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**Origin of *de novo* daptomycin non susceptible enterococci**

KelesidisT.*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

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**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 DNSEwas 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 days of daptomycin therapy[49]. Patients with end stage renal disease have lower Cmax 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.

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