Open Forum Infectious Diseases

MAJOR ARTICLE

Understanding and Application of Daptomycin-Susceptible Dose-Dependent Category for *Enterococcus*: A Mixed-Methods Study

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Background. In 2018, the Clinical Microbiology Laboratory at our institution adopted updated daptomycin *Enterococcus*–susceptible dose-dependent breakpoints. While the introduction of susceptible dose-dependent (SDD) was intended to guide practice toward optimal dosing, the understanding and application of daptomycin SDD breakpoints for enterococci were unknown.

Methods. This mixed-methods study combined a clinician survey with a retrospective pre–post prescribing analysis. An 8-question survey was distributed to infectious diseases (ID) and internal medicine (IM) clinicians. A retrospective chart review of hospitalized adults with infections due to *Enterococcus* spp. was conducted before (pre-SDD) and after (post-SDD) adoption of SDD reporting for enterococci.

Results. Survey response rates were 40 of 98 (41%) for IM and 22 of 34 (65%) for ID clinicians. ID clinicians scored significantly higher than IM clinicians in knowledge of SDD. Chart review of 474 patients (225 pre- vs 249 post-SDD) showed that daptomycin dosage following susceptibility testing was significantly higher post-SDD compared with pre-SDD (8.5 mg/kg vs 6.4 mg/kg; $P < .001$) with no difference in empiric dosing (6.3 mg/kg vs 6.2 mg/kg; $P = .67$). Definitive daptomycin use varied between the pre- and post-SDD periods (35.1% vs 16.9%; $P < .001$).

Conclusions. The survey revealed that ID clinicians placed more importance on and had more confidence in the SDD category over IM clinicians. SDD reporting was associated with a change in definitive daptomycin dosing. ID specialist involvement is recommended in the care of infections due to enterococci for which daptomycin is reported as SDD given their expertise.

Keywords. antimicrobial stewardship; daptomycin; *Enterococcus*; microbial sensitivity tests.

Daptomycin is a broad-spectrum, cyclic lipopeptide used to treat serious infections caused by gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus* species [1]. Studies have demonstrated daptomycin treatment failure in enterococci with elevated minimal inhibitory concentrations (MICs), leading to concerns that standard doses of 4–6 mg/kg may not attain pharmacodynamic targets for select enterococci. In 2018, the Clinical and Laboratory Standards Institute (CLSI) approved a susceptible dose-dependent (SDD) breakpoint range of 2–4 mcg/mL for *Enterococcus* spp., which was subsequently published in the M100 guidelines in 2019; the SDD breakpoints were based on a dosage regimen of 8–12 mg/kg administered every 24 hours for serious infections due to enterococci [2–6]. In 2020, the CLSI again revised the daptomycin breakpoints [3, 5].

While the SDD category is intended to guide practice toward optimal dosing of daptomycin, it is unknown if the breakpoint changes and introduction of the SDD category have influenced clinical practice. We performed a mixed-methods study to assess infectious diseases (ID) and internal medicine (IM) clinicians' understanding of daptomycin SDD as it relates to enterococci and its practice implications.

METHODS

The study was conducted at an academic medical center where daptomycin is restricted to use for MRSA and vancomycin-resistant *Enterococcus* (VRE) infections, situations of vancomycin intolerance, empiric therapy for neutropenic fever in VRE-colonized patients, or in accordance with ID consultation. All daptomycin orders are reviewed by antimicrobial stewardship program personnel on Monday–Friday as part of the

Received 22 September 2021; editorial decision 24 November 2021; accepted 2 December 2021; published online 10 January 2022.

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Open Forum Infectious Diseases®2021

https://doi.org/10.1093/ofid/ofab611

routine prospective audit with intervention program. Thus, ID clinician involvement in patient cases where daptomycin is used is common at this institution. Of note, daptomycin is dosed locally using adjusted body weight. Since September 2018, susceptibility testing results have been provided with a report comment in the electronic health record (EHR) outlining appropriate dosages (ie, 8–12 mg/kg) for the daptomycin SDD category. At our institution, the SDD interpretive category is reported alongside the MIC, similar to the reporting of other interpretive categories. On the isolate report, the dosage guidance is provided as a footnote stating, "SDD for daptomycin in the treatment of *Enterococcus* sp. is based on a higher dosage of 8–12 mg/kg in adults. Infectious Diseases consultation recommended if daptomycin is used in this setting." During the preperiod, MICs were interpreted according to the 2018 CLSI guidelines, and the post-SDD time period used the 2019 guidelines (Supplementary Data 1) [2, 3]. Isolates were identified to the species level (via MALDI-TOF [matrix-assisted laser desorption/ionization time-of-flight] MS), and the Etest (bioMérieux) was performed and was reported in doubling dilutions, with the exception that in the preperiod urinary isolates were identified only to the genus level. Daptomycin susceptibility testing was performed on sterile sources and on VRE isolated from the urine and was not reported on lower respiratory isolates. The presence of van A/B gene was reported from Biofire Diagnostic Film Array blood culture panel.

