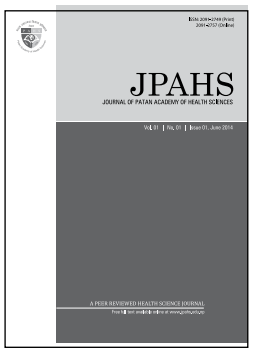

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Outbreak of Extended Spectrum Beta Lactamase Producing *Klebsiella* Species Causing Neonatal Sepsis at Patan Hospital in Nepal

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ABSTRACT

Introductions: *Klebsiella* sepsis is the most important nosocomial infection in neonates. The objectives of this study were to review an outbreak in a neonatal unit caused by *Klebsiella* species, to identify the source of the infections, and to identify infection control measures for eradication and prevention of these infections.

Methods: The case notes and investigation reports of all sepsis cases admitted in neonatal units of Patan hospital from July to December 2011 caused by *Klebsiella* species were retrospectively reviewed. The demographic profile, risk factors along with clinical features and management of sepsis were reviewed.

Results: Twenty three out of 37 neonatal blood cultures grew *Klebsiella* species. Thirty one were *K. pneumoniae* and six *K. oxytoca*. Seventeen of the 31 (55%) *K. pneumoniae* isolates were multidrug resistant and extended spectrum beta lactamase producers. Eighteen of 23 (78%) neonates with *Klebsiella* sepsis died. After extensive cleaning methods and identifying an intermittently leaking roof in one of the nurseries below a vescicovaginal fistula room of gynecological ward above, the infection outbreak was finally controlled.

Conclusions: Infections with extended spectrum beta lactamase producing *Klebsiella spp.* are a threat in neonatal units because of limited treatment options for these multidrug resistant organisms. Identification of the source and control of the outbreak can be a challenge.

Keywords: extended spectrum beta lacatamase, *Klebsiella*, multi drug resistant, neonates

Plain Language Summary

The study was done to review an outbreak caused by *Klebsiella* species, to identify the source of the infections along with infection control measures for eradication and prevention of these infections in neonate unit. Identification of the source and eradication of the outbreak of *Klebsiella* species can be a challenge. Hand washing remains one of the most important methods to prevent cross infections and nosocomial infections.

INTRODUCTIONS

Klebsiella pneumoniae is the most common pathogen among the *Klebsiella* species,[1] and there has been an increase in the incidence of nosocomial infections caused by *K. pneumoniae* strains producing extended-spectrum beta-lactamases (ESBL).[2-4] The widespread use of broad-spectrum antibiotic in intensive care units (ICU) favors development of multidrug resistant (MDR) organism.[5,6]

There was an outbreak of ESBL producing MDR *Klebsiella* species in a neonatal unit of Patan hospital. All the neonates infected with ESBL *Klebsiella* had similar signs and symptoms. The retrospective review of charts was done to identify the source of infections, measures to control and prevent such incident.

METHODS

This cross sectional, descriptive study was performed in three sites of neonatal units: nurseries (clean and septic), neonatal intensive care unit (NICU) and pediatric intensive care unit (PICU) of Patan Hospital, a tertiary care teaching hospital of Patan Academy of Health Sciences. Approval was taken from Institutional Review Committee. Neonates without any risk factors for sepsis are admitted to the clean nursery, while neonates with risk factors for sepsis, and those who have positive blood, urine or stool cultures, diarrhoea, conjunctivitis or skin infections are kept in a 'septic nursery'. Among the neonates requiring ICU care, the inborn babies (delivered in Patan Hospital) are admitted to NICU while the outborn neonates (born outside Patan Hospital) are admitted to PICU. The case notes of all babies infected with *Klebsiella* during the six month duration (July to December 2011) were reviewed. Clinical and demographic data for each patient were recorded. The maternal case-notes were reviewed to evaluate maternal risk factors for the infection like history of premature rupture of membrane, foul smelling liquor and maternal fever.

While reviewing the maternal case-notes, we looked for antenatal risk factors such as history of premature rupture of membrane (PROM), maternal fever, number of per vaginum examination and use of antepartum antibiotics.

