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Original article

Phased outbreak of *Burkholderia cepacia* complex and multi-drug resistant *Klebsiella pneumoniae* causing neonatal sepsis in a tertiary hospital in Benin City, Nigeria: Investigation and mitigation

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ABSTRACT

Background: *Burkholderia cepacia* complex (Bcc) is an emerging pathogen known to contaminate pharmaceutical solutions and medical devices, but has largely been underreported as causing infections in Nigeria. This study presents detailed microbiological and environmental surveillance activities of a sequential outbreak of Bcc and extended-spectrum beta-lactamase (ESßL)-producing *Klebsiella pneumoniae* causing neonatal sepsis in a tertiary hospital in Benin City, Nigeria. **Methods:** Blood culture requests were made for neonates upon clinical suspicion of sepsis. Blood specimens were collected in duplicates in BactT/Alert bottles and incubated in the BacT/Alert machine. Further processing of culture-positive bottles was carried out. Identification and antimicrobial susceptibility tests (AST) of emergent organisms were carried out using the VITEK-2 COMPACT system. Environmental surveillance was also done following standard guidelines. **Results:** During the study period, a total of 303 blood culture requests were received out of which 101 (33.3%) yielded growth of Gram-negative bacilli. Thirty-three (10.9%) yielded Bcc and 41(13.7%) yielded *K. pneumoniae* (ESßL-producing). All Bcc isolates had similar AST patterns. Various samples from the medical solutions, disinfectants, and environment were negative for the Bcc and *K. pneumoniae*. However, Bcc and *K. pneumoniae* (ESßL-producing) were recovered from tap heads and sink drains. Timely infection prevention and control (IPC) interventions led to a decline in the incidence rate. **Conclusion:** An interplay of proper microbial identification, keen observation, and inter-professional collaboration was key in detailing the phased outbreak of Bcc and *K. pneumoniae* causing neonatal sepsis. The study highlights the significance of IPC measures in preventing and mitigating the spread of multidrug resistant pathogens.

Introduction

Neonates are at increased risk of developing sepsis in Low- and resource-limited countries; 99% of the global chunk of neonatal deaths are known to occur in such settings [1]. In neonatal wards, overcrowding, understaffing and gaps in Infection Prevention and Control (IPC) practices have been identified as being critical and contributing to the burden of neonatal sepsis in these countries [2]. Neonatal mortality rate in Nigeria is 37 per 1000 live births [3], alongside perinatal

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asphyxia and prematurity, neonatal sepsis is a prime contributor to this unenviable statistic [1,3].

Burkholderia cepacia complex (Bcc) is a multi-species of aerobic bacteria comprising 24 closely related organisms that are Gram-negative and non-fermenting [4]. They are non-fastidious and ubiquitous, occasionally present as contaminants of fruits, vegetables, soil, water as well as some biological cleaning solutions including disinfectants and antiseptics [2,4]. Within the past three decades, however, there have been reports of these organisms being implicated in cases of pulmonary infections in cystic fibrosis patients [5]. Outbreaks of sepsis attributable to Bcc have also been documented in pediatric populations and among immunocompromised patients in wards [5-9]. *Burkholderia cepacia* complex has also been implicated in causation of sepsis in immunocompetent children, cases of peritonitis, and urinary tract infection (UTI) in patients with indwelling urinary catheters [6,7]. Previous investigation of such outbreaks has been traced to contaminated mouth gels, intravenous fluids, ward sinks, nebulizer solutions and respiratory therapy devices [10,12].

Klebsiella pneumoniae, one of the ESKAPE (*Enterobacter cloacae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterococcus faecium*) pathogens that are renown for antimicrobial resistance and ability to cause healthcare associated infections (HAIs), has been comparatively more frequently implicated in outbreaks than Bcc [2]. Previous reports from Nigerian studies have implicated this organism as the leading cause of neonatal sepsis [13-15]. Although these studies elucidated likely gaps in IPC practices that may have played roles in infection, few studies documented evidence of investigative steps taken to explore the link with the environment. In this study, we explored the role of the environment in sequential outbreak of Bcc and ESßL-producing *K. pneumoniae* causing neonatal sepsis at the University of Benin Teaching Hospital (UBTH), Benin City, Nigeria.

