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MAJOR ARTICLE

Carbapenem Treatment and Outcomes Among Patients With Culture-Positive Complicated Intra-abdominal Infections in US Hospitals: A Retrospective Cohort Study

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Background. Carbapenems are a frequent firstline therapy in complicated intra-abdominal infections (cIAIs). We examined the microbiology, epidemiology, and outcomes among patients hospitalized in the United States with culture-positive cIAIs in the context of their exposure to empiric carbapenem treatment (ECT).

Methods. We performed a multicenter retrospective cohort study of Premier database of ~180 hospitals, 2013–2017. Using an International Classification of Diseases (ICD)-9/10-based algorithm, we identified all culture-positive adult patients hospitalized with cIAI and examined their microbiology, epidemiology, and outcomes.

Results. Among 4453 patients with cIAIs, 3771 (84.7%) had a gram-negative (GN) and 1782 (40.0%) a gram-positive organism; 1185 (26.6%) received ECT. Compared with those on non-ECT, patients on ECT were less frequently admitted from home (82.5% vs 86.0%) or emergently (76.0% vs 81.4%; $P < .05$ for each); *E. coli* were less frequent, whereas *P. aeruginosa* and *Enterococcus* spp. were more prevalent and resistance to third-generation cephalosporins (C3R; 10.1% vs 5.1%; $P < .001$) and carbapenems (CR; 3.6% vs 1.2%; $P < .001$) was more common. In adjusted analyses, ECT was associated with no rise in mortality, shorter postinfection length of stay (–0.59 days; 95% confidence interval [CI], –1.15 to –0.03), but higher postinfection costs ($3844; 95% CI, $1921 to $5767) and risk of *Clostridioides difficile* (odds ratio, 2.15; 95% CI, 1.02 to 4.50).

Conclusions. Among patients hospitalized with cIAI, the majority were gram-negative. Despite a 10% prevalence of C3R, fully one-quarter of all empiric regimens contained a carbapenem. ECT was a marker for slightly lower postinfection length of stay, but higher costs and risk of hospital complications.

Keywords. intra-abdominal infection; carbapanems; ESBL; carbapenem-resistant; outcomes.

Complicated intra-abdominal infections (cIAIs) remain a substantial challenge in US hospitals. Those suffering from a cIAI often require complex management that includes source control and proper antimicrobial coverage [1]. Because of the severity of illness associated with cIAI and the need for complex care, these patients face a considerable risk of death [2]. The potential for mortality increases further when the patient is exposed to inappropriate empiric therapy (IET). In the current era of escalating rates of antimicrobial resistance, the potential for IET is significant [3–18].

Conversely, overuse of broad-spectrum agents where they are not necessary to cover potential pathogens drives up rates of resistance. This phenomenon has been particularly evident in the case of carbapenems, which are often recommended as broad-spectrum empiric treatment in high-risk cIAI patients. In part, concern about the prevalence of extended-spectrum beta-lactamase (ESBL)–producing Enterobacteriaceae and *Pseudomonas aeruginosa* has contributed to greater use of carbapenems in cIAI. However, because of broader reliance on carbapenems, once considered a "last-resort" antibiotic for those with life-threatening infections, the class is losing its in vitro potency, and now resistance to carbapenems is often seen in *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and Enterobacteriaceae [19–21].

Balancing the need for sufficiently broad-spectrum agents with the need to curtail resistance is a challenge for the bedside clinician. Often treatment decisions derive from information generalized at the level of the pathogen, failing to consider its prevalence in the specific disease state necessary to make treatment choices. Additionally, to make recommendations regarding appropriate carbapenem use and to benchmark rates of compliance with formal guideline recommendations, one must understand current practices. To address these issues, we examined the microbiology and outcomes of patients in the United

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States hospitalized with cIAI in the context of their exposure to empiric treatment with a carbapenem (ECT).

METHODS

We performed a multicenter retrospective cohort study of hospitalized patients with International Classification of Diseases (ICD)-9-CM codes (or their ICD-10 equivalents after October 2015) indicating cIAI (the details of the algorithm are presented in the Supplementary Data) [18]. In addition, we required that there be evidence of antibiotic treatment that began on the day culture was obtained and was continued for at least 3 consecutive days, or until discharge [22–24].

Because this study used already existing fully de-identified data, it was exempt from institutional review board review under 45 CFR 46.101(b)4 [25].

Study Population

Patients were included if they were adults (aged ≥18 years) whose hospitalization of 2 days or longer included a diagnosis of cIAI. We required that an abdominal and/or blood culture drawn during or within 48 hours after laparotomy/laparoscopy be positive for a causative organism (list below), as well as evidence of antibiotic treatment on the day of surgery or index culture that continued for ≥3 consecutive days. Patients not meeting these criteria were excluded from the cohort. Additionally, we excluded patients with a concurrent urinary tract infection diagnosis at any time during the hospitalization in order to minimize the risk of source misattribution of positive blood cultures. Finally, we excluded patients transferred from another acute care facility, as our primary interest focused on the empiric treatment period.