Patient Consent

The Institutional Review Board deemed this study exempt. This study does not include factors necessitating patient consent.

Study Design

This study was divided into 2 parts: clinical survey and retrospective chart review.

Part 1: Clinician Survey

Recruitment

The survey was open from January through February 2021 to fully licensed IM and ID physicians and advanced practice providers as identified through the local human resources department and confirmed by the study team. Medical residents, fellows, pharmacists, and clinical microbiologists were excluded. The survey included 4 knowledge-based questions, 4 attitude-based questions, and 3 demographic questions (Supplementary Data 2). Knowledge-based questions were designed to cover the meaning of SDD in general, then the meaning of SDD applied to daptomycin specifically, and case-based questions were meant to assess the application of this knowledge. Attitude-based questions were designed to assess clinicians' self-perceived understanding and application of SDD. Before distribution, the survey questions were independently reviewed by each member of the study team and by the Mayo Clinic Survey Center.

Data Collection

The Mayo Clinic Survey Center distributed the survey via email using Qualtrics Survey Software. The parameters of study participation were provided in an introductory email, which outlined the purpose of the survey, the approach to protecting respondent confidentiality, and the voluntary nature of involvement. After the initial distribution email, up to 4 automated reminder emails were sent. Respondents were entered in a drawing to receive 1 of 6 remunerations (3 per each specialty). Participants could leave questions unanswered. Any surveys left unfinished at the date of closure were still collected and available answers included in data analysis. Survey responses were analyzed for the percentage of knowledge questions answered correctly, the attitudes of clinicians were assessed with Likert scale responses, and demographic information of survey participants was collected. Survey results were de-identified for analysis.

Statistical Analysis

The responses to survey questions were summarized using frequencies and percentages. Questions on the Likert scale were compared between IM and ID clinicians using Wilcoxon rank-sum tests. The remaining responses were compared between clinician groups using either a chi-square or Fisher exact test, as appropriate. All tests were 2-sided, and P values ≤.05 were considered statistically significant. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Part 2: Retrospective Chart Review

Population

A retrospective chart review was conducted from 1 year pre–SDD reporting (5/1/2017–5/1/2018) to 1 year post–SDD implementation (9/1/2019–9/1/2020). Time periods were chosen to allow adequate time for full implementation of SDD reporting. Inclusion criteria were inpatient admission at the study site and *Enterococcus* spp. cultured from sterile sources or VRE from urine with a daptomycin MIC of 2 or 4 mcg/mL. Patients were excluded for the following reasons: age <18 years, presence of pulmonary infection, current incarceration, currently pregnant, or lack of Minnesota research authorization on file.

Data Collection

A microbiology report identifying patients with an *Enterococcus* spp. isolate with daptomycin susceptibilities performed within the study time frame was reviewed for inclusion and exclusion criteria. The following were collected on patients who met study criteria: demographics, height/weight/laboratory values at the time of culture sample collection, concomitant use of serotonergic medications and/or statin therapy, species of *Enterococcus* when applicable, antimicrobial susceptibilities, poly- or monomicrobial infection, and empiric and definitive antibiotics administered. The doses (ie, total daily doses and

mg/kg doses) of daptomycin given before and after susceptibility results were reported, as well as record of ID consultation. Data were stored in a Research Electronic Data Capture (REDCap) database.

Statistical Analysis

Data were summarized using frequencies and percentages for categorical variables and medians and interquartile ranges (IQRs) for continuous variables. Comparisons were made between time periods using the chi-square test or Fisher exact test for categorical data and the Wilcoxon rank-sum test for continuous data. Univariable and multivariable logistic regression was used to assess the association between time period and daptomycin prescribing rates. In the multivariable model, we adjusted for serotonergic medication use, allergies, statin use, and ID consultation. These variables were chosen a priori. Associations were summarized using odds ratios (ORs) and 95% CIs. A multivariable linear regression model was used to evaluate the variables of time period (pre or post), ID consultation, culture source, and MIC on daptomycin dosing. All tests were 2-sided, and P values ≤.05 were considered statistically significant. All analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Part 1: Clinician Survey

