JMM Correspondence

# Emergence of daptomycin-non-susceptible enterococci urinary tract isolates

Daptomycin-non-susceptible enterococci (DNSE) infections are emerging (Kelesidis *et al.*, 2011, 2012b) but limited data are available regarding DNSE urinary tract infections (UTIs) (Kelesidis *et al.*, 2011; Storm *et al.*, 2012). We describe herein clinical, microbiological and epidemiological characteristics for 11 DNSE urine isolates.

All patients with at least one positive urine culture for DNSE, defined as enterococci with a daptomycin MIC $>4$ μg ml$^{-1}$ (Kelesidis *et al.*, 2011) determined by reference broth microdilution (BMD) (Clinical and Laboratory Standards Institute, 2009) in a 5-year (2007–2012) period, were included in this study after institutional review board approval. All DNSE were confirmed by repeat BMD testing at the time of isolation. Daptomycin MICs for isolates included in this study were later confirmed by Etest (bioMérieux) following storage of the isolates at $-70$ °C in Brucella broth $+15$ % glycerol (BD). Strain typing was performed by repetitive element PCR (DiversiLab, bioMérieux) (Kelesidis *et al.*, 2012b). Colonization versus UTI with DNSE was determined using established criteria (CDC/NHSN, 2013).

Eleven DNSE were isolated from the urine of 11 patients (9 female, median age 57 years, range 18–80 years). Over this same time period, 4557 [27 % vancomycin-resistant enterococci (VRE)] enterococci were isolated from the urine of 3525 patients (930 with VRE), yielding an overall incidence of 0.2 % among all enterococcal urinary isolates, and 0.4 % among VRE.

In three cases (27.3 %) (1, 5 and 8), there was no history of prior daptomycin exposure (*de novo* DNSE) (Table 1; Kelesidis *et al.*, 2012b), similar to another study in which 7/12 (58.3 %) DNSE urine isolates were de *novo* (Storm *et al.*, 2012). For the eight exposed patients, the mean duration of daptomycin treatment was 31.3 days (mean dosage 7.3 mg kg$^{-1}$ day$^{-1}$; range, 6–10 mg kg$^{-1}$ day$^{-1}$). Eight (72.7 %) patients were immunosuppressed, similar to other studies of patients with DNSE infections (Storm *et al.*, 2012; Kelesidis *et al.*, 2011). Recent admission to hospital or a long-term health care facility was observed in five (45.5 %) cases (Table 1). DNSE was isolated on the day of admission in five patients, including the three *de novo* cases. Surprisingly, only two (18.2 %) patients had urinary tract catheters at the time of the culture and nine patients had no indwelling catheters or had undergone no urological procedures at least 1 week prior to the day that the urine culture was obtained.

Recent use of vancomycin, third generation cephalosporins, or agents with activity against anaerobes is known to be associated with emergence of VRE and may have a role in the emergence of DNSE (Kelesidis *et al.*, 2012a); such use was identified in 8 (72.7 %; mean duration 16.8 days, range 7–34), 4 (36.4 %; mean duration 18.8 days, range 8–42) and 7 (63.6 %; mean duration 44.1 days, range 14–90) patients, respectively. Of the 11 DNSE isolates, 5 (45.5 %) were *Enterococcus faecalis* and 6 (54.5 %) *Enterococcus faecium*. Strain typing by repPCR revealed two clonally related isolates (cases 5 and 8) that were 98.5 % related to a third *E. faecalis* strain isolated from a patient at our institution after 90 days of daptomycin treatment. Six DNSE (54.5 %) isolates (5 *E. faecalis* and 1 *E. faecium*) were considered colonizers. In 6/11 (54.5 %) cases, other concomitant potential urinary pathogens were also identified (Table 1).

