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Treatment preferences by infectious diseases clinicians for carbapenem-resistant Enterobacterales infections

Samuel E. Cincotta [1]*, Belinda E. Ostrowsky[1], Jessica Howard-Anderson [2], Susan E. Beekmann [3], Philip M. Polgreen[3] and Maroya S. Walters[1]

[1]*Division of Healthcare Quality Promotion, U.S. Centers for Disease Control and Prevention, 1600 Clifton Road NE, Atlanta, GA 30329, USA;* [2]*Division of Infectious Diseases, Emory University School of Medicine, 100 Woodruff Circle, Atlanta, GA 30322, USA;* [3]*Division of Infectious Diseases, University of Iowa Carver College of Medicine, 451 Newton Road, Iowa City, IA 52242, USA*

*Corresponding author. E-mail: ven5@cdc.gov

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Background and objectives: New antibiotics effective against carbapenem-resistant Enterobacterales (CRE) provide additional treatment options, but data on clinician decision-making are limited. We sought to understand treatment preferences, factors influencing antibiotic selection for CRE infections and barriers to prescribing newer agents.

Methods: We surveyed infectious disease clinicians through the Infectious Diseases Society of America (IDSA) Emerging Infections Network (EIN) about their experience treating CRE infections, availability of resistance mechanism testing, antibiotic choices in four CRE infection scenarios and barriers to using newer antibiotics. We used the 2023 IDSA Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections to classify antibiotic selections for the scenario-based questions as preferred approach, alternative option or not in guidance.

Results: Overall, 441 EIN members responded. Among these, 337 (76%) reported treating a CRE infection in the last year. For the clinical scenarios, 851 (63%) of 1356 selections were IDSA-preferred approaches; of these, 653 (77%) were for ceftazidime-avibactam, either alone ($n=456$) or in combination with aztreonam ($n=197$), more than for other β-lactam/β-lactamase inhibitor combination agents active against CRE. For an uncomplicated urinary tract infection caused by carbapenem-resistant *Klebsiella pneumoniae*, where no preferred approaches were available, the most common antibiotic selected was oral fosfomycin (169/343 (49%)).

Conclusions: Most clinicians selected antibiotics aligned with the IDSA guidance for serious CRE infections, although the frequent selection of an agent not in the guidance for uncomplicated cystitis suggests that treatment selection is complex and may depend on infection severity, among other factors. The preference for ceftazidime-avibactam among similar agents is notable and may reflect its longer market availability.

Background

Since 2014, the US FDA has approved six new antimicrobials effective against carbapenem-resistant Enterobacterales (CRE), expanding treatment options. We sought to understand treatment preferences, factors influencing antibiotic selection for CRE infections and barriers to prescribing newer agents.

Methods

The Emerging Infections Network (EIN; https://ein.idsociety.org/) is a provider-based network of infectious disease (ID) physicians and other ID professionals (e.g. pharmacists, nurse practitioners, physician assistants), primarily from North America, supported by the CDC and the Infectious Diseases Society of America (IDSA).[1] In fall 2023, we sent a survey to network members to understand antibiotic selection and factors influencing antibiotic choice for infections caused by CRE.

The survey (https://ein.idsociety.org/surveys/survey/171/) asked EIN members about their experience treating patients infected with CRE, resistance mechanism testing available to them, most likely antibiotic selection for four infection scenarios and barriers to using three specific antibiotics: cefiderocol, ceftazidime-avibactam and eravacycline. For clinical scenarios, participants were asked which antibiotic they would select for treatment based on their primary inpatient facility's antibiotic formulary and to indicate the two factors that most influenced their choice. The first set of scenarios involved a patient with uncomplicated cystitis (Scenario 1) or pyelonephritis (Scenario 2) caused by *Klebsiella pneumoniae* resistant to meropenem, ertapenem, nitrofurantoin, trimethoprim/sulfamethoxazole and ciprofloxacin, without carbapenem mechanism

testing results. The second set asked about a patient with peritonitis and an intra-abdominal abscess with a peritoneal fluid culture growing *Escherichia coli* resistant to meropenem and ertapenem with carbapenemase testing pending (Scenario 3) or producing a New Delhi metallo-β-lactamase (NDM; Scenario 4). We interpreted responses to clinical infection severity within the scenario context, considering cystitis as less severe and abdominal infections as more severe. In all scenarios, respondents were instructed to assume that the organism was susceptible *in vitro* to the provided antibiotic options.

We used the 2023 IDSA Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections to classify antibiotic selections for the scenario-based questions as preferred approach, alternative option or not in guidance.[2] We performed descriptive analyses and bivariate comparisons using χ^2 or Fisher's exact tests ($\alpha = 0.05$) to evaluate practice-related factors associated with antibiotic selections.

