An outbreak of ESBL-producing \textit{E. coli} in a NICU

In 2011 the neonatal unit at Singleton Hospital, Swansea experienced an outbreak of extended-spectrum beta-lactamase (ESBL)-producing \textit{Escherichia coli}. The lessons learnt from a root cause analysis of the events and rapid response to the infection are presented.

Singleton Hospital, Swansea is one of three designated level 3 neonatal units (NNUs) for Wales. The adjacent maternity unit and labour ward has approximately 3,600 deliveries annually and the population served has around 10,000 births per annum. In 2011 the unit experienced an outbreak of ESBL-producing \textit{E. coli}. The lessons learnt from a root cause analysis of the events and rapid response to the infection are very relevant, especially given the increasing incidence of ESBL-producing \textit{E. coli} in the neonatal population\textsuperscript{1,2}.

\textbf{Index case: woman A}

Woman A, a primigravida with a high-risk obstetric history, had undergone intracytoplasmic sperm injection IVF conception abroad, and conceived a twin pregnancy. A Shirodkar suture was inserted at 15 weeks. On her return to the UK at 25 weeks of gestation, she transferred her maternity care to her local district general hospital. Eleven days later she presented with spontaneous pre-labour premature rupture of membranes. She was transferred from her local unit to the maternity unit at Singleton Hospital, Swansea. Antenatal dexamethasone was administered. Soon after arrival, she progressed to premature labour and required an emergency caesarean section in the main operating theatre on the maternity unit because of transverse lie.

Infants A1 and A2 were successfully delivered at 27 weeks' gestation. Infant A1 weighed 880g, was intubated, given surfactant and required assisted ventilation from birth. She was transferred to the NNU (Day 1) where benzylpenicillin and gentamicin were commenced and umbilical lines were inserted.

Infant A2 weighed 1,050g and was also intubated, received surfactant and ventilated from birth. He was transferred separately in a transport incubator to the NNU (Day 1). Intravenous benzylpenicillin and gentamicin were also administered. Infant A1 had an initial C-reactive protein (CRP) of 17, whereas infant A2 had an initial CRP of 1.

On Day 2, infant A2 improved, was extubated, and placed on continuous positive airway pressure (CPAP) ventilation. Infant A1 deteriorated with a raised CRP of 47 and clinical signs suggesting sepsis. Meningitis was suspected and antibiotic therapy was changed empirically to cefotaxime and vancomycin. A cerebral spinal fluid (CSF) analysis for infant A1 was undertaken and was later reported as negative. During the evening, woman A also developed signs of sepsis, with pyrexia and tachycardia. Blood and urine samples were sent for microbiological investigations, a malaria screen was initiated and a chest radiograph was arranged. A provisional diagnosis of an atypical pneumonia was made.

On Day 3 post-delivery, Woman A remained unwell with signs of worsening sepsis. The results of high vaginal swabs taken pre-delivery were now available and showed group B Streptococcus (GBS) as well as ESBL-producing \textit{E. coli}. Also endotracheal aspirates from infant A2 were reported to grow ESBL-producing \textit{E. coli}, but the infant remained well on CPAP. The NNU and maternity wards were informed and, following repeat blood cultures, intravenous meropenem was commenced for woman A, and infants A1 and A2 and barrier nursing commenced for all three.
**Woman B**

Infant B1 was born at 26+5 weeks’ gestation weighing 730g, 16 hours after the births of infants A1 and A2, in the main theatre of the labour ward by caesarean section. Woman B had a history of four previous unsuccessful pregnancies and, on this occasion, conceived naturally. She had a Shirodkar suture inserted early on in her pregnancy. She was transferred to Singleton maternity unit from the same district general hospital as woman A with pre-labour premature rupture of membranes four days prior to delivery. She was unwell with fever, neutrophilia and high CRP. A high vaginal swab grew only anaerobic organisms. Antenatal dexamethasone and clindamycin were administered, as she was allergic to penicillin.

Infant B1 was born by emergency section due to compound presentation in labour. At birth she was in good condition but needed intubation and ventilation. After transfer to the NNU, infant B1 was nursed in the adjacent cot to infant A1. Intravenous benzylpenicillin and clindamycin were commenced, as she was allergic to penicillin.

Over the next five days, woman A and infant A2 improved. Unfortunately, infant A1’s infection, which was also confirmed later as blood culture positive for ESBL-producing *E. coli*, responded poorly to treatment and infant A1 gradually deteriorated. On Day 8, infant A1 was critically unwell with severe systemic sepsis, unresponsive to antibiotics and brain scans revealed large intracranial haemorrhage. Following extensive discussions between the family and medical team, care was withdrawn and infant A1 died a short time later.

