

Prevalence of carbapenem resistance and carbapenemase production among Enterobacteriaceae isolated from urine in the UK: results of the UK infection-Carbapenem Resistance Evaluation Surveillance Trial (iCREST-UK)

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Objectives: Although carbapenem susceptibility testing has been recommended for all Enterobacteriaceae from clinical specimens, for practical reasons a carbapenem is not included in many primary antibiotic panels for urine specimens. The 'iCREST' study sought carbapenemase-producing Enterobacteriaceae (CPE) in routine urine specimens yielding Gram-negative growth in five diagnostic laboratories in the UK. We sought also to compare locally and centrally determined MICs of meropenem and ceftazidime/avibactam.

Methods: Positive growth from up to 2000 urine specimens per laboratory was plated onto chromID[®] CARBA SMART agar. Suspected CPE colonies were tested locally by Etest for susceptibility to meropenem and ceftazidime/avibactam, and referred to central laboratories for PCR confirmation of CPE status and microbroth MIC determination.

Results: Twenty-two suspected CPE were identified from 7504 urine specimens. Ten were confirmed by PCR to have NDM (5), IMP (2), KPC (2) or OXA-48-like (1) carbapenemases. Locally determined ceftazidime/avibactam MICs showed complete categorical agreement with those determined centrally by microbroth methodology. The seven ceftazidime/avibactam-resistant isolates (MICs ≥ 256 mg/L) had NDM or IMP metallo-carbapenemases.

Conclusions: The frequency of confirmed CPE among Gram-negative urinary isolates was low, at 0.13% (10/7504), but CPE were found in urines at all five participating sites and the diversity of carbapenemase genes detected reflected the complex epidemiology of CPE in the UK. These data can inform local policies about the cost-effectiveness and clinical value of testing Gram-negative bacteria from urine specimens routinely against a carbapenem as part of patient management and/or infection prevention and control strategies.

Introduction

Enterobacteriaceae are a common cause of community- and hospital-acquired urinary tract infections, and have become increasingly multiresistant to first- and second-line antibiotics.¹ Carbapenems are used to treat patients with severe life-threatening infections caused by MDR Enterobacteriaceae, including those with ESBLs.¹ The rapid global increase in carbapenem

resistance due to carbapenemase-producing Enterobacteriaceae (CPE) has become a public health crisis, threatening delivery of healthcare and patient safety.²

In 2013–14, the European Survey on Carbapenemase-Producing Enterobacteriaceae (EuSCAPE) investigated the incidence of CPE among carbapenem-non-susceptible isolates of *Klebsiella pneumoniae* and *Escherichia coli* from 36 European

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countries.³ As part of this survey, 32 CPE isolates were confirmed from among 102 suspected non-susceptible *K. pneumoniae* and *E. coli* submitted from 21 sentinel UK laboratories. The period prevalence of CPE in participating UK laboratories was 0.02%, and producers of KPC, OXA-48-like, NDM and VIM carbapenemases were detected, indicating a continuing diverse epidemiology in the UK.⁴

To improve rapid detection of CPE, it has been suggested that all Enterobacteriaceae from clinically significant specimens should ideally be tested against a carbapenem.⁵ However, for practical reasons, a carbapenem is not included in many primary antibiotic panels for urine specimens; many diagnostic laboratories have local algorithms and test a carbapenem only against isolates found resistant to primarily tested β -lactams, such as co-amoxiclav.⁶ The Infection-Carbapenem Resistance Evaluation Surveillance Trial (iCREST) is an *in vitro* sentinel surveillance programme, which aimed, therefore: (i) to investigate the potential for under-detecting CPE in urine specimens collected in five European countries with differing CPE epidemiologies,³ specifically France, Germany, Italy, Spain and the UK; and (ii) to determine the susceptibility of urinary CPE to ceftazidime/avibactam, a new cephalosporin/ β -lactamase inhibitor combination with *in vitro* activity that includes many MDR Enterobacteriaceae,^{2,7} and comparator antibiotics. Here we present the results from the iCREST-UK study.

