows[70]. *E. faecalis* may harbor resistance genes and can be passed to humans through meat consumption[71]. Poultry might be a source for *E. faecalis* infections[72] and may harbor *E. gallinarum*[73] which may also be daptomycin non-susceptible[49]. Similarly, all three *de novo* urine DNSE isolates, were *E. faecalis,* may cause zoonosis[74]. In our study 4/9 (44.4%) subjects with *de novo* DNSE infections reported consumption of beef[5]. Thus, it remains to be shown whether DNSE may be foodborne pathogenes[5,65].

Limited data from epidemiological studies and case series suggest that DNSE may have a zoonotic potential

Humans who are exposed to farm animals may be at risk increase to be colonized with multidrug resistant bacteria[75]. We found that in contrast to patients with daptomycin-exposed DNSE, the majority (78%) of *de novo* DNSE infections lived in areas with increased prevalence of agricultural exposures[76]. In our study of *de novo* DNSE infections 33.3% of patients had prior exposure to farm animals[5]. Thus, further epidemiological studies need to confirm if it is possible that exposure of humans to farm animals may increase the risk for isolation of DNSE[63].

Limited data from observational studies suggest that transfer of genes that determine antimicrobial resistance between anaerobes and DNSE may contribute to emergence of de novo DNSE

Enterococci and anaerobes are gastrointestinal tract flora in humans and may exchange antibiotic resistance genes[77,78]. Mutations in phospholipid biosynthesis and lac operon expression exist in facultative anaerobic[79] and anaerobic bacteria[80] may also lead to emergence of DNSE[30,34]. In addition, the use of antibiotics with activity against anaerobes may increase the spread of VRE and DNSE[81] while recent use of metronidazole may be a risk factor for emergence of DNSE[42]. Use of prior antibiotics with activity against anaerobes was found less in patients with *de novo* DNSE compared to daptomycin-exposed patients with DNSE infection[49]. Finally, daptomycin nonsusceptibility has been

described in anaerobes[53]. Thus, further studies need to confirm that the cross talk among anaerobic bacteria and enterococci may contribute to dissemination of DNSE[82].

CONCLUSION

Treatment of DNSE infections is a challenge for clinicians. Daptomycin non-susceptible enterococcal strains may develop after exposure to daptomycin. Since DNSE are usually isolated from patients with many comorbidities such as immunocompromised and end stage renal disease patients, strict infection control and prudent use of daptomycin are needed for these patients to limit the emergence and spread of DNSE.

However, DNSE may emerge without prior use of daptomycin. Recent epidemiological data suggest the presence of a community reservoir for DNSE which may be associated with environmental, foodborne and agricultural exposures. The mechanisms of development of daptomycin resistance remain unclear. The identification of daptomycin resistance genes in an ancient ecosystem[60], in anaerobes[53] and in farm animals[70] suggest that the environmental reservoir for *de novo* DNSE may be larger than previously thought. In most of the studies with reported DNSE isolates complete medical records were not reviewed and interview of patients was not performed and thus potentially relevant occupational or dietary exposures among patients with DNSE were not identified. Epidemiological investigations focused on environmental exposures in the community may help elucidate the origin of *de novo* DNSE. Further studies to identify the mechanisms of *de novo* daptomycin nonsusceptibility in enterococci are needed.

REFERENCES

1 **Eliopoulos GM**. Microbiology of drugs for treating multiply drug-resistant Gram-positive bacteria. *J Infect* 2009; **59** Suppl 1: S17-S24 [PMID: 19766885 DOI: 10.1016/S0163-4453]

2 **Kelesidis T**, Humphries R, Uslan DZ, Pegues DA. Daptomycin nonsusceptible enterococci: an emerging challenge for clinicians. *Clin Infect Dis* 2011; **52**: 228-234 [PMID: 21288849 DOI: 10.1093/cid/ciq113]

3 **Clinical and Laboratory Standards Institute**. Performance standards for antimicrobial susceptibility testing; Twentieth Informational Supplement [assessed 2012 Jan]. Available from: URL: http://antimicrobianos.com.ar/ATB/wp-content/uploads/2012/11/M100S22E.pdf

