Intravenous glucose preparation as the source of an outbreak of extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* infections in the neonatal unit of a regional hospital in KwaZulu-Natal

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In the last week of May 2005, staff at Mahatma Gandhi Memorial Hospital in KwaZulu-Natal realised that many babies in the high-care nursery ward had bloodstream infections involving *Klebsiella pneumoniae* bacteria. Attempts to identify a common source of infection failed. The ward was therefore closed and new babies needing high care were admitted to another empty ward. Despite this, babies still became infected. This resulted in a request for assistance from the Department of Medical Microbiology of the Nelson R Mandela School of Medicine.

A search for common factors through case history studies of the 26 infected babies showed that blood cultures of the babies remained positive despite the administration of appropriate antibiotics. Different options that could explain this were investigated. The organism was found in intravenous glucose preparations used for multiple dosing. Unopened vials of the same medication were sterile. The nursery was found to lack proper hand-wash facilities and to be overcrowded and understaffed. Reinforcement of hand hygiene and a ban on the multiple dosing of medicines stopped the outbreak.

In conclusion, this outbreak resulted from a combination of factors among which lack of hand hygiene and multiple dosing of an intravenous glucose preparation were most significant.

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Klebsiella pneumoniae is a bacterial species within the family of Enterobacteriaceae. Although it is a normal inhabitant of the human gut it can cause a wide variety of infections including pneumonia, bloodstream infections (BSIs) and urinary tract infections. As early as 1970 it was recognised as a cause of nosocomial infection when Price and Sleigh[1] demonstrated the link between the use of the ampicillin-cloxacillin combination and infection with *K. aerogenes* (now *K. pneumoniae*) in an adult intensive care unit. This landmark paper signalled for the first time the fact that uniform antibiotic prescriptions create a selective advantage for the spread of an organism resistant to these drugs. Since then, *K. pneumoniae* has evolved into a multidrug-resistant species, with numerous reports of outbreaks in hospitals, especially in neonatal units. These outbreaks occur throughout the world in industrialised[2-4] as well as developing countries.[5,6] Reports from South Africa describe outbreaks at R K Khan Hospital in Durban in 1992[7] and at Tygerberg Hospital in Cape Town in 2001.[8]

Although no source other than colonisation of the babies could be identified in most of the reported outbreaks, some outbreaks have been linked to an identified single source. These include disinfectant solutions,[9] dextrose-containing intravenous solutions[10] and artificial nails of health care workers.[4] We report on an outbreak of *K. pneumoniae* BSIs caused by multiple dosing with an intravenous glucose solution.

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Material and methods

Setting

The outbreak occurred in the neonatal unit of Mahatma Gandhi Memorial Hospital (MGMH) in Phoenix, a suburb on Durban's northern border. Commissioned in 1997 as a new district hospital to serve the Phoenix community, its status was changed to regional hospital in order to serve a much larger population living in two newly identified health districts. The neonatal unit consists of one ward divided into an intensive care/high care area with 10 beds and an intermediate/low care area with 15 beds. These areas are separated by a dividing wall. In addition, there is 1 isolation cubicle and 8 kangaroo-mother-care beds. The unit has 3 ventilators. During the period January - May 2005, the average number of staff was 7.5 (range 6 - 9), including 2 nursing assistants. The average number of patients admitted per day was 37.5 (range 35.1 - 41), resulting in an average occupancy of 110% and an average of 5.1 patients per staff member.

Description of the outbreak

In the last week of May 2005 staff at MGMH realised that there was a problem with *K. pneumoniae* infections in the neonatal unit. An attempt was made to identify the source.

K. pneumoniae was grown from the hands of 3 of the 33 staff members present during the survey. Hand-wash practices were reinforced but this did not stop the outbreak. On 9 June 2005 the unit was closed and no new admissions were accepted. Women identified as likely to deliver a neonate needing admission to a neonatal unit were referred to other hospitals for delivery where possible. Babies delivered at MGMH were admitted to a newly opened ward. Despite this, new infections kept occurring. This resulted in a request for help from the Department of Medical Microbiology at the Nelson R Mandela School of Medicine. The outbreak analysis commenced on 20 June 2005.

Outbreak analysis

Information on *K. pneumoniae* BSIs was obtained from the information system of the diagnostic laboratory at MGMH. Isolates still available were brought to the laboratories at medical school for further analysis. A chart review was performed on babies with positive blood cultures involving the possible outbreak strain to identify common factors. Hypotheses were formulated based on the findings and investigations were performed based on these hypotheses.