Materials and methods

Participating laboratories

Five diagnostic laboratories in London (four) and Birmingham (one) participated in the iCREST-UK study. Prior to this survey, all had identified CPE occurring sporadically, but none was considered to have an endemic problem with these organisms. Only one of the participating laboratories routinely tested urinary Gram-negative isolates for resistance to carbapenems in its primary antibiotic panels. For iCREST-UK, each laboratory was required to screen up to 2000 consecutive positive urine specimens for suspected CPE.

Local CPE screening and susceptibility testing

Primary plating of urine specimens collected from inpatients and outpatients was performed according to each participating laboratory's routine practices. The laboratories sought CPE from urine specimens that were positive for Gram-negative bacteria, including those that yielded mixed growth. Growth from the medium specified in each laboratory's relevant Standard Operating Procedures (SOPs) was suspended in saline, calibrated to a 0.5 McFarland standard to reach an inoculum of 10^5 cfu/mL, and then cultured on chromID[®] CARBA SMART agar (bioMérieux, Marcy-l'Étoile, France) and incubated aerobically at 35 ± 2 °C for 18–24 h, in accordance with the manufacturer's instructions. Quality control strains *K. pneumoniae* ATCC[®] BAA-1705[™] (which produces a KPC carbapenemase) and *K. pneumoniae* ATCC[®] 700603[™] (which produces SHV-18 ESBL, but is carbapenemase negative) were used in each participating laboratory.

Colonies considered indicative for CPE showed the following characteristic colours, according to the manufacturer, on chromID[®] CARBA SMART agar: *E. coli*, pink to burgundy colonies or translucent colonies with a pink to burgundy centre; and *Klebsiella* spp., *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp., bluish-green to bluish-grey colonies. Identification was determined according to each participating laboratory's routine practices. One suspected CPE colony of each of these colours (where possible) was subcultured from each specimen yielding growth on this selective medium. Colonies growing on chromID[®] CARBA SMART agar but identified (by characteristic colour) as non-Enterobacteriaceae were discarded and were not studied further.

The selected colonies of suspected CPE were tested locally for susceptibility to both meropenem and ceftazidime/avibactam using Etest (bioMérieux) according to the manufacturer's instructions and were submitted for further centralized testing.

Centralized confirmation and characterization of CPE

On receipt in the two central reference laboratories (PHE's Birmingham laboratory and the PHE AMRHAI Reference Unit), the species identification of all suspected CPE was confirmed by MALDI-TOF MS (Bruker Daltonik GmbH, Bremen, Germany), and genes encoding KPC, NDM, OXA-48-like and VIM carbapenemases were sought by PCR according to the EuSCAPE project protocols.^{3,4} Two PCR-negative isolates were later screened for other metallo-carbapenemase genes,⁸ because their presence was suggested by microbroth susceptibility results.

Isolates were tested for susceptibility to a range of antibiotics, including imipenem, meropenem, ceftazidime, ceftazidime/avibactam, aztreonam, amikacin, colistin, levofloxacin and tigecycline, using a broth microdilution method (Sensititre[®], TREK Diagnostic Systems, Cleveland, OH, USA). MICs were interpreted using EUCAST v. 7.1 breakpoints.⁹

Data capture and ethics consideration

All participating diagnostic laboratories and the central reference laboratories entered their anonymized study data into a centralized electronic database (Micron Research Ltd, Ely, UK), including: patient's age range (<18, 18–65 and >65 years); patient's gender; isolate identification; locally determined Etest MICs of ceftazidime/avibactam and meropenem; centrally determined broth microdilution MICs; and any carbapenemase gene detected.

The iCREST-UK study protocol was submitted to PHE's Research and Development Office and was determined to be a surveillance study, not research, and therefore did not require ethical approval. This decision was communicated and agreed with all participating laboratories.