Data Source

The data for the study were obtained from the Premier database, an electronic laboratory, pharmacy, and billing data repository, for the years 2013 through 2017. The database represents ~15% of all hospitalizations nationwide. For further description of the database, see the Supplementary Data.

Baseline Measures

cIAI was classified as community-onset (CO) if present on admission or if the index culture was obtained within the first 2 hospital days. CO cIAI was further classified as health care–associated (HCA) if 1 or more of the following risk factors was present: (1) prior hospitalization within 90 days of the index hospitalization, (2) hemodialysis, (3) admission from a long-term care facility, and (4) immune suppression. All other CO infections were defined as community-acquired (CA). All cIAIs occurring on or after hospital day 3 were considered hospital-onset (HO). In addition to infection classification, patient factors examined included history of exposure to antibiotics within 90 days before the index admission, exposure to antibiotics during the index hospitalization before the onset of cIAI if HO, demographic variables, and comorbid conditions. We computed the Charlson comorbidity score as a measure of the burden of chronic illness, whereas ICU admission, need for mechanical ventilation, presence of severe sepsis or septic shock, and use of dialysis and/or vasopressors at baseline (day of surgery/index culture) served as markers for acute disease severity. Organisms and their susceptibilities were identified, and empiric antibiotic treatment was considered appropriate if the patient received a regimen that covered the corresponding organism within 2 days of the culture being obtained. The prevalence of carbapenem as empiric therapy in each institution was derived as a baseline hospital-level variable. We also explored hospital structural characteristics (eg, size, teaching status, urbanicity) and processes of care (eg, choices of antimicrobials), as they impacted patient outcomes.

Microbiology and Antimicrobial Treatment Variables and Definitions

Organisms of Interest

To be included, a patient had to grow out at least 1 qualifying organism in the abdominal fluid or blood, including any of the gram-negative organisms listed below. The first culture growing out one of the organisms of interest served as the index culture.

Gram-negative organisms of particular interest were *Pseudomonas aeruginosa, Acinetobacter baumannii*, *Stenotrophomonas maltophilia,* and Enterobacteriaceae. The Supplementary Data lists organisms included as Enterobacteriaceae.

The prevalence of the following frequent cIAI pathogens was also examined: *Enterococcus* spp., *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]), *Bacteroides fragilis*, and *Candida* spp. In addition, we noted if a polymicrobial infection was present.

Definitions of carbapenem resistance (CR), third-generation cephalosporin resistance (C3R), and inappropriate empiric therapy (IET) can be found in the Supplementary Data.

Outcomes

The primary outcome of interest was hospital mortality as it relates to ECT. Secondary outcomes included hospital length of stay (LOS; in days, total and post–infection onset for all and for survivors only), total costs and total post–infection onset costs, and 30-day readmission rates among survivors. We further explored several additional outcomes associated with ECT as compared with other regimens (non-ECT):

1. Development of *Clostridioides difficile*
   a. *C. difficile* (ICD-9-CM 008.45) not principal diagnosis or present on admission
   b. *C. difficile* included as secondary diagnosis
   c. *C. difficile* treatment (oral metronidazole OR oral vancomycin OR fidaxomicin) started on either:

   i. Hospital day 3 or later, if index surgery/culture was on hospital day 1–2, or
   ii. On day of surgery or later, if index surgery/culture was on hospital day 3 or later
2. Development of acute kidney injury (AKI) or AKI requiring dialysis (AKI-D), as identified by a previously published algorithm, on the day of index surgery/culture or later [26]
3. Clinical deterioration, defined as institution of vasopressors and/or mechanical ventilation (MV) within 3 days after the index surgery/culture if not present on index day
4. Treatment failure

   a. Recurrence of infection, defined as re-initiation of antimicrobial treatment with the same or broader-spectrum regimen after a treatment-free period of ≥3 days
   b. Treatment escalation, defined as addition of an antimicrobial or switch to a new antimicrobial with a broader spectrum of coverage within 7 days after the index surgery [27]
   c. Need for a repeat laparotomy/laparoscopy or percutaneous drainage within 7 days after the index surgery [27]

Statistical Analyses

All demographics, comorbidities, hospital characteristics and processes, and hospital outcomes were compared between the ECT and non-ECT groups using standard summary statistics. Continuous variables were reported as means with standard deviations and as medians with 25th and 75th percentiles (interquartile range). Differences between mean values were tested via the Student *t* test, whereas those between medians were examined using the Mann-Whitney *U* test. Categorical data were summarized as counts and frequencies, and the chi-square test or Fisher exact test for cell counts <4 was used to examine between-group differences. Inference tests with a *P* value <.05 were considered statistically significant.