Clinician Recruitment

Thirty-five ID clinicians and 111 IM clinicians were identified as potential survey participants based on an organizational report provider by our institution's department of human resources. One and 13 clinicians from ID and IM were excluded, respectively, due to inactive practice status. This resulted in 34 ID clinicians and 98 IM clinicians who were approached as possible survey participants. The response rate among ID clinicians was 65% (22/34), and among IM clinicians it was 41% (40/98). Of all clinicians who started the survey, there were a total of 6 surveys (4 from IM and 2 from ID) that were left with at least 1 incomplete response. There were no significant differences in credentials (MD/DO, APRN, PA) between ID and IM clinicians (P = .17) or in the years of experience in their respective specialty training (P = .12).

Knowledge-Based Questions

Overall, ID clinicians scored significantly higher in 3 of 4 knowledge-based questions compared with IM (Figure 1A). The single multiple-choice question (Question 1, Supplementary Data 2) in which IM and ID clinicians performed similarly related to the ability to correctly define SDD, where 36 of 39 (92%) IM and 20/21 (95%) ID clinicians answered correctly (P = .99). More ID clinicians than IM clinicians correctly answered the question focused on dose selection for treatment of infections due to isolates reported as SDD (Questions 5 and 6) and the questions assessing case-based application (Questions 7 and 8) of knowledge (Table 1). In total, more ID clinicians answered all 4 knowledge-based questions correctly compared with IM clinicians (Table 1).

Attitude-Based Questions

Based on the 4 attitude questions (Supplementary Data 2), ID clinician responses significantly differed from IM clinician responses (Figure 1B). ID clinicians answered "agree" or "strongly agree" to attitude-based questions at a higher rate, indicating that they placed more importance on and had more confidence in using the SDD category compared with IM clinicians (Figure 1B).

Part 2: Retrospective Chart Review

Demographics

A total of 2118 enterococcal isolates were identified by microbiology report; these included all *Enterococcus* spp. with daptomycin susceptibility testing results from 5/1/2017 to 5/1/2018 and 9/1/2019 to 9/1/2020. Following application of inclusion/exclusion criteria (Figure 2), 474 patients were included in the final analysis—225 patients in the pre-SDD period and 249 patients in the post-SDD period. Patient demographics were similar between the 2 groups, with the exception of the median age being higher in the post-SDD group (65 years vs 62 years; P = .022) (Table 2A).

Enterococci Characteristics

A difference in the number of *Enterococcus* spp. was identified between the pre- and post-SDD periods (Table 2B). There was a higher number of *Enterococcus faecium* isolates observed in the post-SDD period (55.1% vs 66.7%). Penicillin susceptibility was significantly increased in the post-SDD period as compared with the pre-SDD period, and no difference in linezolid susceptibility patterns was noted. No statistically significant difference was identified in vancomycin susceptibilities in the pre- vs post-SDD cohorts. There was a significantly higher percentage of isolates with a daptomycin MIC of 4 mcg/mL in the post-SDD period.

Antibiotic Administration

There is a notable distinction when taking into consideration whether a susceptibility report was available at the time of administration. Before susceptibility reporting (ie, empiric antimicrobial administration), daptomycin was used with equal frequency in the pre- and post-SDD time periods (14.7% vs 14.5%; P = .95). When daptomycin use was empiric, the median dose did not differ between the pre-SDD and post-SDD periods (6.3 mg/kg vs 6.2 mg/kg; P = .67). After susceptibility reporting was made available, daptomycin was used significantly less often in the post-SDD time period as compared with the pre-SDD period (16.9% vs 35.1%; P < .001). When used