Results and discussion

Isolation of suspected CPE from urines

Between September 2016 and January 2017, a total of 7504 consecutive Gram-negative urinary isolates were cultured on chromID[®] CARBA SMART agar plates in the five participating UK diagnostic laboratories. Of these, 22 (0.3%) yielded appropriately coloured colonies that were suspected to be CPE: *E. coli* (31.8%, 7/22), *K. pneumoniae* (27.3%, 6/22), *Enterobacter cloacae* (22.7%, 5/22) and one isolate each of *Citrobacter freundii*, *Enterobacter aerogenes*, *Morganella morganii* and *Serratia marcescens*. Participating diagnostic laboratories did not observe non-CPE growth on the selective agar plates. Furthermore, the local SOPs and algorithms in each participating laboratory also identified these isolates as suspect CPE, so none would have been missed without participation in the iCREST study.

Of the patients with suspected CPE in urine specimens, 64% (14/22) were female, 50% (11/22) were aged >65 years, 46% (10/22) were aged 18–65 years and 4% (1/22) were aged <18 years.

Locally determined antibiotic susceptibilities

Despite growth on chromID[®] CARBA SMART agar, locally performed Etests indicated that most (19/22; 86.4%) suspected CPE were susceptible to meropenem using EUCAST breakpoints (MIC range for all suspected CPE, 0.008 to ≥ 32 mg/L; MIC₅₀, 0.5 mg/L; MIC₉₀, 8 mg/L); the exceptions were single isolates of *E. coli* (MIC, 8 mg/L) and *C. freundii* (MIC, 4 mg/L), both with intermediate

Table 1. *In vitro* activity of ceftazidime/avibactam and comparators against confirmed CPE (*n* = 10) and non-CPE (*n* = 11)^a from urines

Species	Carbapenemase ^b	MIC (mg/L)								
		IPM	MEM	CAZ	CAZ/AVI	ATM	AMK	CST	LVX	TGC
<i>E. cloacae</i>	IMP	2	4	>64	>32	4	2	1	0.06	0.5
<i>K. pneumoniae</i>	IMP	4	>8	>64	>32	0.12	2	1	0.12	0.5
<i>E. cloacae</i>	KPC	8	4	32	0.5	>64	1	1	0.5	1
<i>E. cloacae</i>	KPC	>8	>8	>64	1	>64	1	0.5	1	1
<i>C. freundii</i>	NDM	>8	>8	>64	>32	>64	>64	1	8	2
<i>E. coli</i>	NDM	4	8	>64	>32	0.25	2	1	>8	0.5
<i>E. coli</i>	NDM	8	>8	>64	>32	>64	>64	1	>8	0.5
<i>K. pneumoniae</i>	NDM	>8	>8	>64	>32	>64	>64	0.5	>8	>2
<i>K. pneumoniae</i>	NDM	>8	>8	>64	>32	>64	>64	0.5	>8	1
<i>E. coli</i>	OXA-48-like	1	2	>64	4	>64	4	0.5	>8	0.5
<i>E. aerogenes</i>	none detected	2	0.25	64	2	16	2	1	>8	1
<i>E. cloacae</i>	none detected	0.5	0.12	64	1	4	1	0.5	8	4
<i>E. cloacae</i>	none detected	4	0.12	4	1	1	1	0.5	0.25	2
<i>E. coli</i>	none detected	0.12	0.03	0.12	0.12	0.06	4	0.5	0.06	0.5
<i>E. coli</i>	none detected	2	0.25	8	0.12	32	8	1	2	0.5
<i>E. coli</i>	none detected	2	0.25	>64	1	>64	4	1	>8	0.5
<i>K. pneumoniae</i>	none detected	1	0.12	32	0.25	8	2	1	1	0.5
<i>K. pneumoniae</i>	none detected	0.25	0.03	0.25	0.12	0.06	1	0.5	0.06	1
<i>K. pneumoniae</i>	none detected	4	2	>64	1	64	>64	0.5	>8	2
<i>M. morgani</i>	none detected	4	0.12	1	0.5	0.25	2	>8	0.06	1
<i>S. marcescens</i>	none detected	4	0.25	0.5	0.5	0.5	8	>8	0.12	1

IPM, imipenem; MEM, meropenem; CAZ, ceftazidime; CAZ/AVI, ceftazidime/avibactam; ATM, aztreonam; AMK, amikacin; CST, colistin; LVX, levofloxacin; TGC, tigecycline.

