Outbreak of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* and multidrug-resistant *Acinetobacter baumannii* in the neonatal intensive care unit, Dr Soetomo General Hospital, Indonesia: A case series

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Introduction

Nosocomial outbreaks caused by Extended-Spectrum Beta-Lactamase (ESBL) producing *Klebsiella pneumoniae* strains and Multi-Drug-Resistant (MDR) *Acinetobacter baumannii* have been described by many authors but never from our region. *Klebsiella pneumoniae* is the commonest cause of Neonatal Intensive Care Unit (NICU) outbreaks and potentially causes morbidity and mortality as a hospital-acquired pathogen[1]. The newborn immune system is still immature, making it more prone to infections as well as Low Birth Weight (LBW), and the frequent use of invasive devices and antibiotics[2]. A study from Bosnia found a 35.3% neonatal mortality rate (NMR) from MDR *Acinetobacter baumannii*, while some studies reported NMRs between 22% and 83%[3]. We report an outbreak of ESBL producing *Klebsiella pneumoniae* strains concurrent with MDR *Acinetobacter baumannii* in the NICU of Dr Soetomo General Hospital, Indonesia. We describe the Hospital-Acquired Infection (HAI) caused by *Klebsiella pneumoniae* and *Acinetobacter baumannii* and the control measure from the NICU outbreak to interrupt the chain of transmission.

Case Reports

Case 1: A baby boy was delivered at the 34th week of gestation by caesarean section due to severe preeclampsia with no maternal risk factors for sepsis during pregnancy. Born on 1st April 2017 with LBW (1700g), physical examination showed tachypnoea and increased work of breathing. The baby was suspected of early-onset sepsis (EOS). He was admitted to the NICU for nasal continuous positive airway pressure (CPAP). After initial resuscitation, injections of ampicillin and gentamicin were given as empirical antibiotics. On 2nd April he developed fever (38°C), severe apnoea, and desaturated. Physical evaluation revealed a rash, purple lesions, sclerema on the upper and lower extremities and a capillary refill time (CRT) of 5 seconds. Three days later, baby's condition worsened and he was switched to meropenem injection before the blood culture result was received but unfortunately, he passed away shortly thereafter. Blood culture was performed at two days of age (3rd April) and the result, which was received on 5th April, yielded a growth of ESBL producing *Klebsiella pneumoniae* susceptible only to levofloxacin and trimethoprim-sulfamethoxazole.

***Case 2*:** A baby girl was born spontaneously on 28th March 2017 with LBW (1500g) at the 30th week of gestation with premature rupture of membrane (PROM) of 14 hours. She received ampicillin and gentamicin as empirical treatment of suspected EOS for three days until 31st March. The first blood culture performed after admission did not grow any organisms. On 1st April she had hyperbilirubinaemia and received phototherapy for two days. On 3rd April, at the age of 6 days, she had a temperature of 38.5 °C, an apnoea episode, multiple rashes and purple lesions on the lower extremities, nose and upper lip, bullae on the right upper extremity, as well as sclerema on the upper and lower extremities (Figure 1). After initial resuscitation, she received meropenem injection, and the second blood culture was performed on 4th April. Her condition worsened a day after meropenem injection and she passed away shortly thereafter. Blood and bullae' swab culture results, which were received on 6th April, revealed growth of MDR *Acinetobacter baumannii* sensitive to cefoperazone/ sulbactam.

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Figure 1: ***showing multiple rashes and purple lesions***

Case 3: A baby girl delivered spontaneously at the 34th week of gestation on April 1st 2017. The baby was born with LBW (1700g) with PROM for more than 18 hours. Several hours post-partum, she developed tachypnoea, retraction of the chest wall, and grunting. She was suspected of EOS, treated with nasal CPAP, and was given ampicillin and gentamicin as empirical antibiotics. On the third day of age on April 4th, she developed fever (38.1°C), worsened grunting, nasal flaring, and lethargy. The next day her condition deteriorated. Physical examination showed pale skin, haematin via orogastric tube, sclerema on upper and lower extremities and a CRT of 5 seconds. We discontinued the previous antibiotic used and gave empirical treatment with meropenem and amikacin. Blood culture was taken on April 5th and the result, which was received on 7th April, showed ESBL producing *Klebsiella pneumoniae* susceptible to levofloxacin and trimethoprim-sulfamethoxazole. Levofloxacin was immediately administered. The fever, haematin and apnoea abated but abdominal distention and cholestasis developed. The second blood culture was taken on 12th April and revealed ESBL producing *Klebsiella pneumoniae* susceptible to fosfomycin and trimethoprim-sulfamethoxazole. She was then treated with trimethoprim-sulfamethoxazole and her condition improved.