Results

Overall, 441 (28%) of 1566 EIN members who have ever participated in EIN surveys responded. All respondents practiced adult ID; most were physicians (383, 87%), worked in teaching hospitals (279, 63%) and had ≥5 years of experience since ID fellowship (345, 78%), with more than a quarter having ≥25 years of experience (127, 29%; Table 1). Among respondents, 337 (76%) reported treating a CRE infection in the last year; of the 104 who did not, 93 (89%) chose not to answer mechanism testing, scenario or barrier questions.

Table 1. Practice characteristics of Emerging Infections Network survey respondents ($n = 441$)

Member practice characteristic	No. (%) of respondents	
Practice		
Adult infectious diseases	441	(100)
Member type		
Infectious diseases physician	383	(87)
Healthcare professional	58	(13)
Experience since fellowship		
<5 years	96	(22)
5–14 years	144	(33)
15–24 years	74	(17)
≥25 years	127	(29)
Primary location		
Community hospital	109	(25)
Non-university teaching hospital	105	(24)
University hospital	174	(39)
VA hospital or Department of Defense hospital	26	(6)
City or county hospital	21	(5)
Outpatient only	6	(1)
US Census Bureau region		
Midwest	114	(26)
Northeast	105	(24)
Puerto Rico	3	(1)
South	128	(29)
West	91	(21)

VA, Veterans Affairs.

Figure 1 shows respondents' antibiotic selections for the clinical scenarios. For uncomplicated cystitis caused by CRE resistant to all preferred approaches [nitrofurantoin, trimethoprim/sulfamethoxazole and ciprofloxacin; Figure 1 (1)], respondents chose an agent not in guidance more frequently than an alternative option [189/343 (55%) versus 154 (45%); $P = 0.06$]. Respondents most frequently selected oral fosfomycin (169, 49%; not in guidance), followed by single-dose amikacin (98, 29%; alternative option). For pyelonephritis [Figure 1 (2)], 325/343 (95%) respondents selected preferred approaches, mainly ceftazidime-avibactam (272, 79%). For treating an intra-abdominal infection caused by carbapenem-resistant *E. coli* with pending carbapenem resistance mechanism testing [Figure 1 (3)], 247 (74%) of 335 respondents chose preferred approaches, mainly ceftazidime-avibactam (184, 55%), while 87 (26%) selected alternative options. For treating an intra-abdominal infection caused by NDM-producing *E. coli* [Figure 1 (4)], 279 (83%) of 335 respondents selected preferred approaches: 197 (71%) chose ceftazidime-avibactam with aztreonam, and 82 (24%) chose cefiderocol. Most scenario responses were similar across provider experience levels, facility teaching status and geographical regions; however, Scenario 1 had a higher proportion of experienced respondents and those in the Northeast or West selecting an agent not in the guidance compared to less experienced providers or those in other U.S. regions (Table S1, available as Supplementary data at *JAC* Online).

Overall, respondents indicated that drug availability and infection severity were the most common factors influencing treatment selection (Figure S1). For uncomplicated cystitis (Scenario 1), where oral fosfomycin was the most chosen treatment, infection severity (126, 75%) and efforts to preserve antibiotic activity (74, 44%) drove selection. For pyelonephritis and carbapenem-resistant intra-abdominal infection with unknown mechanism (Scenarios 2 and 3, respectively), where ceftazidime-avibactam, imipenem-relebactam and meropenem-vaborbactam were all preferred approaches, availability influenced the selection of ceftazidime-avibactam more frequently (255/456, 56%) than imipenem-relebactam (6/16, 30%, $P = 0.01$) and meropenem-vaborbactam (31/79, 39%, $P = 0.01$). Familiarity also affected selection: ceftazidime-avibactam (215/456, 47%) compared to imipenem-relebactam (2/14, 14.3%, $P < 0.001$) and meropenem-vaborbactam (24/79, 30%, $P < 0.001$).

When asked about barriers to selecting ceftazidime-avibactam, cefiderocol and eravacycline, 57% of respondents indicated no barriers for ceftazidime-avibactam, compared to 27% for cefiderocol and 16% for eravacycline (Table S2). Among those who identified barriers, the most common for cefiderocol were cost (84/236, 35%) and not being on formulary (81/236, 34%); for ceftazidime-avibactam, they were resistance (68/130, 52%) and cost (54/130, 42%); and for eravacycline, not being on formulary (152/278, 55%) and insufficient or concerning clinical evidence (86/278, 31%).

