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An outbreak of two strains of OXA-48 producing *Klebsiella pneumoniae* in a teaching hospital

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SUMMARY

OXA-48 producers can be difficult to detect in clinical specimens due to phenotypic low-level resistance to carbapenems. Additionally, low infection rates make clinical specimens poor sentinels for the presence of OXA-48 producers within a healthcare institution.

We report an outbreak of OXA-48-producing *Klebsiella pneumoniae* (OXAKp) that was discovered following culture of OXAKp in a urine specimen from a patient with no known risk factors for acquisition. Widespread screening across medical wards in the trust revealed evidence of transmission across several wards. Samples from 60 patients were positive for OXAKp. Five patients had OXAKp clinical infection, four of whom were treated with ceftazidime/avibactam. Variable number tandem repeat analysis of the OXAKp isolates revealed two predominant strain types clustered around two groups of wards.

Infection prevention measures included isolation and cohort nursing of infected and colonized patients, restriction of affected ward areas to new admissions, stringent hand hygiene and use of personal protective equipment. Environmental cleaning of patient areas was carried out using chlorine-releasing disinfectants and hydrogen peroxide vapour. Entire wards were decanted to enable effective cleaning of empty ward areas. The outbreak lasted almost five months and is estimated to have cost around £400 000.

During the course of the outbreak, there were five reported prescription and administration incidents related to confusion between ceftazidime and ceftazidime/avibactam. No patient harm resulted from these incidents and the implementation of brand name prescribing for ceftazidime/avibactam prevented further incidents.

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Introduction

OXA-48, an Ambler Class D β-lactamase, was first detected in an isolate of *Klebsiella pneumoniae* from Turkey in 2001 [1]. Since then, it has spread widely across Europe including the UK [2]. Although most commonly found in *K. pneumoniae*, OXA-48 is also frequently found in other Enterobacteriaceae due to the high conjugation rate of the pOXA-48a plasmid [3].

We report an outbreak of OXA-48-producing *K. pneumoniae* (OXAKp) involving two distinct strains of *K. pneumoniae* in our hospital where such concealed spread became evident.

Methods

University Hospitals of Leicester is a large secondary/tertiary healthcare organisation with three hospital sites. The outbreak occurred on one site with an approximate 1000 bed capacity.

In July 2018, an isolate of *K. pneumoniae* cultured from a urine sample from an inpatient with a suspected urinary tract infection on a geriatric medicine ward (Ward A) was identified as an OXAKp. The isolate was resistant to all tested penicillins and cephalosporins except for pivmecillinam and ceftazidime/avibactam. Disc-diffusion testing showed resistance to ertapenem and intermediate sensitivity to meropenem. This prompted further testing for carbapenemase by PCR which showed the isolate to possess the blaOXA-48-like carbapenemase gene.

The sample came from a patient admitted a month earlier and who had no history of travel or hospitalisation outside of Leicestershire in the previous 12 months. Consequently, the patient had not met our organisation's criterion for screening for carbapenemase producing enterobacteriaceae (CPE) (hospitalisation outside Leicestershire for at least one night in the previous 12 months). The discovery of this OXAKp isolate in a patient without known risk factors for acquisition prompted immediate screening of all Ward A patients. The first round of screening identified 6 CPE colonised patients (5 OXAKp and one *K. pneumoniae* NDM-1). During the same period, another OXAKp infection was identified on Ward A in a patient with OXAKp in blood cultures and a urine sample. An outbreak was declared and contact tracing was undertaken for all patients who had been on Ward A for up to five days prior to the first positive sample being identified and who were still in-patients on other wards. These patients were screened, along with their contacts on the new ward. This exercise showed that transmission had occurred on secondary wards beyond Ward A. The outbreak control team extended CPE screening to all medical wards at the affected hospital site.

Ceftazidime/avibactam was included in the empirical treatment of serious infection in patients on the ward areas where transmission had occurred due to its activity against OXA-48 producers. In UHL, prescriptions of ceftazidime/avibactam require prior approval from an infection specialist and prescriptions and reported incidents were monitored prospectively.