The environmental sampling included laryngoscope blades, ventilator, stethoscopes, equipment trolleys, incubators, central lines, tip of endotracheal tubes, suction tubes, tap water, floor and door handles. These environmental cultures were obtained fortnightly and sent to microbiology laboratory of Patan hospital. Hand swabs and rectal swabs from all the staffs working in the neonatal units, culture of purified water and disinfectants, and swabs from the air conditioning unit were also sent. All neonatal nurseries and ICUs were inspected in detail for any source of infection such as leaking roofs, damp walls and plumbing defects.

Klebsiella isolates from cases not responding to antimicrobial therapy reported as susceptible were also sent to the Microbiology Unit at Canterbury Health Laboratories (CHL), Christchurch, New Zealand.

The isolates were also screened for the production of ESBL by the double disk diffusion procedure. The presence of *Klebsiella* producing carbapenamases (KPC) and metallo-β-lactamase (MBL) enzymes were tested by the inhibition of the enzyme using boronic acid for KPC and dipicolinic acid for MBL.[7] The presence of a carbapenemase was confirmed using a multiplex PCR[8] and DNA sequencing on a representation of each *K. pneumonia* antibiogram pattern; four patterns were seen. Microsoft excel 2010 was used fro descriptive analysis.

RESULTS

Twenty three neonates were included. All 23 neonates had hypotension, respiratory failure, acute renal failure, and disseminated intravascular coagulation with Multiorgan Dysfunction Syndrome (MODS).

Eighteen out of 23 neonates (78%) died. Out of 23 neonates, sixteen (70%) were males and seven (30%) were females. Twenty out of 23 (87%) were premature and low birth weight.

Fifteen out of 23 (65%) neonates were delivered by normal vaginal delivery and eight out of 23 (35 %) were born through caesarean section. Of the twenty-three babies, 15 were admitted in NICU, five in PICU, two in the septic nursery and one in the clean nursery. Out of 23 neonates, ten (44%) neonates acquired *Klebsiella* infection in NICU, seven (30%) in septic nursery, five (22%) in PICU and one (4%) acquired in clean nursery. Out of 23 neonates, 18 needed mechanical ventilation and only two survived. Eight infants had umbilical venous catheter and five had umbilical arterial catheter inserted. Out of thirteen umbilical catheters, eleven were kept for more than three days. Meningitis was present in five neonates and *Klebsiella pneumoniae* was isolated from cerebrospinal fluid (CSF) in one.

There were no associated maternal risk factors for neonatal sepsis in these babies The first blood culture taken within 72 hours of birth were negative in all neonates.

Out of thirty-seven *Klebsiella* isolates, 23 were from blood, eight were from the endotracheal tube-tip, three from urine, two from umbilical catheters and one from CSF.

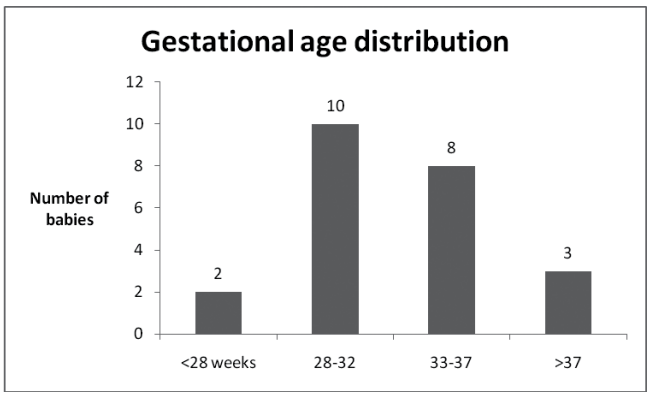

Figure 1. Frequency distribution of neonates with sepsis across different gestational age (n=23)

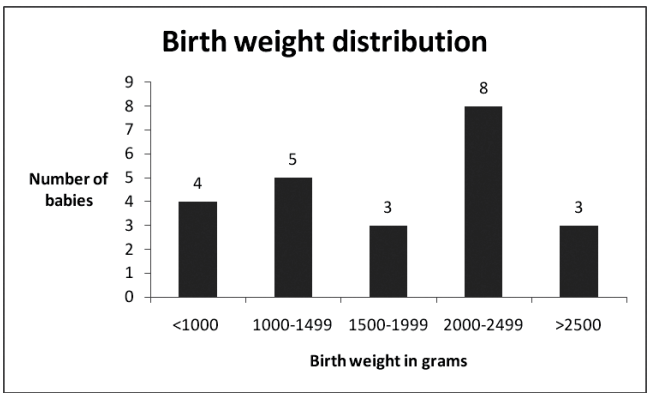

Figure 2. Frequency distribution of neonates with sepsis across different birth weights (n=23)

