First isolation and outbreak of OXA-48-producing *Klebsiella pneumoniae* in an Irish hospital, March to June 2011

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Five OXA-48-producing *Klebsiella pneumoniae* were detected in a tertiary referral hospital in Ireland between March and June 2011. They were found in the clinical isolates of five cases that were inpatients on general surgical wards. None of the cases had received healthcare at a facility outside of Ireland in the previous 12 months. This is the first report of OXA-48-producing *K. pneumoniae* in Ireland.

Background

OXA-48 carbapenemases were first isolated from *Enterobacteriaceae* in Turkey in 2008 [1]. Since then outbreaks have been described throughout Europe (France, Germany and the United Kingdom [2,3]) and worldwide (Argentina, Lebanon, Israel, Morocco and Tunisia [2,4,5]). In November 2010, Ireland was ranked by the European Centre for Disease Prevention and Control (ECDC) as a country with sporadic occurrence of carbapenem-resistant *Enterobacteriaceae* (CRE) [5]. We describe here the first cases of OXA-48-producing *Klebsiella pneumoniae* in Ireland.

Case descriptions

Case 1 was admitted to Surgical ward A for a Whipple's procedure for duodenal adenocarcinoma. Post-operatively he developed an intra-abdominal collection secondary to a hepato-jejunal anastomotic leak. A drain was inserted radiologically, and he was transferred to the intensive care unit (ICU). He was treated with piperacillin/tazobactam and gentamicin and clinically improved. *K. pneumoniae* was grown from intra-abdominal drain fluid taken seven days following drainage of the collection. The isolate was resistant to ertapenem with a minimum inhibitory concentration (MIC) of 8 mg/L but susceptible to meropenem with a MIC of 0.5 mg/L, and to the third- and fourth-generation cephalosporins (Table). Modified Hodge test showed carbapenemase production and the isolate was referred to a reference laboratory for molecular evaluation, where it was confirmed by PCR to be

an OXA-48 carbapenemase producing *K. pneumoniae*. Regular weekly inpatient screening for OXA-48 carriage was initiated in the ICU and no additional cases were detected in the ICU. The patient initially improved, but died later from complications of a gastrointestinal haemorrhage not related to infection.

Case 2 was admitted to Surgical ward A two days after Case 1. He developed an intra-abdominal collection following reversal of a Hartman's procedure. Two weeks after detection of the first case, *K. pneumoniae* with the same susceptibility pattern as Case 1 was isolated from infected pelvic material. This was subsequently confirmed to be an OXA-48 producer. The patient was treated with tigecycline with successful resolution of the collection. He subsequently developed a bloodstream infection caused by the same isolate and was successfully treated with cefepime.

Case 3 was an inpatient in the same hospital on Surgical ward B and transferred to Surgical ward C during her hospitalisation. She developed a subphrenic collection following colectomy from which *E. coli* (susceptible to carbapenems) was grown. She was treated with drainage of the collection and piperacillin/tazobactam and made a good recovery and antibiotic treatment was discontinued. OXA-48-producing *K. pneumoniae* was subsequently isolated from a midstream urine specimen (Table). She did not have any clinical signs of infection and did not require further antimicrobial treatment.

Case 4 was admitted to Surgical ward A 63 days after Case 1 was discharged and underwent a Whipple's procedure. *K. pneumoniae* (susceptible to carbapenems) was isolated from biliary drain fluid samples taken pre- and post-operatively. Cases 2 and 3 were still inpatients on Surgical ward B at his time of admission. OXA-48-producing *K. pneumoniae* was subsequently isolated from a midstream specimen of urine taken 23 days post-operatively. There was no clinical evidence of infection and he did not require antimicrobial treatment.

Case 5 was an inpatient on Surgical ward B. He was initially admitted in April 2011. He had a negative rectal CRE screen at this stage. He was re-admitted for a Whipple's procedure in June 2011. *K. pneumoniae* susceptible to carbapenems was isolated from a biliary drain removed at operation. He deteriorated acutely five days after the operation following massive pulmonary aspiration of gastric contents and was transferred to the ICU. OXA-48 producing *K. pneumoniae* was isolated from a rectal swab taken to screen for CRE and drain fluid taken at that time. Of note, CRE was not isolated from a rectal screen five days earlier.