Screening and laboratory methods

Ward A patients were screened according to local trust policy using three rectal swabs per patient taken 48 hours apart. Patients at high-risk of CPE were isolated until three negative screens were returned. OXA-48-positive patients were isolated or cohort nursed with other OXAKp-colonised patients until discharge.

Swabs were plated onto COLOREX™ mSuperCARBA™ medium, a selective chromogenic medium developed for the detection and isolation of CPE, with subsequent carbapenemase gene detection for suspect isolates using Xpert® Carba-R (Cepheid) PCR. Antibiotic susceptibility testing was performed according to EUCAST methodology [4].

When the decision was taken to widen screening to the rest of Medicine screening was performed using three rectal swabs obtained 24 hours apart to accommodate operational pressures. OXAKp isolates were sent to the Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit in Colindale, London for variable number tandem repeat (VNTR) typing.

Case definitions

An **infected patient** was defined as a patient within UHL with clinical features of infection and from whom OXAKp was cultured from a relevant clinical microbiology specimen from June 2018 onwards.

A **colonised patient** was a patient within UHL with a positive rectal swab or stool sample with OXAKp from June 2018 onwards. Colonised patients could become infected patients.

Cases were notified electronically to the infection prevention team and by telephone to the ward. All infected or colonised patients had ward reviews conducted by the infection prevention team during the outbreak.

Results

Between July and October 2018, over 900 patients were screened for CPE. Ninety samples were identified as positive for OXA-48 of which 60 were OXAKp. Of the OXAKp isolates, six were from clinical specimens (4 urine samples, 1 blood culture, 1 pus sample). The majority of carriers were positive on the first screen (Table 1). Antibiotic susceptibility patterns are reported in Table 2. Two of these (urine and blood culture) were from the same patient. Thus the ratio of OXAKp infected to colonized patients was 0.08. Four infected patients were treated with ceftazidime/avibactam, and one with surgical incision and drainage. No infected patients died within 30 days of diagnosis of OXAKp infection.

We also identified a number of other non-*K. pneumoniae* OXA-48-producing isolates from screening during this period.

Table 1
Number of rectal screens performed before OXAKp was detected during the outbreak period

Number of screening samples before positive result obtained.	Number of patients
1	39
2	8
3	5
4	1
5	1

Table 2
Antibiotic susceptibility results for the OXAKp isolates

Antimicrobial	Percentage of isolates appearing sensitive on disc diffusion testing (EUCAST methodology)
Amikacin	100
Gentamicin	68
Co-amoxiclav	0
Piperacillin-tazobactam	2
Ceftobiprole	0
Ceftazidime	62
Ceftolozane-tazobactam	51
Ceftaroline	0
Cefotaxime	25
Cefuroxime	36
Ceftazidime-avibactam	100
Ertapenem	0
Meropenem	90
Trimethoprim	56
Ciprofloxacin	49

These included 21 isolates of *E. coli*, five of *Enterobacter cloacae*, three of *Citrobacter* spp and one *Serratia marcescens*. Four patients had both OXAKp and OXA-48-producing *E coli* isolated from rectal screen samples.

Numbers of OXA-48 producers detected were highest during August when pro-active screening took place on the medical wards (Figure 1). The second, smaller spike in the epidemic curve in early September 2018 was attributed to readmission of a previously unidentified contact from the initial outbreak ward into an open ward area. This prompted further screening of all patients on that ward and identification of new positives. Thus, the peaks in the epidemic curve were a reflection of screening activity and the subsequent discovery of colonized patients rather than the identification of new clinical cases. Environmental screening of Ward A did not detect an environmental source for the OXAKp.

VNTR typing of the *K. pneumoniae* isolates were carried out on all 60 OXAKp strains and revealed two predominant strain types clustered around two distinct ward groups (Figure 2). There were also a small number of unique strains as well as untypeable isolates. *K. pneumoniae* VNTR strain type 1, 2, 4, 1, 0, 2, 1, 4, 4, 4, 5 was predominantly detected on the initial outbreak ward, ward A. A second strain, *K. pneumoniae* VNTR strain type 6, 3, 4, 0, 1, 1, 4, 1, 4, 2, 3 was found clustered around wards B, C and D.

