

Recent emergence of carbapenem-resistant organisms in a low prevalence UK setting in London

John Hughes, Simon D Goldenberg, Olga Tosas, Jonathan D. Edgeworth, Jonathan A. Otter*.

Centre for Clinical Infection and Diagnostics Research (CIDR), Department of Infectious Diseases, King's College London & Guy's and St. Thomas' NHS Foundation Trust, London, UK.

* Address for correspondence.

Dr Jonathan Otter, Centre for Clinical Infection and Diagnostics Research (CIDR), Department of Infectious Diseases, King's College London, and Guy's and St. Thomas' Hospital NHS Foundation Trust SE1 9RT, UK.
Telephone: +44(0)207 188 7188
Email: jonathan.otter@kcl.ac.uk

Keywords: carbapenem resistant organism, CRO, CRE, *Acinetobacter baumannii*, *Klebsiella pneumoniae*

Running title: Emergence of CRO in London

25 **Abstract**

26

27 Carbapenem-resistant organisms are emerging as a global health threat. The
28 prevalence of carbapenem-resistant organisms in London is largely unknown. A
29 retrospective review of microbiology records indicates an increased in carbapenem-
30 resistant *Klebsiella pneumoniae* (none in 2011 to 1.3% of 386 in 2013, $p=0.073$) and
31 *Acinetobacter baumannii* (9.1% of 11 in 2011 to 31.2% of 16 in 2013, $p=0.001$) in a
32 background of low prevalence at a London hospital. This suggests that carbapenem-
33 resistant organisms may be emerging in our patient population. These increases
34 demand an urgent enhanced surveillance response.

35

Introduction

Carbapenem-resistant organisms have emerged in recent years as a significant public health threat.¹⁻⁴ Therapy for carbapenem-resistant organisms relies on older, less effective and less well tolerated antimicrobials such as the polymyxins.³ Carbapenem resistance is most commonly mediated through a combination of impermeability and AmpC/ESBL activity or acquired carbapenemase production.³ Carbapenemases (typically KPC, VIM, IMP, NDM and OXA-48 types) are encoded by genes on mobile genetic elements, allowing rapid dissemination in the clinical setting.^{5,6} Carbapenemase genes can be acquired by the Enterobacteriaceae such as *Klebsiella pneumoniae* and lactose non-fermenters such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.^{1,4,6}

Carbapenem-resistant organisms are emerging worldwide.^{1,3,6} The European surveillance network EARS-Net suggests that the prevalence of carbapenem-resistant Enterobacteriaceae (CRE) is low in invasive isolates throughout most of Europe.⁷ However, the rate of carbapenem-resistant *Klebsiella pneumoniae* (CRKP) increased from 28% in 2005 to 68% in 2011 in Greece from 1% in 2009 to 27% in 2011 in Italy. Rates of carbapenem-resistance in *Pseudomonas aeruginosa* also vary across Europe, with high rates in Greece (54% in 2011) and Cyprus (43% in 2011). The rate of carbapenem resistance among *P. aeruginosa* in the UK has been fairly stable at around 5% and the prevalence of CRKP is low at <1%.⁷ However, outbreaks of carbapenem-resistant organisms have been reported^{1,4,8} and Public Health England reports an increasing number of carbapenemase-producing Enterobacteriaceae referrals from <100 in 2009 to 800 in 2012.⁹ In light of the increasing global and national CRO trends, we evaluated the prevalence of carbapenem-resistant organisms in recent years at our hospitals.

Methods

We investigated the prevalence of carbapenem-resistant organisms in the microbiology database from Guy's and St Thomas' Hospital NHS Foundation Trust (GSTT), which comprises approximately 1200 beds in two hospitals in central London. The microbiology laboratory processes samples from in-patients, specialist referrals from across the South East of England and patients seen in primary care facilities in the community. Culture results of all samples from which Enterobacteriaceae or non-fermenting Gram-negative bacteria were identified between April 2011 and June 2013 were downloaded into a database. Our study was restricted to April 2011 to June 2013 because prior to April 2011 we had a different laboratory system, and changes in standard antimicrobial testing protocols and methods, including a change from disc diffusion to semi-automated broth microdilution (Vitek), meant that meropenem susceptibility was rarely tested in Gram-negative bacteria prior to 2011. After June 2013, enhanced surveillance for CRE began, which would skew the findings. Samples from Enterobacteriaceae or non-fermenting Gram-negative bacteria comprised mainly clinical cultures (99.5%) and some screens (0.5%). During the study period, the routine hospital surveillance programme for resistant organisms included rectal swabs on admission and throughout the stay of patients on ICU and HDU cultured using gentamicin as a selective agent. We determined the proportion of patients who had a positive culture for carbapenem-resistant organism. Antimicrobial susceptibility was determined through semi-automated broth micro-dilution (Vitek) or disc diffusion according to BSAC guidelines, depending on the specimen type. Isolates resistant to meropenem were considered carbapenem resistant. Data collected included the date of collection, specimen type, the organism grown and the antibiogram. All Enterobacteriaceae and non-fermenting Gram-negative bacteria tested for meropenem sensitivity (comprising 99.6% of the total) were included in the analysis.