We developed multilevel (hierarchical) mixed-effects logistic regression models with hospitals treated as random effects to examine the contribution of empiric carbapenem treatment to clinical deterioration, *C. difficile* development, AKI and AKI-D onset, mortality, and 30-day readmissions. A competing risk regression model (with mortality as the competing risk) was used to model treatment failure. The impact of empiric carbapenem treatment on costs (both total and post–infection onset) and hospital LOS (both total and post–infection onset) was examined using multilevel mixed-effects generalized linear models with a logarithmic link function and a gamma distribution (or a normal distribution for postinfection LOS, as some values equaled 0). In all models, we examined the covariates present from the start of hospitalization through the day of the onset of the index infection.

All statistical analyses were done with Stata/MP 15.1 for Windows (StataCorp, LLC, College Station, TX, USA).

RESULTS

Among 321 317 patients with cIAI, 4453 (1.4%) were culture-positive, met all the inclusion criteria, and were analyzed in the cohort (Supplementary Figure 1). The most common reason for exclusion was the absence of a positive culture (81.1%).

A little over one-third of the cultures came from an abdominal source only (n = 1686), with an additional 545 (12.2%%) from blood only, and another 2222 (49.9%) from both. Although the majority of all cIAIs had gram-negative (GN) organisms, a substantial minority had a gram-positive (GP) pathogen (40.0%), among which *Enterococcus* sp. was the most frequent (60.2%) (Table 1). A total of 4032 GN organisms were isolated from 3771 patients, with *E. coli* being the most common (56.7%), with a C3R prevalence of 4.9% and CR of 0.3%. Overall, C3R and CR prevalence was 7.6% and 2.2%, respectively, among all GN isolates, and *A. baumannii* was most likely to be C3R and CR (21.4% for each) (Table 1). Approximately one-third of the cohort suffered from polymicrobial infections (n = 1512), with the rest growing a single organism. Among those with a polymicrobial infection, 1100 (72.8%) were mixed GN and GP.

Approximately one-quarter (n = 1185) of all patients received antimicrobial regimens that included ECT. Patients on ECT did not differ from those on non-ECT with regard to age, gender distribution, or race (Table 2). Compared with those on non-ECT, patients on ECT were less likely to be admitted from home (82.5% vs 86.0%) and more likely to be admitted from a non–acute care facility (6.4% vs 5.0%), but also less likely to be admitted emergently (76.0% vs 81.4%; $P < .05$ for each) (Table 2). Additionally, ECT (1.8 ± 2.2) patients had a higher mean Charlson comorbidity score than non-ECT (1.6 ± 2.1) patients. ECT was more likely to be given in hospitals in the South in medium-sized (200–399 beds), nonacademic, and urban institutions than non-ECT. Similarly, by all measures of severity of acute illness, those in the ECT group were sicker than those in the non-ECT group (Table 2).

There were limited differences in organism distribution between the ECT and non-ECT groups (Table 3). *E. coli* were less likely, whereas *P. aeruginosa* and *Enterococcus* spp. were more likely to be isolated in the ECT group. Notably, both C3R (10.1% vs 5.1%; $P < .001$) and CR (3.6% vs 1.2%; $P < .001$) infections were more frequent in the ECT than in the non-ECT group. In other words, although a presumptive ESBL pathogen was observed more often in those prescribed ECT, the actual prevalence of ESBL organisms was low even among those treated with a carbapenem. On average, compared with those treated with non-ECT, patients on ECT developed their cIAI later in the hospitalization (5.5 ± 11.8 vs 3.2 ± 5.2 days; $P < .001$) and were more likely to have their infections classified as HCA or HO than CA (Table 3). Of the individual and combination regimens commonly used in cIAI, ertapenem was the most common in the ECT group (57.1%), and meropenem was the second most common

Table 1. Microbiology of cIAIa

	Patients With a GN Isolate (n = 3771)				
	GN Isolates (n = 4032)				
	All	CR		C3R	
Overall	3286	84	2.23%	288	7.64%
Organism					
Klebsiella pneumoniae	655	12	1.55%	19	2.45%
Proteus mirabilis	103	7	5.98%	5	4.27%
Escherichia coli	2285	7	0.27%	129	4.92%
Enterobacter cloacae	191	9	3.96%	46	20.26%
Providencia spp.	9	1	10.00%	0	0.00%
Serratia marcescens	19	0	0.00%	1	4.17%
Morganella morganii	44	4	9.09%	5	11.36%
Enterobacter aerogenes	52	4	6.67%	12	20.00%
Proteus other	18	2	8.70%	2	8.70%
Citrobacter freundii	85	1	1.02%	19	19.39%
Klebsiella oxytoca	133	2	1.31%	4	2.61%
Enterobacter other	24	3	10.34%	5	17.24%
Citrobacter other	52	0	0.00%	8	12.50%
Serratia other	5	0	0.00%	1	14.29%
Klebsiella other	9	0	0.00%	0	0.00%
Pseudomonas aeruginosa	331	31	7.60%	30	7.35%
Acinetobacter baumannii	12	3	21.43%	3	21.43%
Other	94	3	2.40%	13	10.40%
	Patients With a GP Isolate (n = 1782)				
	GP Isolates (n = 2333)				
Enterococcus spp.	1072		45.95%		
Enterococcus faecalis	431		18.47%		
Enterococcus faecium	354		15.17%		
Staphylococcus aureus	241		10.33%		
MRSA	83		3.56%		
Bacteroides spp.	152		6.52%		
	Patients With a Polymicrobial Infection				
Polymicrobial	1512		33.95%		
2 organisms	1118		25.11%		
3 or more organisms	394		8.85%		