Case 4*:* A LBW (1550g) newborn baby boy was delivered at the 34th week of gestation on 3rd April 2017 by caesarean section with a history of maternal hypothyroidism, intrauterine growth restriction (IUGR) and flat fetal non stress test. He was suspected of EOS and was treated with nasal CPAP and was given empirical antibiotics, ampicillin and gentamicin. On the fourth day, April 5th, his condition worsened and he developed grunting, nasal flaring and lethargy. His complete blood count revealed thrombocytopenia of 35x10^3/µL, with normal leucocyte and haemoglobin counts. He was given meropenem, amikacin, mechanical ventilation and supportive treatment. His condition deteriorated a day later and physical examination showed pale skin, haematin via orogastric tube (Figure 2), sclerema on upper and lower extremities, severe lethargy and a CRT of 4 seconds. Mother's Apt test was positive. His blood culture was taken on 5th April and the result, received on 7th April, showed ESBL producing *Klebsiella pneumoniae* susceptible to levofloxacin and trimethoprim-sulfamethoxazole. Levofloxacin was immediately given but his condition worsened and he died on the seventh day of age (8th April).

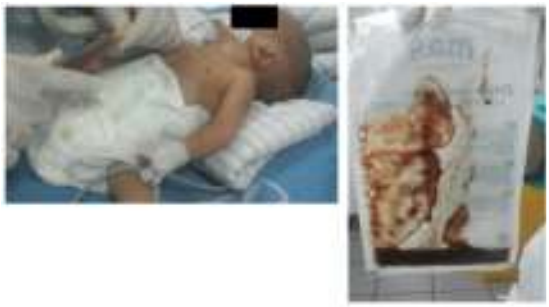

Figure 2: ***showing haematin via orogastric tube***

Case 5: A newborn baby boy was delivered spontaneously at the 31st week of gestation on 15th April with a very low birth weight (1350g) by a mother who had PROM for more than 72 hours. Shortly after birth, he was tachypnoeic, with chest wall indrawing, and grunting. A routine blood count examination showed no abnormality. He was suspected of EOS, treated with nasal CPAP and was given meropenem and amikacin. On the fifth day, 20th April, his condition worsened, as seen by his grunting, nasal flaring and lethargy, and multiple petechiae on the chest and abdomen. His blood count revealed a leucopenia of 1.22 x 10^3/µL and thrombocytopenia of 36 x 10^3/µL. He was immediately supported with

mechanical ventilation and the antibiotic changed to intravenous levofloxacin. His condition deteriorated after the injection and the baby died. His blood culture was taken on 20th April and the result, received on 23rd April, showed the MDR type of *Acinetobacter baumannii*.

Case 6*:* A newborn baby girl was referred from another hospital due to pneumonia and suspected of sepsis at age of 19 days on 31st March. She was a term baby with a birth weight of 2950g and had been treated with meropenem injection and mechanical ventilation at the previous hospital for one week. During the outbreak, we changed her antibiotics to levofloxacin injection. She developed fever (39-40°C), grunting and nasal flaring at the age of 29 days. The first blood culture taken on admission was sterile but the second culture on 20th April revealed an MDR type of *Acinetobacter baumannii*. Sputum culture taken on 20th April from the endotracheal tube aspirate also revealed MDR type *Acinetobacter baumannii*. Consultation with the tropical infection division suggested changing antibiotics to cefoperazone. sulbactam and vancomycin. After 45 days of hospitalization, her condition worsened and she passed away.

Discussion

An outbreak is defined as two or more sterile site isolates of the same species, with the same antibiogram, from different babies (not twins) within the space of 2 weeks[4]. NICU outbreaks represent 37.9% of all ICU outbreaks and Enterobacteriaceae account for 52.9% of NICU outbreaks[5]. Our outbreak happened for two weeks. The baseline characteristics in our outbreak are shown in table 1.