4 **Humphries RM**, Pollett S, Sakoulas G. A current perspective on daptomycin for the clinical microbiologist. *Clin Microbiol Rev* 2013; **26**: 759-780 [PMID: 24092854 DOI: 10.1128/CMR.00030-13]

5 **Kelesidis T**, Humphries R, Uslan DZ, Pegues D. De novo daptomycin-nonsusceptible enterococcal infections. *Emerg Infect Dis* 2012; **18**: 674-676 [PMID: 22469288 DOI: 10.3201/eid1804.110932]

6 **Debono M**, Abbott BJ, Molloy RM, Fukuda DS, Hunt AH, Daupert VM, Counter FT, Ott JL, Carrell CB, Howard LC. Enzymatic and chemical modifications of lipopeptide antibiotic A21978C: the synthesis and evaluation of daptomycin (LY146032). *J Antibiot* (Tokyo) 1988; **41**: 1093-1105 [PMID: 2844711 DOI: 10.7164/antibiotics.41.1093]

7 **Carpenter CF**, Chambers HF. Daptomycin: another novel agent for treating infections due to drug-resistant gram-positive pathogens. *Clin Infect Dis* 2004; **38**: 994-1000 [PMID: 15034832 DOI: 10.1086/383472]

8 **Debbia E**, Pesce A, Schito GC. In vitro activity of LY146032 alone and in combination with other antibiotics against gram-positive bacteria. *Antimicrob Agents Chemother* 1988; **32**: 279-281 [PMID: 2834999 DOI: 10.1128/AAC.32.2.279]

9 **Leclercq R**, Bingen E, Su QH, Lambert-Zechovski N, Courvalin P, Duval J. Effects of combinations of beta-lactams, daptomycin, gentamicin, and glycopeptides against glycopeptide-resistant enterococci. *Antimicrob Agents Chemother* 1991; **35**: 92-98 [PMID: 1849711 DOI: 10.1128/AAC.35.1.92]

10 **Louie A**, Baltch AL, Ritz WJ, Smith RP, Asperilla M. Comparison of in vitro inhibitory and bactericidal activities of daptomycin (LY 146032) and four reference antibiotics, singly and in combination, against gentamicin-susceptible and high-level-gentamicin-resistant enterococci. *Chemotherapy* 1993; **39**: 302-309 [PMID: 8396526 DOI: 10.1159/000239141]

11 **Sader HS**, Moet GJ, Farrell DJ, Jones RN. 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). *Diagn Microbiol Infect Dis* 2011; **70**: 412-416 [PMID: 21546202 DOI: 10.1016/j.diagmicrobio.2011.02.008]

12 **Pfaller MA**, Sader HS, Jones RN. Evaluation of the in vitro activity of daptomycin against 19615 clinical isolates of Gram-positive cocci collected in North American hospitals (2002-2005). *Diagn Microbiol Infect Dis* 2007; **57**: 459-465 [PMID: 17240105 DOI: 10.1016/j.diagmicrobio.2006.10.007]

13 **Sader HS**, Jones RN, Stilwell MG, Dowzicky MJ, Fritsche TR. Tigecycline activity tested against 26,474 bloodstream infection isolates: a collection from 6 continents. *Diagn Microbiol Infect Dis* 2005; **52**: 181-186 [PMID: 16105562 DOI: 10.1016/j.diagmicrobio.2005.05.005]

14 **Sader HS**, Fritsche TR, Streit JM, Jones RN. Daptomycin in vitro activity tested against Gram-positive strains collected from European and Latin American medical centers in 2003. *J Chemother* 2005; **17**: 477-483 [PMID: 16323435 DOI: 10.1179/joc.2005.17.5.477]

15 **Sader HS**, Flamm RK, Jones RN. Antimicrobial activity of daptomycin tested against Gram-positive pathogens collected in Europe, Latin America, and selected countries in the Asia-Pacific Region (2011). *Diagn Microbiol Infect Dis* 2013; **75**: 417-422 [PMID: 23514757 DOI: 10.1016/j.diagmicrobio.2013.01.001]