Materials and methods

Study site

The study followed a cross-sectional analytical design and was conducted at the University of Benin Teaching Hospital (UBTH), Benin City, Nigeria. The hospital comprised of 30 wards and 850 beds, being a tertiary health institution serving the specialist health needs of the state's teeming population and six neighboring states. The specimens were collected from the neonatal ward, also called special care baby unit (SCBU) and were processed in the medical microbiology laboratory, UBTH. The ward comprised of 50 beds and six subunits namely inborn, out-born, high dependency unit, neonatal intensive care unit (NICU) 1 and NICU 2. The study was carried out between January and September 2022. Ethical approval was received from the ethics committee of UBTH with reference/protocol number: ADM/E22/A/VOL VII/VII/1483011853.

Sample collection

Venous blood pairs (1-3 ml) were aseptically collected from neonates admitted in the SCBU with clinical signs and symptoms of sepsis, including fever, lethargy, hypothermia, irritability, bulging fontanelle, apnea, seizures, poor feeding, inconsolable cry and failure to thrive. The specimens were immediately dispensed aseptically into BacT/Alert PF plus culture bottle (Biomerieux, France) and transported immediately to the medical microbiology laboratory, UBTH.

Specimen processing

The pair of BacT/Alert bottles (into which blood samples were dispensed) were incubated in the automated BacT/Alert instrument (BACTEC 9050, Becton Dickinson) and for a maximum of 5 days. Bottles flagged as positive by the system were removed, Gram stained and sub-cultured onto appropriate media such as blood, chocolate and MacConkey agar and incubated at 37 °C for 24–48 h. Emergent colonies were Gram stained, while identification and susceptibility tests were performed using VITEK-2 COMPACT machine following manufacturer's guidelines. VITEK GN-ID identification card (lot 2411830403) was used to characterize Gram negative bacteria and VITEK GN-AST identification card (lot 5952019203) was used to perform antimicrobial susceptibility tests (AST).

Rationale for environmental surveillance

The increased frequency of isolation of Bcc from blood cultures of neonates of consistent antimicrobial susceptibility profile prompted the environmental surveillance. The same observation was equally noted for *K. pneumoniae* that was ESßL-producing. Most of the strains isolated had similar susceptibility pattern.

Environmental surveillance

This was conducted from March 7th to March 25th and July 12th to July 18th, 2022. A total of 33 environmental samples and disinfectants were collected from SCBU aseptically for microbiological processing. The samples included tap water, air-conditioner waste, povidone iodine, methylated spirit and liquid soap. The following items/surfaces were swabbed using moistened sterile swab sticks: feeding cups, incubator, door handles, drip stand, tap head, faucets and sink drains in all the subunits. All samples were immediately sent to the medical microbiology laboratory and were processed following standard guidelines and as previously described [9]. The swab samples were inoculated on blood agar and MacConkey agar plates which were incubated for 48 h at 37°C. Tap water samples which was collected in pairs at one minute interval per tap was centrifuged at 3000 rpm for 15 min and the sediment was processed [9].

All liquid samples were inoculated directly on blood agar, MacConkey agar and in brain heart infusion broth (BHIB) (1:5 dilution). Plates were incubated at 37°C for about 2 days. Brain heart infusion broth was incubated at 37°C for about 5 days and checked for turbidity daily. Subcultures from BHIB were made on blood agar and MacConkey agar plates on the 5th day or earlier in case of turbidity [9,14]. All positive cultures that were Gram negative bacilli (after microscopy) were identified and AST was also performed using the VITEK machine as earlier described. The clinical procedures and practices undertaken by the staff of the unit were observed to identify potential sources of infection.

Results

A total of 303 blood culture requests were made from SCBU during the period under review. Out of this number, 134 (44.2%) were culture positive and 101 (33.3%) yielded growth of Gram-negative bacilli. Of the Gram-negative bacilli, 33 (10.9%) yielded Bcc and 41(13.7%) yielded *K. pneumoniae* (ESßL-producing).