Woman A made a gradual recovery and on Day 9, following discussion with the medical team, she disclosed medical notes from treatment she had received abroad. A review of these notes revealed that she had positive urine cultures for ESBL-producing *E. coli* during her treatment there. This had not been disclosed to the staff prior to this point.

**Outbreak analysis**

The ESBL-producing *E. coli* was resistant to gentamicin, amoxicillin/clavulanic acid, cefuroxime and cefotaxime. It was sensitive to amikacin, meropenem and piperacillin/tazobactam. The earlier decision to change the antibiotics of infant A1 to cefotaxime and vancomycin was empirical, made prior to the knowledge or availability of any of the culture results of any of the patients. The choice was made to cover the possibility of meningitis and long line infection, though the latter appeared unlikely. Neither these antibiotics, nor the gentamicin were effective against the ESBL-producing *E. coli*.

How and exactly when the infection spread from infant A1 to infant B1 could not be ascertained. If the information in mother A’s medical case notes from abroad had been requested by and made available to the clinical team at an early stage, the choice of the initial antibiotics might have been more appropriate. This may have

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**FIGURE 1** The results of pulsed-field gel electrophoresis (PFGE) of isolates of ESBL-producing *E. coli*. The same strain was identified in woman A, infants A1 and A2 and infant B1. PFGE was performed on XbaI-digested genomic DNA using a Bio-Rad CHEF-DR II system. Conditions were 6V/cm for 30 hours at 12°C, with ramping times of 5–35 seconds in a 1.2% (w/v) agarose gel in 0.5x tris borate EDTA buffer. Gel images were compared using BioNumerics software.
prevented infant A1 becoming so unwell and might also have prevented the spread to infant B1. Several other aspects of the outbreak were revealed in a detailed root cause analysis.

The reference laboratory undertook detailed analysis of the isolates of ESBL-producing *E. coli* and the same strain was identified by pulsed-field gel electrophoresis (PFGE) in mother A, infants A1 and A2 and infant B1 (FIGURE 1).

While the organism spread vertically from woman A to infants A1 and A2, either *in utero* or at birth, the information extracted from the analysis suggested cross infection between infant A1 or A2 to infant B1 on the NNU. The infants were delivered on the same day and in the same theatre at a time of high capacity and occupancy and were cared for in adjacent cot spaces on the NNU; all are significant risks for horizontal transmission.

To exclude further transmission during the outbreak, asymptomatic mothers and infants on the neonatal and maternity units were tested for the presence of ESBL-producing *E. coli* via rectal swabs taken after Day 3, a practice endorsed by recent guidelines for gram negative bacteria outbreaks supported by the British Association of Perinatal Medicine. These included the 10 infants delivered in theatre between the deliveries of infants A2 and B1 and infants who had been nursed on the NNU and discharged to the postnatal ward. All of these results were negative. Furthermore weekly rectal swabs of all infants on the NNU were cultured, to screen for ESBL-producing *E. coli* during the outbreak.

**Woman C** grew a different strain of ESBL-producing *E. coli* in her post-caesarean section scar swab. She had also had a Shirodkar suture inserted earlier in the pregnancy. Infant C was born at 31 weeks' gestation by emergency lower segment caesarean section (LSCS) in good condition and required minimal non-invasive ventilator support. A rectal swab on Day 23 grew the same ESBL-producing *E. coli* as woman C, but infant C remained well without antibiotics.

**Woman D** grew another strain of ESBL-producing *E. coli* in a urine sample post-delivery. Infant D had been delivered by spontaneous vaginal delivery at 40 weeks' gestation. He was admitted to the NNU at 20 hours of age for clinical deterioration, initially thought to be most likely GBS sepsis in view of known colonisation in the mother. This was not identified on any culture results from infant D. However skin swabs grew the same ESBL-producing *E. coli* strain as woman D. Initially benzylenepicillin and gentamicin were commenced; these were changed to amikacin and meropenem with the above result. Infant D improved and remained well thereafter.

Finally through routine screening of all infants on the NNU, a further strain of ESBL-producing *E. coli* was isolated on a rectal swab of infant E, who had been born at 38 weeks' gestation by emergency LSCS with a background history of pre-labour rupture of membranes. Infant E had been admitted to the NNU due to clinical deterioration at six hours of age. Benzylenepicillin and gentamicin were administered due to the initial clinical presentation but there was no growth in blood or CSF analysis and he subsequently improved.

