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Risk factors and outcome associated with infection or colonization due to carbapenem-heteroresistant *Escherichia coli*

Karen Tan [1], Corey Kelsom[1,2], Amanda Chron[1], Paul Nieberg[3], Holly Huse[4] and Annie Wong-Beringer [1,2]*

[1]*Department of Clinical Pharmacy, University of Southern California (USC) School of Pharmacy, Los Angeles, CA, USA;* [2]*Department of Pharmacy, Huntington Hospital, Pasadena, CA, USA;* [3]*Department of Infectious Diseases, Huntington Hospital, Pasadena, CA, USA;* [4]*Department of Microbiology, Huntington Hospital, Pasadena, CA, USA*

*Corresponding author. Present address: University of Southern California, School of Pharmacy, 1985 Zonal Avenue, Los Angeles, CA 90089, USA. E-mail:anniew@usc.edu

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Background: Up to 32% of ESBL-producing Enterobacterales strains display a carbapenem-heteroresistant (cHR) phenotype but its clinical relevance is unknown.

Objectives: To determine risk factors and clinical outcome associated with infection due to cHR ESBL-producing *Escherichia coli* (ESBL-EC).

Methods: A retrospective, case–control study was conducted on patients from whom a pair of clonally related *E. coli* strains were isolated during separate healthcare encounters with (case) or without (control) development of cHR phenotype in the latter strain. Study groups were compared for host and microbial characteristics and carbapenem exposure. Outcome measures included ICU admission, length of hospitalization, and mortality.

Results: Study patients (15 cases, 10 controls) were elderly (median age: 74 years) with half admitted from home (52%), most (80%) having ≥3 comorbid conditions and severe functional impairment. Case patients were more likely to have 'index' ESBL-EC isolating from blood (27% versus 0%; $P = 0.125$) and have greater cumulative amount and duration of carbapenem exposure than controls. All control 'subsequent' isolates were from urine whereas five cHR case isolates were from blood or respiratory sources. More hospitalized case patients required ICU admission (23% versus 0%; $P = 0.257$) and prolonged hospital stay (>7 days) than controls (62% versus 38%%; $P = 0.387$).

Conclusions: Our findings deserve confirmation with a larger study population and call attention to the potential for increased morbidity with cHR ESBL-EC infections, which underscores the need to screen for cHR phenotype in patients with repeated growth of ESBL-EC, particularly from systemic sites and patients that have had extensive carbapenem exposure.

Introduction

Extended spectrum β-lactamase-producing Enterobacterales (ESBL-E) remain a serious antibiotic resistance threat.[1] The incidence of ESBL-E infections in the United States continues to rise with a 53% increase in new cases reported between 2012 and 2017.[2] Therapy with a carbapenem agent is preferred for serious, invasive ESBL-E infections.[3–6] However, reports of clinical and microbiological failure in a subset of carbapenem-treated patients with ESBL-E infections are concerning and require further investigation.[7–9] One potential explanation for treatment failure, despite apparent *in vitro* susceptibility, may be attributed to the antibiotic heteroresistance phenotype.[10]

Cases of carbapenem-heteroresistance (cHR) among ESBL-E have been reported in several countries.[11–15] We previously reported the prevalence of cHR in clinical isolates of ESBL-producing Enterobacterales ($n = 173$) at a community-teaching hospital. We found 32% (55/173) of tested isolates expressed heteroresistance to at least one carbapenem agent using the modified population analysis profile method.[16] ESBL-producing *Escherichia coli* (ESBL-EC) was the most common organism (89%, 49/55) evaluated in that study, with urine as the most common source (69%, 38/55) of isolation. Interestingly, cHR isolates were more likely than non-cHR isolates to be cultured from non-urinary source (31% versus 19%, $P = 0.018$), particularly from a respiratory

site. As a follow-up study, we sought to identify factors predisposing to the subsequent acquisition of ESBL-EC with cHR phenotype in patients who had repeated hospital encounters and to evaluate the clinical outcomes associated with infection or colonization due to cHR ESBL-EC.