Discussion

In our survey of EIN members, most respondents reported treating a patient with a CRE infection within the last year and favoured newer agents across various CRE infection scenarios. Respondents overwhelmingly selected IDSA-recommended

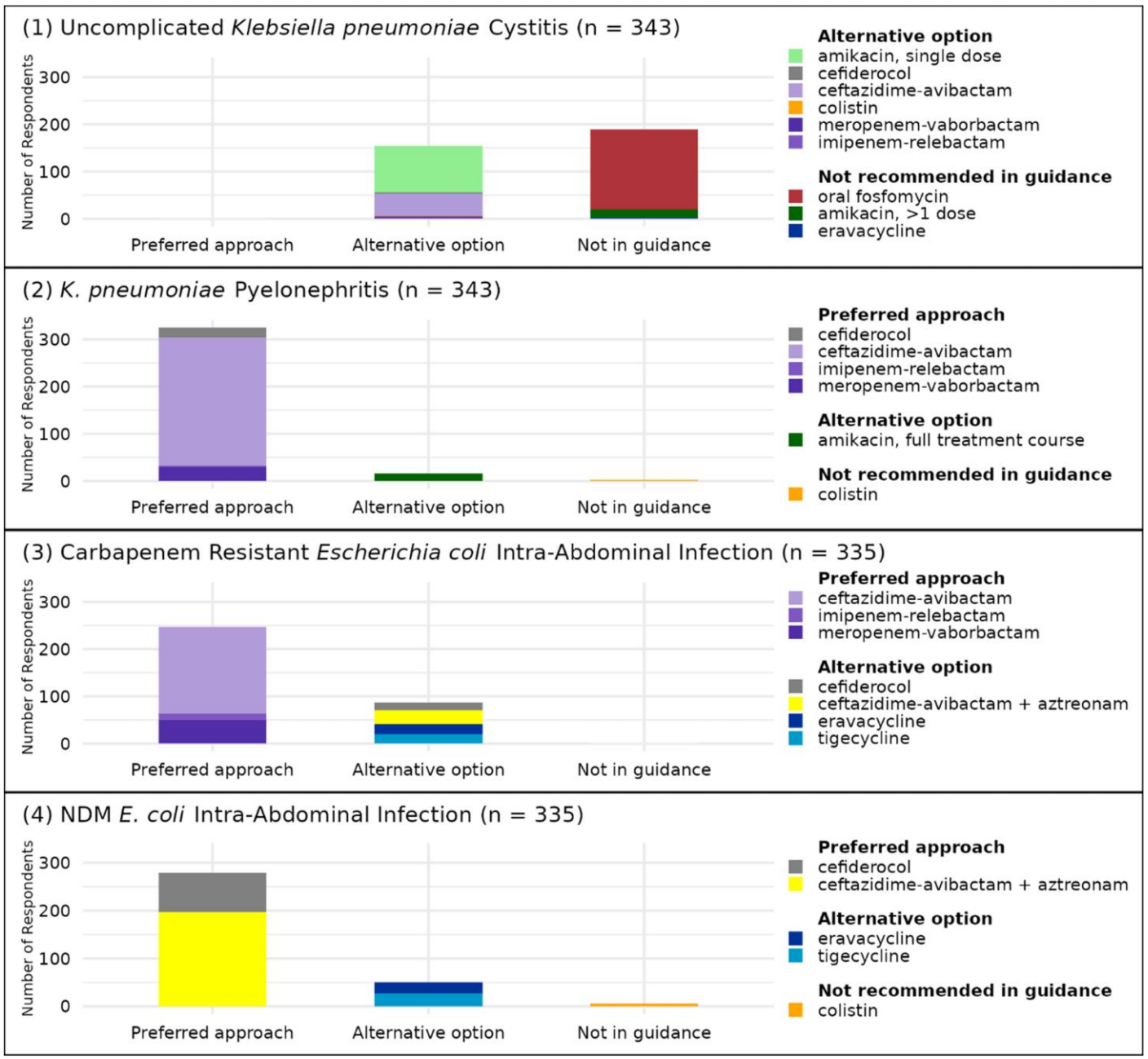

Figure 1. Antibiotic selections for CRE infection scenarios, among respondents to Emerging Infections Network survey, fall 2023. All survey options selected by at least one respondent are shown in the legend. 'Preferred approach', 'Alternative option' and 'Not recommended in guidance' categorizations made based on the Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections. Scenarios 1 and 2: A 57-year-old female with a history of recurrent urinary tract infections but who is otherwise healthy with good renal function presented to the hospital with urinary tract infection symptoms. (1) A urine culture grew *Klebsiella pneumoniae* resistant to meropenem, ertapenem and the preferred suggested treatment options for uncomplicated cystitis caused by CRE (nitrofurantoin, trimethoprim-sulfamethoxazole and ciprofloxacin). (2) The same patient, organism and susceptibility testing results as in Scenario 1, presenting with pyelonephritis. Scenarios 3 and 4: A 64-year-old intensive care unit patient without history of international travel and with new onset fever has peritonitis and an intra-abdominal abscess. Peritoneal fluid culture grows *E. coli* resistant to meropenem and ertapenem. (3) Blood cultures are negative and carbapenemase testing is pending. (4) The lab reports that carbapenemase testing detects the presence of New Delhi metallo-beta-lactamase (NDM) for this isolate. For Scenario 3, no respondent selected the antibiotic survey options meropenem (extended infusion) plus amikacin or meropenem (extended infusion) plus colistin (both classified as not in guidance).