Laboratory investigations

All of the *K. pneumoniae* isolates had elevated MICs for carbapenem (Table) in automated susceptibility testing (VITEK II, Biomerieux) and in the e-test (Biomerieux) and showed production of carbapenemase enzyme by modified Hodge test. Activity of the carbapenemase was not inhibited by boronic or dipicolinic acid. The presence of OXA-48 carbapenemase in all isolates was confirmed by PCR (as described by Kaczmarek et al. [7]). Comparison of the isolates from cases 1, 2 and 3 using Variable Number Tandem Repeat (VNTR) analysis at nine loci showed similarity between the strains, confirming the existence of a clonal outbreak.

Control measures

After cases 2 and 3 were confirmed to be OXA-48 producers, Surgical wards A, B and C were closed to patient admissions and transfers. Weekly screening for rectal CRE carriage which had previously commenced in the ICU following detection of the first case of CRE was extended to include all patients on the Surgical wards A, B and C. In addition, all inpatients that had been on any of the affected wards at the same time as any of the confirmed OXA-48 cases were screened for

rectal carriage of CRE. As of 20 July 2011, an additional four cases of OXA-48 rectal carriage had been detected in contacts of confirmed cases.

All CRE-colonised in-patients were placed in single room isolation with contact precautions (long-sleeved gowns and gloves). A programme of enhanced environmental cleaning and disinfection, including disinfection by vapourised hydrogen peroxide, was implemented. Environmental screening of frequently touched surfaces in the ICU and on Surgical wards A, B and C was carried out. Some 150 samples were taken using flocked swabs, which were cultured with a broth enrichment step. CRE was not isolated from any of these samples.

All cases had been in-patients on one of three adjacent surgical wards between which patients are frequently transferred. Most of the ward accommodation consists of six-bedded rooms that share toilet facilities. A detailed epidemiological investigation of the first four cases, including the interventional radiology and theatre departments, did not identify any other link between the cases. Epidemiological investigation is ongoing.

Discussion

In Ireland, CRE were first reported in 2009; however, these were an isolated case of VIM-producing *K. pneumoniae* [8] and cases of KPC-producing strains [9]. This is the first report of OXA-48 producing *K. pneumoniae* in Ireland. All five cases were patients who had undergone complex abdominal surgery. All had required broad-spectrum antimicrobial treatment (either as antimicrobial prophylaxis for surgery or as treatment for infection) but it is notable that, although carbapenems are used in these wards, none of the cases ever had a

TABLE

Minimum inhibitory concentration profiles of OXA-48 producing *Klebsiella pneumoniae*, Ireland, March–June 2011 (n=5)

Antibiotic	Case 1 MIC mg/L	Case 2 MIC mg/L	Case 3 MIC mg/L	Case 4 MIC mg/L	Case 5 MIC mg/L	EUCAST 2011 clinical breakpoints [6]
Ertapenem	8	13	16	1	2.0	R>1
Meropenem	0.5	8	2	2	0.5	R>8
Cefuroxime	4	4	16	4	>64	R>8
Ceftazidime	1	0.5	2	<1	<1	R>4
Cefotaxime	1	2	2	<1	2	R>2
Cefepime	<1	<1	<1	<1	<1	R>4
Aztreonam	0.5	<1	<1	<1	<1	R>4
Piperacillin/tazobactam	>64	>64	>64	>64	>64	R>16
Ciprofloxacin	>8	>8	>8	1	4	R>1
Gentamicin	>32	>32	>32	>16	>16	R>4
Amikacin	8	4	4	<2	<2	R>16
Tigecycline	1	2	8	<0.5	8	R>2
Colistin	1	1	1	<0.5	<0.5	R>2

EUCAST: European Committee on Antimicrobial Susceptibility Testing; MIC: Minimum inhibitory concentration.

history of carbapenem exposure prior to the detection of OXA-48 producing *K. pneumoniae*. None of the OXA-48 carrying patients had received healthcare outside Ireland in the previous year. The occurrence of this outbreak of OXA-48 has dramatically changed the epidemiology of CRE in Ireland.

OXA-48 producing *Enterobacteriaceae* remain difficult to detect as they are often susceptible to third and fourth generation cephalosporins and monobactams, as was the outbreak strain found in our healthcare facility, and therefore vigilance is required. CRE cases have been notifiable in Ireland since March 2011; however, to date, no national compulsory screening programme exists.

As the optimal method of screening for CRE remains to be determined and as CRE may be shed in varying concentrations from the bowel, it is possible that CRE may not be detected in rectal screens of all patients who are colonised. Of note one of the cases reported here had two negative rectal CRE screens but the third screen was subsequently positive. We use the methodology recommended by the United States Centers for Disease Control and Prevention for the detection of CRE in our laboratory [10].

Ongoing rectal screening for CRE carriage continues in all areas where these cases have been found.

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