Table 1

Baseline character of outbreak cases (n=6)

Characteristic	Number
Sex	
Male	03
Female	03
Birth weight	
1000 - < 1500g	01
1500 -< 2500g	04
>2500g	01
Place of labour	
Inside hospital	05
Outside hospital	01
Type of labour	
Vaginal delivery	04
Caesarean section	02
Suspicious of chorioamnionitis	04

Enterobacteriaceae are normal stool flora, transmitted at birth or acquired in the nursery. The longer the hospital stay, the higher the risk for a newborn to acquire the flora[6-8]. Enterobacteriaceae are usually transmitted hand-to-hand[8]. Major risk factors associated with nosocomial infection were VLBW, lower gestational age and central venous catheter (CVC)[2,6,7]. Our case series found 5 out of the 6 neonates were LBW and had gestational week 34th or less, and 5 out of the 6 neonates had a central venous catheter inserted before the development of sepsis. Intravenous catheters and continuous infusion of lipid mixtures are known to play a role in the genesis of nosocomial infection. The catheter material predisposes to bacterial coloniation whenever placed inside the vein[2,7]. A vulnerable host, premature and low birth weight infants need a more invasive therapeutic approach such as mechanical ventilation, length of stay, and empiric antimicrobial treatment. Inadequate infant bed spacing, high cot occupancy rates, and low nurse-to-infant ratios promote errors and reduce the proper management for infection prevention[6]. Nasal CPAP and caesarean section were reported risk factors for Methicillin Resistant Staphylococcus Aureus (MRSA) acquirement[5,6].

We formed a team of Neonatologist, Hospital Director, Head of Emergency Department, Microbiologist, Infection Prevention Control, Antimicrobial Resistance Control Team, Environmental Health Team, Infrastructure Hospital Team, Head Nurse, NICU Staff, and Pharmacist as soon as the outbreak happened. Investigation found low compliance on hand hygiene of NICU staff (<70%). We re-educated and monitored hand hygiene via direct supervision and CCTV. It should lead to >95% compliance[5,6].

We performed throat swabs and microbiological cultures of health personnel. There were normal flora on all cultures. Understaffing and overcrowding have been repeatedly described as risk factors for increased infection rates and the occurrence of outbreaks[9,10]. The lack of an ideal nurse-to-infant ratio is still an issue in our NICU. The nurse-to-infant ratio in our NICU was 4:1 when a 1:1 nurse-to-infant ratio is required for neonatal intensive care qualified nurses and 2:1 for the high-dependency unit[9,10]. Outbreak control was achieved by reducing infant beds or closing the admissions to improve spacing and nurse-to-infant ratios. It was necessary as 16.3% NICU outbreaks last for about 14 days[5,11].

The NICU environmental quality monitoring in March revealed that an air germ number of 296 CFU/m^3 (more than 200 CFU/m^3) and temperature of 26.7°C

(more than 23°C) do not meet the criteria of indoor air condition. We did a general room cleaning and continuing air culture every 3 months. In July, the air germ number improved to 52 CFU/m^3 but the temperature was 23.5°C, still above the upper limit standard. Microbiological cultures of all surfaces and devices found *Pseudomonas spp*. in two stethoscopes, *Escherichia coli* in incubator bed, *gram negative cocci* in suctioning devices, *Staphylococcus epidermidis* in ventilator devices, breast milk heater, sink, infusion handle, and *Streptococcus spp.* in one incubator bed and on phone handle. To stop the transmission, daily cleaning using chlorine-based solution every week, incubator and surface tools cleaning using chlorhexidine-based solution every day, maintained incubator standard turnover every week, a general incubator cleaning 24 hours after been used and strict monitoring of the ETT suctioning procedure. We also provide a stethoscope, height gauge, gloves, and wall suction unit for each patient; a weight and diaper scale for every room. We added more air and oxygen outlets, provided exhaustion, a new separate isolation room, a closed toilet inside NICU surgery room, and improved the air conditioner system.

A separate group of nurses and doctors should look after infected babies, supported with an adequate supply of protective equipment[6,7,9]. Isolating affected patients is a common method to prevent the disease spread, such as contact precautions for the MDR[6,9]. Our team had developed a new approach to the management of neonates with suspected or proven EOS and commitment to sustainable antimicrobial sensitivity pattern: ampicillin and gentamicin for first-line antibiotic choice, cefoperazone-sulbactam and amikacin as a second line, and meropenem as a third line. Regular surveillance of antibiotic susceptibility patterns is very important to guide the clinician in choosing empirical or directed therapy of infected patients.

Conclusion

Although this outbreak duration was short, there was a high mortality. HAIs, major risk factors in NICUs, are difficult to eliminate. Multifactorial interventions that improve hygiene and safe procedure have been shown to be able to lower the incidence of HAIs[7,12,13,14]. We now have a NICU with adequate space, standardized room and equipment, a new approach to neonatal management with suspected or proven EOS, new antibiotic choice guidelines, and sustainable antimicrobial sensitivity patterns. In the following month in May, we only had one sepsis case and none in June.

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