16 **Wang JT**, Chen YC, Chang SC, Chen ML, Pan HJ, Chang YY, Sun CC, Wang LH, Wang SH, Lin HC, Chien SF, Tseng MS. Control of vancomycin-resistant enterococci in a hospital: a five-year experience in a Taiwanese teaching hospital. *J Hosp Infect* 2004; **58**: 97-103 [PMID: 15474179 DOI: 10.1016/j.jhin.2004.06.005]

17 **Edelsberg J**, Weycker D, Barron R, Li X, Wu H, Oster G, Badre S, Langeberg WJ, Weber DJ. Prevalence of antibiotic resistance in US hospitals. *Diagn Microbiol Infect Dis* 2014; **78**: 255-262 [PMID: 24360267 DOI: 10.1016/j.diagmicrobio.2013.11.011]

18 **Biedenbach DJ**, Bell JM, Sader HS, Fritsche TR, Jones RN, Turnidge JD. Antimicrobial susceptibility of Gram-positive bacterial isolates from the Asia-Pacific region and an in vitro evaluation of the bactericidal activity of daptomycin, vancomycin, and teicoplanin: a SENTRY Program Report (2003-2004). *Int J Antimicrob Agents* 2007; **30**: 143-149 [PMID: 17531446 DOI: 10.1016/j.ijantimicag.2007.03.015]

19 **Snydman DR**, McDermott LA, Jacobus NV. Evaluation of in vitro interaction of daptomycin with gentamicin or beta-lactam antibiotics against Staphylococcus aureus and Enterococci by FIC index and timed-kill curves. *J Chemother* 2005; **17**: 614-621 [PMID: 16433191 DOI: 10.1179/joc.2005.17.6.614]

20 **Fluit AC**, Schmitz FJ, Verhoef J, Milatovic D. Daptomycin in vitro susceptibility in European Gram-positive clinical isolates. *Int J Antimicrob Agents* 2004; **24**: 59-66 [PMID: 15225863 DOI:

10.1016/j.ijantimicag.2003.12.014]
21 **Bryant KA**, Roberts AL, Rupp ME, Anderson JR, Lyden ER, Fey PD, Van Schooneveld TC. Susceptibility of enterococci to daptomycin is dependent upon testing methodology. *Diagn Microbiol Infect Dis* 2013; **76**: 497-501 [PMID: 23719086 DOI: 10.1016/j.diagmicrobio.2013.04.019]
22 **Montero CI**, Stock F, Murray PR. Mechanisms of resistance to daptomycin in Enterococcus faecium. *Antimicrob Agents Chemother* 2008; **52**: 1167-1170 [PMID: 18180351 DOI: 10.1128/AAC.00774-07]
23 **Critchley IA**, Blosser-Middleton RS, Jones ME, Thornsberry C, Sahm DF, Karlowsky JA. Baseline study to determine in vitro activities of daptomycin against gram-positive pathogens isolated in the United States in 2000-2001. *Antimicrob Agents Chemother* 2003; **47**: 1689-1693 [PMID: 12709341 DOI: 10.1128/AAC.47.5.1689-1693.2003]
24 **Silverman JA**, Oliver N, Andrew T, Li T. Resistance studies with daptomycin. *Antimicrob Agents Chemother* 2001; **45**: 1799-1802 [PMID: 11353628 DOI: 10.1128/AAC.45.6.1799-1802.2001]
25 **Friedman L**, Alder JD, Silverman JA. Genetic changes that correlate with reduced susceptibility to daptomycin in Staphylococcus aureus. *Antimicrob Agents Chemother* 2006; **50**: 2137-2145 [PMID: 16723576 DOI: 10.1128/AAC.00039-06]
26 **Sakoulas G**, Alder J, Thauvin-Eliopoulos C, Moellering RC, Eliopoulos GM. Induction of daptomycin heterogeneous susceptibility in Staphylococcus aureus by exposure to vancomycin. *Antimicrob Agents Chemother* 2006; **50**: 1581-1585 [PMID: 16569891 DOI: 10.1128/AAC.50.4.1581-1585.2006]
27 **Sakoulas G**, Bayer AS, Pogliano J, Tsuji BT, Yang SJ, Mishra NN, Nizet V, Yeaman MR, Moise PA. Ampicillin enhances daptomycin- and cationic host defense peptide-mediated killing of ampicillin- and vancomycin-resistant Enterococcus faecium. *Antimicrob Agents Chemother* 2012; **56**: 838-844 [PMID: 22123698 DOI: 10.1128/AAC.05551-11]
28 **Mishra NN**, Bayer AS, Tran TT, Shamoo Y, Mileykovskaya E, Dowhan W, Guan Z, Arias CA. Daptomycin resistance in enterococci is associated with distinct alterations of cell membrane phospholipid content. *PLoS One* 2012; **7**: e43958 [PMID: 22952824 DOI: 10.1371/journal.pone.0043958]
29 **Munita JM**, Panesso D, Diaz L, Tran TT, Reyes J, Wanger A, Murray BE, Arias CA. Correlation between mutations in liaFSR of Enterococcus faecium and MIC of daptomycin: revisiting daptomycin breakpoints. *Antimicrob Agents Chemother* 2012; **56**: 4354-4359 [PMID: 22664970 DOI: 10.1128/AAC.00509-12]
30 **Arias CA**, Panesso D, McGrath DM, Qin X, Mojica MF, Miller C, Diaz L, Tran TT, Rincon S, Barbu EM, Reyes J, Roh JH, Lobos E, Sodergren E, Pasqualini R, Arap W, Quinn JP, Shamoo Y, Murray BE, Weinstock GM. Genetic basis for in vivo daptomycin resistance in enterococci. *N Engl J Med* 2011; **365**: 892-900 [PMID: 21899450 DOI: 10.1056/NEJMoa1011138]
31 **Humphries RM**, Kelesidis T, Tewhey R, Rose WE, Schork N, Nizet V, Sakoulas G. Genotypic and phenotypic evaluation of the evolution of high-level daptomycin nonsusceptibility in vancomycin-resistant Enterococcus faecium. *Antimicrob Agents Chemother* 2012; **56**: 6051-6053 [PMID: 22948885 DOI: 10.1128/AAC.01318-12]
32 **Kelesidis T**, Tewhey R, Humphries RM. Evolution of high-level daptomycin resistance in Enterococcus faecium during daptomycin therapy is associated with limited mutations in the bacterial genome. *J Antimicrob Chemother* 2013; **68**: 1926-1928 [PMID: 23580562 DOI: 10.1093/jac/dkt117]
33 **Tran TT**, Panesso D, Gao H, Roh JH, Munita JM, Reyes J, Diaz L, Lobos EA, Shamoo Y, Mishra NN, Bayer AS, Murray BE, Weinstock GM, Arias CA. Whole-genome analysis of a daptomycin-susceptible enterococcus faecium strain and its daptomycin-resistant variant arising during therapy. *Antimicrob Agents Chemother* 2013; **57**: 261-268 [PMID: 23114757 DOI: 10.1128/AAC.01454-12]
34 **Palmer KL**, Daniel A, Hardy C, Silverman J, Gilmore MS. Genetic basis for daptomycin resistance in enterococci. *Antimicrob Agents Chemother* 2011; **55**: 3345-3356 [PMID: 21502617 DOI: 10.1128/AAC.00207-11]