Patients and methods

Study design

We conducted a case-control study at a 619 bed community-teaching hospital. This study was approved by the local institutional review board (IRB). Study patients met the following inclusion criteria: age ≥18 years, isolation of clonally related ESBL-EC strains from two separate hospital encounters, and medical records available for review.

Microbiological testing

Methods to screen and confirm cHR in clinical isolates were previously published.[16] Briefly, cHR phenotype was screened by disc diffusion which was identified as growth of colonies within the zone of inhibition for all isolates with susceptible zone diameter, as defined by CLSI breakpoints.[17] cHR phenotype was then confirmed by a modified population analysis profile (PAP) method based on growth on carbapenem-containing Mueller-Hinton agar plates at 8-fold MIC, as determined by broth microdilution.[16] To determine clonality of study strains, we performed random amplification of polymorphic DNA (RAPD)-PCR. Genomic DNA was extracted from clinical strains of *E. coli* by Qiagen DNeasy Blood & Tissue Kits (Cat No. #69506) per manufacturer's instructions and PCR assay was performed using previously published primer (AP4) and protocol.[18,19]

Study definitions

Each patient had two isolates included in this study, 'index' and 'subsequent' isolates. The 'index' isolate represents the earliest clinical ESBL-EC isolate saved in the biorepository, determined as non-cHR by modified PAP method, and collected during a hospital admission. The 'subsequent' isolate was the most recent clinical ESBL-EC collected subsequent to the 'index' isolate, determined as either cHR or non-cHR based on PAP method, and saved from any type of hospital encounter, defined as either an emergency department visit or a hospital admission. Patients were grouped as either cases or controls based on their 'subsequent' isolate. Case patients were those with a non-cHR ESBL-EC 'index' isolate followed by subsequent isolation of a cHR ESBL-EC 'subsequent' isolate. Control patients had non-cHR ESBL-EC for both 'index' and 'subsequent' isolates. All 'index' isolates were collected from patients with an ESBL-EC infection defined by criteria established by the CDC/NHSN. 'Subsequent' isolates were collected from patients with either an infection or colonization with ESBL-EC; colonization was defined by the lack of signs and symptoms of infection or as documented by the treating physician in the medical record and without the need for antibiotic therapy.

Clinical data collection

Medical records were reviewed for pertinent demographics, clinical presentation, microbiology results, treatment details and outcomes at 'index' and 'subsequent' isolate hospital encounters. Demographic data included age, sex, residence prior to admission, and comorbidities. Cardiovascular disease included the following: hypertension, hyperlipidaemia, congestive heart failure, and/or coronary artery disease. Liver disease was defined as total bilirubin >2.5 mg/dL. Charlson Comorbidity Index (CCI) scores were calculated. Katz Index of Independent Activities of Living score to characterize functional status were recorded. Recent antimicrobial exposure, within 90 days of admission, was noted. Outcome measures included need for ICU admission, length of hospital stay, total number of hospital encounters between 'index' and 'subsequent' isolate pairs, and in-hospital mortality at 'subsequent' isolate visit. Carbapenem therapy prescribed during 'index' isolate visits and during the interval between 'index' and 'subsequent' isolate visits was detailed for each patient. Study data were managed using the Research Electronic Data Capture (REDCap) software hosted at the University of Southern California.

Data analysis

Case and control patients were compared on demographics, clinical presentation, laboratory data, carbapenem exposure, and outcomes including need for ICU admission, length of hospital stay, and in-hospital mortality. Additionally, hospital encounters between 'index' and 'subsequent' isolates were detailed to include the time between isolate pair, frequency of total emergency department and hospital admissions, and the time interval between discharge to next documented hospital admission. Katz Index scores calculated at 'index' and 'subsequent' isolate visits for each patient were compared for change in functional status over time and between cases and controls. At 'subsequent' isolate admission, in-hospital mortality was compared between cases and controls.

