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Prevalence of beta-lactam nonsusceptible Gram-negative bacilli and use and interpretation of current susceptibility breakpoints: a survey of infectious disease physicians☆,☆☆,★

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Abstract

Beta-lactam–resistant *Enterobacteriaceae* represent an important public health problem; however, questions exist about their prevalence and the impact of recent breakpoint changes on clinical practice. We surveyed infectious disease physicians to better understand these issues. Many reported encountering resistant Enterobacteriaceae; respondents generally favored a more conservative interpretation of antimicrobial susceptibility results.

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Multidrug-resistant *Enterobacteriaceae*, including those resistant to beta-lactams, represent a growing public health problem (Bilavsky et al., 2010; CDC, 2009). Control and treatment of these organisms require that they be reliably identified in the laboratory. Changes in the 2010 Clinical and Laboratory Standards Institute (CLSI) (M100-S20 and M100-S20U) guidance for cephalosporin and carbapenem susceptibility breakpoints for *Enterobacteriaceae* have potential to change the way laboratories and clinicians approach these organisms by lowering breakpoints used for interpreting minimum inhibitory concentrations (MICs) (CLSI, 2010a, 2010b). Furthermore, this change removes the need to identify mechanisms of resistance (e.g., extended-spectrum beta-lactamase [ESBL] production) and adjust test results. In order to better understand the prevalence of these resistant organisms and the use of the current CLSI susceptibility breakpoints for *Enterobacteriaceae*, we surveyed infectious disease clinicians who were members of the Emerging Infections Network (EIN).

The EIN of the Infectious Disease Society of America consists of 1332 clinically oriented adult and pediatric infectious disease physicians who can be rapidly queried about important public health issues. In November 2010, EIN conducted a 1-time survey about the prevalence of beta-lactam–resistant Gram-negative bacilli and use and interpretation of the current CLSI breakpoints. Surveys were sent by email and/or fax to all US EIN members ($N = 1307$). The survey consisted of 6 questions in the following 3 domains: prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE) and ESBL-producing *Enterobacteriaceae*, use of the current CLSI breakpoints, and comfort with the current cephalosporin breakpoints for clinical decision making. For simplicity, *Enterobacteriaceae* were considered carbapenem-resistant if they were nonsusceptible to at least 1

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carbapenem and ESBL producers if they were nonsusceptible to any extended-spectrum cephalosporin.

Overall, 569 of 1307 clinicians responded to the survey (response rate 44%). Respondents more often cared for adults (416 [73%]) than for children (126 [22%]) or both (27 [5%]); respondents were categorized as caring for any adults (adults and both children and adults) or only children for this analysis. Most respondents were from the South Atlantic census region (114 [20%]), followed by the Pacific region (101 [18%]), and the Mid-Atlantic (92 [16%]). The least represented census area was New England (26 [5%]). Most respondents practiced in a university or medical school (212 [37%]) and had between 15 and 24 years of infectious diseases practice experience (177 [31%]); 160 (28%) had less than 5 years' experience.

The frequency with which providers cared for patients with ESBL-producing *Enterobacteriaceae* and CRE is shown in Table 1. The majority of respondents in each census region reported that they had treated patients infected or colonized with ESBLs in the last 3 months (range 87% to 97%). The percentage of respondents reporting they had treated patients infected or colonized with CRE in the last 3 months varied by census region: New England 31%, Mountain 33%, Pacific 42%, West North Central 47%, East North Central 52%, East South Central 54%, South Atlantic 55%, Mid-Atlantic 59%, and West South Central 60%.

Overall, 144 (31%) respondents reported they were unfamiliar with the current CLSI breakpoints for *Enterobacteriaceae*. Of those who were aware of the changes, respondents were nearly evenly split between those whose laboratories were currently using them and those not (Table 2). About half of those not using the current breakpoints had plans to adopt them. Most respondents reported they were using the current breakpoints to make clinical decisions (Table 2). However, responses to several clinical scenarios suggested respondents were using a combination of the old and current recommendations (Table 3). Specifically, the majority of respondents favored using the current lower cephalosporin breakpoints combined with tests for ESBL detection before making treatment recommendations.

Respondents were asked what they considered to be the most important problem with regard to diagnosis and treatment of multidrug-resistant Gram-negative bacilli. Respondents (179 [44%]) cited the lack of new effective antimicrobials most commonly (179 [%]) followed by diagnostic/clinical laboratory issues (103 [25%]) (e.g., need for more rapid, reliable, and reproducible testing methods). Smaller numbers of respondents listed the following: inappropriate antimicrobials use (24 [6%]), differentiating colonization from infection (23 6[%]), lack of information on optimal treatment regimens (22 [5%]), lack of a clear consensus on recommended infection prevention practices to reduce transmission (20 [5%]), difficulty with dosing polymyxin antimicrobials (10 [2%]), and lack of pediatric-specific treatment/diagnostic recommendations (8 [2%]). Fifteen (4%) responses could not be further categorized.