Table 1. Culture and sensitivity pattern of Klebsiella isolates in twenty-three neonates

Antibiotics	1	2	3	4	5	6.	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Augmentin.	-	-	-	-	-	-	-	-	-	R	-	-	-	R	-	-	-	R	R	R	R	R	-
Ampicillin.	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Amikacin	S	S	I	S	R	R	S	R	S	R	R	S	S	R	S	R	R	R	R	R	R	R	R
Cefepime.	-	-	-	-	-	R	-	-	-	R	-	S	S	R	-	-	-	R	R	R	R	R	-
C-S	-	-	I	S	R	R	R	R	R	R	R	S	R	R	-	R	R	R	R	R	R	R	R
Cefoxitin.	-	-	-	I	-	R	-	-	-	R	-	-	-	R	-		-	R	R	R	R	R	-
Cefotaxim	R	R	R	R	R	S	R	R	R	R	R	S	S	R	R	R	R	R	R	R	R	R	R
Ceftriaxone.	-	-	-	-	-	-	-	-	-	R	-	-	-	R	-	-	-	R	R	R	R	R	-
Chloram	R	R	R	S	R	S	S	S	S	R	R	S	S	R	S	R	R	R	R	R	R	R	S
Cefuroxime.	-	-	-	-	-	-	-	-	-	R	-	-	-	R	-	-	-	R	R	R	R	R	-
Cipro.	R	R	R	R	R	S	R	R	R	R	R	S	S	R	R	R	R	R	R	R	R	R	R
CTZ.	R	R	R	R	R	R	R	R	R	R	R	S	S	R	S	R	R	R	R	R	R	R	R
Colistin.	-	-	-	-	-	S	-	-	-	S	-	S	S	S	S	S	S	S	R	S	S	S	S
Etrapenem.	-	-	-	-	-	R	-	-	-	R	-	-	-	R	-	-	-	R	R	R	R	R	-
Gentamicin.	R	S	I	S	R	S	R	R	R	R	R	S	S	R	R	R	R	R	R	R	R	R	R
Imipenem.	S	S	S	S	R	R	S	R	S	I	R	S	S	I	R	S	R	R	I	I	I	I	S
Meropenem.	S	S	S	S	S	S	S	S	S	I	S	S	S	R	S	S	S	R	I	I	I	I	S
Nalidixic acid	R	R	R	R	R	S	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Nitro	S	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Ofloxacin	S	R	R	R	R	S	S	S	S	R	R	S	S	R	R	R	R	R	R	R	R	R	S
Pip/Taz	-	-	R	S	R	R	R	R	-	R	R	R	R	R	-	R	R	R	R	R	R	R	R
Tazocin.	-	-	-	-	-	R	-	-	-	R	-	-	-	R	-	-	-	R	R	R	R	R	-
Tobramycin.	-	-	-	-	-	R	-	-	-	R	-	-	-	R	-	-	-	R	R	R	R	R	-
Species	KPNE	KPNE	KPNE	KPNE	KPNE	KPNE	KPNE	KPNE	KPNE	KPNE	KPNE	KOXY	KOXY	KPNE	KOXY	KPNE	KPNE	KPNE	KPNE	KPNE	KPNE	KPNE	KPNE
ESBL screen	-	-	-	-	P	-	-	-	-	P	P	-	-	P	-	P	P	P	P	P	P	P	-
MBL PCR										NDM-1				NDM-1				NDM-1		NDM-1	-	NDM-1	
Specimen	Urine	Blood	Blood ET UVC	Blood	Blood ET	Blood	Blood	Blood	Blood	Blood Urine	Blood UVC	Blood ET	Blood	Blood	Blood ET	Blood Urine	CSF	Blood	Blood	Blood	Blood ET	Blood	Blood

Out of twenty-three *Klebsiella* isolates in blood, two neonates had repeated positive blood cultures; out of which four were from one neonate and two from another neonate. Out of eight *Klebsiella* isolates in endotracheal tube-tip, in two neonates, it was isolated on two different occasions. In those who had positive isolates in urine, umbilical catheter and endotracheal tube-tip, the same organisms were also isolated in blood cultures. The infant who had positive CSF culture for *Klebsiella* had negative blood cultures.

