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Journal

Zoonoses and Public Health, 62(1)

ISSN

1863-1959

Author

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Publication Date

2015-02-01

DOI

10.1111/zph.12091

Peer reviewed

HHS Public Access

Author manuscript

Zoonoses Public Health. Author manuscript; available in PMC 2021 April 19.

Published in final edited form as:

Zoonoses Public Health. 2015 February ; 62(1): 1–6. doi:10.1111/zph.12091.

The Zoonotic Potential of Daptomycin Non-susceptible Enterococci

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Summary

Daptomycin non-susceptible Enterococcus (DNSE) is an emerging clinical problem. Little is known about how de novo DNSE infections develop or the risk factors associated with them. Determining risk factors associated with de novo DNSE infections will aid in understanding the mechanisms of daptomycin non-susceptibility. Humans in contact with animals worldwide are at risk of carriage of multidrug-resistant bacteria. Herein, I review the scientific evidence that supports the hypothesis that transport of daptomycin non-susceptibility genes between animals and humans may be a possible mechanism for development of de novo daptomycin non-susceptibility in enterococci.

Keywords

Daptomycin; resistance; enterococci; animals

Introduction

Daptomycin non-susceptible Enterococcus (DNSE) is an emerging problem (Kelesidis et al., 2011). Although most daptomycin non-susceptible *Enterococcus* isolates develop after daptomycin therapy (Kelesidis et al., 2011), we have recently reported DNSE infections in patients with no previous therapy with daptomycin (Kelesidis et al., 2012b). It remains to be determined how these infections develop. Elucidating risk factors associated with de novo DNSE infections will contribute to the identification of mechanisms of daptomycin non-susceptibility. Humans in contact with animals may be carriers of multidrug-resistant bacteria such as methicillin-resistant Staphylococcus aureus (MRSA; Geenen et al., 2012), and many zoonoses can be transmitted from livestock to humans (Aslam et al., 2012). Another emerging infection that may be associated with livestock is DNSE (Kelesidis et al., 2011). Herein, I review the scientific evidence that supports the hypothesis that transport of genes responsible for daptomycin resistance between humans and animals may be a mechanism for development of de novo DNSE.

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Competing interests

None declared.

Anti-microbial Resistance may Derive from Environmental Bacteria

Antibiotic resistance genes may be mobilized from the environmental resistome and transferred to potentially pathogenic to humans bacteria (Canton, 2009; Wright, 2010). The level of anti-microbial resistance in these bacteria may indicate selection pressure by antibiotic use (O'Brien, 2011). Indeed, antibiotic resistance has been reported even in bacteria isolated from human use of antibiotics for million years (Bhullar et al., 2012). Thus, the genes encoding antibiotic resistance may derive from environmental bacteria that are reservoirs of resistance genes for pathogenic bacteria (O'Brien, 2011).

The Soil is a Major Environmental Source for Antibiotic Resistance Genes

Soil-dwelling bacteria are a reservoir of resistance genes that can be transported to other bacteria (D'Costa et al., 2006). These risks might be very high for agricultural areas in which wastewater is used for irrigation (Heuer et al., 2011; Dalkmann et al., 2012). Wastewater may harbour bacteria resistant to antibiotics (Ansari et al., 2008; Munir and Xagoraraki, 2011). However, resistance genes may also be common in soils (Allen et al., 2010). Thus, an understanding of the soil resistome, the resistance determinants present in the soil, will provide information about new mechanisms of antibiotic resistance that may emerge as clinical problems.

Enterococci are Common Environmental Bacteria that Originate from Animal and Human Faeces

Enterococci are common gut bacteria in mammals and birds (Byappanahalli et al., 2012) that are commonly used as hygienic indicator in the environment because they can be cultured easily, are shed in human and animal faeces, and predict human health risks from exposure to contaminated waters (Frahm and Obst, 2003; Dalkmann et al., 2012). The widespread reservoirs of enterococci indicate the need to better understand their roles as opportunistic pathogens.

De Novo DNSE may Originate from Soil Bacteria

Acquired antibiotic resistances in enterococci have increasingly been reported. Daptomycin has activity against gram-positive bacteria (Kelesidis et al., 2011) and is indicated for skin and soft tissue infections, *S. aureus* endocarditis (Kelesidis et al., 2011) and may also be used for treatment of vancomycin-resistant enterococci (VRE) infections (Kelesidis et al., 2011). Although daptomycin resistance has increasingly been reported among enterococci (Kelesidis et al., 2011), the exact mechanisms of development of resistance are largely unknown. It was found initially that soil actinomycetes species may inactivate daptomycin and may demonstrate very high (~80%) levels of daptomycin resistance (Debono et al., 1988; D'Costa et al., 2006). However, multiple mechanisms of inactivation of daptomycin may create a selective pressure for dissemination of resistance genes (D'Costa et al., 2012). Daptomycin resistance genes such as an inducible daptomycin hydrolase were identified in bacteria that have been isolated for over 4 million years (Bhullar et al., 2012). Finally, we identified nucleotide mutations in DNSE isolates in genes that have also been described in

