Daptomycin Non-susceptible *Enterococcus faecium*: Emerging Pathogen or Microscan™ Pseudo-Phenomenon?

#40452

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Abstract

Background: Although reported rates of daptomycin non-susceptible Enterococcus (DNSE) isolates remain low (0.3% of isolates from 2002-08 US surveillance data), recent publications suggest a higher occurrence. At Lahey Hospital & Medical Center (LHMC), emergence of DNSE (MIC > 4 mg/mL) increased from 0% of initial E. faecium isolates tested in 2008 to 17% in 2010, then 12% in 2012.

Methods: We reviewed all patients with DNSE identified by Microscan™ from 1 Jan 2008 to 31 Dec 2012. DNSE susceptibility was verified by E-test at LHMC and by broth dilution MIC and E-test at Cubist Pharmaceuticals, Lexington, MA. Patient isolates sorted into 3 categories: confirmed DNSE (MIC > 4 mg/mL in Microscan™ and by another test), non-confirmed DNSE (MIC > 4 mg/mL for Microscan™ but MIC ≤ 4 mg/mL in all other tests), and isolates unavailable for confirmatory testing (MIC > 4 mg/mL in Microscan™ only).

Results: 99 patients (126 isolates) from 2008 to 2012 with DNSE were reviewed. Of 50 patient isolates available for additional testing, 21 had confirmed and 29 had non-confirmed DNSE. DNSE was hospital-acquired in 43% of inpatients (>3 days from admission to positive culture). Two DNSE isolates were also resistant to linezolid and vancomycin.

Of patients with confirmed DNSE, 86% were inpatients. 43% had hepatobiliary disease and/or procedures. 57% and 29% of first isolates of DNSE were in urine and blood cultures, respectively. 76% of patients had antibiotic exposure within 30 days prior to positive DNSE culture: 57%, 57%, and 24% received cefepime, vancomycin, and daptomycin, respectively.

Patients with confirmed DNSE were not statistically different in characteristics from non-confirmed DNSE patients or those with no confirmation data. Treatment changed to linezolid following report of DNSE in 29 patients. All groups had similar mortality (21.8% died or were discharged to hospice).

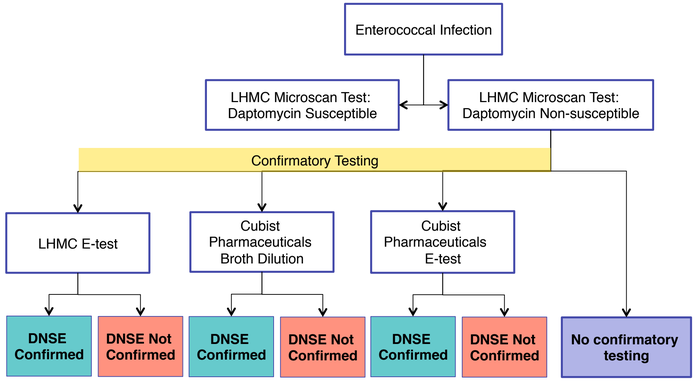
Conclusions: Rates of DNSE rose rapidly at LHMC from 2008-2012. It is unclear whether isolates deemed resistant by Microscan™ are truly daptomycin-non-susceptible or represent a pseudo-phenomenon. However, we were unable to distinguish between non-confirmed and confirmed DNSE. In practice, reports of DNSE generated frequent linezolid use, raising the potential risk of combined resistance to daptomycin, linezolid, and vancomycin.

Background

- Daptomycin non-susceptible Enterococcus (DNSE) isolates remain low (0.3% of isolates from 2002-08 US surveillance data), but recent studies suggest higher occurrence
- At Lahey Hospital & Medical Center (LHMC), emergence of DNSE (MIC > 4 mg/mL) increased from 0% of initial E. faecium isolates tested in 2008 to 19% in 2011, then 12% in 2012.

Methods

- All patients with DNSE identified by Microscan™ at LHMC from 1 Jan 2008 to 31 Dec 2012 were reviewed.
- DNSE susceptibility was verified by E-test at LHMC, broth dilution MIC and/or E-test at Cubist Pharmaceuticals, Lexington, MA.
- Patient isolates sorted into 3 categories: confirmed DNSE (MIC > 4 mg/mL in Microscan™ and by another test), non-confirmed DNSE (MIC > 4 mg/mL for Microscan™ but MIC ≤ 4 mg/mL in all other tests), and isolates unavailable for confirmatory testing (MIC > 4 mg/mL in Microscan™ only).
- Univariate statistical analysis was conducted among the three groups using WinPEPI Statistical software.

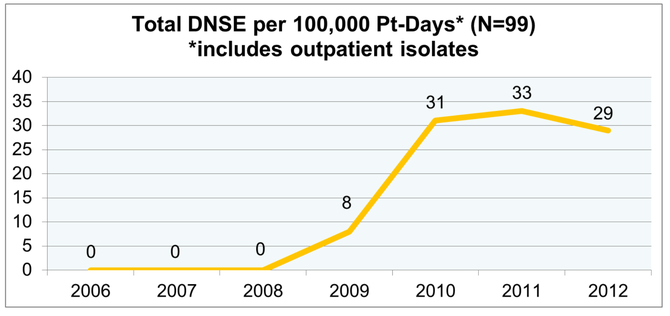


DNSE infection is considered confirmed if daptomycin MIC is greater than 4 mg/ml in at least one of the three confirmatory tests. DNSE infection is considered not confirmed if daptomycin MIC in all confirmatory tests is less than or equal to 4 mg/ml.

