Outbreak of extended spectrum $\beta$ lactamase producing *Klebsiella pneumoniae* in a neonatal unit

Jennifer Royle, Sharon Halasz, Gillian Eagles, Gwendolyn Gilbert, Dianne Dalton, Peter Jelfs, David Isaacs

Abstract

An outbreak of extended spectrum $\beta$ lactamase producing *Klebsiella pneumoniae* (ESBLKp) in a neonatal unit was controlled using simple measures. Normally, the control of such infections can be time consuming and expensive. Seven cases of septicaemia resulted in two deaths. ESBLKp isolates were subtyped by pulse field gel electrophoresis, and four of the five isolates typed were identical. Control of the outbreak was achieved by altered empiric antibiotic treatment for late onset sepsis and prevention of cross infection by strict attention to hand washing. Widespread colonisation of babies in the unit was presumed, so initial surveillance cultures were not performed. No further episodes of sepsis occurred.

Keywords: $\beta$ lactamase producing Klebsiella pneumoniae; antibiotic resistance; hygiene; sepsis

Gram negative bacillary sepsis is a common nosocomial problem in neonatal units. Australian data from 1992–3 revealed coagulase negative *Staphylococcus* as the pathogen in about half the late onset cases of sepsis and that Gram negative bacteria were responsible for around 20% of late onset infections. Reports of recent outbreaks highlight the problem of multiresistant strains of *Klebsiella*. The presence of *Klebsiella* in high numbers in the stool provides a reservoir for spread from baby to baby, with transfer on the hands of staff, and, indeed, positive culture results from staff members’ hands have been obtained. Colonised babies are the commonest reported source of infection, although many primary environmental reservoirs of Gram negative bacteria have been reported in epidemics, including distilled water bottles, resuscitation apparatus, hand washing brushes and bottles of 1% chloroxylenol soap.

Methods reported to control outbreaks have included reducing implementing “antibiotic pressure” by changing the antibiotic policy, introducing methods to improve hand washing, cohorting (nursing together) infected and colonised babies, and varying levels of surveillance cultures to detect environmental contamination. These methods can prove very expensive.

We describe a first stage approach to an outbreak of a multiresistant extended spectrum $\beta$ lactamase producing *Klebsiella pneumoniae* (ESBLKp), which involves education of staff to improve hand washing and changes to the antibiotic policy. No initial surveillance cultures of babies or environment were done. Since the epidemic resolved after these simple measures had been taken, further more costly methods were not required.

Methods

The neonatal unit at The Royal Alexandra Hospital for Children is a tertiary referral centre. All babies are referred from outside hospitals, there being no attached obstetric unit. There are 27 beds: 10 intensive care, 12 extended care, and five isolation beds in two isolation rooms. Twelve members of the nursing team are on duty at any one time, one, two or three of whom are senior staff. Three neonatologists work one week on at a time. Day shifts are staffed by one medical registrar and two residents. Overnight cover is provided by one medical registrar. The unit moved in October 1995 from an old hospital site in Camperdown to a new site in Westmead.

Routine surveillance cultures of babies are not performed in the unit. In general, babies over 48 hours old with suspected late onset sepsis are treated empirically with vancomycin and gentamicin. A third generation cephalosporin (cefotaxime) is used in place of gentamicin when Gram negative sepsis is strongly suspected.

Pulsed field gel electrophoresis (PFGE) was performed on available isolates. Agarose plugs containing the isolates were each digested overnight using the restriction endonucleases XbaI and NsiI. PFGE was performed using a Biorad Chef-Mapper. The digested plugs were incorporated into a 1% agarose gel which was electrophoresed using the following conditions: a 21 hour run time, temperature of 14°C, voltage of 6.0 volts/cm and switch times of 2 seconds to 40 seconds linear ramping.

The babies’ characteristics are shown in table 1. On 30 July 1995, a full term baby with bladder extrophy (case 1) became clinically septic. She was known from superficial wound cultures to be colonised with an ESBLKp. Empiric treatment was started using flucloxacinil and amikacin. Blood and urine cultures subsequently grew ESBLKp that was sensitive to amikacin. The baby recovered uneventfully.

The second case occurred three months later, when a term baby who had been treated...
Table 1 Cases of ESBLKp sepsis

<table>
<thead>
<tr>
<th>Cases</th>
<th>Sex</th>
<th>Gestation (weeks)</th>
<th>Birthweight (kg)</th>
<th>Underlying problems</th>
<th>Age at sepsis onset (days)</th>
<th>Date of ESBLKp sepsis</th>
<th>Sites of positive cultures</th>
<th>Antibiotics before and days of use</th>
<th>Empirical antibiotics</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>35</td>
<td>2.82</td>
<td>Meningitis</td>
<td>15</td>
<td>1/3/96</td>
<td>Blood</td>
<td>A, G, M, Ami, F</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>24</td>
<td>2.0</td>
<td>NEC</td>
<td>9</td>
<td>3/3/96</td>
<td>Blood</td>
<td>A, G, M, Ami, F</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>24</td>
<td>2.0</td>
<td>NEC</td>
<td>14</td>
<td>3/3/96</td>
<td>Blood</td>
<td>A, G, M, Ami, F</td>
<td>Survived</td>
<td></td>
</tr>
</tbody>
</table>