Thirty-one were identified as *K. pneumoniae* and six were *K. oxytoca*. Infection with *K. pneumoniae* was associated with disseminated intravascular coagulation (DIC) and refractory hypotension. Seventeen out of 18 neonates who died had *K. pneumoniae*, and one had *K. oxytoca*.

Seventeen out of 37 *K.* pneumoniae isolates were MDR and ESBL producers. They were resistant to all the first line, ampicillin and amikacin and second line drugs, cefotaxim/chloramphenicol and ofloxacin, and

some were resistant to third line drugs, meropenem/ imipenem/piperacillin-tazobactum/cefoperazone-sulbactum and colistin used in our neonatal units. Twentythree isolates were sent to CHL, New Zealand for microbiological confirmation and subtyping. Nine out of eleven isolates were confirmed as *K. pneumoniae* and two as *K. oxytoca*. All nine *K. pneumoniae* isolates were confirmed as MDR and ESBL producers. The *K. pneumoniae* isolates showed intermediate resistance to meropenem and imipenem except in one which showed complete resistance to meropenem. These *Klebsiella* isolates were only sensitive to colistin. Out of these nine, seven *Klebsiella pneumoniae* isolates were reported sensitive to carbapenems in Patan Hospital. Out of the five neonates who survived, three had received colistin. The details of culture and sensitivity patterns along with subtyping of *Klebsiella* isolates in twenty three neonates are shown in Table 1.

The subtyping of *Klebsiella* isolates were done at CHL, New Zealand and the strain was found to be NDM-1 (New Delhi Metallo-beta-lactamase) strain in five neonates which was resistant to all beta lactams.

Klebsiella was isolated in various environmental cultures such as laryngoscope blades, suction jar, jar containing purified water, tap water, and a hand of health care worker. Additionally, swab from the air conditioner also grew *Klebsiella* species. None of these environmental isolates were MDR or ESBL. Rectal swab of all health care workers in our neonatal units were found to be negative for ESBL producing *Klebsiella* species.

An intermittent leaking roof with a toilet drain pipe was noted in one of the nurseries situated below the vescicovaginal fistula (VVF) room of Gynecology ward. Further investigation revealed that MDR *Klebsiella* were isolated in the urine specimens of patients in the VVF room and in the surface cultures of the room.

DISCUSSIONS

Eighteen out of 23 neonates died in this study. Thirty-seven *Klebsiella* species were isolated in six months duration. Out of 37 isolates, 17 were extended spectrum beta lactamase producers and multidrug resistant *Klebsiella* which were resistant to all first and second line antibiotics.

Several outbreaks of infection caused by *K. pneumoniae* isolates that are simultaneously resistant to broad-spectrum cephalosporins and aminoglycosides have been widely reported.[9-12] *Klebsiella* can cause serious infections such as bacteremia, pneumonia, and urinary tract and soft tissue infections, particularly in immunosuppressed and hospitalized patients. Bacteremia and meningitis are common in pediatric patients, especially those in NICUs.[13,14] These infections are frequently caused by multidrug-resistant strains and have a high mortality rate.[15] Low birth weight, mechanical ventilation, prolonged hospitalization, use of third-generation cephalosporins, and invasive procedures are important risk factors for the emergence of nosocomial infections in intensive care units and for high mortality.[16,17] More than 50% of the neonates affected in this study had low birth weights and were premature. Out of twenty-three, 18 required mechanical ventilation and eight had central (umbilical) venous or arterial catheters. *Klebsiella* was isolated in eight out of 18 endotracheal tube-tip cultures and six out of eight neonates died who grew *Klebsiella* in their endotracheal tip. Two out of 13 umbilical lines grew *Klebsiella* and both neonates died. *Klebsiella* infections may spread rapidly from medical devices, soap and disinfectants, blood products, and the hands of hospital staff.[13,18]