Clonal relatedness was analysed by visually comparing banding patterns for all study isolates and between 'index' and 'subsequent' isolates from the same patients. Strains with banding patterns that differed by <2 bands were considered to be clonally related.[20]

Statistical analysis

Univariate analyses were performed for clinical, microbiological, and outcomes data. Categorical and continuous variables were analysed using Fisher's exact test and Mann–Whitney U test where appropriate. Statistical analyses were performed using SPSS Version 26 (IBM Corp., Armonk, NY) and GraphPad Software version 8.4.2 (La Jolla, CA).

Results

Study population

All patients hospitalized during the study period (2012 to 2017) and from whom growth of ESBL-EC was saved on at least two hospital encounters were screened for inclusion. A total of 25 patients met inclusion criteria; all had an 'index' non-cHR ESBL-EC isolate while 15 (cases) had a 'subsequent' culture positive for cHR ESBL-EC confirmed by modified PAP method and 10 (controls) had 'subsequent' non-cHR strain. 'Index' and 'subsequent' isolates from each study patient were shown to be clonally related.

Risk factors for subsequent development of cHR phenotype in ESBL-EC

'Index' hospital encounter

Clinical and microbial characteristics at 'index' and 'subsequent' encounters for study groups are summarized in Table 1. The overall median age was 74 years (IQR: 62–87) and 76% (19/25) of study patients were female. About half of the study patients resided at home (52%, 13/25) prior to admission, while 40% (10/25) were admitted from a skilled nursing facility. Most patients (80%, 20/25) had at least three comorbid conditions; cardiovascular disease (80%, 20/25), diabetes (44%, 11/25), and chronic kidney disease (24%, 6/25) were the most common comorbid conditions. About 24% of patients (6/25) had at least one indwelling medical device. Most patients (84%, 21/25) presented with a Katz Index Score of

Table 1. Comparison of patient characteristics between cases and controls during admissions for 'index' and 'subsequent' isolates causing infection

	'Index' isolate			'Subsequent' isolate		
	Case ($n = 15$)	Control ($n = 10$)	*P* value	Case ($n = 15$)	Control ($n = 10$)	*P* value
Demographics						
Age, years, median (IQR)	74 (63–92)	75 (62–84)	0.683	76 (63–92)	76 (62–84)	0.723
Female, *n* (%)	11 (73%)	8 (80%)	>0.99	unchanged from index admission		
Residence prior to admission, *n* (%)						
Home	7 (46%)	6 (60%)	0.6882	unchanged from index admission		
SNF/LTAC	6 (40%)	4 (40%)	>0.99	unchanged from index admission		
OSH	1 (7%)	0	>0.99	unchanged from index admission		
Homeless	1 (7%)	0	>0.99	unchanged from index admission		
Comorbidities						
≥3 different comorbidities	13 (87%)	7 (70%)	0.358	13 (87%)	8 (80%)	>0.99
Cardiovascular disease	12 (80%)	8 (80%)	>0.99	unchanged from index admission		
Diabetes	8 (53%)	3 (30%)	0.414	9 (60%)	4 (40%)	0.428
Chronic kidney disease	5 (33%)	1 (10%)	0.3449	2 (13%)	3 (30%)	0.358
Cerebral vascular accident	3 (20%)	0	0.250	3 (20%)	1 (10%)	0.626
Chronic obstructive lung disease	3 (20%)	3 (30%)	0.653	unchanged from index admission		
Malignancy	2 (13%)	1 (10%)	>0.99	2 (13%)	3 (30%)	0.358
Neurogenic bladder	1 (7%)	0 (0%)	>0.99	unchanged from index admission		
Liver disease	0	0	>0.99	1 (6.7%)	1 (10%)	>0.99
Benign prostatic hypertrophy	0	0	>0.99	2 (13%)	1 (10%)	>0.99
Charlson Comorbidity Index, median (IQR)	6 (3–6)	5 (4–7)	0.935	6 (4–7)	6 (4–7)	0.495
Katz Score of ≤2 Severe impairment[a]	12 (80%)	9 (90%)	0.626	13 (93%)	7 (70%)	0.272
Worsened score from index				5 (36%)	1 (10%)	0.341
Improved score from index				3 (21%)	4 (40%)	0.393
Requires indwelling medical device	4 (27%)	2 (20%)	>0.99	7 (47%)	1 (10%)	0.088
Requires chronic indwelling foley	2 (13%)	2 (20%)	>0.99	6 (40%)	1 (10%)	0.179
Any antimicrobial exposure within 90 days	9 (60%)	5 (50%)	0.697	10 (67%)	7 (70%)	>0.99
Source of infection						
Blood	4 (27%)	0	0.125	4 (27%)	0	0.125
Respiratory	0	0	>0.99	1 (7%)	0	>0.99
Urine	11 (73%)	10 (100%)	0.125	10 (67%)	10 (100%)	0.001
Culture site differed from index				5 (33%)	0 (0%)	0.061