Abbreviations: C3R, resistant to third-generation cephalosporin; cIAI, complicated intra-abdominal infection; CR, carbapenem-resistant; GN, gram-negative; GP, gram-positive.
[a]Denominators for percentages are as follows: all GN isolates for GN; all GP isolates for GP; overall cohort (n = 4453) for polymicrobial infections.

(39.3%). In the non-ECT group, piperacillin-tazobactam was used in nearly three-quarters of all patients (72.6%). Among patients for whom appropriateness of the empiric regimen could be determined, there was no difference in exposure to IET between the ECT and non-ECT groups (Table 3).

All the examined unadjusted outcomes were worse in the group on ECT than non-ECT (Table 4). Adjusting for confounders known at the onset of cIAI, including demographics, hospital characteristics, and chronic and acute illness markers, worsening of some, though not all, of the outcomes persisted in association with receiving ECT (Table 5). Though hospital mortality, 30-day readmission, and AKI/AKI-D incidence were not increased in the ECT group compared with non-ECT, and though ECT was associated with significant independent excess in the total hospital LOS (0.96 days; 95% confidence interval [CI], 0.29 to 1.64), total hospital costs ($3897; 95% CI, $2001 to $5792), postinfection costs ($3844; 95% CI, $1921 to $5767), and in the risk of HO-CDI (odds ratio [OR], 2.14; 95% CI, 1.02 to 4.47), clinical deterioration (OR, 1.26; 95% CI, 1.04 to 1.52), and treatment failure (subhazard ratio, 1.62; 95% CI, 1.41 to 1.86), the postinfection LOS in the ECT group was shorter than in the non-ECT group (–0.61 days; 95% CI, –1.18 to –0.04).

In contrast, the postinfection LOS in the ECT group was statistically similar to the non-ECT group. Sensitivity analyses produced similar results (Supplementary Data). We did observe a modest excess in postinfection LOS in the ECT group relative to the non-ECT group (0.25 days; 95% CI, 0.03 to 0.48).

DISCUSSION

We demonstrate that among hospitalized patients with cIAI, only a small minority (1.4%) had a positive culture. The use of ECT, employed in over one-quarter of all patients, exceeded

Table 2. Demographic, Clinical, and Hospital Characteristics Present at Hospital Admission Among Patients With ≥1 Gram-Negative Organism

	ECT, No.	ECT, %	Non-ECT, No.	Non-ECT, %	
	n = 1185 (26.61%)		n = 3268 (73.31%)		*P*
Mean age (SD), y	61.1 (17.0)		61.0 (17.0)		.910
Gender: male	617	52.07%	1765	54.01%	.251
Race					
White	910	76.79%	2435	74.51%	.439
Black	114	9.62%	331	10.13%	
Hispanic/other	150	12.66%	470	14.38%	
Unknown	11	0.93%	32	0.98%	
Admission source					
Home	978	82.53%	2810	85.99%	.014
Clinic	94	7.93%	247	7.56%	
Transfer from another non–acute health care facility	76	6.42%	150	4.59%	
Other	37	3.12%	59	1.80%	
Admission type					
Emergency	900	75.95%	2659	81.36%	
Urgent	120	10.13%	237	7.25%	
Elective	155	10.95%	358	10.95%	<.001
Trauma	4	0.34%	9	0.28%	
Unknown	6	0.51%	5	0.15%	
Elixhauser comorbidities					
Congestive heart failure	158	13.33%	397	12.15%	.290
Valvular disease	64	5.40%	170	5.20%	.793
Pulmonary circulation disease	34	2.87%	76	2.33%	.302
Peripheral vascular disease	112	9.45%	254	7.77%	.071
Paralysis	24	2.03%	77	2.36%	.512
Other neurological disorders	95	8.02%	228	6.98%	.237
Chronic pulmonary disease	240	20.25%	614	18.79%	.273
Diabetes without chronic complications	191	16.12%	535	16.37%	.840
Diabetes with chronic complications	98	8.27%	286	8.75%	.613
Hypothyroidism	154	13.00%	379	11.60%	.204
Renal failure	188	15.86%	469	14.35%	.208
Liver disease	73	6.16%	211	6.46%	.721
Peptic ulcer disease with bleeding	31	2.62%	59	1.81%	.089
AIDS	6	0.51%	4	0.12%	.027
Lymphoma	16	1.35%	28	0.86%	.141
Metastatic cancer	62	5.23%	149	4.56%	.350
Solid tumor without metastasis	67	5.65%	156	4.77%	.234
Rheumatoid arthritis/collagen vascular	33	2.78%	104	3.18%	.497
Coagulopathy	187	15.78%	349	10.68%	<.001
Obesity	245	20.68%	677	20.72%	.976
Weight loss	325	27.43%	630	19.28%	<.001
Fluid and electrolyte disorders	661	55.78%	1537	47.03%	<.001
Chronic blood loss anemia	40	3.38%	63	1.93%	.005
Deficiency anemia	309	26.08%	721	22.06%	.005
Alcohol abuse	58	4.89%	163	4.99%	.899
Drug abuse	26	2.19%	88	2.69%	.352
Psychosis	91	7.68%	190	5.81%	.024
Depression	154	13.00%	356	10.89%	.052
Hypertension	623	52.57%	1715	52.48%	.955
Charlson comoribidity score					
0	469	39.58%	1406	43.02%	.097
1	884	18.82%	661	20.23%	
2	169	14.26%	415	12.70%	
3	97	8.19%	253	7.74%	
4	72	6.08%	166	5.08%	
5+	155	13.08%	367	11.23%	