Interestingly, all *de novo* DNSE were *E. faecalis* and had a lower median daptomycin MIC than the *E. faecium* isolates (6 versus 28 μg ml$^{-1}$; Table 1). In only one *de novo* DNSE isolate the repeat daptomycin MIC was $>4$ μg ml$^{-1}$ following 1 year of storage at $-70$ °C. All isolates (100 %) and all *E. faecium* isolates were susceptible to linezolid and quinupristin/dalfopristin, respectively. Tigecycline, fosfomycin, vancomycin, nitrofurantoin, ampicillin, ciprofloxacin and doxycycline had activity against 10 (90.9 %), 8 (72.7 %), 7 (63.6 %), 5 (45.5 %), 4 (36.4 %), 3 (27.3 %) and 2 (18.2 %) of the DNSE isolates, respectively. While not all (4/6, 66.7 %) DNSE *E. faecium* isolates were VRE, all DNSE *E. faecalis* isolates were susceptible to vancomycin.

In this series, four cases were treated with linezolid, three with vancomycin and four with daptomycin, as DNSE was not identified at the time of treatment (Table 1). In one case (no. 4), there was eradication from the urine without specific treatment targeted to DNSE while in three cases (6–8) there was eradication from the urine after treatment with antimicrobials that had activity against DNSE. Two (20.0 %) patients expired while receiving DNSE directed therapy (Table 1); one (case 10) was considered to be colonized with DNSE and the other patient (case 3) had multiple comorbidities and death could not be attributed to DNSE.

There are limited data regarding DNSE urine isolates (Kelesidis *et al.*, 2011; Storm *et al.*, 2012). The identification of two clonally related DNSE isolates in patients with no hospitalization in the previous 12 months may indicate either long-term DNSE colonization in patients or a community reservoir of DNSE. Nevertheless, nosocomial acquisition of DNSE for these patients cannot be entirely ruled out due to lack of information on enterococci from other clinical sites that may have previously colonized the patients and persisted for years (Baden *et al.*, 2001).

We have recently described *de novo* urinary DNSE isolates (Kelesidis *et al.*, 2012a, b). Herein, we now confirm this finding in our expanded case series of DNSE UTIs. Similarly, Storm and colleagues found 7 of 12 (58.3 %) DNSE UTIs were in patients with no prior obvious exposure to

**Table 1.** Summary of patient and treatment characteristics of 11 patients with DNSE urinary tract isolates

| Patient | Age | Sex | Comorbidities* | Hospitalization† | Enterococcus species | MIC (E-test) | Day of isolation of DNSE | Other pathogens (urine) | UTI | Bacteriologic eradication§ | Treatment | Clinical outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 73 | F | Hypertension | No | *E. faecalis* | 6 | 0 (outpatient) | CNS | No | ND | None | Remained asymptomatic |
| 2 | 18 | F | AML, neutropenia, renal failure | Yes | *E. faecalis* | 4 | 3 | No | No | Yes | Vancomycin | Recovered |
| 3 | 43 | F | AML | Yes | *E. faecium* | 96 | 2 | No | Yes | No | Daptomycin, linezolid | Died |
| 4 | 80 | F | Diabetes, CHF, | Yes | *E. faecium* | 64 | 30 | *Candida* spp. | Yes | Yes | Daptomycin | Recovered |
| 5 | 53 | F | CNS tumour | No | *E. faecalis* | 3 | 0 (outpatient) | No | No | ND | None | Remained asymptomatic |
| 6 | 58 | F | Diabetes, CHF, colitis | Yes | *E. faecium* | 16 | 92 | *Candida* spp. | Yes | Yes | Linezolid | Recovered |
| 7 | 56 | M | CHF, endocarditis | Yes† | *E. faecium* | 24 | 87 | *Candida* spp. | Yes | Yes | Linezolid | Recovered |
| 8 | 75 | M | CVA | No | *E. faecalis* | 12 | 1 | No | No | Yes | Linezolid, vancomycin | Recovered |
| 9 | 70 | F | TCC, multiple UTIs, COPD | Yes‖ | *E. faecalis* | 4 | 1 | *Candida* spp. | Possibly | Yes | Tigecycline, vancomycin | Recovered |
| 10 | 50 | F | Diabetes, SLE, corticosteroids | No | *E. faecium* | 32 | 95 | *Pseudomonas*, *Stenotrophomonas* spp. | No | No | Daptomycin, cefepime | Died |
| 11 | 28 | F | Diabetes, cancer, intraabdominal abscesses | Yes | *E. faecium* | >256 | 28 | No | No | Yes | Daptomycin | Remained clinically stable |

