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What may be lurking in the hospital undergrowth? Inapparent cross-transmission of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae*

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SUMMARY

Background: Extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* pose an increasing challenge in hospitals.
Aim: To describe the benefits of using molecular techniques to investigate the spread of ESBL-producing *Klebsiella pneumoniae* (ESBL-KP) within a tertiary referral centre.
Methods: Following the identification of a cluster of five ESBL-KP on one ward, a hospital-wide retrospective epidemiological investigation was undertaken into the incidence and spread of these organisms. Variable number tandem repeat (VNTR) profiles were used to assign patients to possible clusters. Patient outcome and length of hospital stay were reviewed. Locations of patients assigned to each cluster were investigated as possible sources of spread. Antimicrobial prescribing practices and hand hygiene compliance on affected wards were also reviewed.
Findings: Twenty-four ESBL-KP isolates were characterized by VNTR. The mean length of stay was 102.5 days for patients with ESBL-KP, which was significantly longer compared with the mean length of stay for all patients (10.1 days, $P < 0.01$). Nineteen patients were assigned to clusters with shared VNTR profiles. Review of patient transfer histories identified two instances where cross-transmission may have occurred. In both cases, compliance with good hand hygiene practice and antimicrobial prescribing was suboptimal.
Conclusion: Molecular typing provided a valuable insight into the clones of ESBL-KP circulating within the study institution. Increased surveillance to identify colonization among patients and routine typing of isolates should be considered, but the resource implications for patient isolation are considerable.

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Introduction

Healthcare-associated extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* are an increasing challenge in hospitals. Production of beta-lactamase enzymes is the most common mechanism of resistance to beta-lactam antimicrobial agents amongst Gram-negative bacilli, including *Escherichia coli* and *Klebsiella pneumoniae*.[1] Infections due to ESBL-producing *Enterobacteriaceae* are associated with a delay in the initiation of appropriate antibacterial therapy, prolonged hospital stay, increased morbidity and mortality, and increased hospital costs.[2,3] Antimicrobial selective pressure plays a central role in the acquisition, selection, persistence and transmission of resistant pathogens.[3] Combined interventions are necessary to control spread, including optimal hand hygiene, education of healthcare professionals and adherence to antimicrobial prescribing policies.[4] In Europe, antimicrobial susceptibility information is available on invasive cases of ESBL-producing *E. coli* and *K. pneumoniae* through the European Antimicrobial Resistance Surveillance Network (EARS-Net).[1] In many settings, sources of infection and patterns of spread are only investigated in more depth as part of an outbreak investigation. Molecular typing is often required to confirm transmission, but it is not performed routinely in the hospital setting.[5] This paper describes a retrospective epidemiological study using molecular typing and routine surveillance to detect inapparent transmission of ESBL-producing *K. pneumoniae* (ESBL-KP).

Methods

The study hospital is a tertiary referral centre with over 800 beds, and includes national specialties in neurosurgery, renal and pancreatic transplantation, and cochlear implantation. Routine surveillance includes a review of new ESBL isolates from all patients attending the hospital at a weekly infection prevention control team meeting. All new clinical isolates of ESBLs are stored routinely within the microbiology laboratory. Currently, inpatients with ESBL producers that are resistant to either carbapenems or to both second-generation fluoroquinolones and aminoglycosides are prioritized for single-room accommodation. Due to limited single-room facilities, risk assessment on a case-by-case basis is employed for inpatient placement decisions.

During the latter part of 2011, routine surveillance of ESBL isolates indicated a possible cluster of ESBL-KP on a single ward. Antibiogram data from five isolates prompted further investigation, and additional isolates were sent to the reference laboratory in London for analysis of variable tandem repeat (VNTR) profiles to investigate possible cross-infection. Loci A, E, H, J, K and D (described previously) and three additional loci (N1, N2 and N4) were used.[6] This VNTR scheme was designed by the laboratory and is used routinely for typing services. The profiles were identical in four of the five cases. However, as no information was available regarding circulating strains of ESBL-KP isolates within the hospital, it was not known if this represented a cluster or if this profile was one characteristic of other isolates in the hospital. As such, a larger hospital-wide investigation was undertaken.

VNTR profiles of isolates were used to assign patients to possible clusters. A cluster was defined as two or more isolates with the same VNTR profile. Capsular types K1, K2, K5, K20, K54 and K57 were sought by multiplex polymerase chain reaction.[6] Once assigned to a cluster, antibiogram data of isolates within that cluster were compared for similarity and the potential usefulness of such data for identifying ESBL-KP clusters. Possible sources of transmission were identified by reviewing patient journeys, the clinical teams in charge of care, and exposure to nursing and other care staff. The findings of contemporaneous audits of healthcare worker hand hygiene on the affected wards were also reviewed.

Antimicrobial prescribing on two wards with evidence of possible cross-transmission was audited in September 2011 as part of the annual hospital-wide antimicrobial prevalence survey, and again in May 2012 as part of a European point prevalence survey. A similar protocol was used for both audits.[7] The audit results were used as a proxy for compliance with antimicrobial guidelines on the affected wards.

Statistical analysis was performed using STATA Version 9.1 (StataCorp, College Station, TX, USA). Independent sample *t*-test was used to compare the average length of hospital stay between groups. $P < 0.05$ was considered to indicate significance.

Results

Twenty-four ESBL-KP isolates were identified in 2011. Nineteen further isolates were typed in addition to the original five isolates sent for typing. Patients with ESBL-positive isolates had a mean age of 67 years (range 26–88 years), with a male:female ratio of 1.8:1. Twenty-three specimens were taken from inpatients and one specimen was taken from an outpatient who was subsequently admitted. Only one sample positive for ESBL-KP was identified within 48 h of admission. Twelve isolates were cultured from urine (including one taken from an outpatient), seven from a variety of swabs samples, three from theatre tissue samples, one from blood and one from a femoral catheter tip.

In 2011, the mean length of hospital stay was significantly longer for patients with ESBL-KP (102 days, median 57 days, range 7–427 days) compared with the mean length of stay for all patients (10.1 days; $P < 0.01$). Just over half ($N = 13$, 52%) of the patients with ESBL-KP were discharged home, 31% were discharged to other facilities such as long-term care facilities and 17% died ($N = 4$). The contribution of ESBL-KP to patient death was not investigated.

VNTR groups

Nine distinct VNTR profiles were reported, and four of these were identified on more than one occasion. The remaining five profiles were only found from one patient in each case, and these patients were excluded from further analysis (Figure 1). The remaining 19 patients were assigned to one of four clusters based on the finding that their isolates shared a common VNTR pattern (Table I). Ten patients shared a single strain with VNTR profile 6,3,4,0,1,1,4,1,1 and capsular type K2 (referred to as Group K2). A further two patients were assigned to VNTR profile 7,3,1,5,1,2,4,1,1 and capsular type K54 (referred to as Group K54). Both capsular types K2 and K54 have previously been associated with invasive disease.[6] There were a further two clusters with VNTR profiles