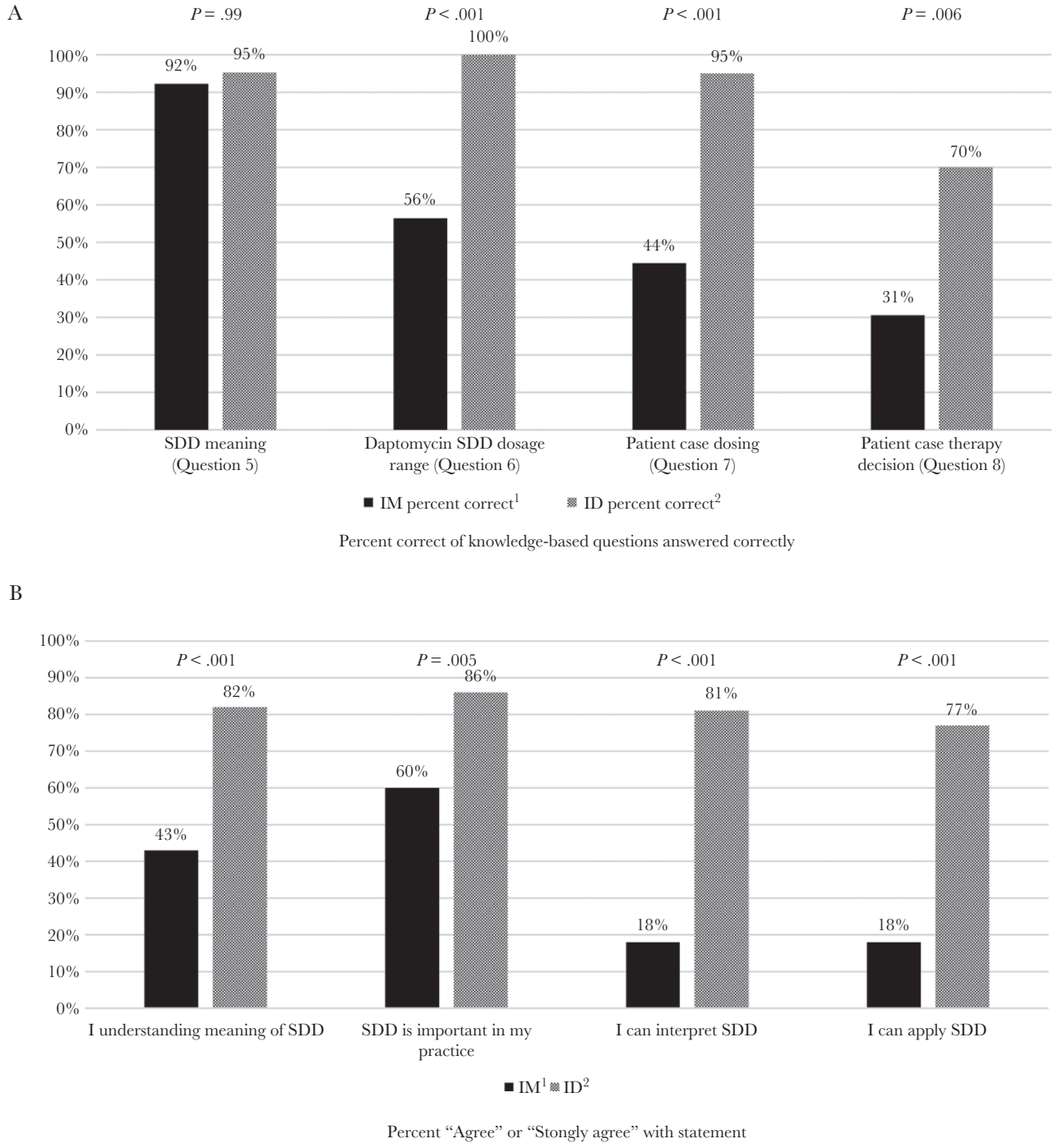

Figure 1. A, Responses to knowledge-based questions. B, Responses to Likert-scale attitude-based questions. Abbreviations: ID, infectious disease clinicians; IM, internal medicine clinicians; SDD, susceptible dose-dependent.

for definitive treatment (ie, after susceptibility reports were released), the median daptomycin dose was significantly higher in the post-SDD group (6.4 mg/kg vs 8.5 mg/kg; $P < .001$). Additionally, dosing in the post-SDD period when the isolates were stratified by MIC displayed a slightly higher dose utilized in isolates with an MIC of 2 mcg/mL (8.2 mg/kg) vs 4 mcg/mL (9.0 mg/kg). However, in both the pre- and post-SDD periods, a trend toward high dosing was observed in isolates with an MIC of 4 mcg/mL compared with 2 mcg/mL (7.6 mg/kg vs 6.5 mg/kg). Overall, the median daptomycin dose differed significantly by culture source comparing blood, urine, and other in the pre period (overall $P = .003$) but not in the post period (overall $P = .71$). ID was consulted in 60.8% of all patients, and in 93.4% of patient cases when daptomycin was utilized. In both pre- and post-SDD periods, the median daptomycin dose was significantly higher when an ID consult was present (pre-SDD period, 5.2 mg/kg vs 6.4 mg/kg; $P = .040$; post-SDD period, 6.2 vs 8.7 mg/kg; $P = .041$). When evaluating cases for which

