

## Neonatal Sepsis Outbreak due to Carbapenamase Producing *Klebsiella pneumoniae*

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### Abstract

Neonatal sepsis forms the most common cause of mortality in the first month of life. *Klebsiella* species are the most commonly implicated pathogen in neonatal sepsis and the emergence of carbapenam-resistant *Klebsiella pneumoniae* (CPKP) has resulted in high morbidity and mortality. The study was undertaken in the department of Microbiology and Infection Prevention and Control of Alman General Hospital, Saudi Arabia when in the month of January 2018, a sudden rise in positive blood cultures due to phenotypically identical *K. pneumoniae* from patient samples received from neonatal intensive care unit (NICU) raised an alarm. Out of 19 blood culture samples obtained from neonates, 5 were positive for *K. pneumoniae* and they were positive for carbapenamase production when tested by modified Hodge test. Environmental sampling revealed similar growth from door handle of clean linen cabinet within the NICU. Infection prevention and control breach by healthcare providers was identified as the most critical cause for this outbreak in NICU. The study focuses on the prevention of hospital outbreak by stringent infection control measures and judicious use of antibiotics in healthcare settings.

**Keywords:** Carbapenamase; *Klebsiella pneumoniae*; Outbreak; Blood Cultures; Neonatal Intensive Care Unit

### Introduction

*Klebsiella pneumoniae* is a well recognized cause of neonatal infections with case fatality rate ranging from 18 to 68% [1]. Infants, particularly those with a low gestational age and low birth weight, are at increased risk for developing healthcare associated infections in neonatal intensive care unit (NICU). Neonatal infections acquired in hospital increases the length of hospital stay, exposes patients to central venous catheters, mechanical ventilation, total parenteral nutrition, and exposure to broad spectrum antimicrobials. Carbapenam-resistant *K. pneumoniae* (CPKP) sepsis has serious implications because of the limited choices of antibiotics available for therapy, resulting in high morbidity and mortality [1,2]. Environmental contamination serves as a reservoir for this pathogen, encouraging cross infections through equipments and hands of health care providers. Hence, the most important factor in hospital outbreaks is poor adherence to infection control policies and practices [3].

### Materials and Methods

The study was undertaken in the department of Microbiology and Infection Prevention and Control of Alman General Hospital, Al Khobar located in the Eastern Province of Saudi Arabia. During the month of January 2018, a sudden rise in positive blood cultures from NICU patients, due to phenotypically identical *K. pneumoniae* raised an alarm. By this time, 5 phenotypically identical *K. pneumoniae* had been

isolated from 5 patient's blood culture samples. Isolates were identified by standard microbiological methods [4]. The antibiotic susceptibility testing was done by Kirby-Bauer disc diffusion test according to Clinical and Laboratory Standards Institute, 2017 guidelines [5]. Antibiotics tested include, Amoxicillin (10 µg), amoxicillin clavulanate (20/10 µg), cephalexin (30 µg), cefuroxime (30 µg), cefotaxime (30 µg), ceftriaxone (30 µg), ceftazidime (30 µg), cotrimoxazole (30 µg), gentamicin (10 µg), amikacin (30 µg), ciprofloxacin (5 µg), piperacillin/tazobactam (100/10 µg), meropenem (10 µg), imipenem (10 µg) and colistin (10 µg). In addition, E-test strip was used to ascertain the minimum inhibitory concentration (MIC) for meropenem, imipenem and colistin. The strains were tested for carbapenamase production by Modified Hodge test and presence of a cloverleaf shaped zone of inhibition due to carbapenamase production by the test strains was considered positive after overnight aerobic incubation at 37°C [5].

### Outbreak investigation

To trace out the possible source of this outbreak, specimens were collected from varied possible sources of infection including high touch surfaces, samples from instruments, medical equipments, hands of nursing staff and physicians. All the samples were collected in brain heart infusion broth and sub cultured after overnight incubation on MacConkey agar and sheep blood agar and checked for the growth of *K. pneumoniae* having similar biochemical profile and antibiogram pattern to patient samples.

### Results and Discussion

Out of 19 blood culture samples obtained from neonates, 5 (26%) were positive for *K. pneumoniae*. Neonates with positive blood culture samples for CPKP were also harboring the same isolate within their gastrointestinal tract as evident by rectal swab culture. Following this sudden rise in the number of CPKP isolates, all neonates admitted within the NICU underwent baseline screening and 3 more patients were found to be asymptotically colonized in their gastrointestinal tract, urine and or umbilical swab. Hence in total, 8 patients were infected and or colonized with CPKP. The index patient was a preterm baby with multiple congenital anomalies including tracheo-oesophageal fistula (TEF), cleft lip and imperforate anus. This patient underwent surgical repair of TEF and a colostomy tube was created for imperforate anus. This patient could be the most probable primary source for the CPKP outbreak in NICU. Apart from this, environmental sampling revealed CPKP isolate from the handle of clean linen cabinet within the linen storage room. All patient and environmental isolates produced similar biochemical reactions and similar antibiogram pattern inferring that they belonged to a single strain. All CPKP isolates were showing resistance to all tested antimicrobials and the only active antimicrobial was colistin.