The index case of Bcc which occurred in February 2022 was a preterm baby, a female from a set of twins being managed for preterm low birth weight and was referred from a secondary care facility within Benin City, Nigeria. Blood culture was collected on the 9th day of admission on suspicion of sepsis. This yielded Bcc which was sensitive to ceftazidime, meropenem and sulfamethoxazole-trimethoprim, but resistant to piperacillin, amikacin, ceftriaxone, cefepime, gentamicin and tobramycin **(Table 1)**. The second case was a one-day old male neonate who was referred from a private hospital on account of cyanotic congenital heart disease (with patent ductus arteriosus and patent foramen ovale). Blood culture sample collected on day three of admission on suspicion of sepsis yielded Bcc. Subsequent cases of Bcc which comprised both inborn and referred patients followed in succession with similar AST pattern, thereby raising the suspicion of an outbreak of same source.

The index case that heralded the spike in *K. pneumoniae* causing neonatal sepsis was defined as the first case in May 2022 and was a 3-day old febrile baby who was referred from a secondary hospital within Benin City on account of abdominal distention. A blood culture test was done on admission and was positive for ESßL-producing *K. pneumoniae*. The strain was sensitive to ertapenem and meropenem, but resistant to ampicillin, ampicillin-sulbactam, piperacillin, ceftazidime, ceftriaxone, cefepime, gentamicin, tobramycin and trimethoprim-sulfamethoxazole **(Table 1)**. The second case that was culture positive for *K. pneumoniae* was a four-day old baby born in the hospital and was admitted on account of portal intestinal obstruction secondary to an intestinal stenosis in a child with perinatal asphyxia. The other 39 cases followed in quick succession and had similar AST pattern.

The incidence rate per month of Bcc and *K. pneumoniae* causing neonatal sepsis is shown in **figure (1)**. The peak months of the infection for Bcc and *K. pneumoniae* were April and June 2022, respectively before the decline.

Various samples from the environment were culture negative for the organisms of interest (Bcc and *K. pneumoniae*). However, 2 samples from sink drains in a subunit (NICU-2) yielded growth of Bcc, 3 sink drains and one tap head yielded growth of *K. pneumoniae* (ESßL-producing). All solutions (Tap water, povidone iodine, methylated spirit and liquid soap) did not yield Bcc and *K. pneumoniae* **(Table 2)**.

Table 1. Susceptibility profile of *Burkholderia cepacia* and *Klebsiella pneumoniae* isolates recovered from blood of patients admitted in the special care baby Unit (SCBU), University of Benin Teaching Hospital, Benin City, Nigeria.

Organism	CN	CIP	LVX	SXT	ETP	MEM	AMK	SAM	AMP	PRL	CMP	CRO	CAZ
Burkholderia cepacia (n = 33)	0	0	0	33 (100)	NA	33 (100)	0	NA	NA	0	0	0	33 (100)
K. pneumoniae (ESßL positive) (n = 41)	3 (7.7)	31 (75.6)	35 (85.4)	0	41 (100)	41 (100)	40 (97.6)	0	0	0	0	0	0

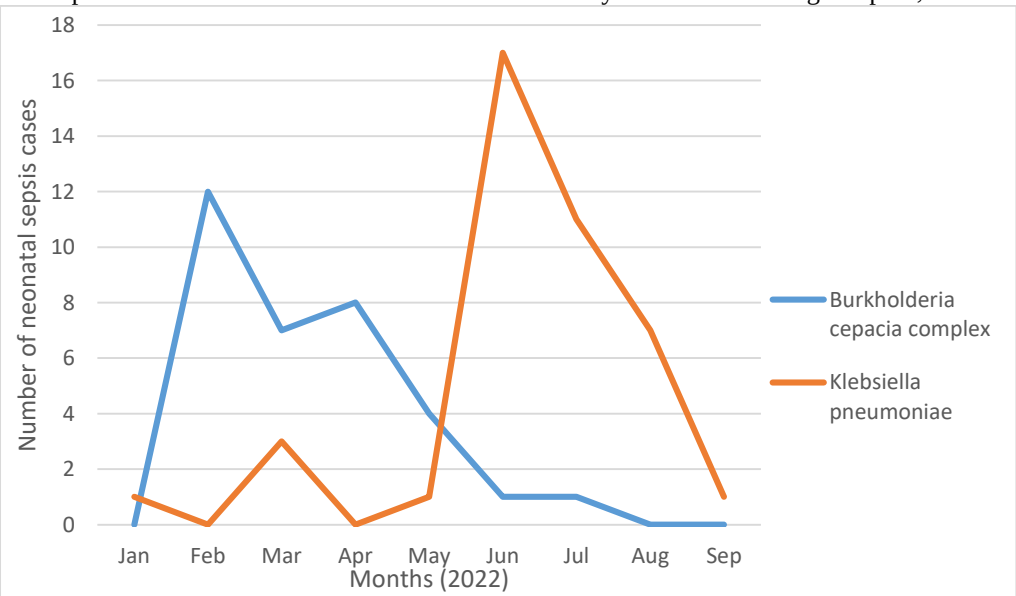
NA-Not applicable, number in brackets = value in percentage, CN-gentamicin, CIP-ciprofloxacin, LVX-levofloxacin, SXT-trimethoprim -sulfamethoxazole, ETP-ertapenem, MEM-meropenem, AMK-amikacin, SAM- ampicillin-sulbactam, AMP-ampicillin, PRL-piperacillin, CMP-cefepime, CRO-ceftriaxone, CAZ-ceftazidime, NA-not applicable.