Table 1. Responses to Knowledge-Based Questions

Knowledge-Based Responses Correct by Individual Question				
	IM Number Correct (%)	ID Number Correct (%)	Overall Number Correct (%)	*P* Value
SDD meaning (Question 5)	36/39 (92.3)	20/21 (95.2)	56/60 (93.3)	.99
Daptomycin SDD dosage range (Question 6)	22/39 (56.4)	21/21 (100.0)	43/60 (71.7)	<.001
Patient case dosing (Question 7)	16/36 (44.4)	19/20 (95.0)	35/56 (62.5)	<.001
Patient case therapy decision (Question 8)	11/36 (30.6)	14/20 (70.0)	25/56 (44.6)	.006
Overall Performance on Knowledge-Based Questions				
	IM Clinicians, %		ID Clinicians, %	*P* Value
1 question correct	97.2		100.0	<.001
2 questions correct	63.9		100.0	
3 questions correct	44.5		95.0	
4 questions correct	16.7		65.0	

Abbreviations: ID, infectious diseases; IM, internal medicine; SDD, susceptible dose-dependent.

daptomycin was utilized, rates of ID specialist involvement were similar between the 2 time periods. Uni- and multivariable analyses showed a higher likelihood of receipt of daptomycin in the pre-SDD period or when ID was consulted (Table 3). There was no significant effect of serotonergic medication use, antibiotic allergy reported, or statin use on the utilization of daptomycin. The associated time period (pre vs post) was found to remain a statistically significant variable when the data were analyzed using a multivariable linear regression model for daptomycin dosing ($P < .001$) (Supplementary Data 3).

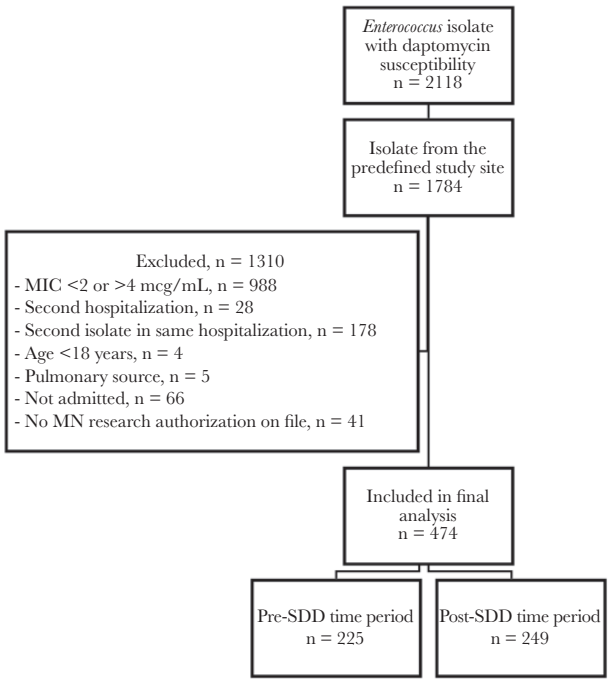

Figure 2. Patient recruitment. Abbreviations: MIC, minimum inhibitory concentration; MN, Minnesota; SDD, susceptible dose-dependent.

DISCUSSION

Proper daptomycin dosing for enterococcal infections with an SDD susceptibility result is an important facet of ensuring appropriate antibiotic therapy. Despite the release of the new SDD interpretive criteria several years ago, little is known about how well this information is understood and practically applied by clinicians. The current study was developed to evaluate ID and IM clinicians' understanding and attitudes toward the SDD interpretive criteria for daptomycin in enterococcal isolates and to assess the integration of this into real-world clinical practice. The novel mixed-methods study design allowed us to evaluate current knowledge and attitudes of clinicians and assess whether changes in practice occurred following implementation of SDD reporting, thereby allowing an assessment of both quantitative and qualitative data on the criteria's use [7].

In Part 1 of this study, a significant difference was identified between ID and IM clinicians in both the knowledge of the SDD interpretive category as it applies to daptomycin and enterococci and the subjective attitudes of utilizing this category. While this may be anticipated given the additional training that ID clinicians receive, there are still important observations from these results. Notably, at an institution such as our study site, there is guidance provided on the susceptibility report as to how daptomycin doses should be optimized in the case of an SDD isolate. Even with the presence of this guidance in clinical practice, IM clinicians were less knowledgeable of the interpretation of the SDD category when presented with a patient case in the absence of a guiding statement provided within the patient case. This observation is potentially of greater importance at institutions without a specialty ID service to assist with antibiotic optimization. In such institutions, the clinical practice may benefit from increased provider education as well as from pharmacist involvement in daptomycin dosing.