Enterobacteriaceae and non-fermenting Gram-negative bacteria were analysed separately. Trends were analysed using Chi-squared tests.

Results

CRE were identified from 25 (0.14%) of 18279 patients who had a positive culture for Enterobacteriaceae. The prevalence of CRE doubled from 15 (0.1%) of 12931 in 2011/2 to 10 (0.2%) of 5348 in 2013 ($p=0.107$). Importantly, the prevalence of CRKP increased from none of 82 in 2011 to 5 (1.3%) of 386 in 2013 ($p=0.073$) (Figure). The characteristics of the 25 CRE isolates are summarized in the Table. The most common CRE identified was *Klebsiella* species (12/25, 48.0%). CRE were identified from surgery, medicine, critical care, paediatrics and the community. Only 2 CRE were identified on screens alone; 10/25 were from urine samples. No epidemiological links were obvious between the isolates. Of the 16 meropenem resistant Enterobacteriaceae detected between 2002 and 2009, 88% were susceptible to another carbapenem (imipenem), whereas only two of the 10 meropenem-resistant Enterobacteriaceae identified between 2011 and 2013 that were tested for susceptibility were resistant to another carbapenem (ertapenem) ($P=0.001$, Fisher's exact test). This supports an increase in carbapenemase-producing Enterobacteriaceae in recent years.

Carbapenem-resistant non-fermenters were identified from 129 (2.6%) of 4779 patients. The prevalence of carbapenem resistance among the non-fermenters did not increase over the study period overall but carbapenem-resistant *A. baumannii* increased from 3 (10.3%) of 29 in 2011 to 5 (31.2%) of 16 in 2013 ($p=0.001$) (Figure). Analysis of the carbapenem-resistant *A. baumannii* isolates from 2013 indicated a range of specialties and antibiograms, indicating that a clonal outbreak was not responsible for the increase.

Discussion

Our study confirms the low prevalence of carbapenem-resistant organisms in the population studied amounting to <1% of all Enterobacteriaceae and <5% of non-fermenters. However, we demonstrate an apparent increase in the proportion of Enterobacteriaceae that are CRE in recent years, particularly in *K. pneumoniae*. Although these increases were not statistically significant due to the low number of cases, the trends are concerning given rapid increases of CRE in Greece, Italy and Israel,^{5,10} and suggests that the increase in CRE reported by Public Health England is not solely explained by 'referral bias'.⁹ Only two CRE cases were reported in 2011 compared with 10 in the first half of 2013, suggesting an increase. CRE were most frequently identified from clinical cultures, indicating that they are likely to cause infection, and represented sporadic cases. The discovery of CRE in a range of species and specialties suggests repeated introduction with limited horizontal transmission. There is some evidence of a community reservoir, with 24% of cases from general practice / outpatient clinics. However, many of these patients are likely to have had healthcare contact. While there is some evidence that CRE are emerging globally and nationally in the UK, prevalence studies are lacking.^{5,6,8}

The epidemiology of non-fermenting Gram-negative bacteria such as *A. baumannii* is distinct from CRE. While resistance to carbapenems in these organisms is problematic and has been associated with outbreaks, particularly in critical care, the explosive spread associated with CRE has not been reported.^{1,4,6} We detected a significant increase in the rate of carbapenem resistance in *A. baumannii*, reaching more than 30% in 2013. *A. baumannii* is an uncommon cause of serious infection in the UK, and tends to cause clinical infection in the immunocompromised or those in the intensive care units. While the emergence of carbapenem resistance in *A.*

baumannii is consistent with global trends, we cannot explain the rapidity of the increase over the past few years since the antibiogram and epidemiology of individual cases did not appear to be linked.¹

Our pragmatic prevalence survey has several important limitations. We were reliant on electronic records that had only limited patient data. In particular, we were not able to investigate travel related risk factors, which have been associated with CRE, and which are a common feature in our population characterised by frequent overseas travel.^{5,6} Although no changes to the screening policy occurred during the study period, our survey included a small number of resistance screens, which may skew apparent prevalence. We also did not perform molecular analysis to determine the mechanism of carbapenem resistance, though the rapid emergence is indicative of carbapenemase spread.