35 **Rice LB**, Carias LL, Rudin S, Hutton R, Marshall S, Hassan M, Josseaume N, Dubost L, Marie A, Arthur M. Role of class A penicillin-binding proteins in the expression of beta-lactam resistance in Enterococcus faecium. *J Bacteriol* 2009; **191**: 3649-3656 [PMID: 19304851 DOI: 10.1128/JB.01834-08]
36 **Zhang X**, Paganelli FL, Bierschenk D, Kuipers A, Bonten MJ, Willems RJ, van Schaik W. Genome-wide identification of ampicillin resistance determinants in Enterococcus faecium. *PLoS Genet* 2012; **8**: e1002804 [PMID: 22761597 DOI: 10.1371/journal.pgen.1002804]
37 **Sakoulas G**, Okumura CY, Thienphrapa W, Olson J, Nonejuie P, Dam Q, Dhand A, Pogliano J, Yeaman MR, Hensler ME, Bayer AS, Nizet V. Nafcillin enhances innate immune-mediated killing of methicillin-resistant Staphylococcus aureus. *J Mol Med* (Berl) 2014; **92**: 139-149 [PMID: 24297496 DOI: 10.1007/s00109-013-1100-7]
38 **Munita JM**, Tran TT, Diaz L, Panesso D, Reyes J, Murray BE, Arias CA. A liaF codon deletion abolishes daptomycin bactericidal activity against vancomycin-resistant Enterococcus faecalis. *Antimicrob Agents Chemother* 2013; **57**: 2831-2833 [PMID: 23507277 DOI: 10.1128/AAC.00021-13]
39 **Miller C**, Kong J, Tran TT, Arias CA, Saxer G, Shamoo Y. Adaptation of Enterococcus faecalis to daptomycin reveals an ordered progression to resistance. *Antimicrob Agents Chemother* 2013; **57**: 5373-5383 [PMID: 23959318 DOI: 10.1128/AAC.01473-13]
40 **Tran TT**, Panesso D, Mishra NN, Mileykovskaya E, Guan Z, Munita JM, Reyes J, Diaz L, Weinstock GM, Murray BE, Shamoo Y, Dowhan W, Bayer AS, Arias CA. Daptomycin-resistant Enterococcus faecalis diverts the antibiotic molecule from the division septum and remodels cell membrane phospholipids. *MBio* 2013; **4**: pii: e00281-13 [PMID: 23882013]
41 **Steed ME**, Vidaillac C, Rose WE, Winterfield P, Kaatz GW, Rybak MJ. Characterizing vancomycin-resistant Enterococcus strains with various mechanisms of daptomycin resistance developed in an in vitro pharmacokinetic/pharmacodynamic model. *Antimicrob Agents Chemother* 2011; **55**: 4748-4754 [PMID: 21788457 DOI: 10.1128/AAC.00084-11]
42 **Judge T**, Pogue JM, Marchaim D, Ho K, Kamatam S, Parveen S, Tiwari N, Nanjireddy P, Bheemreddy S, Biedron C, Reddy SM, Khammam V, Chalana IK, Tumma RS, Collins V, Yousuf A, Lephart PR, Martin ET, Rybak MJ, Kaye KS, Hayakawa K. Epidemiology of vancomycin-resistant enterococci with reduced susceptibility to daptomycin. *Infect Control Hosp Epidemiol* 2012; **33**: 1250-1254 [PMID: 23143365 DOI: 10.1086/668438]
43 **Bubalo JS**, Munar MY, Cherala G, Hayes-Lattin B, Maziarz R. Daptomycin pharmacokinetics in adult oncology patients with neutropenic fever. *Antimicrob Agents Chemother* 2009; **53**: 428-434 [PMID: 19015332 DOI: 10.1128/AAC.00943-08]
44 **Enoch DA**, Bygott JM, Daly ML, Karas JA. Daptomycin. *J Infect* 2007; **55**: 205-213 [PMID: 17629567 DOI: 10.1016/j.jinf.2007.05.180]
45 **Mushatt DM**, Mihm LB, Dreisbach AW, Simon EE. Antibiotic dosing in slow extended daily dialysis. *Clin Infect Dis* 2009; **49**: 433-437 [PMID: 19580416 DOI: 10.1086/600390]
46 **Kielstein JT**, Eugbers C, Bode-Boeger SM, Martens-Lobenhoffer J, Haller H, Joukhadar C, Traunmüller F, Knitsch W, Hafer C, Burkhardt O. Dosing of daptomycin in intensive care unit patients with acute kidney injury undergoing extended dialysis--a pharmacokinetic study. *Nephrol Dial Transplant* 2010; **25**: 1537-1541 [PMID: 20031929 DOI: 10.1093/ndt/gfp704]
47 **Burkhardt O**, Joukhadar C, Traunmüller F, Hadem J, Welte T, Kielstein JT. Elimination of daptomycin in a patient with acute renal failure undergoing extended daily dialysis. *J Antimicrob Chemother* 2008; **61**: 224-225 [PMID: 17965030 DOI: 10.1093/jac/dkm405]
48 **Hanberger H**, Nilsson LE, Maller R, Isaksson B. Pharmacodynamics of daptomycin and vancomycin on Enterococcus faecalis and Staphylococcus aureus demonstrated by studies of initial killing and postantibiotic effect and influence of Ca2+ and albumin on these drugs. *Antimicrob Agents Chemother* 1991; **35**: 1710-1716 [PMID: 1659305 DOI: 10.1128/AAC.35.9.1710]
49 **Kelesidis T**, Chow AL, Humphries R, Uslan DZ, Pegues D. Case-control study comparing de novo and daptomycin-exposed

