Outbreak of extended spectrum β-lactamase producing *Klebsiella pneumoniae* in a neonatal unit

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Abstract

An outbreak of extended spectrum β-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 pulsed 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: β-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.1

Outbreaks of Klebsiella infections in neonatal units have been widely reported and are frequently associated with widespread colonisation of babies, systemic infections, and death.2–5 Reports of recent outbreaks highlight the problem of multiresistant strains of Klebsiella.6–8 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.9–11

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 containers,12 resuscitation apparatus,13 hand washing brushes14 and bottles of 1% chlorhexidine soap.15

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 β-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 fluoroxacillin 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...
for necrotising enterocolitis, and not known to be colonised with ESBLKp, developed septi-
cæmia. Treatment with cefotaxime and gent-
amicin was started, as Gram negative sepsis
was suspected. After ESBLKp had been
isolated amikacin was substituted and the baby
recovered.

Cases 3 and 4 occurred after a further 10
weeks, and cases 5 and 6 another five weeks
later. Two babies died; in each case empirical
antibiotic treatment was begun to which the
ESBLKp subsequently proved resistant. Case 7
occurred one week after cases 5 and 6, by
which time the empiric antibiotic choice had
been changed in view of the outbreak. The
organisms in cases 1 and 2 were sensitive to
amikacin and imipenem. Cases 3 to 6 grew
organisms resistant to amikacin and sensitive
only to imipenem.

One other unit baby developed endotracheal
tube colonisation with the ESBLKp strain on 2
March 1996. This baby died on 4 March from
cases other than sepsis. In March 1996 an
urgent meeting was held with the infection
control team and the neonatologists to decide
strategies to prevent further cases, and to
decide how the unit antibiotic policy should be
changed.

INTERVENTION
The infectious diseases team and neonatolo-
gists decided on strategies to deal with the out-
break. The empirical antibiotic policy for
suspected late onset sepsis was changed to imi-
penem and vancomycin. Surveillance cultures
of babies or of the environment were not
performed immediately, as negative cultures
would not reliably exclude colonisation or con-
tamination. The primary source of infection
was presumed to be colonised infants, with gut
colonisation as the major reservoir.

All babies in the unit at the time of the out-
break were presumed to be colonised. Case 6
was placed in one of the two isolation rooms, as
she was known to be colonised. All babies were
to be regarded as potential reservoirs for
further spread. New (presumably uncolonised)
babies admitted to the unit were nursed in
areas within the two main rooms of the nursery
with the colonised babies.

The primary focus for preventing cross con-
tamination was hand washing. In-service edu-
cation sessions explaining the outbreak to the
nursing staff and unit nursing educators were
conducted. The importance of hand washing
to prevent baby to baby spread of gut colonis-
ing organisms was stressed. The wearing of
disposable gloves for nappy changing, a policy
previously only variably practised, was rein-
forced.

Nurses were declared to be the advocates for
the babies. Each nurse was given the responsi-
bility to act on behalf of the babies under his or
her care, and to insist that all attending person-
nel wash hands before and after handling the
baby. Any medical or paramedical staff refusing
to wash his or her hands after being asked to
do so by the attending sister was to be reported
to the infection control team. A high level of
motivation emerged among the nursing staff:
“nurse power” advocacy was well received by
visiting staff.

Attendance of at least one of the infectious
disease team at a weekly neonatal ward round
was routine. However, on each occasion during
the subsequent 10 weeks, the outbreak was
discussed and the importance of hand washing
reiterated.

Results
No further episodes of sepsis occurred after
case 7. Ten weeks after the antibiotic policy was
changed, fecal or rectal swab cultures from all
the babies in the unit were taken to assess the
point prevalence of colonisation.

Fecal culture from case 6 was positive for
ESBLKp but only one other baby, admitted
two weeks earlier, was positive. This baby was
placed in the isolation room with case 6. Apart
from case 6, all babies on the unit had been
admitted after the epidemic intervention had
started. Repeat surveillance cultures per-
formed one week later on all babies on the unit
confirmed positive cultures only in the same
two babies in the isolation room.

The empirical antibiotic policy for suspected
late onset sepsis was changed back to vancomy-
cin and gentamicin for all unit babies, other
than for the two babies in isolation who were to
be treated empirically with vancomycin and
imipenem if they became clinically septic.

Subtyping of the ESBLKp isolates was
performed on cases 3–7. The isolates from the
earlier two cases were not available for testing.