Table 2. Continued

	ECT, No.	ECT, %	Non-ECT, No.	Non-ECT, %	
	n = 1185 (26.61%)		n = 3268 (73.31%)		*P*
Mean (SD)	1.8 (2.2)		1.6 (2.1)		.011
Median [IQR]	1 [0–3]		1 [0–2]		.006
Hospital characteristics					
Census region					
Midwest	342	28.86%	941	28.79%	<.001
Northeast	137	11.56%	525	16.06%	
South	558	47.09%	1204	36.84%	
West	148	12.49%	598	18.30%	
No. of beds					
<100	36	3.04%	142	4.35%	
100–199	141	11.90%	376	11.51%	<.001
200–299	318	26..84%	686	20.99%	
300–399	200	16.88%	451	13.80%	
400–499	145	12.24%	571	17.47%	
500+	345	29.11%	1042	31.88%	
Teaching	501	42.28%	1532	46.88%	.006
Urban	1042	87.93%	2738	83.78%	.001

Abbreviations: ECF, extended care facility; ECT, empiric carbapenem treatment; IQR, interquartile range.

the prevalence of C3R by a factor of 3. Importantly, the organisms with the highest prevalence of C3R, where carbapenems may represent the treatment of choice (*Enterobacter* spp., *A. baumannii*), were an order of magnitude less common as causes of cIAI than those with the lowest rates of resistance (*E. coli*, *K. pneumoniae*). Despite this, the most common C3R pathogen was *E. coli*, accounting for nearly half of all C3R organisms. Importantly, although hospital mortality and 30-day readmission rates in the 2 groups were similar, ECT was associated with a reduction in the postinfection LOS. Higher postinfection costs were associated with ECT despite a modest reduction in postinfection LOS.

The dissociation between costs and LOS may be due to several factors. One possibility is that the higher raw mortality in the ECT group implies greater resource utilization without extension of life. Another potential explanation is a statistical anomaly known as Simpson's paradox. This arises essentially because of potentially heterogeneous groups combined into a single mean value, as well as the presence of residual confounding. It would be useful to examine this issue in future research.

The discordance between the total and postinfection LOS between the 2 groups suggests that the overall prolongation of LOS in the ECT group occurred largely in the pre-infection period, possibly pointing to, along with prior exposure to antimicrobials and history of C3R, an increased probability of a resistant organism. In this way, LOS is a marker for ECT use, rather than its consequence. ECT was also linked with an increase in the risk of developing HO-CDI, as well as of clinical deterioration, and treatment failure relative to other empiric treatments, even after adjusting for many confounders known at cIAI onset. Together, these findings, along with the stably low prevalence of CR, suggest that opportunities exist for carbapenem-sparing strategies in cIAI. Shifting away from ECT in cIAI, therefore, could potentially reduce selection pressure for carbapenem resistance and limit rates of important, publicly reported complications such as CDI.

Carbapenems have been increasingly relied upon in cIAI for many years. However, the Surgical Infections Society (SIS) in 2017 updated its evidence-based guidelines for the treatment of cIAI [28]. At that time, the SIS indicated that carbapenems were not recommended as routine empiric agents. Carbapenems, though, were noted to serve a role in select "higher-risk" patients, namely those at risk for a resistant pathogen (HCA and HO cIAI) or those who exhibit severe signs of acute decompensation, such as the need for vasopressors and/or mechanical ventilation. Our data suggest that, on one level, practitioners appear to heed this advice. Specifically, we saw that ECT was administered more frequently than non-ECT to HCA- and HO-cIAI patients. We further observed that all markers of acute illness severity were higher in patients in the ECT group than those in the non-ECT group, thus comporting with the recommendations. Nonetheless, the majority of patients with ECT suffered from a CO-cIAI.