Based on the apparent emergence of carbapenem resistance in both Enterobacteriaceae and non-fermenters in our hospitals over the past few years, there is an urgent need to prospectively define the prevalence of carbapenem-resistant organisms in order to evaluate the risk and implement effective interventions to prevent the sporadic cases developing into an epidemic. In response to our findings and the threat of carbapenem-resistant organisms, we are embarking on enhanced surveillance including screening a wider group of patients for carbapenem-resistant organisms to identify the hidden burden. We hope that targeted interventions in our low prevalence setting will prevent the widespread emergence of carbapenem-resistant organisms in our patient population, which would have grave implications.

Acknowledgements

176 Conflict of interest: JAO is employed part-time by Bioquell. All other authors have no
177 conflicts to declare.

178

179 Funding sources: None.

180

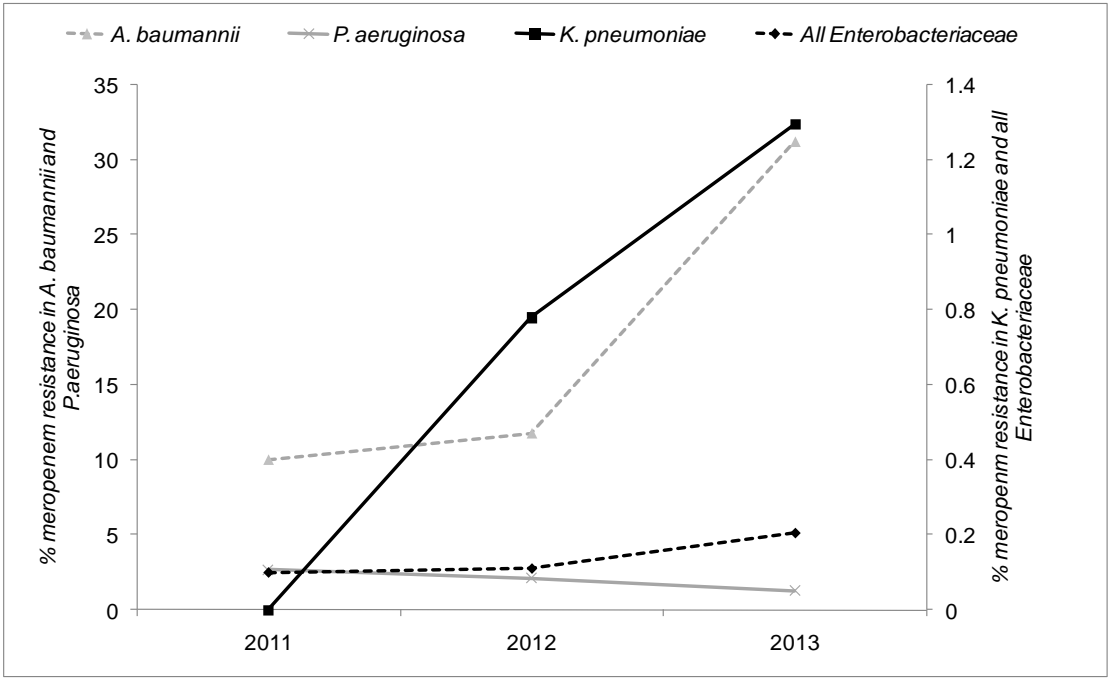
181

182 Table. Characteristics of the 25 carbapenem-resistant Enterobacteriaceae detected.

Patient Number	Age	Sex	Year Of Sample	Wards	Specimen Location	Subsequent clinical sample	Organism	Outcome	Antibiogram									
									AMC	AMO	CAZ	CTX	CXM	ERT	FEP	FOX	MER	TAZ
1	83	M	2011	Outpatient	Urine		<i>E.cloacae</i>	Died 125 days later	R	R	R	R	R	R	R	R	R	R
2	62	M	2011	Haemoncology	Sputum		<i>E.cloacae</i>	Died 30 Days later	R	R	R	R	R	R	R	R	R	R
3	67	F	2012	Surgery	Drain fluid		<i>Enterobacter sp</i>	Died 71 Days later	R	R	R	-	R	-	-	-	R	R
4	80	M	2012	ICU	Resistance Screen	Yes	<i>K.pneumoniae</i>	Survived	R	R	R	R	R	R	R	R	R	R
5	57	F	2012	Community	Urine		<i>Klebsiella sp</i>	Survived	R	R	R	R	R	R	R	R	R	R
6	75	M	2012	ICU	Sputum		<i>K.pneumoniae</i>	Died 61 days later	R	R	R	R	R	-	R	R	R	R
7	86	M	2012	ICU	Sputum		<i>S.marcescens</i>	Survived	R	R	R	-	R	-	-	-	R	R
8	66	M	2012	Surgery	Urine		<i>K.oxytoca</i>	Survived	R	R	R	R	R	-	R	R	R	R
9	53	F	2012	Surgery	Unknown		<i>K.pneumoniae</i>	Survived	R	R	R	R	R	-	R	R	R	R
10	42	F	2012	Medicine	Urine		<i>K.pneumoniae</i>	Survived	R	R	R	R	R	R	R	R	R	R
11	89	F	2012	Surgery	Urine		<i>M.morganii</i>	Survived	R	R	R	-	R	-	-	-	R	R
12	46	F	2012	Surgery	Abdominal swab		<i>K.pneumoniae</i>	Died 11 Days Later	R	R	R	R	R	R	R	R	R	R
13	88	M	2012	Surgery	Specimen		<i>E.coli</i>	Survived	R	R	R	-	R	R	-	-	R	R
14	U	U	2012	Unknown	Lung		<i>E.coli</i>	Survived	R	R	R	R	R	-	R	R	R	R
15	0.92	M	2012	Paediatrics	Resistance Screen	Yes	<i>K.pneumoniae</i>	Survived	R	R	R	R	R	-	R	R	R	R
16	33	M	2013	Haemoncology	Blood - culture		<i>E.coli</i>	Died 25 Days later	R	R	R	R	R	-	R	R	R	R