[a]Number of patients included for Katz score: index visit (15 cases, 10 controls), subsequent visit (14 cases, 10 controls).

≤2, suggesting severe impairment of independence in activities of daily living. No differences in the above characteristics were observed at 'index' hospital encounter except that recent antibiotic exposure prior to admission was numerically greater in cases than controls (60%, 9/15 versus 50% 5/10; $P = 0.70$).

All index visits were due to infection by ESBL-EC isolate. Urine was the most common culture site (84%, 21/25). Four case patients, but no controls, had ESBL-EC bacteraemia ($P = 0.125$). The majority of infections were treated with carbapenem therapy (76%, 19/25) (Table 2). Importantly, of those who received either meropenem or ertapenem therapy, a trend towards longer treatment duration (5 days versus 3 days, $P = 0.295$) was observed for cases compared with control patients. Overall, one-third of patients (36%, 9/25) required a hospital stay of >7 days during 'index' isolate visits; more than twice as many cases compared with control patients required prolonged hospital stay (47%, 7/15 versus 20%, 2/10, $P = 0.229$) (Table 3).

Hospital encounters between 'index' and 'subsequent' isolates

A median time interval of 169 days (IQR: 67–295) had elapsed between 'index' and 'subsequent' isolates for our study patients, where case patients had a longer time interval between pairs than controls (254 days versus 79 days; $P = 0.023$) (Table 2). During this interval, case patients had a longer total healthcare exposure (26 days versus 18 days; $P = 0.186$) and were more likely to have had carbapenem exposure (87%, 13/15 versus 60%, 6/10;

Table 2. Carbapenem exposure and healthcare encounters between 'index' and 'subsequent' isolates

	'Index' isolate			Interval between 'Index' and 'Subsequent' isolates		
Characteristic	Case ($n = 15$)	Control ($n = 10$)	*P* value	Case ($n = 15$)	Control ($n = 10$)	*P* value
Had exposure to any carbapenem[a]	11 (73%)	8 (80%)	>0.99	13 (87%)	6 (60%)	0.1753
Ertapenem	5 (33%)	5 (50%)	0.442	8 (53%)	5 (50%)	>0.99
Meropenem	7 (47%)	6 (60%)	0.688	12 (80%)	5 (50%)	0.194
Days of cumulative carbapenem exposure, median (IQR)	5 (3–8) $N = 11$	3 (2–7) $N = 8$	0.295	11 (4–14) $N = 13$	9 (2–13) $N = 6$	0.506
Ertapenem, median, IQR	4 (3–6) $N = 5$	2 (2–5) $N = 5$	0.333	5 (3–7) $N = 8$	2 (2–11) $N = 5$	0.269
Meropenem, median, IQR	5 (3–8) $N = 7$	2 (2–4) $N = 6$	0.131	8 (3–11) $N = 12$	5 (3–8) $N = 5$	0.339
Cumulative carbapenem exposure, grams						
Ertapenem, median, IQR	–	–		7 (3–8) $N = 10$	4 (2–16) $N = 7$	0.375
Meropenem, median, IQR	–	–		11 (6–19) $N = 12$	4 (2–8) $N = 7$	0.0371
Events between index and subsequent isolates				Case	Control	
Time between index and subsequent isolates, days, median (IQR)				254 (124–403)	79 (25–169)	0.023
Cumulative duration of healthcare exposure, days, median (IQR)				26 (14–37) $N = 14$	18 (11–28) $N = 10$	0.186

