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CONCISE COMMUNICATION

Challenges in the Management of Infections due to Carbapenem-Resistant Enterobacteriaceae

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Carbapenem-resistant Enterobacteriaceae (CRE) infections are increasing and are associated with considerable morbidity and mortality. Members of the Emerging Infections Network treating CRE encountered difficulties in obtaining laboratory results and struggled with limited treatment options. In addition, many treated patients experienced an alarming degree of drug toxicity from CRE therapies.

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Multidrug-resistant gram-negative organisms are a major concern,[1] especially since antimicrobial development has stagnated.[2] This is particularly true for carbapenem-resistant Enterobacteriaceae (CRE), which are resistant to the traditional drugs of last resort for serious gram-negative infections. Because CRE are resistant to empiric antimicrobials typically prescribed for suspected gram-negative infections, effective therapy may be delayed, increasing morbidity and mortality. Currently available agents to treat CRE include colistin, tigecycline, and fosfomycin, but each has limitations. Little is known regarding challenges encountered while treating CRE infections; we queried Emerging Infections Network (EIN) members to better understand challenges in treating CRE infections in the United States.

METHODS

In July 2012, EIN members were invited to complete a report form describing their experiences with treating CRE infections to enable a case series. The Centers for Disease Control and Prevention funds the EIN through a cooperative agreement with the Infectious Diseases Society of America to maintain a provider-based network for emerging infections (http://ein.idsociety.org). Because laboratories differ in defining and detecting CRE, we asked that respondents use their local laboratory definition. The 17-question report form included source patient information, treatments, organism information, outcome data, and complications encountered.[3] Research oversight committees at the primary investigators' institutions (D.M.D. and S.J.W.) approved the protocol.

RESULTS

An electronic link to the report form was sent to all EIN members, and 54 members provided information regarding

TABLE 1. Reported Susceptibility Profile of 98 Carbapenem-Resistant Enterobacteriaceae Reported by Respondents

Antimicrobial	*N*	Susceptible	Intermediate	Resistant
Amikacin	78	32 (41)	11 (14)	35 (45)
Aztreonam	52	0	0	52 (100)
Cefepime	77	9 (12)	2 (3)	66 (86)
Ceftazidime	73	7 (10)	0	66 (90)
Ciprofloxacin	92	16 (17)	1 (1)	75 (82)
Colistin	63	52 (83)	7 (11)	4 (6)
Doripenem	32	2 (6)	3 (9)	27 (84)
Ertapenem	54	0	1 (2)	53 (98)
Fosfomycin	15	11 (73)	0	4 (27)
Gentamicin	91	35 (38)	3 (3)	53 (58)
Imipenem	74	4 (5)	14 (19)	56 (77)
Meropenem	70	8 (11)	6 (9)	56 (80)
Nitrofurantoin	38	4 (11)	3 (8)	31 (82)
Piperacillin/tazobactam	78	5 (6)	2 (3)	71 (91)
Tigecycline	58	31 (53)	11 (19)	16 (28)
Tobramycin	82	19 (23)	3 (4)	60 (73)
Trimethoprim/sulfamethoxazole	87	19 (22)	0	68 (78)

NOTE. Data are no. (%), unless otherwise indicated.

TABLE 2. Demographic and Travel Characteristics of the 85 Source Patients from Whom 98 Carbapenem-Resistant Enterobacteriaceae (CRE) Were Isolated

Characteristic	Patients
Age, median, years[a]	31
Sex	
Male	46 (54)
Female	35 (41)
Not reported	4 (5)
Race	
White	40 (47)
Black	14 (16)
Hispanic	10 (12)
Asian	3 (4)
Unknown/other	18 (21)
Travel outside United States in 6 months prior to CRE isolation	
No	66 (78)
Yes	12 (14)
Unknown	7 (8)
Received medical care outside United States in 6 months prior to CRE isolation	
No	73 (86)
Yes	6 (7)
Unknown	6 (7)

NOTE. Data are no. (%), unless otherwise indicated.
[a] Age range, 1 month to >89 years.

85 source patients; for 13 patients, information on 2 separate CRE was provided, for a total of 98 isolates. Hospital settings represented by respondents included university (24), nonuniversity teaching (13), community (8), Veterans Administration/Department of Defense (5), and city/county (4) facilities. Infections were reported from 22 states, with the most reports from California (20), Pennsylvania (19), and Ohio (8). An additional 213 respondents indicated that CRE infections were not encountered in their practice.

Reported pathogens included 68 *Klebsiella* species; 12 *Enterobacter* species; 12 *Escherichia coli*; 2 *Citrobacter* species; and 1 each of *Proteus*, *Pseudomonas* (though not an Enterobacteriaceae), *Salmonella*, and *Serratia* species. Antimicrobial resistance was prevalent (Table 1), with only 3 drugs testing as susceptible for more than 50% of the isolates (tigecycline, fosfomycin, and colistin). Colistin was the drug to which the highest percentage of isolates was susceptible (83%), but susceptibility was known for only 63% of isolates. Fosfomycin susceptibility testing was even less common, with only 15% of isolates tested.