*AML, acute myelogenous leukaemia; CHF, congestive heart failure; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; SLE, systemic lupus erythematosus; TCC, transitional cell carcinoma.

†Recent (within 12 months prior to isolation of DNSE) admission to hospital or long-term health care facility and/or surgery.

§A bacteriologic eradication was defined by a urine culture negative for DNSE at least 2 weeks after therapy, or was considered undetermined if there were no available follow-up urine cultures.

‖Had placement of nephrostomy tubes.

ND, Not determined.

daptomycin, although the authors suggested that daptomycin consumption could not be completely excluded in these cases (Storm *et al.*, 2012). Interestingly, all our *de novo* DNSE urine isolates were *E. faecalis*. *E. faecalis* might be a reservoir of resistance genes that may be transferred to humans through consumption of contaminated meat (Aslam *et al.*, 2012). Contaminated meat may also be a possible reservoir for DNSE isolates (Kelesidis *et al.*, 2012b; Zhang *et al.*, 2010). However, the origin of community-acquired DNSE remains unknown.

More than half of the DNSE urine isolates in our study were considered colonizers. Similarly, in another study, 8/12 (66.7 %) cases with DNSE urine isolates were considered colonizers (Storm *et al.*, 2012). In addition, in one case (no. 4), there was eradication from the urine without specific treatment targeted to DNSE. Thus, urine DNSE may not always represent infection and the clinical significance of these isolates should always be determined.

All DNSE *E. faecalis* isolates were susceptible to vancomycin. Thus the incidence of DNSE urine isolates may be higher than expected, since daptomycin MIC may not be reported if the isolate is vancomycin-susceptible.

Limited data exist regarding treatment of DNSE UTIs (Kelesidis *et al.*, 2011). Daptomycin MIC is not routinely reported for vancomycin-susceptible enterococci (VSE). Thus, in our case series, daptomycin was given empirically for nosocomial infection in four cases (3, 4, 10 and 11) and the DNSE urine isolates were identified retrospectively. Interestingly, two of these patients (4 and 11) had bacteriologic eradication of urine DNSE while receiving daptomycin. This observation indicates the need to define urine susceptibility MIC breakpoints for DNSE. Clinical success in >90 % of patients with UTI treated with daptomycin has been reported (Fisher and North, 2009). Standard doses of daptomycin result in urine concentrations of daptomycin of 44.9–103 μg $ml^{-1}$ (Cubist Pharmaceuticals, personal communication), well above the MICs for the majority of DNSE. Thus, since Clinical and Laboratory Standards Intitute daptomycin interpretive criteria are based on serum achievable drug concentrations, urine susceptibility MIC breakpoints for DNSE need to be further evaluated. Finally, variable susceptibility to oral antimicrobials that may be considered for outpatient treatment of DNSE UTIs, including linezolid, nitrofurantoin, fosfomycin, was noted in our cohort.

The epidemiological conclusions about clonal spread or *de novo* resistance development are limited by small numbers of patients, retrospective single centre nature of study and lack of a comparator group. Further case–control studies comparing patients with and without DNSE and/or prior daptomycin exposure may better define the epidemiology of DNSE urine isolates.

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Abbreviations: DNSE: daptomycin-non-susceptible enterococci; UTI, urinary tract infection; VRE, vancomycin-resistant enterococci; VSE, vancomycin-susceptible enterococci.

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