daptomycin-nonsusceptible Enterococcus infections. *Antimicrob Agents Chemother* 2012; **56**: 2150-2152 [PMID: 22252808 DOI: 10.1128/AAC.05918-11]

50 **Hume ME**, Poole TL, Pultz NJ, Hanrahan JA, Donskey CJ. Inhibition of vancomycin-resistant enterococcus by continuous-flow cultures of human stool microflora with and without anaerobic gas supplementation. *Curr Microbiol* 2004; **48**: 364-367 [PMID: 15060733 DOI: 10.1007/s00284-003-4112-7]

51 **Sun Y**, Smith E, Wolcott R, Dowd SE. Propagation of anaerobic bacteria within an aerobic multi-species chronic wound biofilm model. *J Wound Care* 2009; **18**: 426-431 [PMID: 19816382 DOI: 10.12968/jowc.2009.18.10.44604]

52 **Ballard SA**, Grabsch EA, Johnson PD, Grayson ML. Comparison of three PCR primer sets for identification of vanB gene carriage in feces and correlation with carriage of vancomycin-resistant enterococci: interference by vanB-containing anaerobic bacilli. *Antimicrob Agents Chemother* 2005; **49**: 77-81 [PMID: 15616278 DOI: 10.1128/AAC.49.1.77-81.2005]

53 **Goldstein EJ**, Citron DM, Merriam CV, Warren YA, Tyrrell KL, Fernandez HT. In vitro activities of daptomycin, vancomycin, quinupristin- dalfopristin, linezolid, and five other antimicrobials against 307 gram-positive anaerobic and 31 Corynebacterium clinical isolates. *Antimicrob Agents Chemother* 2003; **47**: 337-341 [PMID: 12499210 DOI: 10.1128/AAC.47.1.337-341.2003]

54 **Sader HS**, Streit JM, Fritsche TR, Jones RN. Antimicrobial activity of daptomycin against multidrug-resistant Gram-positive strains collected worldwide. *Diagn Microbiol Infect Dis* 2004; **50**: 201-204 [PMID: 15541606 DOI: 10.1016/j.diagmicrobio.2004.07.002]

55 **Salama NN**, Segal JH, Churchwell MD, Patel JH, Gao L, Heung M, Mueller BA. Intradialytic administration of daptomycin in end stage renal disease patients on hemodialysis. *Clin J Am Soc Nephrol* 2009; **4**: 1190-1194 [PMID: 19541812 DOI: 10.2215/CJN.01650309]

56 **Salama NN**, Segal JH, Churchwell MD, Patel JH, Gao L, Heung M, Mueller BA. Single-dose daptomycin pharmacokinetics in chronic haemodialysis patients. *Nephrol Dial Transplant* 2010; **25**: 1279-1284 [PMID: 20007981 DOI: 10.1093/ndt/gfp655]

57 **Butterfield JM**, Mueller BA, Patel N, Cardone KE, Grabe DW, Salama NN, Lodise TP. Daptomycin pharmacokinetics and pharmacodynamics in a pooled sample of patients receiving thrice-weekly hemodialysis. *Antimicrob Agents Chemother* 2013; **57**: 864-872 [PMID: 23208714 DOI: 10.1128/AAC.02000-12]