Laboratory methods

Specimens collected in the course of the outbreak analysis were inoculated onto McConkey no. 1 and cysteine lactose electrolyte deficient agar plates. The media were incubated overnight in a regular incubator at 37°C. Gram stain and the API 20E (Biomerieux, Marcie L'Etoile, France) identification system were used to identify colonies suspected of being klebsiella to species level and to compare biochemical profiles of the isolates. Susceptibility tests were performed using the Kirby-Bauer disc diffusion test to compare antibiograms. Double disc diffusion tests with cefotaxime and ceftazidime were done to establish the production of extended-spectrum β-lactamase (ESBL).[11]

Results

The laboratory database revealed 26 neonates with a blood culture from which klebsiella was grown, and 1 with a related species (*Enterobacter cloacae*). One of the isolates was a *K. oxytoca* with a susceptibility pattern different from the others. Only 5 of the isolates were still available for further analysis, including the *E. cloacae*. Further investigations of these 5 isolates revealed that the *E. cloacae* had been misidentified and was in fact *K. pneumoniae*. All 5 had identical susceptibility patterns and were ESBL producers.

The first culture became positive on 30 April 2005. Seven days after collection of this blood culture the baby died as a result of sepsis. The relevant clinical characteristics of all babies with *K. pneumoniae* BSI are summarised in Table I. All but 3 (88%) were born before a gestational age of 36 weeks. The mean weight at birth was 1 845 g, with 9 babies (35%) weighing less than 2 500 g. All were judged by the clinician to be at risk for developing a neonatal infection; according to protocol they were therefore commenced on antimicrobial treatment with penicillin and gentamicin. Of the 26 infected babies 22 (85%) died, with a mean age at death of 6.5 days.

Table I. Characteristics of babies infected with *Klebsiella pneumoniae* (*N* = 26)

Mean (range) gestational age at birth (weeks)	33.4 (30 - 42)
Mothers known to be HIV-infected (*N* (%))	6 (22)
Delivered by caesarean section (*N* (%))	8 (31)
Mean weight at birth (g)	1 845
Normal birth weight (> 2 500 g) (*N* (%))	6 (23)
Low birth weight (1 500 - 2 500 g) (*N* (%))	11 (42)
Very low birth weight (1 000 - 1 500 g) (*N* (%))	7 (27)
Extremely low birth weight (< 1 000 g) (*N* (%))	2 (8)
Deaths (*N* (%))	22 (85)
Mean (range) age at death (days)	6.5 (1 - 13)

Table II. Common factors in 26 neonates infected with *K. pneumoniae*

	N (%)
Ventilated	10 (38)
Central venous line	26(100)
Intravenous fluids	26(100)
Penicillin/gentamicin on admission	26(100)
Piperacillin-tazobactam/amikacin for BSI	26(100)
Positive blood culture while on treatment	19(73)

BSI = bloodstream infection.

Table III. Possible causes of persistently positive blood cultures and investigations performed

Reason for persistent positive blood cultures	Investigation
Collection of pus	Review of clinical history
Colonised/infected gastro-intestinal tract	Stool/rectal swab culture Cultures of formula feeds in use Cultures from expressed breastmilk (when applicable)
Infected intravenous fluids or medication	Culture of all fluids in use Culture of all medication in use
Poor blood culture technique	Skin and environmental cultures

Table II shows the common factors identified. When blood cultures became positive with *K. pneumoniae*, antimicrobial treatment was changed to piperacillin-tazobactam and amikacin. This decision was directed by susceptibility test results. Despite this, 19 (73%) had 1 or more positive blood cultures with *K. pneumoniae* while on appropriate treatment. The susceptibility patterns of the subsequent isolates did not differ from the initial ones. Success with this antimicrobial regimen has been shown in infants infected with ESBL-producing *K. pneumoniae* infections.[12] We therefore based our outbreak investigations on the observation that blood cultures remained positive in patients on appropriate antimicrobial treatment. The possible reasons for this and the related

investigations are shown in Table III. No indications for pus collections were found in any of the patients. The outbreak klebsiella was not found in any of the stool or rectal swab cultures of the 6 babies still present at the time of the investigations. Although contaminated, formula feeds and expressed breastmilk did not grow the outbreak klebsiella. The possibility of a pseudo-epidemic was excluded because no klebsiellas were found on the skin of the babies or on environmental surfaces in the areas where blood was collected for culture. All intravenous fluids and medications were sterile with the exception of the Vamin-with-Glucose preparation. All 4 bottles in use grew *K. pneumoniae* with identical biochemical and antibiogram profile to the outbreak strain. Two bottles of the same preparation that had not been opened were sterile. On enquiry the staff volunteered that they had used these bottles for multiple dosing despite the fact that the instructions printed on the label of the vials advise to the contrary.