many soil bacteria (Table 1; Humphries et al., 2012). Indeed, transfer of resistance between soil bacteria and enterococci has previously been documented (Johnston and Jaykus, 2004). However in another study, DNSE *E faecium* developed independently of daptomycin resistance mechanisms previously identified in soil bacteria (Montero et al., 2008). Thus, further studies are needed to investigate the hypothesis that transfer of resistance between soil bacteria and enterococci may also be responsible partially for development of daptomycin non-susceptibility in enterococci.

Acquired Daptomycin Resistance among *Enterococcus* spp. may be Mediated by Transferable Transposons from Bacteria of Animal Origin

Enterococcus spp. display a variety of anti-microbial resistance mechanisms which may be mediated by transferable transposons or plasmids encoding resistance cassettes (Johnston and Jaykus, 2004; van den Bogaard and Stobberingh, 2000; Zhang et al., 2010). *Enterococci* of animal origin such as *E. faecalis* could act as donors of anti-microbial resistance genes for other enterococci (Hammerum, 2012). Genetic mutations that may explain daptomycin resistance in enterococci that were exposed to daptomycin may have derived from recombination between adjacent repetitive nucleotide sequences (Arias et al., 2011). However, the mechanisms of development of DNSE among patients without prior exposure to daptomycin (de novo DNSE) remain to be determined (Kelesidis et al., 2012b).

Farm Animals may be a Source for Development of De Novo DNSE Isolates

Enterococci are isolated from the gastrointestinal tract flora in humans and most animals (van den Bogaard and Stobberingh, 2000; Zhang et al., 2010). Multidrug-resistant enterococci, such as vancomycin-resistant enterococci can be found in food and animal species, can emerge among farm animals and become widespread within just a few years (van den Bogaard and Stobberingh, 2000; Zhang et al., 2010). Environmental reservoirs of antibiotic resistance can develop in farmland (van den Bogaard and Stobberingh, 2000; Johnston and Jaykus, 2004) since food and animal Enterococcus species can efficiently transfer antibiotic resistance to human strains in inter-specific matings (van den Bogaard and Stobberingh, 2000; Zhang et al., 2010). Consistent with the hypothesis that DNSE isolates may develop in animal Enterococcus species, we found nucleotide mutations in DNSE isolates (Humphries et al., 2012) in genes that have also been described in many bacteria found in poultry such as putative lipoprotein (Johnson et al., 2011), regulatory protein spx (Voget et al., 2011), protein DNAB (Lowder et al., 2009). Thus, a possible mechanism of resistance in DNSE could be transfer of antibiotic resistance genes encountered in animal products (Kelesidis et al., 2012b).

DNSE as a Foodborne Zoonosis

In addition, the daptomycin-resistant enterococci may have developed in animals and then passed to humans via the food chain (Kelesidis et al., 2012b). In a recent study, up to 25% of enterococci that were frequently (up to 62%) isolated from beef products were resistant to daptomycin (Zhang et al., 2010). We recently reported that four of nine (44.4%) patients with de novo DNSE infections had frequent ingestion of beef, and no clonal spread was

detected, indicating that gene transfer may have contributed to the dissemination of antibiotic resistance (Kelesidis et al., 2012b).

Enterococci faecalis can be transferred to humans through consumption of contaminated undercooked meat and is a reservoir of resistance genes (Aslam et al., 2012). *Enterococcus gallinarum* can occur in high numbers in production animals like poultry (Klein, 2003) and daptomycin non-susceptible isolates have previously been isolated from humans (Kelesidis et al., 2012a). The homology of *E. faecalis* isolates from poultry and urine in recent studies suggests that poultry may be a source for urinary tract infections (UTIs) caused by *E. faecalis* in humans (Poulsen et al., 2012). Consistent with these data and the hypothesis of a foodborne source of DNSE urine isolates, all the three de novo DNSE isolates in our recent cohort of 11 DNSE isolated from the urinary tract, were *E. faecalis,* known to have zoonotic potential (Kelesidis et al., 2013). Thus, it is possible that DNSE may be transferred to humans through the food supply as meat can be a reservoir for DNSE isolates (Zhang et al., 2010; Kelesidis et al., 2012b).