Review of the potential origins of the outbreak identified a Ward A patient who, prior to admission to UHL, had been living in Spain. CPE screening was not done during the admission due to the lack of a clear history of hospitalisation within the last 12 months. Although this patient had been discharged from UHL before the outbreak was recognised, screening swabs taken in the community showed that the patient was colonised with OXAKp VNTR strain type 1, 2, 4, 1, 0, 2, 1, 4, 4, 4, 5, the strain associated with ward A.

CPE-positive patients were isolated in side rooms or cohort nursed in bays when affected patient numbers exceeded side room capacity. Wards with evidence of on-going transmission were classed as uncontrolled environments and restricted from receiving new admissions. Entry to affected wards was strictly limited through the use of prominently displayed signs and, where possible, electronic keypad access. Intensive daily infection prevention support was provided to staff, patients and their families on affected wards via ward visits and telephone follow-up.

Ward staff working on restricted wards were required to practice stringent hand hygiene and wear theatre scrubs instead of usual uniforms. Healthcare workers involved with hands-on patient care were provided with appropriate single-use PPE including gloves and long sleeved gowns. Twice daily full cleaning of the affected environments was required with particular attention paid to touch points, toilets and bathrooms.

Once affected patients were either isolated or discharged, the patient environment was deep cleaned with chlorine-releasing disinfectants (ChlorClean) and decontaminated with 35% hydrogen peroxide vapour (HPV) (Bioquell). In many cases this required the decanting of the entire ward prior to re-opening it to new admissions. A total of 10 wards were

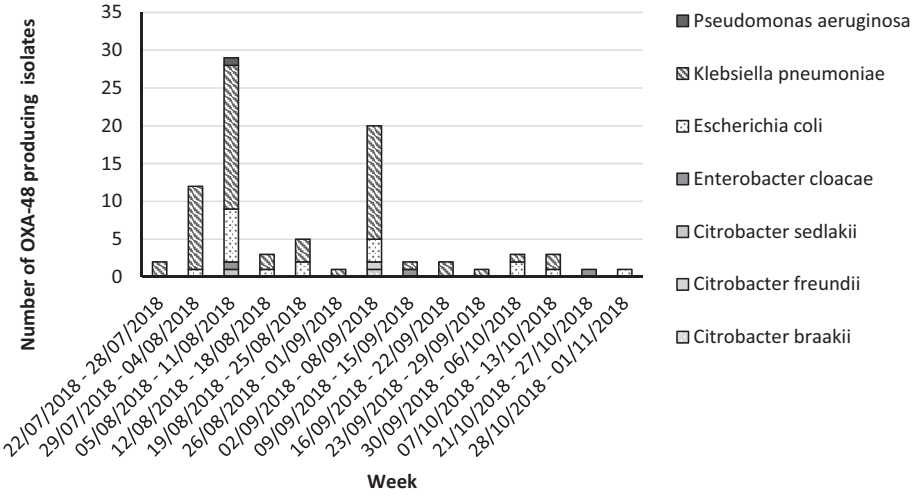

Figure 1. Epidemic curve by specimen date and organism type.