HMD = hyaline membrane disease; CLD = chronic lung disease; FTT = failure to thrive; NEC = necrotising enterocolitis; ESBLKp = extended spectrum β-lactamase producing Klebsiella pneumoniae; A = ampicillin; Cl = clindamycin; Imi = imipenem; Am = amoxycillin; Ctx = cefotaxime; M = metronidazole; Ami = amikacin; F = flucloxacillin; V = vancomycin; G = gentamicin.
With each restriction endonuclease enzyme, identical banding patterns were displayed by isolates from cases 3–6, with case 7 having a distinctly different pattern (fig 1).

Discussion

Hospital neonates develop gastrointestinal tract colonisation with *Klebsiella, Enterobacter*, and *Citrobacter* species (KEC species) at high rates compared with well babies at home in whom *Escherichia coli* is the predominant bowel flora. The risk of stool colonisation with KEC species is increased with over three days of antibiotic use and with duration of hospital stay, 60% being colonised by day 15 and over 90% by day 30.27 Microbial drug resistance is an inescapable consequence of the widespread use of antimicrobial agents. Outbreaks of infection with resistant strains of Gram negative organisms create the situation where empirical antibiotic choice may not cover the causative organism. Resistance to aminoglycosides has been the focus of many reported outbreaks.6 16 19 Amikacin resistant Entero-bacteriaceae were reported from Louisville in 1980; colonised babies were the only source discovered and there were three deaths.23 Extended spectrum β-lactamase (ESBL) producing strains of Gram negative bacilli were first reported in Germany in 1983. These organisms showed decreased susceptibility to the third generation cephalosporins, due to a plasmid mediated β-lactamase identified as a mutational modification of the *Klebsiella* SHV-1 enzyme, designated *Klebsiella* SHV-2.21 More than 27 distinct enzymes have been described, with worldwide distribution. The selective pressure of heavy cephalosporin use has probably contributed to the emergence of ESBL producing organisms.22 24 Outbreaks are frequent as host strains are readily transferred.6 25 26 A nursery epidemic can be defined as a significant increase in the rate of certain infections over baseline.27 At our hospital, all episodes of blood culture confirmed sepsis in the nursery have been documented prospectively since 1991, so an increase in the incidence of *Klebsiella* sepsis was not difficult to document. The death of case 5, presumably as a result of cross contamination, caused the infection control team to intervene. In retrospect, earlier intervention—for example, when cases 3 and 4 presented—would have been preferable and might have averted the later cases.

Subtyping revealed that a single epidemic organism was responsible for cases 3–6. The isolates from cases 1 and 2 were not available for subtyping, while case 7 was caused by a different strain of ESBLKp of unknown origin. The origin of the predominant ESBLKp is unknown, although we suspect that it was introduced by the transfer of a colonised baby from another hospital. We looked at the antibiotics received by our colonised and infected babies, and none of them had received any third generation cephalosporins, nor prolonged courses of other antibiotics. However, as we do not perform surveillance cultures on admission to the unit, we are unable to say whether the first baby was already colonised before admission.

The ESBLKp isolate from case 7 occurring at the height of the epidemic was not a genetic match with the other isolates. This highlights the benefits of subtyping organisms in an epidemic and raises further questions relating to the origins of different strains of ESBLKp.

Surgical patients were over represented in our outbreak—six of the seven patients having undergone recent surgical procedures. Because our unit is tertiary referral centre, several surgical patients are on the unit at any one time. Many non-surgical patients were colonised or presumed to be colonised, and only one became septic. This suggests that surgery may be a contributory factor. Gastrointestinal surgery, and in particular, ischaemic bowel, may be an important risk factor for sepsis. Other outbreaks have also reported over representation of surgical patients.8 20 An outbreak of ESBLKp at Guy’s Hospital, London, was mostly seen in neonates recovering from cardiac surgery for congenital defects.8 The increased risk of clinical infection is probably associated with invasive procedures in general, and not restricted to major surgery. This highlights the relative likelihood of such an epidemic becoming a rapid clinical problem in a major surgical neonatal centre compared with smaller units where surgery is not performed on site.

Various outbreak management strategies have been described. The methods used address antibiotic policy, cohorting, hand washing, wearing of gloves and gowns, and environmental swabs. The expense of the management increases as the number of methods instituted rises. In some outbreaks short term antibiotic policy change has been reported as being adequate to prevent further spread of infection.29 30 Occasionally, an environmental source has been found and removal of the environmental source has led to rapid resolution of the outbreak.12 13

Many outbreaks are managed with surveillance cultures and cohorting. If this approach is
Control of Klebsiella infection in a neonatal unit

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