17	U	U	2013	Community	Urine		<i>K.pneumoniae</i>	Survived	R	R	R	R	R	R	R	R	R	R
18	U	U	2013	Community	Urine		<i>E.coli</i>	Survived	R	R	R	R	R	-	R	R	R	R
19	1	M	2013	PICU	Resistance Screen	No	<i>K.pneumoniae</i>	Survived	R	R	R	-	R	-	-	-	R	R
20	34	M	2013	Outpatient	Finger swab		<i>C.freundii</i>	Survived	R	R	R	R	R	S	S	R	R	R
21	51	F	2013	Surgery	Urine		<i>S.marcescens</i>	Survived	R	R	R	R	R	S	R	R	R	R
22	51	F	2013	Surgery	Hip swab		<i>K.pneumoniae</i>	Survived	R	R	R	R	R	-	R	R	R	R
23	2	F	2013	PICU	Resistance Screen	No	<i>K.pneumoniae</i>	Survived	R	R	R	R	R	-	R	R	R	R
24	73	F	2013	Surgery	Urine		<i>K.pneumoniae</i>	Survived	R	R	R	R	R	R	R	R	R	R
25	U	U	2013	Community	Urine		<i>E.coli</i>	Survived	R	R	R	R	R	R	R	R	R	R

209 Co-amoxiclav (AMC), Amoxicillin (AMO), Ceftazidime (CAZ), Cefotaxime (CTX), Cefuroxime (CXM), Ertapenem (ERT), Cefepime
210 (FEP), Cefoxitin (FOX), Meropenem (MER), Piperacillin/Taz (TAZ). Unknown (U) M=Male, F = Female, (P)ICU = (Paediatric)
211 Intensive Care Unit. R = resistant, S = Sensitive.

Figure. The prevalence of carbapenem (meropenem) resistance in key organisms and organism groups, 2011-2013.



References

1. Higgins PG, Dammhayn C, Hackel M, Seifert H. Global spread of carbapenem-resistant *Acinetobacter baumannii*. *J Antimicrob Chemother* 2010; **65**: 233-238.
2. Nordmann P, Poirel L. Strategies for identification of carbapenemase-producing Enterobacteriaceae. *J Antimicrob Chemother* 2013; **68**: 487-489.
3. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. *Clin Infect Dis* 2011; **53**: 60-67.
4. Coelho JM, Turton JF, Kaufmann ME *et al.* Occurrence of carbapenem-resistant *Acinetobacter baumannii* clones at multiple hospitals in London and Southeast England. *J Clin Microbiol* 2006; **44**: 3623-3627.
5. Canton R, Akova M, Carmeli Y *et al.* Rapid evolution and spread of carbapenemases among Enterobacteriaceae in Europe. *Clin Microbiol Infect* 2012; **18**: 413-431.
6. Nordmann P, Naas T, Poirel L. Global spread of Carbapenemase-producing Enterobacteriaceae. *Emerg Infect Dis* 2011; **17**: 1791-1798.
7. EARS-Net. Antimicrobial resistance surveillance in Europe 2012. 2012;
8. Drew RJ, Turton JF, Hill RL *et al.* Emergence of carbapenem-resistant Enterobacteriaceae in a UK paediatric hospital. *J Hosp Infect* 2013; **84**: 300-304.
9. PHE. Interim guidance for the control of Carbapenemase-Producing Enterobacteriaceae in England. 2013;
10. Schwaber MJ, Lev B, Israeli A *et al.* Containment of a country-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* in Israeli hospitals via a nationally implemented intervention. *Clin Infect Dis* 2011; **52**: 848-855.