[a]Had exposure to both ertapenem and meropenem at index visit (1 case, 3 controls) and subsequent visit (7 cases, 4 controls).

Table 3. Comparison of outcome between cases and controls during admissions for 'index' and 'subsequent' isolates

	'Index' isolate, *N* (%)			'Subsequent' isolate, *N* (%)		
Characteristic	Case $N = 15$	Control $N = 10$	*P* value	Case $N = 15$	Control $N = 10$	*P* value
Required hospital admission	15 (100%)	10 (100%)	>0.99	13 (87%)	8 (80%)	>0.99
ICU admission	1 (7%)	0	>0.99	3 (23%)	0	0.257
Length of stay, days, (median, IQR)	6 (4–9)	6 (4–8)	0.765	9 (6–13)	5 (5–10)	0.138
Prolonged stay (>7 days)	7 (47%)	2 (20%)	0.229	8 (62%)	3 (38%)	0.387
In-hospital mortality	0	0	>0.99	1 (8%)	1 (12%)	>0.99

Note: At 'subsequent' visit, a total of 21 patients (13 cases, 8 controls) required hospitalization; need for ICU admission, length of hospital stay, and in-hospital mortality were calculated for this subset of patients.
At last visit, a total of 27 patients (13 cases, 14 controls) required hospitalization; need for ICU admission, length of hospital stay, and in-hospital mortality were calculated for this subset of patients.

$P = 0.175$) compared with controls. Cumulative ertapenem and meropenem exposure during the interval between 'index' and 'subsequent' isolates indicated that case patients had higher cumulative carbapenem exposure than the control group for both ertapenem (7 grams versus 4 grams, $P = 0.375$) and meropenem (11 grams versus 4 grams, $P = 0.037$).

'Subsequent' isolate admission

Detailed clinical characteristics of patients at the 'subsequent' isolate admission are summarized in Table 1. No changes in residence prior to admission were noted. Most patients remained functionally dependent, with a Katz Index score of ≤ 2 (80%, 20/25). Of the 24 patients with scores recorded (14 cases, 10 controls) at both

visits, case patients were more likely to present with a worsened Katz score (36%, 5/14 versus 10%, 1/10; $P = 0.341$). In contrast, control patients had a higher likelihood of an improved Katz score at subsequent admission (21%, 3/14 versus 40%, 4/10; $P = 0.393$). Case patients with a cHR ESBL-EC strain were more likely to present with a chronic indwelling foley catheter (40%, 6/15 versus 10%, 1/10; $P = 0.179$).

In the majority of study patients (80%, 20/25), the 'subsequent' isolate was grown from the same culture site as their 'index' isolate visit. Of those 20 patients, all 10 control patients had a non-cHR ESBL-EC strain collected from the urine (100%, 10/10) while the 8 case patients had cHR ESBL-EC grown from urine (80%, 8/10) and 2 from blood (20%, 2/10). Of the five 'subsequent' isolates cultured from a different site than the 'index' isolate, all were from case patients (33%, 5/15 versus 0%, 0/10, $P = 0.061$) with the respective 'index'–'subsequent' sites as followed: 2 pairs (urine–blood), 2 pairs (blood–urine), 1 pair (urine–respiratory).

