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Active Surveillance for Carbapenem-Resistant Enterobacteriaceae Using Stool Specimens Submitted for Testing for *Clostridium difficile*

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Abstract

Active surveillance to identify asymptomatic carriers of carbapenem-resistant Enterobacteriaceae (CRE) is a recommended strategy for CRE control in healthcare facilities. Active surveillance using stool specimens tested for *Clostridium difficile* is a relatively low-cost strategy to detect CRE carriers. Further evaluation of this and other risk factor-based active surveillance strategies is warranted.

Carbapenem-resistant Enterobacteriaceae (CRE) are increasingly common causes of healthcare-associated infections for which limited therapeutic options exist. Active surveillance—identifying and implementing infection control measures for asymptomatic carriers—has been included in successful multifaceted CRE control programs¹ and is one of several interventions recommended in current Centers for Disease Control and Prevention guidance for CRE control.² Active surveillance for CRE typically uses rectal or perianal swab samples to detect gastrointestinal carriage of CRE. This is resource intensive, incurring the costs of swabs and specimen transportation and the human resources needed to obtain and process patient samples, and it requires patient participation in an activity they may consider unpleasant. Active surveillance strategies that reduce costs and barriers while retaining the ability to identify CRE carriers may be cost effective and better accepted. CRE colonization and *Clostridium difficile* infection share risk factors, including prolonged hospitalization, antibiotic exposure, and severity of illness.³ Thus, a potential alternative active surveillance strategy is to test stool specimens submitted for *C. difficile* testing for the

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presence of CRE. This may increase pretest probability while eliminating the need for perianal swab collection. This strategy has been used successfully to identify carriers of vancomycin-resistant *Enterococcus*,⁴ another enteric organism with similar risk factors. The objectives of this study were, among hospital patients being tested for *C. difficile*, to determine the prevalence of CRE colonization, identify risk factors for CRE carriage, and evaluate the relative cost and yield of active surveillance for CRE.

METHODS

Following institutional review board approval, stool specimens submitted for *C. difficile* testing from February through July 2011 at 2 large academic hospitals in New York City were tested for CRE. Before the study period, hospital A performed active surveillance for CRE among patients on high-risk units using perianal swab sampling at admission and weekly thereafter. There was no active surveillance program at hospital B.

Aliquots of stool specimens were obtained upon submission to the laboratory and frozen at -70°C for subsequent testing. Detection of CRE was performed using previously described methods.⁵ The modified Hodge test was performed to detect carbapenemase production among ertapenem-resistant Enterobacteriaceae. Isolates were also tested for the presence of the *Klebsiella pneumoniae* carbapenemase (KPC) gene (NucliSENSEasyQ system, BioMérieux). Isolates that were carbapenem resistant but KPC negative underwent additional testing to determine the mechanism(s) of carbapenem resistance, including assessment of the presence of the New Delhi metallo- β -lactamase carbapenemase; TEM, SHV, and CTX-M extended-spectrum β -lactamases (ESBLs); the ampC gene; and deletions in outer membrane proteins ompF35, ompF36, and ompF37.^{6–8}

A nested case-control study was performed to identify factors associated with CRE carriage. Cases were subjects with stool specimens from which CRE was isolated. Controls were subjects with CRE-negative specimens matched to cases by study facility and randomly selected at a 3 : 1 ratio. Predefined clinical variables were abstracted using a standardized data collection instrument. Variables were evaluated with a χ^2 , Fisher exact, or Mann-Whitney *U* test, as appropriate. Analyses were performed using Stata (ver. 8.2; StataCorp).

RESULTS

CRE was isolated from 27 (2.6%) of 1,047 specimens. The prevalence of CRE was 2.9% (25/854 unique patients), with 4.0% (11/272 patients) at hospital A and 2.4% (14/582 patients) at hospital B ($P = .18$). Among patients with CRE-positive samples, 10 (40%) had been previously identified as CRE carriers (64% at hospital A, 21% at hospital B). The 25 CRE isolates included *K. pneumoniae* ($n = 23$), *Klebsiella oxytoca* ($n = 1$), and *Enterobacter cloacae* ($n = 1$). The KPC gene was detected in 21 (84%) isolates, including 21 (91%) *K. pneumoniae* isolates. The KPC-negative isolates were all found to contain deletions in 1 or more outer membrane proteins, and 3 of the 4 possessed genes for 1 or more ESBLs (SHV and/or TEM).

Among all tested specimens, patients colonized with CRE were older (median age, 66 vs 59 years; $P = .05$). Rates of CRE positivity did not differ between specimens that tested positive (2/90 [2.2%]) and those that tested negative (25/955 [2.6%]; $P = .82$) for *C. difficile* or by patient sex ($P = .97$). In bivariate analysis of data from the case-control study, several characteristics of the index hospitalization were associated with CRE colonization, including length of stay greater than 1 week before testing ($P = .04$), admission from a skilled nursing facility ($P = .01$), percutaneous tube feeding ($P < .01$), intensive care unit admission before testing ($P < .01$), and mechanical ventilation ($P = .01$; Table 1). In addition, exposure to a β -

lactam/ β -lactamase inhibitor combination, oral vancomycin, and more than 20 days of antimicrobial therapy during the index hospitalization were associated with CRE carriage ($P = .02$, $.04$, and $.02$, respectively). Surgery in the 6 months before CRE testing was also associated with CRE colonization ($P = .04$).