The most common underlying risk factor among the infected neonates was prematurity and low birth weight. Infected neonates birth weight ranged from 815 g to 1,800 g; and was preterm with gestational age ranging from 25 weeks to 36 weeks. Male to female ratio was 4:1. All the neonates had a history of empiric antibiotic therapy with a third generation cephalosporin (cefotaxime or ceftazidime) and amoxicillin. All infected neonates presented with tachypnea, poor feeding, lethargy, cyanosis and jaundice. One of the neonates was diagnosed with hydro anencephaly. All the 5 blood culture positive neonates were with ventilator support because of acute respiratory distress and 3 of these patients had long lines. Laboratory parameters revealed high C-reactive protein levels among all 5 neonates. Based on the culture and sensitivity report on blood culture isolates, the empiric treatment was reviewed with the multidisciplinary team comprising neonatologists, clinical microbiologists, clinical pharmacists and infection control specialists to high dose colistin, meropenem and gentamicin. In spite of early review of antimicrobial therapy based on culture and susceptibility test results, one neonate succumbed to infection and the remaining 4 neonates with evident blood stream infection responded to treatment. Three neonates who were found to be colonized at baseline sites were not treated with antimicrobial and were in stable clinical condition until hospital discharge.

Sepsis, in the first month of life still forms a major cause of mortality and morbidity. Multidrug resistant gram-negative organisms form a big threat to preterm, low birth weight and immunocompromised newborns. *Klebsiella* species are the most commonly implicated pathogen in neonatal sepsis outbreaks followed by *Escherichia coli* and on rare occasions, *Enterobacter* species [6]. Neonatal septicemia is difficult to diagnose clinically as it presents with non-specific signs and symptoms. The main symptoms in our study were tachypnea, with respiratory distress and all 5 neonates required early intubation with ventilator support, poor feeding, lethargy, cyanosis and jaun-

dice. There can be intrinsic risk factors for infection of newborns like gestational age, sex, birth weight and immunologic development [7]. In our study, prematurity and low birth weight was the main underlying condition of the infected neonates. The extrinsic factors which contribute to outbreak are prolonged hospital stay, use of invasive procedures, overcrowding, understaffing, breach in hand hygiene and aseptic techniques and injudicious use of antimicrobials. In this outbreak, understaffing (nurse to patient ratio was 1:3) and breach of standard precautions including inadequate hand hygiene has led to the outbreak. The contaminated environment can serve as reservoirs for this pathogen, which is then spread by hands of health care workers [8].

Following this outbreak, an emergency infection prevention and control meeting was initiated and was attended by the hospital higher management, administration, nursing director, supervisors, the neonatal ICU service chief, infection prevention and control team and clinical microbiologist. The following corrective measures were promptly implemented:

1. Restricted the visitors from entering the NICU and if needed, nursing aide posted at the entry door will educate on adequate hand hygiene and provide personal protective equipment to don.
2. Visitors were always supervised in performing hand hygiene by the patient care nurse.
3. Re-arrangement of nursing staff was done to provide nurse to patient ratio of 1:1 at all the 3 work shifts.
4. Thorough terminal cleaning of the NICU was performed with hospital approved freshly prepared disinfectant solution which was supplemented by fumigation with hydrogen peroxide and silver ions.
5. Stopped unwarranted admission of neonates from within our facility and referral patients.
6. Active Hand hygiene campaign was initiated for NICU healthcare providers and visitors.
7. Baseline screening for CPKP on all new patients at admission was initiated and the sites to be included were rectal or perirectal swabs, if patient is catheterized, urine and any open wounds or vascular catheter exit sites were also screened. All CPKP positive patient files were flagged.
8. Initiated a policy for daily review of invasive devices and early removal, once the clinical need ceases.
9. Early de-escalation of broad-spectrum antimicrobials to narrow spectrum or target specific antimicrobials were strictly implemented based on clinical evaluation along with available microbiology results. Patient care plan was formulated for early discharge based on the clinical condition of the patients.
10. Healthcare workers of NICU were advised to adopt strict aseptic techniques including adequate and appropriate hand hygiene. All reusable medical equipments were sent to the central sterilization services of the hospital for disinfection and sterilization. Wherever possible disposable single use items were introduced within the NICU. All electronic devices within patient care environment underwent regular cleaning and disinfection as per the manufacturer's guidelines.

An important compounding factor in the treatment of these infections is the emergence of multidrug resistance which limits the treatment options [9]. Carbapenemases hydrolyse almost all betalactams and they are associated with diverse mobile genetic elements carrying multiple resistance genes, thereby conferring resistance to several antibiotic classes, including aminoglycosides, fluoroquinolones, trimethoprim, and sulphonamides [10]. The only antimicrobial which had activity against the isolated *K. pneumoniae* was colistin and hence the only treatment option available. MICs of meropenem and imipenem against the isolated CPKP were ranging from 8 µg - 12 µg for 7 isolates and 1 isolate showed an MIC of 64 µg. Colistin MIC was < 0.5 µg for all the isolates. The optimal treatment of infections due to CPKP is unknown, and none of the currently available antibiotics used as single therapy may be effective for treating infections with all types of carbapenamase producers. Source control, in addition to antimicrobial therapy, is essential for the effective management of these infections. Empirical combination therapy including colistin, a carbapenem, or an aminoglycoside, might be justified for severely ill patients with CPKP [11].

## Conclusion

*K. pneumoniae* has been reported as one of most frequent causes of infection outbreaks in NICUs. Neonatal infections due to CPKP are of grave concern due to limitations in treatment options. So, the main focus should be on the prevention of this infectious scourge by implementing adequate infection prevention and control measures by all healthcare providers at all times of patient care. Clinical microbiology laboratories should be well equipped to identify the carbapenamase producing Enterobacteriaceae and as well to promptly notify the patient care team. Early identification should prompt infection control team to stop the spread of infection to other patients, visitors and healthcare providers. Judicious use of all broad-spectrum antimicrobials including carbapenems can prevent the rise in carbapenem resistant isolates. CPKP infections are a significant challenge worldwide, especially as infections caused by these organisms are associated with morbidity and high mortality. Few antimicrobials retain activity against CPKP, and polymyxin based combinations have become an important treatment option for patients with these infections. Some newer agents show promise for treating infections due to KPC producers; however, effective options for the treatment of CPKP remain elusive.

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