Results

- 99 patients (126 isolates) from 2008 to 2012 with DNSE were reviewed.
- Of 50 patient isolates available for additional testing, 21 had confirmed (MIC > 4 mg/ml for at least one other test) and 29 had non-confirmed DNSE (MIC ≤ 4 mg/ml for all additional tests).
- Overall, DNSE was hospital-acquired in 43% of inpatients (>3 days from admission to positive culture).
- Of patients with confirmed DNSE, 86% were inpatients.
- 43% had hepatobiliary disease and/or procedures.
- 57% and 29% of first isolates of DNSE were in urine and blood cultures, respectively.
- 76% of patients had antibiotic exposure within 30 days prior to positive DNSE culture: 57%, 57%, and 24% received cefepime, vancomycin, and daptomycin, respectively.
- Patients with confirmed DNSE were not statistically different from non-confirmed DNSE patients or those with no confirmation data.
- Treatment changed to linezolid following report of DNSE in 29 patients.
- 22% of patients died or were discharged to hospice. All groups had similar mortality.
- Two DNSE isolates were also resistant to daptomycin, linezolid, vancomycin, ampicillin, tetracycline, and tigecycline but susceptible to dalfopristin/quinupristin.

Year	Patients with DNSE	DNSE Confirmed	DNSE Not Confirmed	No Confirmatory Testing
2009	8	0	0	8
2010	31	3	1	27
2011	33	12	13	8
2012	27	6	15	6
Total	99	21	29	49



Variable	DNSE Confirmed N	DNSE Confirmed %	DNSE Not Confirmed N	DNSE Not Confirmed %	No Confirmatory Testing N	No Confirmatory Testing %	p-value*
Demographics							
Female	21	48%	29	38%	49	59%	NS
Male	21	52%	29	62%	49	41%	NS
Inpatient	21	86%	29	86%	49	90%	NS
Admitted from Home	18	44%	25	68%	44	48%	0.22
Admitted from Outside Facility	18	56%	25	32%	44	52%	NS
Hospital Acquired Infection	18	61%	25	32%	44	41%	0.17
Comorbidities							
Hx Cancer	21	38%	29	38%	49	37%	NS
Hx Diabetes	21	29%	29	34%	49	31%	NS
Hx Hepatobiliary Disease	21	43%	29	34%	49	45%	NS
Hx Other GI Disease	21	19%	29	21%	49	45%	NS
Hx Heart Disease	21	33%	29	38%	49	45%	NS
Hx Kidney Disease	21	24%	29	48%	49	49%	0.13
Hx Lung Disease	21	29%	29	24%	49	27%	NS
Procedures							
Surgery at Lahey in Last 365 Days	21	52%	29	62%	49	57%	NS
Hx Chemotherapy	21	24%	29	14%	49	18%	NS
Hx Heart Procedure(s)	21	10%	29	14%	49	18%	NS
Hx GI Procedure(s)	21	14%	29	17%	49	24%	NS
Hx Liver Procedure(s)	21	43%	29	28%	49	31%	NS
Hx Transplant(s)	21	29%	29	14%	49	8%	0.102
Hx Urinary Tract Procedure(s)	21	14%	29	24%	49	22%	NS
Hx Other Procedure(s)	21	24%	29	38%	49	47%	NS
Antibiotics in Last 30 Days							
Any antibiotics	21	76%	29	69%	49	82%	NS
Cefepime	21	57%	29	41%	49	41%	NS
Daptomycin	21	24%	29	7%	49	14%	NS
Vancomycin	21	57%	29	45%	49	53%	NS
Site of First Isolate							
Urine	21	57%	29	34%	49	57%	0.12
Blood	21	29%	29	21%	49	6%	**0.026**
Liver/Asp/Drng	21	29%	29	21%	49	24%	NS
GI/Abdomen	21	0%	29	0%	49	4%	NS
Discharge Disposition							
Died or Discharged to Hospice	18	28%	25	16%	44	23%	NS

* All p-values labeled NS have values ≥ 0.3.

Conclusions

- Rates of DNSE rose rapidly at LHMC from 2008-2012, to as high as 19% of *Enterococcus faecium* isolates.
- Relatively few patients were exposed to daptomycin prior to isolation of DNSE infection.
- 43% of cases were hospital acquired, but many were present on transfer from outside facilities.
- 22% of patients in this population died or were discharged to hospice, but it is unclear how many of these were attributable to DNSE infection.
- It is unclear whether isolates deemed resistant by Microscan™ are truly daptomycin-non-susceptible or represent a pseudo-phenomenon, as we were unable to distinguish clinically between non-confirmed and confirmed DNSE infections.
- In practice, reports of DNSE generated frequent linezolid use, raising the potential risk of combined resistance to daptomycin, linezolid, and vancomycin.
- Two DNSE isolates were also resistant to daptomycin, linezolid, vancomycin, ampicillin, tetracycline, and tigecycline but susceptible to dalfopristin/quinupristin.

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