Discussion

Hospital-acquired or nosocomial infections are defined as infections that occur 48 hours or more after admission. Not all of these infections can be prevented. For instance, state-of-the-art measures to prevent infections after colonic surgery are not 100% effective. If such an infection occurs despite all efforts, it is per definition a hospital-acquired infection. Iatrogenic infections are hospital-acquired infections that could have been prevented if the health care professionals had applied optimal care.

Epidemiologists define an outbreak as an increase in the prevalence of a particular infection above its baseline prevalence. This definition applies to those hospital-acquired infections that cannot be prevented completely. However, it does not apply to iatrogenic infections as such infections are unacceptable in any health care setting. Therefore, an outbreak of iatrogenic infections is defined as two or more cases caused by the same genotype of a microbial species. This can be in one institution or in more than one institution when there is regular transfer of patients between those institutions.

We report on a cluster of infections involving *K. pneumoniae* in the neonatal unit of a regional hospital. The mortality rate within this group of patients was extremely high at 85%, and only comparable to the rate reported from Turkey.[5] Strictly speaking, we have not been able to prove that this was an outbreak as we have not been able to perform genotyping on the isolates. As cultures were performed in a routine laboratory setting over a period of 2 months, most of the isolates had been discarded. In addition, in KwaZulu-Natal there is no specialised infection control laboratory. Therefore, genotyping capacity is only available in research laboratories that are not set up to do this as a service. However, there is strong circumstantial evidence that this was an outbreak as we were able to identify a common source and were able to interrupt transmission by elimination of that source.

K. pneumoniae outbreaks are a major threat in high care and intensive care settings, especially in neonatal units. A review of the literature on such outbreaks in neonatal units lists 52 papers, the first from 1972. Analyses of most of these outbreaks do not reveal an obvious source.[5,16,14-16] However, most studies show a strong association with increased levels of colonisation of the neonates, in particular of the gut.[6,15,16] Increased colonisation is associated with suboptimal infection prevention strategies[3,6] and each day spent in the unit is associated with a reported 26% increase in colonisation.[16] Most reports associate bacterial access to the bloodstream with the presence of central venous lines.[6,16] Only one other study[10] reported on contaminated intravenous preparations as a source. Others[17] strengthen the initial observation by Price and Sleigh[1] that treatment of many patients in one unit with the same antimicrobial drugs is a risk factor for colonisation with a *K. pneumoniae* strain resistant to those drugs.

The current outbreak resulted cumulatively from a number of events. The practice of treating all patients with a gentamicin-containing antimicrobial regimen provided selective advantage for ESBL-producing *K. pneumoniae*. From 1992, when these strains emerged in South Africa, they were resistant to gentamicin.[18] This allowed colonisation of these neonates with this organism. MGMH was built as a district hospital but now serves a much larger area as regional hospital without much increase in space and staffing. Lack of space, understaffing and structural problems such as an insufficient number of wash hand basins, resulted in breaches of infection prevention strategies. Therefore, hands were the most likely vehicle of transmission of the bacteria to the rubber stoppers of the Vamin-with-Glucose vials. However, the role of cockroaches,[19] colonised mothers[6] and other unidentified factors cannot be fully excluded. Multiple sampling of the vials created capillary-sized channels in the colonised rubber stoppers as well as a vacuum. This facilitated the access of *K. pneumoniae* into the vials, where they found a rich culture medium in the form of glucose. Keeping the vials for prolonged periods of time allowed the bacteria to multiply. As a result, the neonates were regularly injected with a culture of Gram-negative bacteria creating recurrent episodes of endotoxaemia.

Closure of units in which an outbreak of bacterial infection is suspected has almost become a default response. While such action can be helpful, one needs to realise that this is in fact a form of cohort nursing. This assumes that isolation of infected from uninfected patients will stop the outbreak. That will only happen if the organism spreads from person to person without a common source. This report shows that closing a ward should not be done without full outbreak analysis.

deaths with similar events that occurred in the past at MGMH and other hospitals in the Durban region. This is a futile exercise as differentiation between incidental infections in neonates at risk and outbreaks of iatrogenic infection can only be done at the time of these infections and not in retrospect.

This outbreak highlights the deficiencies of our health care system in the area of hospital infection control and the urgent need for improved infection prevention. This should include a system of continuous monitoring. Such a system would allow for rapid detection of outbreaks. In addition, proper training of infection control officers through a diploma course offered at our universities needs to be implemented. The current in-service training and educational workshops are insufficient. Without trained specialists in the field of infection prevention, the essential continuous education of hospital staff will be suboptimal, as will be the response to possible outbreaks.

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