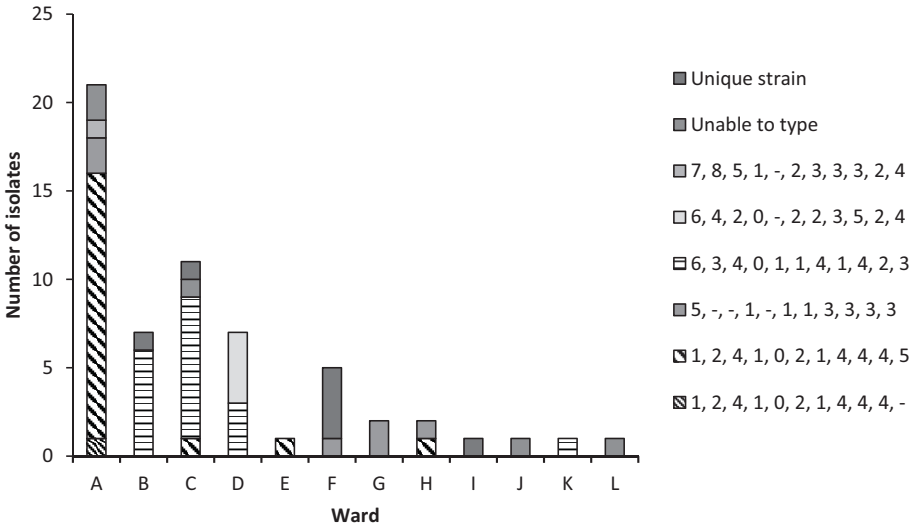

Figure 2. Distribution of OXAKp VNTR starins by ward.

decanted and fully cleaned including the use of hydrogen peroxide vapour.

When affected patients were discharged into another health or social care facility, the receiving organisation was informed by the UHL infection prevention team prior to discharge. Support was also provided by local PHE colleagues where needed. A letter informing neighbouring trusts of the outbreak situation was also sent so that appropriate screening for shared patients could be implemented.

No further cases of evident nosocomial transmission were identified towards the end of September 2018 and a 28-day outbreak closedown period was agreed by the Outbreak Control Team. There was a small number of OXA-48 isolates detected in October, attributed to previously known outbreak contacts or patients with known risk factors unrelated to the outbreak. The outbreak was declared over at the end of October 2018.

During the four-month period of the outbreak, 320 defined daily doses (DDDs) of ceftazidime/avibactam were used in the affected ward areas, a large increase in comparison to 17 DDDs used in the nine months preceding this. In the following six months, 147 DDDs of ceftazidime/avibactam were used; the ongoing use is attributed to OXA-48 colonized patients being treated for suspected or confirmed infection.

There were a number of incidents relating to ceftazidime/avibactam use. Five incidents were due to confusion between ceftazidime and ceftazidime/avibactam; on four occasions ceftazidime was prescribed instead of ceftazidime/avibactam as intended and once ceftazidime was administered instead of ceftazidime avibactam. Other reported incidents included delayed administration, incorrect prescribed dose and incorrect storage. As a result of close stewardship and monitoring of use by the Antimicrobial Pharmacy Team, no errors resulted in patient harm. When the strategy of prescribing by brand name was implemented, no further incidents were reported relating to confusion between the two products.

Discussion

VNTR typing of the OXAKp isolates revealed two predominant strain types. There were also a smaller number of other non-Klebsiella OXA-48-producing Enterobacteriaceae identified during the outbreak period. As the pOXA-48a plasmid is highly transmissible amongst different species of Enterobacteriaceae, it is possible and even highly likely that some of these isolates contained the same plasmid as found within the outbreak OXAKp strain. It is also uncertain if both predominant stains of OXAKp identified had the same plasmid, given that the strains were clustered around different ward areas. Plasmid typing is not readily available via current PHE national reference laboratory service. Based on VNTR results alone, enhanced screening of all medical wards in the Trust detected a previously unknown second outbreak clustered around wards B, C and D.

The discovery of the outbreak in UHL was prompted by the detection of OXAKp in a clinical specimen. In our experience, secondary transmission occurred very rapidly when an OXAKp-colonised patient was nursed on an open ward. Given the low ratio of infection to colonisation of this organism, clinical specimens were an insensitive and late indicator of the presence of OXA-48 in our organisation, a situation made worse by the frequent apparent *in vitro* susceptibility of OXA-48-producing isolates to meropenem [5], which made detection of CPE in clinical specimens challenging.

OXA-48-producing *K. pneumoniae* is the predominant CPE in Spain [6] and in the suspected index patient, initial acquisition was likely to have occurred there. Although OXA-48 colonisation in Spanish hospitals is an established problem [7], the risk of acquisition in residents with other forms of healthcare contact is unclear.