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>Antibiotics before ESBLKp sepsis and days of use</th>
<th>Age at sepsis onset (days)</th>
<th>Date of ESBLKp sepsis</th>
<th>Sites of positive cultures</th>
<th>Empiric antibiotics</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>41</td>
<td>3.5</td>
<td>Bladder exopyd</td>
<td>A2, G2, Am(oral)5 A9, G9, M9</td>
<td>24</td>
<td>30/7/95</td>
<td>Blood, urine</td>
<td>Am, F</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>40</td>
<td>3.7</td>
<td>NEC (day 3)</td>
<td>CI 12, G14, A7, M4</td>
<td>13</td>
<td>29/10/95</td>
<td>Blood</td>
<td>Ctx, G then Ami (at 24 hours)</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>34</td>
<td>2.0</td>
<td>Malrotation; volvulus; NEC (day 25)</td>
<td>A11, Ami11, M5, G5</td>
<td>60</td>
<td>19/9/95</td>
<td>Blood</td>
<td>Ctx, G then Imi (at 24 hours)</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>35</td>
<td>2.4</td>
<td>Gastrochisis</td>
<td>A11, Ami11, M5, G5</td>
<td>56</td>
<td>27/1/96</td>
<td>Blood</td>
<td>V, G then Ctx, G (at 24 hours) then Imi (1 dose)</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>29</td>
<td>1.2</td>
<td>HMD</td>
<td>Nil</td>
<td>6</td>
<td>3/3/96</td>
<td>Blood</td>
<td>V, G</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>25</td>
<td>0.6</td>
<td>CLD, FTT, NEC, multiple gut ressections</td>
<td>A6, G6, M4</td>
<td>195</td>
<td>3/3/96</td>
<td>Blood</td>
<td>A, G then Imi (at 48 hours)</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>37</td>
<td>2.82</td>
<td>Cloacal exopyd; lipomyelo-meningocele</td>
<td></td>
<td>11/3/96</td>
<td>Blood, urine</td>
<td>Imi</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; CI = clindamycin; Imi = imipenem; Am = amoxicillin; 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 30.37

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 18 19 Amikacin resistant *Enterobacteriaceae* were reported from Louisville in 1980; colonised babies were the only source discovered and there were three deaths.39 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.21–24 Outbreaks are frequent as a consequence of the widespread use of antibiotics.25–27

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 ESBL*Kp* of unknown origin. The origin of the predominant ESBL*Kp* 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 ESBL*Kp* 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 ESBL*Kp*.

Surgical patients were over represented in our outbreak—six of the seven patients having undergone recent surgical procedures. Because our unit is a 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.6 28 An outbreak of ESBL*Kp* 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 15

Many outbreaks are managed with surveillance cultures and cohorting. If this approach is
taken, regular, preferably weekly, cultures need to be performed until the outbreak is resolved, to ensure accurate cohorting. The lower cost approach is to assume that all babies are colonised and that strict attention to hand washing is promoted. New admissions are then nursed with babies presumed to be colonised, but are protected by improved hand washing routines.

The outbreak in our unit was managed by this low cost approach. It was felt that immediate surveillance cultures would not significantly change our approach to the outbreak and would add unnecessary cost. Klebsiella outbreaks are consistently associated with high levels of colonisation.245 Regardless of the level of colonisation we could not isolate large numbers of babies in the unit and would still have relied on increased hand washing to eradicate spread. Case 6 was isolated because persistent colonisation was assumed after confirmed infection, and because the increased awareness and discussion of the implications of multireistant organisms, associated with nursing her in isolation, was felt to be advantageous.

In most Klebsiella epidemics, the primary source of infection is gut colonisation of infants.2 4 5 We began stage 1 management without searching for an environmental source and, as no further episodes of sepsis occurred, it is likely that none existed. If further cases had occurred we would have begun a second stage of management and surveyed the unit environment. One may question the possible continued risk to babies by not seeking out a possible external source, but with the change in antibiotic policy the risk to infants was reduced.

There is little published evidence to support the control of outbreaks by improved hand washing and the eventual discharge of colonised babies from the unit. Compliance with hand washing by staff has rarely been observed to occur on more than one third of occasions of patient contact, ranging from 28%–48%.11–14 Tibballs at the Royal Children’s Hospital for Children and the neonatologists Peter Barr, Robert Haliday and Julian Wojtulewicz

We thank the staff of the Grace neonatal unit at the Royal Alexandra Hospital for Children and the neonatologists Peter Barr, Robert Haliday and Julian Wojtulewicz

References