Over 80% of patients (84%, 21/25) required hospitalization at their 'subsequent' visit, with similar proportions between cases and controls (87%, 13/15 versus 80%, 8/10, respectively); the other 4 patients were admitted to emergency department only (Table 3). Of those admitted, 52% (11/21) required a prolonged hospital stay of more than one week with cases almost twice as likely as controls (62%, 8/13 versus 38%, 3/8; $P = 0.387$). Additionally, three case patients (23%) with a cHR ESBL-EC isolate compared with none from the control group required ICU admission ($P = 0.257$). Two deaths (1 case, 1 control) occurred during the 'subsequent' isolate hospitalization. The case patient was a 95-year-old male who presented with altered mental status and shortness of breath and was diagnosed with aspiration pneumonia. Admission blood cultures grew ESBL-EC; no positive cultures from respiratory samples were noted. The patient developed respiratory failure despite receiving 7 days of meropenem therapy and expired. Disc diffusion testing of this isolate revealed heteroresistance to all tested carbapenems, including meropenem. However, only ertapenem tested positive for cHR phenotype by the PAP method. The control patient who died was an 86-year-old female with multiple comorbidities admitted for cellulitis. The patient received daptomycin and cefepime for cellulitis. A urine culture obtained upon admission was positive for ESBL-EC but the growth was attributed to colonization and therefore not treated. On day 5 of hospitalization, the patient developed cardiopulmonary arrest and expired.

Strain typing

Study patients were selected based on isolation of a pair of clonally related 'index' and 'subsequent' ESBL-EC isolates. Altogether, five different banding patterns were identified across 25 pairs from 25 study patients, suggesting that between patients most strains were clonally unrelated. In addition, we compared banding patterns for all heteroresistant isolates side-by-side and found three unique banding patterns among 15 strains.

Discussion

To the best of our knowledge, this study is the first to evaluate both the risk factors for development of a carbapenem-heteroresistant phenotype in patients who had repeated hospital encounters and the outcomes of cHR ESBL-EC infection. In our study of 25 patients with multiple hospital encounters following initial isolation of ESBL-*E. coli*, patients in whom cHR phenotype developed were more likely to have had greater healthcare exposure prior to 'subsequent' admission and received higher cumulative doses of ertapenem and meropenem. At 'subsequent' admission, case patients were more likely to present with a chronic indwelling foley catheter and have a strain isolated from a non-urinary site (e.g. blood) in addition to a focal source such as the urinary tract. cHR phenotype appeared to negatively affect clinical outcomes, where patients hospitalized with a cHR ESBL-EC infection were more likely to require an ICU admission and a prolonged hospital stay compared with control patients.

Our findings show a higher cumulative exposure to carbapenem therapy between 'index' and 'subsequent' visits in case patients who subsequently develop a cHR phenotype isolate. A study focused primarily on the role of antimicrobial exposure on the development of full carbapenem resistance in *E. coli* found prior use of carbapenems (OR 4.56, 95% CI 1.44–14.46) as well as fluoroquinolones (OR 2.81, 95% 1.14–6.99) to be independent risk factors for carbapenem resistance in *E. coli*.[21] cHR phenotype may be a precursor to the emergence of full carbapenem resistance. Prior *in vitro* studies of imipenem-heteroresistant *Klebsiella pneumoniae* reported full resistance following prolonged imipenem exposure.[22] Alternative carbapenem-sparing options to treat ESBL-producing *E. coli* infections may be considered in this setting to slow the development of full carbapenem resistance. We previously screened ESBL-producing Enterobacteriaceae clinical isolates for heteroresistant phenotype with carbapenems (ertapenem, imipenem, meropenem) and ceftolozane/tazobactam (C/T).[16] Nearly all (99%, 171/173) of the clinical isolates screened retained *in vitro* activity and tested negative for ceftolozane/tazobactam heteroresistance. Of the two strains that displayed heteroresistant phenotype to ceftolozane/tazobactam using disc diffusion tests, only one strain was confirmed to be heteroresistant with the PAP method. Future studies should evaluate the clinical efficacy of ceftolozane/tazobactam, as a carbapenem-sparing treatment option, in recurrent ESBL-EC infections where cHR phenotype is suspected or confirmed.