agents for complicated infections; notably, ceftazidime-avibactam, either alone or in combination with aztreonam, was preferred to other β-lactam/β-lactamase inhibitors active against CRE. However, oral fosfomycin, an agent not recommended in current or prior versions of the IDSA guidance, was chosen for uncomplicated *K. pneumoniae* cystitis. This suggests that factors such as ease of treatment in the outpatient setting and the desire to preserve newer antibiotics for more severe infections might influence treatment selection. Additionally, an assessment of barriers for a subset of agents indicated that limited clinical evidence, cost and formulary availability are obstacles to incorporating newer drugs into clinical use.

The preference for ceftazidime-avibactam could be attributed to several factors: its longer market presence, broader availability of antimicrobial susceptibility testing (AST) and greater carbapenemase coverage compared to other new β-lactam/β-lactamase inhibitor agents. Our findings align with two retrospective cohort studies that show ceftazidime-avibactam predominates among recently FDA-approved antibiotics targeting Gram-negative organisms.[3,4] Survey respondents who selected ceftazidime-avibactam over imipenem-relebactam and meropenem-vaborbactam cited availability and familiarity as key influences. This preference may reflect the advantage of being first-to-market; ceftazidime-avibactam received FDA approval in 2015, before meropenem-vaborbactam (2017), imipenem-relebactam (2019) and cefiderocol (2019), allowing for earlier incorporation onto formularies and AST panels. Strich *et al.*[3] reported that AST availability for ceftazidime-avibactam in surveyed hospitals was 47.8%, compared to 29.4% for meropenem-vaborbactam and less than 2% for cefiderocol, suggesting that AST access influences antibiotic selection. Additionally, ceftazidime-avibactam is also the only approved β-lactam/β-lactamase inhibitor that covers CRE producing the OXA-48 carbapenemase[5]; however, its impact on respondent decisions in our survey is unclear, and OXA-48 remains an uncommon cause of carbapenem resistance in the USA.[6]

An unexpected finding in our survey was the frequent selection of oral fosfomycin for treating uncomplicated cystitis caused by carbapenem-resistant *K. pneumoniae*. Oral fosfomycin is approved by the FDA as a one-time dose for the treatment of uncomplicated acute cystitis infections in women due to susceptible strains of *E. coli* and *Enterococcus faecalis*. However, the *fosA* hydrolase gene, which is associated with high-level fosfomycin resistance, is commonly found in Gram-negative organisms outside of *E. coli*, and IDSA guidance has advised against its use for these organisms since first publication in 2020.[7–9] As the question prompt indicated susceptibility to all listed treatment options, it is unclear whether respondents factored this into their selection and whether they deliberately weighed the risk of clinical failure against the low severity of the infection, convenience of a single-dose oral treatment (which we did not directly ask) and desire to preserve novel agents or did not recall that fosfomycin is not recommended for *K. pneumoniae*. Given the frequency of fosfomycin selection, additional pragmatic studies may be warranted to its use for *K. pneumoniae* cystitis and associated clinical outcomes.

The survey had several limitations. First, our survey respondents specialize in ID, but other hospital prescribers may be less familiar with new antibiotic options, limiting the generalizability of our findings. Second, our results primarily reflect the experiences of clinicians who have recently treated CRE, as most participants who had not treated CRE in the past year chose not to complete the survey, contributing to a low overall response rate. Third, respondents largely selecting newer recommended agents over older therapies may reflect social desirability bias; however, Strich *et al.*[3] found that 73.2% of difficult-to-treat Enterobacterales episodes received new antibiotics. A limitation in interpreting why fosfomycin was chosen outside of guidance recommendations is the absence of a direct question asking whether ease of administration influenced the choice.

In conclusion, our findings indicate that antibiotic selection for infections caused by CRE is complex, with clinicians often balancing clinical evidence, severity of infection, formulary availability and the desire to limit the development of additional resistance. As resistance continues to emerge, ensuring the availability and appropriate use of all recommended newer antibiotics in various clinical scenarios will become increasingly important.

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Transparency declarations

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Emerging Infections Network queries are to gauge the current landscape of infectious disease practice. As such, these queries fall within the scope of non-research programme evaluation, as described in current CDC policy.

Supplementary data

Figure S1 and Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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