We further note that in the group receiving ECT, approximately one-third of the patients also received empiric piperacillin-tazobactam. This likely represents a switch during the transfer of care between teams in the emergency department, the ward, the operating room, and/or the ICU. Moreover, nearly three-quarters received piperacillin-tazobactam in the

Table 3. Infection and Treatment Characteristics Among Patients With ≥1 Gram-Negative Organism

	ECT, No.	ECT, %	Non-ECT, No.	Non-ECT, %	
	n = 1185		n = 3268		*P*
Culture source					
Abdominal only	383	32.32%	1303	39.87%	
Both	646	54.51%	1576	48.23%	<.001
Blood only	156	13.16%	389	11.90%	
Organisms					
Gram-negative isolates					
Klebsiella pneumoniae	195	16.46%	579	17.72%	.326
Proteus mirabilis	33	2.78%	84	2.57%	.693
Escherichia coli	641	54.09%	1983	60.68%	<.001
Enterobacter cloacae	58	4.89%	169	5.17%	.711
Providencia spp.	2	0.17%	8	0.24%	1.000
Serratia marcescens	5	0.42%	19	0.58%	.521
Morganella morganii	12	1.01%	32	0.98%	.921
Enterobacter aerogenes	14	1.18%	46	1.41%	.563
Proteus spp.	5	0.42%	18	0.55%	.596
Citrobacter freundii	29	2.45%	69	2.11%	.500
Klebsiella oxytoca	41	3.46%	112	3.43%	.958
Enterobacter other	8	0.68%	21	0.64%	.905
Citrobacter other	13	1.10%	51	1.56%	.251
Serratia other	3	0.25%	4	0.12%	.392
Klebsiella other	5	0.42%	4	0.12%	.062
Pseudomonas aeruginosa	130	10.97%	278	8.51%	.012
Âcinetobacter baumannii	6	0.51%	8	0.24%	.168
Stenotrophomonas maltophilia	2	0.17%	8	0.24%	1.000
Other	22	1.86%	103	3.15%	.021
CR	43	3.63%	41	1.25%	<.001
C3R	120	10.13%	168	5.14%	<.001
Gram positive isolates					
Enterococcus spp.	346	29.20%	726	22.22%	<.001
Staphylococcus aureus	65	5.49%	176	5.39%	.897
Bacteroides spp.	39	3.29%	113	3.46%	.787
Candida spp.	41	3.46%	98	3.00%	.434
Infection characteristics					
Monomicrobial	772	66.15%	2169	66.37%	.774
Polymicrobial					
2 organisms	308	25.99%	810	24.79%	
3 or more organisms	105	8.86%	289	8.84%	
Gram-negative only	669	56.46%	2002	61.26%	
Both gram-negative and gram-positive	306	25.82%	794	24.30%	.006
Gram-positive only	210	17.72%	472	14.44%	
Community-onset cIAI	1028	86.75%	2976	91.06%	
Community-acquired	682	57.55%	2116	64.75%	<.001
Health care–associated	346	29.20%	860	26.32%	
Hospital-onset cIAI	157	13.25%	292	8.94%	
Time to cIAI					
Mean (SD)	5.5 (11.8)		3.2 (5.2)		<.001
Median [IQR]	2 [1–6]		2 [1–3]		<.001
Antibiotics within 90 d before admission	199	16.79%	414	12.67%	<.001
Antibiotics during index hospitalization before cIAI onset	672	56.71%	1738	53.18%	.037
CR organism within 90 d before admission	3	0.25%	4	0.12%	.392
C3R organism within 90 d before admission	11	0.93%	12	0.37%	.032
Illness severity measures at cIAI onset (by day 2 from index infection onset)					
ICU admission	635	53.59%	1167	35.71%	<.001
Mechanical ventilation	517	43.63%	913	27.94%	<.001
Vasopressors	510	43.04%	1076	32.93%	<.001