Early on in the outbreak, the decision was taken to screen using three rectal swabs obtained 24-hours apart. It was not operationally possible to quarantine a suspected CPE carrier for the full week that is necessary if swabs are taken at 48-hour intervals, as recommended in the PHE acute trust toolkit [8], and there was no strong evidence base for that particular time interval recommendation within the toolkit. The current literature suggests that three serial screens do not significantly increase the detection of CPE carriage [9]. However, it was noted during our outbreak that not all patients who screened positive were detected on the first round of screening.

A large number of patients were screened in the course of this outbreak which gave the outbreak control team a good grasp of the scale of the problem. This enabled the identification of the necessary nursing, equipment, housekeeping and estate resources to manage the outbreak. It was operationally extremely difficult to maintain several medical wards in isolation simultaneously.

This outbreak was estimated to cost the Trust £350,000 to £400,000 in at a time of great financial pressure in the NHS. This cost estimate included extra cleaning including HPV, staffing, laboratory costs and treatment with ceftazidime/avibactam. The estimated cost of additional screening alone was £25,000.

The majority of the wards affected during this outbreak were geriatric medicine wards. Thirty-day readmission rates for this population was estimated at 24% [10], making re-admission of carriers highly probable. A proportion of these patients were discharged to nursing and residential homes, in which onward transmission of OXAKp to other residents is likely. Thus, care homes may act as community amplifiers of CPE increasing the probability of re-introduction of CPE back into the hospital setting. Because of our outbreak, we have extended our previous screening policy to include all admissions with a history of hospitalisation to UHL in the preceding 12 months. We have also made the change to screening by direct CPE detection from rectal swabs using PCR. As a result, we are detecting OXAKp in patients who were not known to be contacts of the initial outbreak.

The confusion of ceftazidime/avibactam with ceftazidime is a concern. There is the potential for patient harm if patients with infections caused by OXA-48-producing Enterobacteriaceae requiring ceftazidime-avibactam treatment are given ineffective ceftazidime instead. Another UK hospital has reported incidents relating to the selection of cephalosporin antibiotics for dispensing in pharmacy departments [11]. European Union directives (2001/82/EC, 2001/83/EC, and 2003/63/EC) require the use of International Non-proprietary Names (INN). For established combination products with existing British Approved Names (BANs), e.g. co-amoxiclav, BANs are commonly used in prescriptions. BANs have not been issued for newer combination products. Of the beta-lactam/beta-lactamase-inhibitor combinations without a BAN (e.g. piperacillin/tazobactam, ceftolozane/tazobactam), ceftazidime/avibactam is the first to include a beta-lactam antibiotic already in use as a single agent so this potential for confusion is an emerging concern affecting dispensing, prescribing and administration practice.

Recommendations

Using clinical specimens as sentinels for the detection of the introduction of OXAKp into a healthcare organisation is an insensitive approach and will likely lead to late recognition of a problem. Instead, our experience supports the introduction of pre-emptive screening of higher-risk groups including patients with a history of hospitalisation elsewhere in the previous 12 months.

High rates of re-admission in older patients pose a challenge following an outbreak of OXAKp because of prolonged carriage [12]. Screening strategies should consider the risk of re-introduction of OXAKp in this group of patients.

Enterobacteriaceae with resistance to ertapenem should be considered for molecular testing for carbapenemase genes, especially when there is evidence of transmission of CPE in a healthcare organisation.

Efforts to decontaminate clinical areas affected by CPE transmission may need to include the use of chlorine-releasing agents and hydrogen peroxide vapour disinfection.

Reference to ceftazidime/avibactam by brand name will reduce the risk of confusion with ceftazidime and the chance of patient harm caused by the use of ineffective antibiotic.

Conclusions

OXAKp transmits readily in the acute hospital setting. Clinical specimens are an unreliable marker for the presence of the OXA-48 producers in the organisation and active screening of potentially all patients with previous healthcare contact may be warranted.

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