Root cause analysis uncovered several aspects of the management of the outbreak, which reduced the risk of further transmission. The unit’s practice was in keeping with recently updated NHS guidelines. As soon as the microbiologist identified ESBL-producing *E. coli* in mother A, and infants A1 and A2, the relevant clinicians were notified, new admissions were reduced and reduced barrier nursing was strictly implemented. Space between the cots was increased. No new infants were admitted to the neonatal intensive care area of the unit. This reduced the capacity on the unit. The importance of hand washing was reiterated with more frequent audits. Previously, the unit had regularly obtained results of 100% for monthly hand washing audits. There were twice daily team meetings at the start of each shift to keep staff updated and to reinforce the importance of all infection control measures.

After close liaison with the microbiology and infection control staff, an environmental audit was commenced to ascertain any reservoirs of environmental infection that could put other patients at risk. Subsequently the labour wards, operating theatres, NNU and equipment were swabbed and thoroughly cleaned. ESBL-producing *E. coli* was not identified in any of the 131 environmental swabs undertaken. The unit remained open throughout the outbreak but admission numbers were reduced by collaboratively working across the Welsh neonatal network. A review of all cleaning practices of equipment was undertaken. Cleaning of the ultrasound probe was identified as an issue, as it was difficult to thoroughly decontaminate due to its design. Subsequently, single use disposable sheaths were used for each scan to avoid any possibility of cross colonisation. Also individual patient sterile ultrasound gel sachets were introduced. Prior to the outbreak, the unit had used gel dispensed from a plastic bottle for all patients undergoing ultrasound scans on the unit.

**Discussion**

Among the gram negative bacteria, the production of the enzyme beta-lactamase is the most frequent mechanism of antibiotic resistance. Beta-lactamase production results in resistance to penicillins and third generation cephalosporins through degradation of the antibiotic beta-lactamase ring structure, inactivating the antibiotic. Over the last 30 years, Enterobacteriaceae that produce ESBL have increasingly shown an increased background resistance to other antibiotic classes since the genes encoding ESBLs are located on transferrable plasmids that harbour genes encoding resistance to several other classes of antimicrobial agents. ESBL-producing organisms often exhibit resistance to certain aminoglycosides, co-trimoxazole, tetracyclines and fluoroquinolones and are a formidable challenge with limited therapeutic options.

ESBL-producing organisms have become increasingly prevalent, especially in the developing world. Recent reports from India estimate a prevalence in intensive care units of 23-86% with reported community carrier rates of 1.1% in France (in 2006) and up to 10% in Israel. The availability of antibiotics without prescription and widespread use with suboptimal dosing and duration contribute to the emergence of multidrug-resistant organisms. In 2006, the Antimicrobial Availability Task Force of the Infectious Diseases Society of America listed ESBL-producing Enterobacteriaceae (*Klebsiella* species and *E. coli*) as one of six key problematic drug-resistant pathogens. More recent reports describe ESBL-producing organisms as a significant and
developing global public health threat\textsuperscript{7,18}. ESBL-producing \textit{E. coli} may be associated with higher mortality\textsuperscript{7}, not due to increased disease severity but to inappropriate empirical treatment\textsuperscript{16}. A more recent study has suggested a higher mortality rate could be related to a possible pathological role for the increased expression of fimbrial adhesins and increased cell invasion in some ESBL-producing gram negative bacteria\textsuperscript{20}.

Neonatologists are caught in a conundrum. Appropriate and timely use of broad-spectrum antibiotics is paramount to reduce neonatal deaths from multi-resistant organism sepsis. However the knowledge that injudicious use of such antibiotics is likely to increase the prevalence of multi-resistant organisms in the neonatal environment must be highlighted and considered when making decisions. Early signs of sepsis may be subtle and non-specific and there are no reliable early markers, thereby necessitating the need to commence appropriate antibiotics as soon as clinical suspicions are aroused and after taking appropriate cultures, but before culture results are available. The first line antibiotics for early neonatal sepsis where \textit{E. coli} and GBS are the most common causative agents’ are penicillin and gentamicin. In later sepsis, other organisms are more likely to be responsible. The choice of antibiotics for later sepsis, prior to culture results becoming available, is based on clinical decision making guided by factors such as whether there is a long line in situ, (making coagulase negative Staphylococcus more likely), whether any organisms have been identified from other cultures such as endotracheal aspirates or, in an outbreak, what organisms are prevalent on the unit. Of paramount importance is prevention of spread of infection through good practice including NNU design, hand washing and cleaning of equipment.