The anatomic site appears to play an important role in the isolation of cHR ESBL-EC. In our earlier study, we identified 55 cHR ESBL-E isolates by PAP method.[16] Over 30% of these strains were from a non-urinary source (31%, 17/55). Similarly, in this current study of patients with recurrent ESBL-EC infections, we found that case patients who were subsequently infected with cHR ESBL-EC were more likely to have a strain isolated from blood in addition to urine. Additionally, at subsequent hospital encounters where a cHR strain was collected, cases were more likely to have their ESBL-EC isolate collected from a site different from prior visits. This observation suggests that other body sites where antibiotic exposure is relatively lower compared with urine may contribute towards the selection of strains developing the heteroresistant phenotype. In addition, it is possible that the heteroresistant phenotype may be associated with enhanced virulence, supporting the systemic spread of a focal infection.

The potential mechanism for antibiotic heteroresistance is thought to be mostly attributed to tandem gene amplifications of resistance genes.[11] Tandem gene amplifications in *E. coli* are thought to be attributed to stress-induced cases.[23] Others have

evaluated the impact of imipenem exposure in a transformant *E. coli* TOP10 strain carrying a bla_{KPC-2} gene and found that imipenem induced an oxidative stress response, where activation of the TCA cycle, the electron transport chain pathway and iron metabolism were most notable with high drug concentrations.[24] Future studies elucidating the mechanisms of cHR in *E. coli* may consider evaluating changes in metabolism induced by carbapenem exposure and its contribution to the development of a heteroresistant phenotype.

This study has several limitations. First, due to the retrospective design, we relied on chart review to obtain data. For recent antibiotic exposure and cumulative carbapenem use, it is possible that some prior antibiotics used were not documented. A comprehensive attempt to capture the most accurate data was made. Second, our institution is not a closed system, therefore, other outpatient and outside hospital admissions were not accounted for in this study. Third, our findings are considered exploratory given the limited sample size of patients who had repeated isolation of ESBL-EC with subsequent development of cHR phenotype. Our sample size was limited in part due to our stringent selection criteria to include only patients who have had repeated hospital encounters between the 'index' and 'subsequent' *E. coli* isolates and that the isolate pairs from the same patient are clonally related to allow for the analysis of longitudinal risk factors contributing to the subsequent development of the carbapenem-heteroresistant phenotype. On balance, this stringent selection of patients allowed an unprecedented opportunity to study the real-life evolution of ESBL strains in the development of carbapenem-heteroresistant phenotype in the same patients and its clinical impact on infection characteristics and outcome. Finally, since we captured only clinical events that occurred between the very first non-cHR ESBL-EC isolate designated as 'index' and the 'subsequent' cHR ESBL-EC isolate saved in our biorepository, it is possible that we have missed clinical events and drug exposure that cumulatively contributed to the overall risk of cHR ESBL-EC isolation.

Conclusions

Patients with repeated isolation of ESBL-EC, particularly from a non-urinary systemic site, appear to be at risk over time for infection with strains harbouring the carbapenem-heteroresistant phenotype after multiple hospital encounters. Our findings deserve confirmation with a larger sample size and call attention to the potential increased morbidity in association with cHR ESBL-EC infections, which underscores the need to screen for cHR phenotype and to consider non-carbapenem alternative treatment options for recurrent ESBL-EC infections to limit selection of full carbapenem resistance.

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Transparency declarations

A.W.B., has received grants from Merck and Allergan; and reports consulting fees from Nabriva Therapeutics, Insmed, Rempex Pharmaceuticals, Paratek Pharmaceuticals, Achaogen, Inc, Bayer Healthcare, SIGA Technologies, and GlaxoSmithKline. All other authors: none to declare.

Disclaimer

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