Table 2. Part 2 Characteristics

A, Patient Demographics

	Pre-SDD Period (n = 225)	Post-SDD Period (n = 249)	Total (n = 474)	*P* Value
Age				
Median (IQR), y	62 (52–71)	65 (57–73)	64 (54–72)	.022
Gender				.57
Female	97 (43.1)	101 (40.6)	198 (41.8)	
Male	128 (56.9)	148 (59.4)	276 (58.2)	
Weight				.16
Median (IQR), kg	78.3 (66.5–91.5)	81.8 (66.8–96.1)	80.1 (66.6–95.2)	
BMI				.28
Median (IQR), kg/m^2	26.7 (22.5–31.8)	27.6 (22.9–32)	27.2 (22.8–31.9)	
Statin use, No. (%)	72 (34.6)	67 (27.2)	139 (30.6)	.10
>1 serotonergic medication, No. (%)	11 (4.9)	15 (6.0)	26 (5.5)	.69
Any antibiotic allergy reported, No. (%)	74 (32.9)	82 (32.9)	156 (32.9)	.99

B, Isolate Species Characteristics & Antibiotic Administration

	Pre-SDD Period (n = 225)	Post-SDD Period (n = 249)	Total (n = 474)	*P* Value
Pathogens, No. (%)				.82
Polymicrobial	145 (64.4)	158 (63.5)	303 (63.9)	
Monomicrobial	80 (35.6)	91 (36.5)	171 (36.1)	
Species of *Enterococcus*, No. (%)				<.001[a]
E. faecalis	67 (29.8)	72 (28.9)	139 (29.3)	
E. faecium	124 (55.1)	166 (66.7)	290 (61.2)	
Enterococcus spp.[b]	25 (11.1)	0 (0)	25 (5.3)	
Other species[c]	9 (4)	11 (4.4)	20 (4.2)	
Daptomycin MIC, No. (%)				.004
2 mcg/mL	163 (72.4)	149 (59.8)	312 (65.8)	
4 mcg/mL	62 (27.6)	100 (40.2)	162 (34.2)	
Linezolid susceptibility, No. (%)				.14
Susceptible	111/112 (99.1)	240/240 (100)	351/352 (99.7)	
Resistant	1/112 (0.9)	0/240 (0.0)	1/352 (0.3)	
Penicillin susceptibility, No. (%)				
Susceptible	107/225 (47.6)	142/247 (57.5)	249/472 (52.8)	
Resistant	118/225 (52.4)	105/247 (42.5)	223/472 (47.2)	
Vancomycin susceptibility, No. (%)				.092
Susceptible	124/221 (56.1)	163/248 (65.7)	287/469 (61.2)	
Intermediate	2/221 (0.9)	1/248 (0.4)	3/469 (0.6)	
Resistant	95/221 (43.0)	84/248 (33.9)	179/469 (38.2)	
Empiric antibiotic, No. (%)				
Daptomycin	15 (6.7)	8 (3.2)	23 (4.9)	.081
Vancomycin	92 (40.9)	96 (38.6)	188 (39.7)	.6
Piperacillin-tazobactam	85 (37.8)	86 (34.5)	171 (36.1)	.46
Ampicillin	4 (1.8)	1 (0.4)	5 (1.1)	.14
Linezolid	6 (2.7)	6 (2.4)	12 (2.5)	.86
Ampicillin-sulbactam	1 (0.4)	3 (1.2)	4 (0.5)	.37
Antibiotics administered during course of therapy, No. (%)				
Vancomycin	137 (60.9)	125 (50.2)	262 (55.3)	.019
Piperacillin-tazobactam	112 (49.8)	115 (46.2)	227 (47.9)	.43
Ampicillin	9 (4)	14 (5.6)	23 (4.9)	.41
Linezolid	19 (8.4)	25 (10)	44 (9.3)	.55
Ampicillin-sulbactam	2 (0.9)	8 (3.2)	10 (2.1)	.079
Daptomycin use before susceptibility reporting, No. (%)				.95
Yes	33 (14.7)	36 (14.5)	69 (14.6)	
Daptomycin dose before susceptibility reporting				.67
Median (IQR), mg/kg	6.3 (6.1–7.0)	6.2 (6.0–6.8)	6.3 (6.0–7.0)	
Daptomycin use after susceptibility reporting, No. (%)				<.001
Yes	79 (35.1)	42 (16.9)	121 (25.5)	
Daptomycin dose after susceptibility reporting				
Median (IQR), total, mg/kg	6.4 (6.0–7.1)	8.5 (6.4–10.0)	6.6 (6.1–8.3)	<.001
Median (IQR), excluding *Enterococcus* identified to genus level only,[d] mg/kg	6.4 (6.1–7.0)	8.5 (6.4–10.0)	6.5 (6.1–8.3)	<.001