DNSE may be Transferred to Humans from Animals through the Faecal–oral Route and Direct Contact with Animals

Humans in contact with animals are at risk of being carriers of multidrug-resistant bacteria including methicillin-resistant Staphylococcus aureus (MRSA; Geenen et al., 2012). We have recently conducted an epidemiological investigation of the possible origin of de novo DNSE infections (Kelesidis and Chow, 2013) studying home address data from electronic medical records which may provide useful epidemiologic information regarding emerging infections (Wilson et al., 2010). Of the nine de novo DNSE infections, 4 (44%) patients lived in areas where there were >2 animal operations [as defined by the U.S. Department of Agriculture (USDA)]. Two (9.5%) of 21 in the prior daptomycin exposure group had lived near >50 crop or animal operations (as defined by USDA) compared with three (42.9%) subjects with de novo DNSE ($P = 0.08$). Six of eight (75%) subjects with de novo DNSE lived within a half-mile radius around crop and animal operations. The mean number of crop or animal operations near the residence of subjects with de novo DNSE was 98.6 compared with 13.8 for patients with daptomycin-exposed DNSE ($P = 0.049$; Kelesidis and Chow, 2013). These data suggest that patients with de novo DNSE may have a significantly higher exposure to a crop or animal operation than patients with daptomycin-exposed DNSE. We recently found that three of nine (33.3%) subjects with de novo DNSE had a history of prior exposure to livestock (Kelesidis et al., 2012b). Thus, it is possible that humans in contact with animals are at risk of carriage of DNSE, but this hypothesis remains to be further investigated.

Antibiotic Use for Animal Growth Promotion may Contribute to Development of DNSE in Animals

Antibiotic use for animal growth promotion may promote the dissemination of antibiotic-resistant bacteria that may contaminate meat products and colonize the gut of humans (Johnston and Jaykus, 2004; O'Brien, 2011). Anti-microbial usage in animals has a major

role in the transport of resistance genes via the food chain to humans and the selection of bacterial resistance (Johnston and Jaykus, 2004; O'Brien, 2011). These antibiotic resistance genes can be transferred to other bacteria such as human enterococci (Johnston and Jaykus, 2004; O'Brien, 2011). Indeed extensive use of antibiotics for growth promotion contributed to the spread of VRE among farm animals (Nilsson, 2012). However, it remains to be shown whether antibiotic use for animal growth promotion may also promote development of DNSE.

Conclusion

One can only speculate on what happened when the first de novo DNSE emerged. Similar questions remain to be answered for VRE. Mathematical models suggest that agricultural use of anti-microbials can promote the spread of anti-microbial resistance from animals to humans, by gene transfer between animal and human strains and by spread of resistant bacteria (Smith et al., 2002). These transfers of resistance genes may largely affect public health even when they are rare among human-adapted strains (Smith et al., 2002). Daptomycin resistance among human enterococci is still rare, but DNSE is an emerging infection (Kelesidis et al., 2011). Recent published evidence suggests that the daptomycin resistance genes have developed in the environment millions of years ago (Bhullar et al., 2012). Based on the scientific evidence summarized herein, it is possible that de novo DNSE isolates in humans emerged by horizontal gene transfer of the daptomycin resistance genes from environmental/animal sources (Fig. 1). This hypothesis needs to be further investigated in epidemiologic studies. To safeguard public health, the zoonotic potential of resistant bacteria should be controlled.

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Impacts

- Daptomycin non-susceptible enterococcus (DNSE) is an emerging clinical problem.
- Determining risk factors associated with de novo DNSE infections will aid in understanding the mechanisms of daptomycin non-susceptibility.
- Humans in contact with animals are at risk of carriage of DNSE, and this manuscript reviews the scientific evidence regarding the zoonotic potential of daptomycin non-susceptible enterococci.