58 **Vilay AM**, Grio M, Depestel DD, Sowinski KM, Gao L, Heung M, Salama NN, Mueller BA. Daptomycin pharmacokinetics in critically ill patients receiving continuous venovenous hemodialysis. *Crit Care Med* 2011; **39**: 19-25 [PMID: 20890189 DOI: 10.1097/CCM.0b013e3181fa36fb]

59 **Baden LR**, Thiemke W, Skolnik A, Chambers R, Strymish J, Gold HS, Moellering RC, Eliopoulos GM. Prolonged colonization with vancomycin-resistant Enterococcus faecium in long-term care patients and the significance of "clearance". *Clin Infect Dis* 2001; **33**: 1654-1660 [PMID: 11595985 DOI: 10.1086/323762]

60 **Bhullar K**, Waglechner N, Pawlowski A, Koteva K, Banks ED, Johnston MD, Barton HA, Wright GD. Antibiotic resistance is prevalent in an isolated cave microbiome. *PLoS One* 2012; **7**: e34953 [PMID: 22509370 DOI: 10.1371/journal.pone.0034953]

61 **D'Costa VM**, McGrann KM, Hughes DW, Wright GD. Sampling the antibiotic resistome. *Science* 2006; **311**: 374-377 [PMID: 16424339 DOI: 10.1126/science.1120800]

62 **Johnston LM**, Jaykus LA. Antimicrobial resistance of Enterococcus species isolated from produce. *Appl Environ Microbiol* 2004; **70**: 3133-3137 [PMID: 15128577 DOI: 10.1128/AEM.70.5.3133-3137.2004]

63 **Kelesidis T**. The zoonotic potential of daptomycin non-susceptible enterococci. *Zoonoses Public Health* 2015; **62**: 1-6 [PMID: 24274811]

64 **van den Bogaard AE**, Stobberingh EE. Epidemiology of resistance to antibiotics. Links between animals and humans. *Int J Antimicrob Agents* 2000; **14**: 327-335 [PMID: 10794955 DOI: 10.1016/S0924-8579(00)00145-X]

65 **Zhang J**, Wall SK, Xu L, Ebner PD. Contamination rates and antimicrobial resistance in bacteria isolated from "grass-fed" labeled beef products. *Foodborne Pathog Dis* 2010; **7**: 1331-1336 [PMID: 20618073 DOI: 10.1089/fpd.2010.0562]

66 **Hammerum AM**. Enterococci of animal origin and their significance for public health. *Clin Microbiol Infect* 2012; **18**: 619-625 [PMID: 22487203 DOI: 10.1111/j.1469-0691.2012.03829.x]

67 **Johnson TJ**, Fernandez-Alarcon C, Bojesen AM, Nolan LK, Trampel DW, Seemann T. Complete genome sequence of Gallibacterium anatis strain UMN179, isolated from a laying hen with peritonitis. *J Bacteriol* 2011; **193**: 3676-3677 [PMID: 21602325 DOI: 10.1128/JB.05177-11]

68 **Voget S**, Klippel B, Daniel R, Antranikian G. Complete genome sequence of Carnobacterium sp. 17-4. *J Bacteriol* 2011; **193**: 3403-3404 [PMID: 21551290 DOI: 10.1128/JB.05113-11]

69 **Lowder BV**, Guinane CM, Ben Zakour NL, Weinert LA, Conway-Morris A, Cartwright RA, Simpson AJ, Rambaut A, Nübel U, Fitzgerald JR. Recent human-to-poultry host jump, adaptation, and pandemic spread of Staphylococcus aureus. *Proc Natl Acad Sci USA* 2009; **106**: 19545-19550 [PMID: 19884497 DOI: 10.1073/pnas.0909285106]