Table 2. Continued

A, Patient Demographics				
	Pre-SDD Period (n = 225)	Post-SDD Period (n = 249)	Total (n = 474)	*P* Value
Median (IQR), MIC 2 mcg/mL,[e] mg/kg	6.3 (6.0–6.9)	8.2 (6.2–9.4)	6.5 (6.1–8.0)	<.001
Median (IQR), MIC 4 mcg/mL,[f] mg/kg	6.4 (6.1–7.7)	9.0 (7.9–10.2)	7.6 (6.2–9.0)	.002
Median (IQR), source = blood,[g] mg/kg	6.9 (6.2–8.3)	8.8 (8.0–10.0)	7.9 (6.4–8.7)	.005
Median (IQR), source = urine,[h] mg/kg	5.2 (4.3–7.0)	8.6 (5.3–9.8)	6.2 (4.3–9.4)	.20
Median (IQR), source = other,[i] mg/kg	6.3 (6.0–6.6)	8.3 (6.3–9.7)	6.4 (6.1–7.9)	<.001
Median (IQR), ID consult,[j] mg/kg	6.4 (6.1–7.2)	8.7 (7.9–10.0)	6.6 (6.1–8.4)	<.001
Median (IQR), no ID consult,[k] mg/kg	5.2 (5.2–6.0)	6.2 (6.0–8.1)	6.0 (5.2–7.2)	.18
ID consultation, No. (%)				
All patients	158 (70.2)	130 (52.2)	288 (60.8)	<.001
Patients receiving daptomycin	76 (96.2)	37 (88.1)	113 (93.4)	.088

Abbreviations: BMI, body mass index; ID, infectious diseases; IM, internal medicine; IQR, interquartile range; MIC, minimum inhibitory concentration; SDD, susceptible dose-dependent.

[a]A significant *P* value indicates an imbalance in the spread of *Enterococcus* spp. but does not specify between which values a significant difference lies.

[b]Isolates not identified to the species level depending on specimen source pre-SDD time period; in post-SDD time period, isolates were routinely identified to the species level regardless of source.

[c]Other species: *E. casseliflavus* (1), *E. gallinarum* (12), *E. hirae* (5), *E. mundtii* (1), *E. raffinosus* (1).

[d]Pre: n = 76; post: n = 42.

[e]Pre: n = 54; post: n = 23.

[f]Pre: n = 25; post: n = 19.

[g]Pre: n = 25; post: n = 12.

[h]Pre: n = 7; post: n = 8.

[i]Pre: n = 125; post: n = 159.

[j]Pre: n = 76; post: n = 37.

[k]Pre: n = 3; post: n = 5.

In Part 2 of this study, a change in practice was observed in which higher doses of daptomycin were used in definitive therapy in the post-SDD group. Specifically, the median dose utilized did fall within the recommended range of 8–12 mg/kg, albeit on the lower end of the recommended range and with some patients receiving continued use of 6 mg/kg of daptomycin despite displaying SDD susceptibility. When distinguishing isolates with an MIC of 2 vs 4 mcg/mL, there was a trend toward higher dosing being prescribed for the MIC 4 mcg/mL subgroup (Table 2B). This finding may demonstrate MIC-tailored dosing in these patient scenarios, recognizing that higher MICs within the SDD interpretation require increased daptomycin dosing. Interestingly, before the release of susceptibility results, the dosing in both periods demonstrates a dosing strategy closer to 6 mg/kg. Consideration may be given whether there are situations in which an empiric dosing strategy of 8–12 mg/kg should be indicated to target an *Enterococcus* sp. with an SDD susceptibility. This appears to be a limitation of directing antimicrobial dosing using susceptibility results that are not available empirically.

Table 3. Variable Analyses

	Univariable		Multivariable	
	Odds Ratio[a] (95% CI)	*P* Value	Adjusted Odds Ratio (95% CI)	*P* Value
Time period (pre vs post)	0.38 (0.24–0.58)	<.001	0.50 (0.31–0.80)	.004
Serotonergic medication use	0.87 (0.34–2.22)	.77	0.96 (0.34–2.73)	.94
Allergy reported	1.36 (0.88–2.08)	.17	1.08 (0.66–1.77)	.77
Statin use	1.02 (0.64–1.62)	.94	0.84 (0.50–1.40)	.50
ID consulted	14.36 (6.81–30.30)	<.001	13.80 (6.20–30.73)	<.001

Abbreviations: ID, infectious diseases; OR, odds ratio.