^aOne suspected CPE isolate was not available for central MIC determination.

^bThe iCREST protocol required PCR screening only for KPC, NDM, OXA-48-like and VIM genes. IMP genes were detected in two isolates after expanded PCR screening, as indicated by their antibiograms.

meropenem resistance (MICs 4–8 mg/L), and one *K. pneumoniae* that was fully resistant (MIC, ≥ 32 mg/L). However, the meropenem MICs for 14/22 (63.6%) suspected isolates were >0.12 mg/L, which is the screening criterion recommended by EUCAST to identify suspected CPE.¹⁰

Similarly, most (15/22; 68.2%) suspected CPE isolates were found susceptible to ceftazidime/avibactam by locally performed Etest (MIC range, 0.016 to >256 mg/L; MIC₅₀, 1 mg/L; MIC₉₀, >256 mg/L). The exceptions were two isolates of *E. coli*, three *K. pneumoniae*, one *E. cloacae* and one *C. freundii*, all with MICs ≥ 256 mg/L.

Reference centre characterization of suspected CPE

Twenty-one of the 22 suspected CPE isolates were submitted to the central reference laboratories for confirmatory testing; one *E. coli* isolate was lost to follow-up. Of these, eight (36.4%) were confirmed to be carbapenemase producers in the initial PCR, with two further isolates confirmed as CPE in expanded PCR screening (Table 1). Hence the overall rate of confirmed CPE among Gram-negative urinary isolates from the five participating UK laboratories was 0.13% (10/7504). None of the patients identified with CPE in this study was known to the participating laboratories to have been infected or colonized by CPE previously.

Carbapenemase genes (5 NDM, 2 IMP, 2 KPC and 1 OXA-48-like) were detected in isolates of four species (Table 1): *K. pneumoniae* (*n* = 3), *E. coli* (*n* = 3), *E. cloacae* (*n* = 3) and *C. freundii* (*n* = 1).

Ceftazidime/avibactam MICs: Etest versus microbroth dilution

Locally determined susceptibilities of ceftazidime/avibactam (Etest) showed excellent categorical agreement with those determined centrally by microbroth dilution (Table 2). Seven isolates found resistant by Etest (MICs ≥ 256 mg/L) were all confirmed as such by microbroth dilution (MICs >32 mg/L). Similarly, 14 isolates reported susceptible to ceftazidime/avibactam by Etest were all confirmed susceptible by microbroth dilution; MICs determined by the two methods for most (10/14) susceptible isolates were identical (eight isolates) or differed 2-fold (two isolates) and were 4–16-fold lower by Etest for the remainder.

There was poorer categorical agreement for meropenem, with only one of six isolates found resistant by microbroth dilution also found resistant by Etest in the diagnostic laboratory; two were reported intermediate and three as susceptible to meropenem (Table 2).