It is important to note that two-thirds of responding infectious disease clinicians reported caring for a patient with CRE colonization or infection and nearly all had treated a patient with an ESBL-producing *Enterobacteriaceae* in the

Table 2
Use of current Clinical and Laboratory Standards Institute carbapenem and cephalosporin breakpoints for *Enterobacteriaceae*

Question	For cephalosporins, *n* (%)	For carbapenems, *n* (%)
Is your facility reporting susceptibility or nonsusceptibility based on the current breakpoints today?	*n* = 317	*n* = 317
Yes	140 (44%)	130 (41%)
No	126 (40%)	130 (41%)
Not sure	51 (16%)	57 (18%)
If your facility is using the old breakpoints, does your laboratory plan to change to the current breakpoints?	*n* = 175	*n* = 185
Yes	92 (53%)	95 (51%)
No	6 (3%)	5 (3%)
Not sure	77 (44%)	85 (46%)
Are you currently using the current breakpoints to make treatment decisions?	*n* = 286	*n* = 282
Yes	166 (58%)	150 (53%)
No	97 (34%)	99 (35%)
Not sure	23 (8%)	33 (12%)

Table 1
Reported frequency of patients treated over the prior 3 months with extended spectrum beta-lactamase producing *Enterobacteriaceae* or carbapenem-resistant *Enterobacteriaceae*

Organism	Number of respondents	Over the prior 3 months the number (%) of providers treating			
		0 patients	1 to 2 patients	3 to 5 patients	More than 5 patients
Among providers caring for any adult					
ESBL*	364	13 (4%)	68 (19%)	115 (32%)	168 (46.2%)
CRE†	443	191 (43.1%)	136 (30.7%)	83 (18.7%)	33 (7.4%)
Among providers caring only for children					
ESBL*	91	20 (22.0%)	39 (42.9%)	23 (25.3%)	9 (9.9%)
CRE†	125	92 (73.6%)	27 (21.6%)	6 (4.8%)	0 (0%)

* Extended-spectrum beta-lactamase producing *Enterobacteriaceae*.
† Carbapenem-resistant *Enterobacteriaceae*.

Table 3
Clinical scenarios: use of current cephalosporin breakpoints for clinical treatment decisions

Would you use ceftazidime to treat a *Klebsiella spp.* infection when	Number	Yes	No	Unsure	Ask for ESBL test before deciding
The ceftazidime MIC is 2 μg/mL (susceptible by the current breakpoints) but the isolate meets the previous screening criteria for the ESBL test (using the old breakpoints), *n* (%)	439	111 (25%)	231 (53%)	97 (22%)	Not asked
The ceftazidime MIC is 2 μg/mL (susceptible by the current breakpoints) but the ESBL test is performed and is positive, *n* (%)	438	36 (8%)	360 (82%)	42 (10%)	Not asked
The ceftazidime MIC is 8 μg/mL (intermediate by the current breakpoints, susceptible by the old breakpoints), *n* (%)	426	16 (4%)	356 (84%)	54 (13%)	Not asked
The ceftazidime MIC is 8 μg/mL (intermediate by the current breakpoints, susceptible by the old breakpoints) and the ESBL test is performed and is negative, *n* (%)	433	70 (16%)	284 (66%)	79 (18%)	Not asked
The ceftazidime MIC is 2 μg/mL (susceptible by the current breakpoints) and the ceftriaxone MIC is 4 μg/mL (resistant by the current breakpoints), *n* (%)	434	101 (23%)	133 (31%)	62 (14%)	138 (32%)

last 3 months. Although national data on the prevalence of these organisms are limited, data from the National Healthcare Safety Network from 2006 and 2007 have shown that between 21% and 27% of *Klebsiella pneumoniae* from hospitalized patients were resistant to extended-spectrum cephalosporins and between 4% and 10% were resistant to a carbapenem (Hidron et al., 2008). Taken together, this information reinforces the frequency with which these organisms are being encountered and the need for additional effort aimed at preventing both infections with and transmission of these organisms.

The current CLSI breakpoints (CLSI, 2010a, 2010b) were established to allow for resistance to cephalosporins to be identified without the need for specialized testing (e.g., ESBL testing). However, a number of obstacles have complicated their complete adoption. In addition, controversy has developed about the appropriateness of using the current cephalosporin breakpoints without ESBL testing (Jenkins, 2010; Schreckenberger, 2010). Unfortunately, evidence on treatment outcomes based on use of the current breakpoints alone is lacking and is at times contradictory (Bhavnani et al., 2006; Paterson et al., 2001; Wong-Beringer et al., 2002). Respondents in this survey appear to prefer a more conservative approach: treating potential ESBL-producing *Enterobacteriaceae* with cephalosporins based on parts of both the old and current criteria for susceptibility. Most respondents would not treat based on the current breakpoints alone without ESBL testing as was recommended in the old guidance. However, most would not use a cephalosporin for an *Enterobacteriaceae* that was extended-spectrum cephalosporin susceptible using the old higher breakpoints if it was nonsusceptible using the current lower breakpoints, even if ESBL testing was negative. In addition, most respondents would not use an extended-spectrum cephalosporin that tested susceptible when another extended-spectrum cephalosporin tested nonsusceptible using the current breakpoints.

This report is subject to several limitations. The response rate was less than 50%, which limits conclusions that can be drawn from these data. In addition, EIN is a convenience sample of infectious disease clinicians and results may not be entirely generalizable outside the survey sample.

In summary, infectious disease physicians commonly treat patients with infections caused by *Enterobacteriaceae* that are resistant to broad-spectrum antimicrobials. Although many of the laboratories these physicians use have instituted the current CLSI breakpoints or plan to in the future, it appears that many respondents would not use these current breakpoints without testing for ESBLs as previously recommended.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.diagmicrobio.2011.07.013.

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