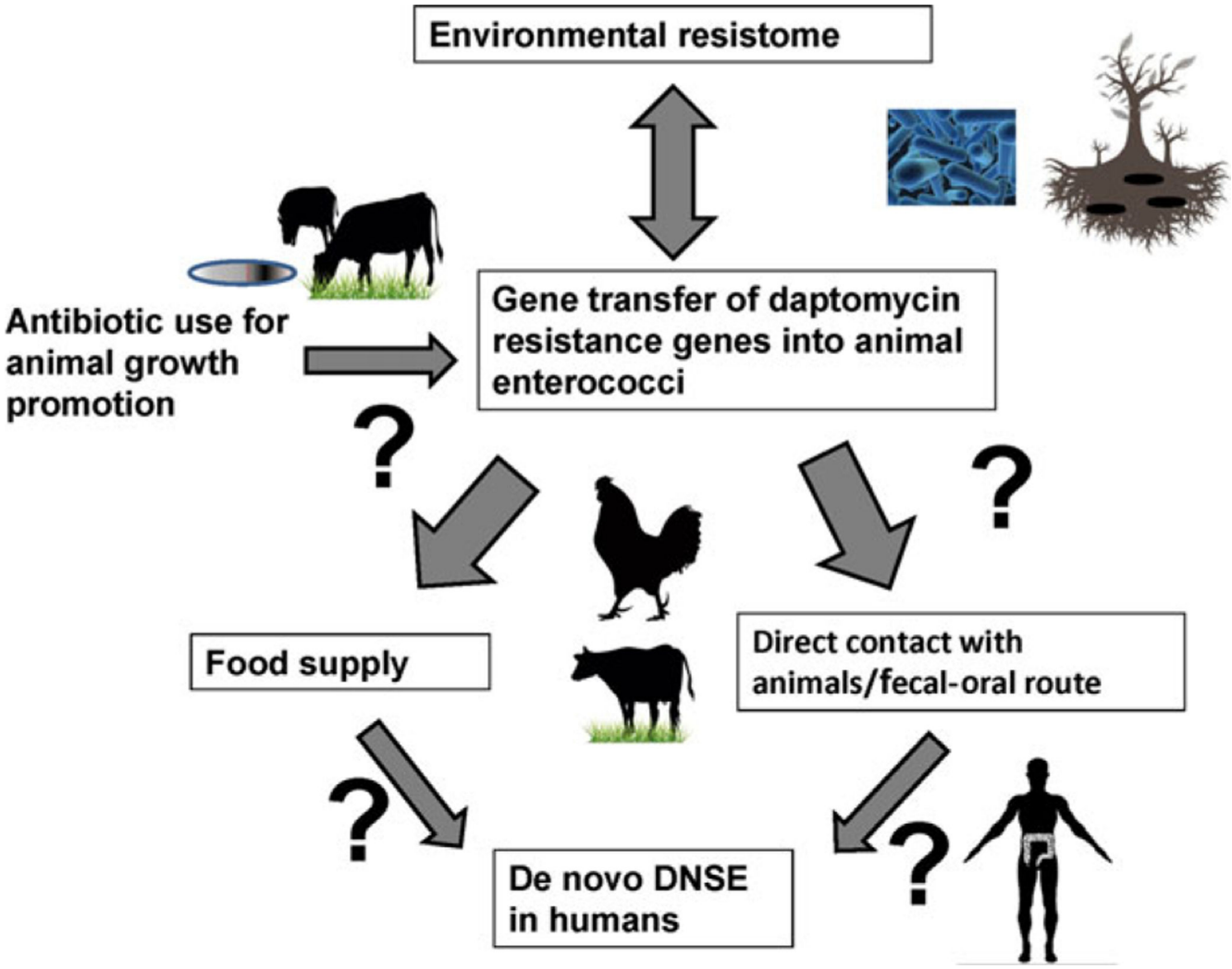

Fig. 1.

Overall hypothesis: Daptomycin resistance genes have been recently found in a culture collection of isolates from an ecosystem that has been isolated for over 4 million years. Enterococci are common environmental bacteria. Daptomycin-resistant genes may be present in many soil bacteria and they may be transferred to enterococci in animals. Farm animals may be a source for the development of de novo daptomycin non-susceptible Enterococcus (DNSE) isolates which may be passed to humans via the food chain or via the faecal–oral route and direct contact. Antibiotic use for animal growth promotion may hasten the appearance of DNSE. These hypotheses need to be further investigated in epidemiological studies.

Table 1.

Polymorphisms in genes that have been identified in daptomycin non-susceptible Enterococcus isolates and also in soil bacteria

Genes that may be involved in daptomycin resistance	References
Enzymes that inactivate daptomycin: deacylases, hydrolases	(Debono et al., 1988; D'Costa et al., 2006; Humphries et al., 2012).
Inducible daptomycin hydrolase	(Bhullar et al., 2012; Humphries et al., 2012)
Putative lipoprotein	(Martinez-Canamero et al., 2002; Sutcliffe and Harrington, 2002; Reffuveille et al., 2011; Humphries et al., 2012)
Nicotinamide mononucleotide transporter	(Vodovar et al., 2006; Gartemann et al., 2008; Humphries et al., 2012)
Septation ring formation regulator EzrA	(Nanninga, 2001; Saw et al., 2008; Humphries et al., 2012)
Conserved hypothetical protein CofD related	(Galperin and Koonin, 2004; Humphries et al., 2012)
Iron-containing alcohol dehydrogenase	(Radianingtyas and Wright, 2003; Humphries et al., 2012)
Pts system, iibc component	(Barabote and Saier, 2005; Humphries et al., 2012)
Replication initiation and membrane attachment protein DnaB	(Hoshino et al., 1987; Humphries et al., 2012)