Infections with gram negative bacteria are a leading cause of neonatal mortality. Previously nosocomial infections were commonly reported as a major problem in NICUs\textsuperscript{10}, especially in long-stay, high-risk infants with regular use of invasive supportive measures\textsuperscript{19}. These, however, are now reducing due to better infection control measures. Contaminated equipment or inanimate objects may play a role in the dissemination of organisms\textsuperscript{21}. These factors, alongside failure of infection control procedures can be responsible for horizontal transmission\textsuperscript{22,24}. It is now also known that ultrasound transmission gel (USTG) can act as a reservoir of infection and has been implicated in several outbreaks, including some on NNUs\textsuperscript{25,26}. Many countries now have guidelines recommending that the use of USTG on NNUs is limited to single-patient use, sterile sachets\textsuperscript{22,26}.

As ESBL-producing \textit{E. coli} infections are increasing significantly worldwide in all patient groups, including pregnant women, it is no surprise that there has also been an increase in the neonatal population\textsuperscript{15} with sustained outbreaks\textsuperscript{14}. It is tempting to speculate that another risk factor for vertical transmission may be the presence of cervical incompetence, as three of the five women who transmitted ESBL-producing \textit{E. coli} in this outbreak had Shirodkar sutures.

Conclusions

One particular strain of ESBL-producing \textit{E. coli} sadly contributed to the deaths of two premature infants. Horizontal transmission was inferred from the results of PFGE typing of the isolates, although the exact pathway by which this transmission occurred has not been identified despite an extensive analysis.

The rapid increase in multidrug-resistant organisms worldwide, especially in developing countries, but increasingly in community settings in the more developed world, will probably result in increasing rates of multidrug-resistant infections in the highly vulnerable neonatal population.

Although a rapid response to the initial detection of a multi-resistant organism can reduce the risk of developing a sustained outbreak, the delay in treating infected patients with appropriate antibiotics significantly increases the morbidity and mortality. It is therefore vital for the neonatal medical community to have a high index of suspicion for multidrug-resistant organisms, especially in mothers who have had recent treatment or travel to a high-risk area, or those who have themselves been inpatients on intensive care units. Wherever possible, maternal notes and culture results will be invaluable in helping to decide the most appropriate antibiotic therapy for the infant.

It is of vital importance that all infection control measures are in place at all times on units as a single lapse may lead to a cross infection.

Once an outbreak is suspected, weekly rectal swabbing of asymptomatic patients and endotracheal aspirates of ventilated patients may well pick up asymptomatic carriers, as described here. Microbiological typing may demonstrate that the strains are unrelated. This may lead to questioning the value of undertaking these in such a situation. The inevitable delay between identification of the ESBL-producing \textit{E. coli}, and the typing results (in the authors’ experience, 1-2 weeks) can lead to anxiety and uncertainty as to whether there has been further cross infection. On the other hand, it did ultimately give some reassurance that further cross infection was prevented and would have enabled choice of appropriate antibiotics, if those infants had shown signs of infection subsequent to organism identification. It also enabled further enhancement of infection control precautions for carriers.

References

Newborn and Infant Physical Examination Programme launches e-learning module

Some infants with certain congenital conditions are diagnosed late, even though early diagnosis reduces the likelihood of morbidity and mortality as well as the associated severe treatment options and the risk of long-term disability.

The NHS Newborn and Infant Physical Examination Programme (NIPE) offer parents of newborn babies in England the opportunity to have a head-to-toe physical examination for their baby to check for problems or abnormalities. The examination is carried out within 72 hours of birth and then again at 6-8 weeks of age, as some conditions can develop or become apparent later. It includes a general all over physical check, as well as specific examination of the infant’s eyes, heart, hips and testes.

To support practitioners, NIPE has launched a state-of-the-art, e-learning module that uses film clips and animations to illustrate best practice and covers the four screening aspects of the examination. It is free, quick-to-register and easy-to-use, offering condensed or full versions.

During the pilot phase, many users described the resource as an excellent refresher for seasoned practitioners and an essential learning resource for anyone new to the programme. In particular, practitioners appreciated the detailed animation of the Ortolani and Barlow manoeuvres to examine infant hips. Dr Simon Mitchell, Consultant Neonatologist and Honorary Professor at the University of Salford says: “There has been a real need to improve training for the physical examination and having used this new e-module I rate it extremely highly. Doctors will be more confident to deliver the examination having used it and the quality of the whole service, as well as the experience of parents, will improve.”

It is recommended that anyone who undertakes the NIPE examination uses the e-learning resource to update their own knowledge and skills (www.newbornphysical.screening.nhs.uk/elearning). The resource, which will be regularly reviewed in light of changes in policy and user feedback, forms part of a suite of antenatal and newborn screening education resources produced by the UK National Screening Committee (UKNSC).