[a]OR >1 means more likely to have had daptomycin administered following susceptibility reports.

While the median definitive therapy daptomycin dose was increased following SDD implementation, the overall rate of daptomycin administration was decreased. Compared with the pre-SDD period, there was an increase in both penicillin and vancomycin-susceptible isolates in the post-SDD period. This variability in susceptibilities, coupled with provider unfamiliarity surrounding the SDD interpretive criteria or a preference for use of an antimicrobial reported as susceptible over SDD (eg, linezolid), may have impacted the agent selected for definitive therapy. A similar finding was seen in a small retrospective analysis of cefepime SDD *Enterobacterales* isolates wherein most infections were treated with a carbapenem instead of cefepime [8]. However, in that study all cefepime SDD isolates were dosed in accordance with CLSI guidance, whereas daptomycin was not always dosed to SDD specifications in our findings. Interestingly, we did not identify a statistically significant shift to a single daptomycin alternative for definitive therapy (eg, linezolid, vancomycin, or ampicillin-based regimens) in the post-SDD period. This considered, definitive antimicrobial therapy selection is a multifactorial decision impacted by the interplay between patient and/or organism characteristics, clinician preferences, and more. Therefore, a singular reason for

the decrease in definitive daptomycin use in the post period was not able to be clearly determined in this study.

Current literature supports the involvement of ID specialists to aid with antimicrobial management in patients with enterococcal infections. Specifically, ID consultation in the treatment of enterococcal bacteremia was associated with lower 30-day mortality compared with patients who did not receive ID consultation, especially when *Enterococcus faecium* was isolated [9]. An additional retrospective analysis assessed the impact of ID consultation in children with enterococcal bacteremia [10]. This analysis showed ID specialist involvement to be associated with a significant improvement in outcomes, such as higher rates of appropriate empiric therapy, appropriate definitive therapy, and increased survival at 1 year [10]. These additional studies emphasize that ID involvement improves patient outcomes for serious enterococcal infections. Our study adds to this literature by demonstrating the importance of ID specialist involvement in the selection of optimal daptomycin doses.

This study has several limitations. First, it was conducted at a single academic medical center and may not be representative of the knowledge, practices, and resources at other institutions. Second, the involvement of ID specialists, clinical pharmacists, and clinical microbiologists in the day-to-day practice may have impacted chart review results, whereas these clinicians were excluded from the survey. Third, an interrupted time series is vulnerable to confounding. Additionally, while survey response rates were similar to those reported in the literature, there were fewer participants in the IM group relative to ID. Next, while the current study evaluated changes and current attitudes in practice, it was not designed to evaluate clinical outcomes. Another limitation is that this study does not assess the 2020 CLSI revised daptomycin breakpoints. Our institution has since adopted these updated breakpoints, but they are not assessed in this study.

The current study was able to identify critical gaps in the understanding and implementation of SDD interpretive criteria when applied to *Enterococcus* spp. and daptomycin. Further studies are needed to evaluate clinical outcomes of both efficacy and toxicity in patients treated with daptomycin 8–12 mg/kg for enterococcal infections. With the most recent CLSI guidance on daptomycin breakpoints, there is now no "susceptible" breakpoint for *E. faecium* for daptomycin, only "SDD" and "resistant," highlighting the importance more than ever of proper understanding and application of SDD [3]. The impact of reporting of SDD interpretive categories at institutions without ID specialty practices and/or without antimicrobial stewardship guidance comments to specify dosages upon which the breakpoints were developed merits further exploration.

CONCLUSIONS

ID clinicians demonstrated better understanding and higher confidence in daptomycin SDD interpretive criteria for *Enterococcus* spp. as compared with IM clinicians. SDD reporting resulted in a modest change in definitive daptomycin dosing and no change in empiric dosing at our institution. ID specialist involvement is recommended when daptomycin is used to treat enterococci with a daptomycin MIC in the SDD range.

Acknowledgments

We would like to thank Mikayla Puskala from the Clinical Microbiology Laboratory for assistance with gathering the microbiology report.

Financial support. This work was supported by the Pharmacy Research Committee from the Department of Pharmacy at Mayo Clinic. REDCap was utilized under grant support (UL1TR002377).

Potential conflicts of interest. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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