Table 3. Continued

	ECT, No.	ECT, %	Non-ECT, No.	Non-ECT, %	
	n = 1185		n = 3268		*P*
Dialysis	82	6.92%	134	4.10%	<.001
Severe sepsis	287	24.22%	520	15.91%	<.001
Severe sepsis present on admission	168	14.18%	326	9.98%	<.001
Septic shock	333	28.10%	576	17.63%	<.001
Septic shock present on admission	179	15.11%	367	11.23%	<.001
Empiric cIAI treatment regimens (by day 2 from index infection onset)					
Cefoxitin	97	8.19%	350	10.71%	.013
Ertapenem	677	57.13%	0	0.00%	<.001/NA
Moxifloxacin	3	0.25%	8	0.24%	1.000
Ciprofloxacin	113	9.54%	502	15.36%	<.001
Levofloxacin	96	8.10%	358	10.95%	.005
Ampicillin-sulbactam	41	3.46%	261	7.99%	<.001
Moxifloxacin + metronidazole	2	0.17%	4	0.12%	.660
Ciprofloxacin + metronidazole	84	7.09%	399	12.21%	<.001
Levofloxacin + metronidazole	62	5.23%	254	7.77%	.004
Cefazolin + metronidazole	32	2.70%	260	7.96%	<.001
Cefuroxime + metronidazole	1	0.08%	0	0.00%	.266
Ceftriaxone + metronidazole	34	2.87%	23	7.19%	<.001
Cefotaxime + metronidazole	0	0.00%	3	0.09%	.570
Imipenem-cilastatin	85	7.17%	0	0.00%	<.001/NA
Meropenem	466	39.32%	0	0.00%	<.001/NA
Doripenem	24	2.03%	0	0.00%	<.001/NA
Piperacillin-tazobactam	383	32.32%	2371	72.55%	<.001
Tigecycline	17	1.43%	24	0.73%	.031
Ticarcillin-clavulanic acid	0	0.00%	0	0.00%	1.000
Cefepime	51	4.30%	241	7.37%	<.001
Ceftazidime	2	0.17%	16	0.49%	.183
Ceftolozane-tazobactam	0	0.00%	0	0.00%	1.000
Ceftazidime-avibactam	0	0.00%	1	0.03%	1.000
Empiric treatment appropriateness					
Non-IET	781	65.91%	2442	74.72%	<.001
IET	77	6.50%	220	6.73%	
Indeterminate	327	27.59%	606	18.54%	

Abbreviations: cIAI, complicated intra-abdominal infection; C3R, resistant to third-generation cephalosporin; CR, carbapenem-resistant; ECT, empiric carbpenem treatment; ICU, intensive care unit; IET, inappropriate empiric therapy; IQR, interquartile range.

non-ECT group, despite the fact that the SIS guidelines also recommend reserving this drug for high-risk patients.

In part, the use of either of these broad agents reflects limitations in rapid diagnostic technologies that might help to alleviate uncertainty about initial empiric therapy. Although bedside rapid molecular testing is on the horizon, until it is widely available, appreciating local antibiograms and the interaction of the hospital's microbiology with the specific syndrome in question will remain critical for limiting the use of broad-spectrum coverage. Furthermore, predictive models, if validated, may prove a useful adjunct to stratifying the risk for resistance [29, 30].

The hospital mortality rate in our cohort did not differ from that reported by other authors, supporting the generalizability and face validity of our results. For example, Solomkin and coworkers examined the outcomes of cIAI treatment with tigecycline in a group of patients conducted using the Premier database between 2009 and 2012 [31]. In propensity score–matched groups, hospital mortality was between 10.2% and 11.1%, or similar to what we observed in the ECT group. One major difference between Solomkin's study and ours is that we required patients to have a positive abdominal or blood culture, thus possibly selecting for sicker patients. In view of this, it is encouraging that we did not detect higher death rates in our cohort.

Our study builds on prior work and adds to the body of knowledge on the outcomes of cIAI in other ways. Although adjusting for factors present at the onset of cIAI eliminated differences in mortality and 30-day readmission, ECT was associated with greater total hospital LOS but a reduction in the postinfection LOS. At the same time, we estimated added postinfection costs of ~$3800. These observations with regard to the potential implications of ECT for resource use are novel and suggest that clinicians rightly target ECT to patients who

Table 4. Unadjusted Hospitalization Outcomes Among Patients With ≥1 Gram-Negative Organism

	ECT	%	Non-ECT	%	
	n = 1185		n = 3268		*P*
Hospital mortality	124	10.46%	213	6.52%	<.001
30-d readmission	144	13.57%	316	10.34%	.004
Hospital costs total, $					
Mean (SD)	56 406 (91 778)		36 289 (50 414)		<.001
Median [IQR]	27 638 [14 495–61 440]		19 616 [11 373–39 361]		<.001
Postinfection hospital costs, $					
Mean (SD)	34 365 (61 421)		22 803 (41 127)		<.001
Median [IQR]	13 927 [5998–36 348]		9070 [3866–23 904]		<.001
Postinfection LOS, d					
Mean (SD)	13.2 (19.4)		9.4 (13.7)		<.001
Median [IQR]	8 [4–15]		6 [3–11]		<.001
Exploratory outcomes					
HO-CDI	14	1.18%	16	0.49%	.013
AKI	414	34.94%	904	27.66%	<.001
Incident AKI	173	14.60%	361	11.05%	.001
AKI POA	240	20.25%	549	16.80%	.008
AKI-D	33	2.78%	55	1.68%	.020
Incident AKI-D	19	1.60%	27	0.83%	.023
AKI-D POA	4	0.37%	12	0.34%	.884
Clinical deterioration	548	46.24%	1292	39.53%	<.001
Treatment failure	510	43.04%	1029	31.49%	<.001

Abbreviations: AKI, acute kidney injury; AKI-D, AKI with dialysis; CDI, *Clostridioides difficile* infection; ECT, empiric carbapenem treatment; HO, hospital onset; IQR, interquartile range; LOS, length of stay; POA, present on admission.

have spent a longer time in the hospital and are more acutely ill, thus raising their risk for a resistant infection. We also examined novel yet important outcomes such as the risk of incident *C. difficile* and other complications that impact hospital course.