Our series included both pediatric and adult patients with a median age of 31 years, with 11% younger than 18 years of age (Table 2). Travel or medical care outside the United States in the 6 months prior to CRE isolation was infrequent, with the most common destination being India ($n = 4$). Underlying medical conditions and risk factors for acquiring a drug-resistant organism at the time of CRE isolation were frequent and included hospitalization or surgery in the prior 6 months (79%) and chronic kidney disease (21%); only 5% of patients were without chronic medical conditions. Common sites of CRE isolation were urine (39%), blood (34%), and sputum (15%).

At the time of CRE isolation, most patients (91%) were hospitalized, with 48% for more than 4 weeks. Almost one-fifth of patients (19%) were in an intensive care unit at the time of CRE isolation, and in 28% of these patients, the CRE infection was considered to have necessitated the intensive care unit care. Overall, 57 patients died (67%); however, respondents reported that death was attributable to the CRE infection for only 16% of these patients. For 76% of patients, the CRE infection was judged to have caused or prolonged the hospitalization.

The most common management challenges were the inability to use first-line antimicrobials (65%), the need to use antimicrobials with increased risk of toxicity (56%), the need to use parenteral antimicrobials due to lack of oral options (44%), and a manifested drug toxicity (16%). Reported toxicities included renal dysfunction (colistin) and pancreatitis (tigecycline). In 11 of 14 patients experiencing drug toxicity, the implicated drug was used because of the patient's CRE resistance profile. Reported challenges did not differ appreciably between the pediatric and adult cases. Other reported challenges included discordant susceptibility results with different testing methods, lack of interpretive criteria for colistin, and inability to obtain susceptibility testing for fosfomycin.

DISCUSSION

This EIN case series provides insight into hurdles associated with the management of CRE infections from a geographically diverse group of infectious disease specialists in the United States. Only tigecycline, colistin, and fosfomycin were active against more than 50% of the isolates tested, and susceptibility testing was not commonly performed for each drug. Comorbidities were frequent, with only a small minority of patients having no chronic medical conditions or healthcare exposure.

There are few antimicrobials available to treat CRE, and all have substantial limitations, including nephro- and neurotoxicity (colistin),[4] unavailability of a parenteral formulation (fosfomycin), concerns about inadequate blood levels (tigecycline),[5] and increased mortality (tigecycline).[6] Surprisingly, susceptibility testing to these agents was often not obtained, and respondents reported difficulty in obtaining and interpreting the results of such testing. Of these 3 antimicrobials, susceptibility testing was most commonly performed for colistin (64%), followed by tigecycline (59%) and fosfomycin (15%). Since the EIN is comprised of infectious disease physicians, difficulty in obtaining and interpreting susceptibility results may be even more challenging for non–infectious disease providers, who may be unaware of the limited treatment options available and where isolates might be sent for testing. Ensuring that providers are aware of these

first-line agents for CRE infections and that appropriate susceptibility testing is available should be a high priority for all healthcare facilities.

Additional management challenges were reported by the majority of respondents. Most indicated that they were unable to use what they considered to be first-line agents or had to use a parenteral agent when otherwise an oral agent would have been indicated, potentially exposing patients to additional risks, including those associated with the need for long-term intravenous access. While the questionnaire did not elicit a comprehensive antimicrobial history for each reported case, antimicrobial agents mentioned in the comments included colistin, tigecycline, extended-infusion carbapenems, ciprofloxacin, and trimethoprim/sulfamethoxazole. Although ciprofloxacin and trimethoprim/sulfamethoxazole are both relatively nontoxic and convenient, colistin and tigecycline have the previously discussed disadvantages. Extended infusions of carbapenems is a strategy used to optimize drug levels, although the effectiveness of this strategy for the treatment of CRE infections is unknown. No respondents utilized colistin plus rifampicin, a strategy used in non-CRE gram-negative infections.[7]

Potential limitations include recall bias—with respondents preferentially reporting cases that are difficult to manage—or increased reporting from areas newly affected by CRE. Conversely, clinicians experienced in managing CRE may view these issues as routine and underreport cases. This may explain the limited number of cases reported from areas with a high prevalence of CRE, such as New York,[8] where only 4 isolates were reported. Respondent bias is another potential limitation. CRE cases may have been present at the institutions of the approximately 1,000 EIN members who did not respond to the survey; the members may have made a decision not to report them. Thus, the cases reported herein may not be representative of all CRE cases that might have been available through the EIN network.

This report provides details regarding clinical challenges that a geographically diverse group of EIN members encountered during the management of CRE infections, including problems with susceptibility testing, the necessity of using antimicrobials with increased toxicity, and the lack of oral options. These issues are likely more challenging without access to an infectious disease consultant, a situation that will become increasingly common as CRE continue to proliferate. Efforts to control the spread of CRE, improve access to appropriate susceptibility testing, and further investigate the safest and most effective treatment strategies should be prioritized.

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