Table 2. Environmental and pharmaceutical items surveillance report from SCBU ward, UBTH.

UNIT	Sampling site/sample	Culture report (Bcc or *K. pneumoniae*)
NICU-1	Sink Tap head (n = 1)	*Klebsiella* pneumoniae (ESßL-producing) grown
	Tap water (n = 2)	Not grown
	Incubator (n = 2)	Not grown
	Air-conditioner vent/waste (n = 2)	Not grown
HDU	Sink drain (n = 1)	Not grown
	Tap head (n = 2)	Not grown
Lactation room	Tap head (n = 1)	Not grown
	Door handle (n = 2)	Not grown
	Sink drain (n = 1)	*Klebsiella pneumoniae* (ESßL-producing)
NICU-2	Sink Tap head (n = 2)	Not grown
	Sink drain (n = 2)	*Burkholderia cepacia* complex grown
	Air-conditioner vent/waste (n = 2)	Not grown
	Tap water (n = 2)	Not grown
	Povidone iodine (n = 2)	Not grown
	Methylated spirit (n = 2)	Not grown
	Incubator (n = 2)	Not grown
Out-born	Sink drain (n = 1)	*Klebsiella pneumoniae* (ESßL-producing)
	Tap water (n = 2)	Not grown
	Liquid soap in use (n = 2)	Not grown

NICU- neonatal intensive care unit, HDU- High dependency unit, Bcc- *Burkholderia cepacia* complex.

Figure 1. Curve showing incidence rate of Bcc and *K. pneumoniae* causing neonatal sepsis between January and September 2022 at the neonatal unit in the University of Benin Teaching Hospital, Benin City, Nigeria.



Discussion

The ecological niche for Bcc seems to have evolved over the last three decades as these organisms have thrived as opportunists, having been isolated from clinical specimens of immunocompromised patients [9], preterm babies [2,8], patients having vertebral osteomyelitis following surgical intervention and surprisingly, from immunocompetent pediatric patients [5,6]. This is very much unlike their natural habitat, on fruits, on soil, and in water, owing to their intrinsic tolerance to nutrient scarcity [4]. Literature survey shows that Bcc has been largely underreported as causing neonatal sepsis in Nigeria due mainly to challenges in identification and its being an infrequent pathogen [13,15-17]. *Klebsiella pneumoniae* (ESßL-producing), of diverse sequence types have been known to cause outbreak of neonatal sepsis in both high income countries and resource-constrained settings [2,3,18,19]. In this study, we document the first sequential outbreak of Bcc and *K. pneumoniae* from babies diagnosed of neonatal sepsis in Nigeria within a nine month period.

Isolation of a causative agent of neonatal sepsis (Bcc) that had not been previously isolated from the blood of neonates in quick succession and of same susceptibility pattern was a key finding in defining an outbreak in the neonatal ward as had been done in previous studies [2, 8, 9].