Though rare in both groups, CDI was strongly associated with ECT, occurring at more than double the rate seen with other regimens. This nexus between ECT and CDI is worrisome and may reflect the important impact of carbapenems on gastrointestinal flora. This finding contrasts with that of Metzger et al., who in a single-center cohort failed to find a connection in cIAI between CDI and any specific antimicrobial class [32]. This relationship requires further examination in future research.

Incident AKI, on the other hand, is somewhat more likely in ECT patients. Notably, the AKI prevalence in our cohort was high, with approximately one-third of all patients suffering this outcome. This is considerably higher than what has been described in other studies, though it is not inconsistent with the high degree of acute illness (vasopressor use in one-third of the population) [26]. Given that AKI, and particularly AKI-D, is an important determinant of hospital costs and mortality, future

Table 5. Adjusted Association of ECT With Outcomes

Outcome	Measure	Point Estimate	95% Confidence Interval	*P*
Mortality	Odds ratio	1.11	0.83 to 1.48	.502
30-d readmission	Odds ratio	1.18	0.93 to 1.49	.167
Hospital costs (all)	Excess $	3897	2001 to 5792	<.001
Hospital costs (post–infection onset)	Excess $	3844	1921 to 5767	<.001
Total LOS	Excess days	0.96	0.29 to 1.64	.005
Post–infection onset LOS	Excess days	–0.59	–1.15 to –0.03	.039
Exploratory				
HO-CDI	Odds ratio	2.15	1.02 to 4.50	.044
AKI	Odds ratio	1.09	0.90 to 1.32	.389
Incident AKI	Odds ratio	1.07	0.85 to 1.34	.588
AKI-D	Odds ratio	1.39	0.88 to 2.21	.163
Incident AKI-D	Odds ratio	1.55	0.84 to 2.87	.162
Clinical deterioration	Odds ratio	1.26	1.04 to 1.52	.017
Treatment failure	Subhazard ratio	1.28	1.14 to 1.45	<.001

Abbreviations: AKI, acute kidney injury; AKI-D, AKI with dialysis; CDI, *Clostridioides difficile* infection; ECT, empiric carbapenem treatment; HO, hospital onset; LOS, length of stay.

studies need to examine potential modifiable risk factors for developing AKI in cIAI patients.

Two additional important end points are worth highlighting: the incidence of clinical deterioration and treatment failure. Though their frequency in our study is lower than in that by Solomkin et al., this is most likely due to a different population (theirs did not require a positive culture) and different definitions for these events [31]. Nevertheless, both are common in both groups.

Our study has a number of limitations. As a retrospective cohort study, it is susceptible to various types of bias, most notably selection bias. We attempted to minimize this by defining enrollment criteria prospectively, as well as by enrolling consecutive patients who met the selection criteria. Confounding is another threat to the validity of an observational study, particularly when evaluating treatment effectiveness. Similarly, in the case of any treatment exploration, there is also a possibility specifically of confounding by indication, where broader-spectrum treatment may be a marker of more severe disease. Though we adjusted for illness severity among many other covariates, residual confounding may still be present. For example, we lacked access to information regarding source control, an important determinant of outcomes in cIAI. This implies that the outcome estimates may not be wholly attributable to ECT. However, we minimized residual confounding by using severity of illness variables known at cIAI onset. We also did not stratify by infection source in this analysis. We omitted this, as the recent SIS guideline does not recommend including this as a determinant of risk [28]. Despite these shortcomings, our results may point to potential carbapenem overuse as an empiric regimen.

Misclassification is a possibility as well, particularly given that we relied on administrative coding to identify the cohort and some of the outcomes. We tried to minimize it by (a) using previously published algorithms and (b) erring on the side of specificity at the expense of sensitivity [18, 22–24, 26, 33]. Furthermore, when present, such misclassification would affect both groups equally, thus reducing any actual differences between the groups. Because we used a large multicenter database for our analyses, lack of generalizability is not a major concern. However, given that our cohort includes only culture-positive cIAI patients, the results may not generalize broadly to those cIAI patients who either were not sampled for a pathogen or did not grow one out.

In summary, we show that the prevalence rates of C3R, a surrogate for ESBL, and CR in culture-positive patients with cIAI are still relatively low in the United States. Nevertheless, ECT is used in one-quarter of all cIAI patients, with some associated adverse outcomes, including an increase in the risk of CDI, clinical deterioration, treatment failure, and excess costs. Although it remains difficult to attribute some of these end points specifically to carbapenem use rather than to other underlying factors not captured in the data, these are important associations that future studies should attempt to disentangle. In a broad sense, our findings point to potential opportunities for antimicrobial stewardship programs as a compliment to the care of cIAI patients, so as to address the appropriate use of broad-spectrum therapies.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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