The seven ceftazidime/avibactam-resistant isolates included the five NDM producers, as expected because avibactam does not inhibit metallo-carbapenemases. However, single isolates of *E. cloacae* and *K. pneumoniae* were found to be highly resistant to both unprotected ceftazidime (MICs >64 mg/L) and ceftazidime/avibactam (MICs >32 mg/L), but negative by PCR for genes encoding KPC, NDM, OXA-48-like and VIM enzymes. Neither of these two isolates was resistant to aztreonam (MICs of 4 mg/L, intermediate,

Table 2. Comparison of MICs (mg/L) for 21 suspected CPE isolates determined locally (Etest, five laboratories) and centrally (microbroth dilution, one laboratory)

Microbroth	Etest												
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>32	≥256
Meropenem													
≤0.03	1	1	-	-	-	-	-	-	-	-	-	-	-
0.06	-	-	-	-	-	-	-	-	-	-	-	-	-
0.12	-	-	-	1	1	2	-	-	-	-	-	-	-
0.25	-	-	-	-	3	1	-	-	-	-	-	-	-
0.5	-	-	-	-	-	-	-	-	-	-	-	-	-
1	-	-	-	-	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	1	-	-	1	-	-	-	-
4	-	-	-	-	-	-	1	-	1	-	-	-	-
8	-	-	-	-	-	-	-	1	-	-	-	-	-
>8	-	-	-	-	-	-	-	1	2	1	1	1	-
Ceftazidime/avibactam													
≤0.12	-	-	-	-	3	-	-	-	-	-	-	-	-
0.25	-	1	-	-	-	-	-	-	-	-	-	-	-
0.5	-	-	-	-	1	-	2	-	-	-	-	-	-
1	-	-	-	1	-	1	-	2	1	-	-	-	-
2	-	-	-	-	-	-	-	1	-	-	-	-	-
4	-	-	-	-	-	-	-	-	-	1	-	-	-
8	-	-	-	-	-	-	-	-	-	-	-	-	-
>32	-	-	-	-	-	-	-	-	-	-	-	-	7

EUCAST MIC breakpoints⁹ are indicated by broken lines.

and 0.12 mg/L, susceptible; Table 1), which suggested metallo-carbapenemase activity, and IMP genes were detected in expanded PCR screening.

Considering other antibiotics, many of the suspected CPE were confirmed to be MDR (Table 1). Only colistin remained active against all suspected CPE (MICs 0.5–1 mg/L), when excluding the single isolates of *M. morgani* and *S. marcescens*, both with intrinsic resistance.

In conclusion, the iCREST-UK study found that the rate of confirmed CPE among Gram-negative urinary isolates in the participating UK laboratories was 0.13%. This rate was substantially lower than that observed in some other European countries participating in the iCREST trial, such as Spain.¹¹ The number of positive UK specimens was very low, but higher than the rate reported in the 2013–14 EuSCAPE survey.³ It should be noted that CPE were found in urines at all five participating sites and that the diversity of carbapenemase genes observed (IMP, KPC, NDM and OXA-48-like) reflected the complex epidemiology of CPE in the UK. The proportion of centrally confirmed versus suspected CPE (10/22, 45%) was higher in this study than was reported in the previous EuSCAPE-UK survey (32/102; 31%),⁴ although this may be explained in part because the EuSCAPE study did not seek to detect IMP producers and was limited only to *E. coli* and *K. pneumoniae*. More generally, the reported rates of CPE from urine vary between studies and direct comparison is confounded by differences in their geographical setting, the patient populations sampled and the laboratory methods used.^{12–14}

Ceftazidime/avibactam was the only agent active against all isolates with KPC or OXA-48-like carbapenemases but, as expected, had no activity against the NDM or IMP producers; only colistin was active against all confirmed CPE *in vitro*. Furthermore, although the sample was small, MICs of ceftazidime/avibactam determined locally showed excellent categorical agreement with those determined centrally by microbroth dilution; this concordance must be further investigated against larger panels of isolates and should also consider the accuracy of susceptibilities determined locally by disc diffusion.

This study identified a currently low prevalence of CPE among routinely tested urinary specimens from UK hospital and community settings, but there is potential for under-diagnosis if laboratories do not test a carbapenem (meropenem is recommended by EUCAST¹⁰) in their primary or secondary antibiotic panels. These data can inform local policies and decisions about the cost-effectiveness and clinical value of routinely testing Gram-negative bacteria from these specimens as part of patient management and/or infection prevention and control strategies

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