70 **Kateete DP**, Kabugo U, Baluku H, Nyakarahuka L, Kyobe S, Okee M, Najjuka CF, Joloba ML. Prevalence and antimicrobial susceptibility patterns of bacteria from milkmen and cows with clinical mastitis in and around Kampala, Uganda. *PLoS One* 2013; **8**: e63413 [PMID: 23667611 DOI: 10.1371/journal.pone.0063413]

71 **Aslam M**, Diarra MS, Checkley S, Bohaychuk V, Masson L. Characterization of antimicrobial resistance and virulence genes in Enterococcus spp. isolated from retail meats in Alberta, Canada. *Int J Food Microbiol* 2012; **156**: 222-230 [PMID: 22520502 DOI: 10.1016/j.ijfoodmicro.2012.03.026]

72 **Poulsen LL**, Bisgaard M, Son NT, Trung NV, An HM, Dalsgaard A. Enterococcus faecalis clones in poultry and in humans with urinary tract infections, Vietnam. *Emerg Infect Dis* 2012; **18**: 1096-1100 [PMID: 22709904 DOI: 10.3201/eid1807.111754]

73 **Klein G**. Taxonomy, ecology and antibiotic resistance of enterococci from food and the gastro-intestinal tract. *Int J Food Microbiol* 2003; **88**: 123-131 [PMID: 14596985 DOI: 10.1016/S0168-1605(03)00175-2]

74 **Kelesidis T**, Humphries R, Chow AL, Tsiodras S, Uslan DZ. Emergence of daptomycin-non-susceptible enterococci urinary tract isolates. *J Med Microbiol* 2013; **62**: 1103-1105 [PMID: 23598376 DOI: 10.1099/jmm.0.056630-0]

75 **Geenen PL**, Graat EA, Haenen A, Hengeveld PD, Van Hoek AH, Huijsdens XW, Kappert CC, Lammers GA, Van Duijkeren E, Van De Giessen AW. Prevalence of livestock-associated MRSA on Dutch broiler farms and in people living and/or working on these farms. *Epidemiol Infect* 2013; **141**: 1099-1108 [PMID: 22831886 DOI: 10.1017/S0950268812001616]

76 **Kelesidis T**, Chow AL. Proximity to animal or crop operations may be associated with de novo daptomycin-non-susceptible Enterococcus infection. *Epidemiol Infect* 2014; **142**: 221-224 [PMID: 23587411 DOI: 10.1017/S0950268813000885]

77 **Scott KP**. The role of conjugative transposons in spreading antibiotic resistance between bacteria that inhabit the gastrointestinal tract. *Cell Mol Life Sci* 2002; **59**: 2071-2082 [PMID: 12568333]

78 **Garnier F**, Taourit S, Glaser P, Courvalin P, Galimand M. Characterization of transposon Tn1549, conferring VanB-type resistance in Enterococcus spp. *Microbiology* 2000; **146** (Pt 6): 1481-1489 [PMID: 10846226]

79 **Lapierre L**, Mollet B, Germond JE. Regulation and adaptive evolution of lactose operon expression in Lactobacillus delbrueckii. *J Bacteriol* 2002; **184**: 928-935 [PMID: 11807052 DOI: 10.1128/jb.184.4.928-935.2002]

80 **Silber P**, Borie RP, Mikowski EJ, Goldfine H. Phospholipid biosynthesis in some anaerobic bacteria. *J Bacteriol* 1981; **147**: 57-61 [PMID: 6263870]

81 **Bhalla A**, Pultz NJ, Ray AJ, Hoyen CK, Eckstein EC, Donskey CJ. Antianaerobic antibiotic therapy promotes overgrowth of antibiotic-resistant, gram-negative bacilli and vancomycin-resistant enterococci in the stool of colonized patients. *Infect Control*

Hosp Epidemiol 2003; **24**: 644-649 [PMID: 14510245 DOI: 10.1086/502267]

82 **Kelesidis T**. Comment on: Successful therapy of treatment-emergent, non-clonal daptomycin-non-susceptible Enterococcus faecium infections. *J Antimicrob Chemother* 2012; **67**: 515-516 [PMID: 22052687 DOI: 10.1093/jac/dkr465]

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