The estimated average cost of surveillance testing was \$8.53 per specimen, including technical support and supplies but exclusive of molecular testing. At the prevalence of CRE within the study population, 76 and 68 stool specimens had to be tested at hospitals A and B, respectively, in order to identify 1 previously undetected CRE carrier. Thus, the cost of detecting 1 CRE-colonized patient ranged from \$580 (hospital B) to \$649 (hospital A).

DISCUSSION

In this study, active surveillance for CRE using stool specimens submitted for *C. difficile* testing detected a number of patients with previously unrecognized CRE carriage. While it likely identifies only a small proportion of CRE carriers because of its inclusion of only those patients with signs and symptoms suggestive of *C. difficile* infection, this active surveillance strategy may be of value in some CRE surveillance programs because of its convenience and relatively low cost. For example, this strategy could be implemented in facilities in which CRE have not yet been identified as a potential means of detecting the introduction of CRE carriers into the facility. Alternatively, this strategy could be used as 1 component of a risk factor–based screening program or in conjunction with geographic-based screening programs in facilities in which CRE are prevalent. The findings of the case-control study suggest that certain healthcare-associated exposures may serve as alternative characteristics for use in a risk factor–based active surveillance strategy that may allow identification of a higher prevalence population in which to conduct screening. Previous studies have identified similar healthcare-associated risk factors for CRE colonization and/or infection, including admission from a nursing home, prolonged hospitalization, intensive care unit exposure, mechanical ventilation, and long courses of antimicrobial therapy.^{3,9,10}

This study does have limitations. First, it was performed at 2 academic medical centers in a geographic region with a relatively high prevalence of CRE. It is unknown whether this strategy would yield similar results in other settings. Additionally, the prevalence of and practices regarding testing for *C. difficile* infection may vary among institutions, which could also affect the utility of this type of active surveillance strategy. Finally, the number of cases included in the case-control study was small because of a time-limited funding period and a lower volume of *C. difficile* testing and a lower prevalence of CRE than anticipated, preventing meaningful multivariable analysis of potential CRE risk factors that might allow further refinement of this and other risk factor–based active surveillance strategies. In conclusion, active surveillance for CRE using stool specimens submitted for *C. difficile* testing may represent 1 strategy for a risk factor–based screening program. Further evaluation of this and other risk factor–based active surveillance strategies in other settings is warranted.

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TABLE 1

Demographic Characteristics and Healthcare Exposures Associated with Carbapenem-Resistant Enterobacteriaceae (CRE) Carriage in Bivariate Analysis

Factor	Case subjects (n = 25)	Control subjects (n = 75)	P ^c
Age, years			
>70	11 (44)	20 (27)	.06
50–69	10 (40)	30 (40)	.26
<50	4 (16)	25 (33)	Reference
Healthcare exposures during 6 months before index hospitalization			
Previous hospitalization at study site	15 (60)	44 (59)	.91
Receipt of antibiotics ^a	16 (64)	53 (71)	.53
Any surgery	12 (48)	19 (25)	.04
Healthcare exposures during index hospitalization			
Admitted from skilled nursing facility	7 (29)	6 (8)	<.01
Admitted in transfer from another hospital	6 (24)	12 (16)	.37
Length of admission before CRE testing, median, days	14	7	.02
Length of stay >1 week before test	19 (76)	39 (52)	.04
ICU exposure	15 (60)	18 (24)	<.01
Central venous catheter	18 (72)	39 (52)	.08
Urinary catheter	15 (60)	29 (39)	.06
Mechanical ventilation	11 (44)	14 (19)	.01
Nasogastric tube	5 (20)	20 (27)	.32
Percutaneous feeding tube	9 (36)	6 (8)	<.01
Proton pump inhibitor use	20 (80)	48 (64)	.14
Antibiotic exposures ^b			
β -lactam/ β -lactamase inhibitor	13 (52)	20 (27)	.02
First- or second-generation cephalosporin	2 (8)	6 (8)	1.00
Third-generation cephalosporin	4 (16)	13 (17)	.89
Fourth-generation cephalosporin	7 (28)	18 (24)	.69
Carbapenem	7 (28)	14 (19)	.32
Fluoroquinolone	4 (16)	19 (25)	.34
Metronidazole	9 (36)	16 (21)	.15
Intravenous vancomycin	14 (56)	31 (41)	.20
Oral vancomycin	5 (20)	4 (5)	.04
Antibiotic therapy before CRE test, days			
0	2 (8)	21 (28)	Reference
1–5	7 (28)	18 (24)	.08
6–20	5 (20)	19 (25)	.42
20	11 (44)	17 (23)	.02

NOTE. Data are no. (%) of subjects, unless otherwise indicated. ICU, intensive care unit.

^aIncludes inpatient and outpatient antibiotic use documented in the inpatient medical record.

^b Defined as administration of at least 1 antibiotic dose during the index hospitalization before CRE screening.

^c Values of $P < .05$ were considered statistically significant.