In view of *Klebsiella* outbreak of from contaminated disinfectant in a neonatal and pediatric intensive-care unit,[13] we tested all disinfectant solutions which were used in our neonatal units. All the disinfectants were equally effective for *Klebsiella*. ESBL *Klebsiella* has also been liked to artificial nails.[19] Melek Ayan et al[20] reported *Klebsiella* outbreaks in premature neonates with intravenous catheters, mechanical ventilation or both, and high mortality rate (76.7%) was noted. In this study, more than half of the patients had low birth weight, were premature, or underwent mechanical ventilation. Approximately three-fourths of the patients died. In our series, 87% of the babies with *Klebsiella* sepsis were premature and low birth weight while the mortality rate of 78% is almost comparable to the Melek Ayan's study. More than half of the strains in the study by Melek Ayan were resistant to many beta-lactam antibiotics, amikacin, and trimethoprim/sulfamethoxazole. Resistance to multiple antibiotics, mainly to broad-spectrum beta-lactam antibiotics was observed, particularly in *Klebsiella pneumoniae* isolates. Similarly, resistance to expanded-spectrum cephalosporins is reported for most of the outbreak strains of *Klebsiella* species.[9,15,21] In our study, *Klebsiella pneumoniae* isolates were resistant to all the beta lactams.

There is increasing evidence of the emergence of carbapenem resistant isolates.[22,23] In the study by Hanna Sidjabat et al[24] carbapenem resistance in *Klebsiella pneumoniae* due to NDM-1 beta lactamase was demonstrated. Similarly, study done by Dongeun Young et al[24] also characterized NDM-1 gene and a novel erythromycin esterase gene on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14

from India. Comparing our study with them, six out of eleven patients who were ESBL *K. pneumoniae* were intermediate, two were resistant and the rest were sensitive to meropenem. Regarding imipenem, six were intermediate, four were resistant and only one was sensitive. Carbapenem resistant organisms were of NDM-1 strain. Timothy R Walsh et al[25] found the dissemination of NDM-1 positive bacteria in New Delhi environment (water supply and sewage effluent samples). Similarly, Mariana Castanheira et al[26] found early dissemination of NDM-1 producing enterobacteriaceae in Indian hospitals. Although we cannot extrapolate these data for our country, with emerging carbapenem resistant NDM-1 strain *Klebsiella pneumoniae*, there is a need for a broad environmental survey.

In addition to surveillance cultures, various infection control strategies were implemented. Revised cleaning policy was added to our infection control protocol. 1% virkon was used for cleaning equipments after testing its efficacy to inhibit *Klebsiella* species in-vitro. After each new MDR *Klebsiella* infection, surface cleaning, high dusting, and fumigation of neonatal units were done. The routine chlorination of water sources was inspected. Purified water was used in humidifiers of ventilators. Disposable paper-towels were used instead of cloth towels in all neonatal units. Staffs and visitor gowns were changed every morning. All visitors were advised to use gowns hung in the designated pegs. All visitors were informed about hand washing policy. Air conditioner was cleaned. Disposable tubings for ventilators were used. Discarding of infected equipments was done. Cleaning protocols for ventilators were implemented. The importance of hand washing was emphasized to all the staffs working in neonatal units. Bedside cleansing solution Microshield (chlorhexidine) was used in all neonatal units. Universal decontamination using daily chlorhexidine bath for all neonates was implemented. The nursery with the leaking roof was eventually closed and was shifted to another room.

After implementation of these infection control measures, we have now reduced the infection with MDR and ESBL *Klebsiella* species. Hence, we need to do prospective studies to conclude that how useful these measures are to prevent the outbreak.

According to our hospital policy, the microbiology laboratory does test the antimicrobial sensitivity on surface swabs culture. Therefore, we were unable to prove that the leaking roof was indeed the source of the outbreak. However, closing this nursery below the VVF room finally eradicated the infection outbreak. In addition, some patients who were admitted in the VVF room also had similar *Klebsiella* infection to the infants in the nursery, which strengthens the speculation. The main limitation of our study is that, this being a retrospective study, some of the information were missing on the medical notes especially information regarding the risk factors for sepsis.-

CONCLUSIONS

Infections with ESBL *Klebsiella pneumoniae* was a major cause of morbidiry and mortality among neonates in Patan Hospital during the outbreak with the limited treatment options for MDR organisms**.** The emergence of ESBL and carbapanem resistant *Klebsiella pneumonia* pose a great challenge for clinicians.

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