In previous studies, upon environmental surveillance occasioned by outbreak of Bcc, the organism was recovered from normal saline (opened bottles), continuous positive airway pressure humidifier water, sealed injection vial rubber stopper of antimicrobials (amikacin), respiratory therapy devices and sink drains [8, 9, 20, 21]. When these were removed or successfully disinfected, there was a sharp decline in incidence rate. During the first environmental surveillance occasioned by the marked increase in cases of Bcc in this study, the organism was not isolated from all samples, sink drains were not sampled during the first outbreak. However, implementation of IPC interventions by way of emphasis on the hand hygiene among healthcare workers (HCWs) in the unit led to a marked decline in incidence. Following the outbreak of *K. pneumoniae*, environmental sampling was focused mainly on tap water and sink drains as reported in literature [22]. *Klebsiella pneumoniae* and Bcc were thereafter isolated from sink drain of two sinks. The finding was surprising as repeated cultures of tap water were negative for Bcc. The reason for our finding could be that Bcc being able to thrive in water, could form biofilms in tanks and water pipes from where it could occasionally be dislodged and contaminate water and the environment [4,21]. The organism may also have been introduced in the ward by an engineering activity such as construction, contaminated food or an extraneous item which may have been rinsed in the sink. Being intrinsically resistant to certain biocides and low nutrients, this organism may have self-perpetuated and multiplied to outbreak proportions, while gaps in hand hygiene practices by HCWs in the unit facilitated the outbreak.

Although *K. pneumoniae* is one of the most common causes of neonatal sepsis in Nigeria [13, 15], a significant upsurge in the number of cases as the first outbreak of Bcc was receding confirmed another outbreak, all strains being ESßL-producing. Following the outbreak of *K. pneumoniae*, environmental sampling was focused mainly on tap water and sink drains as reported in literature [22]. *Klebsiella pneumoniae* and Bcc were thereafter isolated from sink drain of two sinks in the neonatal unit. The finding was surprising as repeated cultures of tap water were negative for Bcc. The reason for our finding could be that Bcc being able to thrive in water, could form biofilms in tanks and water pipes from where it could occasionally be dislodged and contaminate water and the environment [4, 23, 24]. Previous outbreaks of Bcc have been linked to to contaminated sink drains [24,25]. The propensity for contaminated environmental surfaces to facilitate HAI has been established and depends on several factors, including frequency with which organisms contaminate environmental surfaces, ability of pathogens to remain viable on surfaces, location of pathogen reservoirs, hand-touch frequency of surfaces, adequate level of contamination required to pose a transmission risk, and pathogen infectivity index [20]. The organism may also have been introduced in the ward by an engineering activity such as construction, contaminated food or an extraneous item which may have been rinsed in the sink. Being intrinsically resistant to certain biocides and low nutrients, this organism may have self-perpetuated and multiplied to outbreak proportions, while the hands of HCWs and mothers may have been the vehicle of transfer to susceptible neonates. Gaps in hand hygiene practices by HCWs, lapses in standard contact precautions and aseptic precautions in the unit may have facilitated the outbreak.

Conversely, in previous studies, *K. pneumoniae* outbreaks were associated with water shortages in resource-limited settings [2,13]. However, this was not the case in our setting. *K. pneumoniae* has been isolated from the hands of HCWs during outbreak investigations; the hands of HCW has been shown to facilitate the spread of this organism in settings where there were gaps in hand hygiene adherence. Our interview sessions and observations showed gaps in compliance to hand hygiene. Alongside disinfection of sinks, a decline in the isolation rate of this organism coincided with improved hand hygiene practices. Although not the organism of interest, a strain of carbapenemase-producing *Enterobacter cloacae* was also recovered from the sink drain. This study therefore highlights the sink as an overlooked reservoir of multidrug resistant organisms that may occasionally be involved in outbreaks and HAIs in wards. Environmental surveillance during outbreak investigations should therefore include this site.

The similarity in susceptibility pattern for Bcc recovered from blood samples of all neonates in this study was noteworthy and raised the index of suspicion of an outbreak of an organism from same source. Similar observations had been previously made by other investigators [2,8,9]. The high resistance rate to aminoglycosides namely gentamicin and amikacin was not too surprising as Bcc is known to have intrinsic resistance to the aminoglycosides [4,9]. With the exception of ceftazidime, other third generation cephalosporins showed poor activity to Bcc while meropenem and trimethoprim-sulfamethoxazole showed good activity against the organism. This susceptibility pattern is consistent with the finding from a previous study [8]. In a recent study which strikingly documented sequential outbreak of these two organisms in Gambia, but used molecular techniques to analyze the genomic characteristics of both organisms, it was shown that the Bcc had been in the environment for at least 3 years before the outbreak [2]. This may mean that exposure to suboptimal doses of biocides and antimicrobials may exert selective pressure and lead to survival and proliferation of these strains in wards that can subsequently cause occasional outbreaks with attendant morbidity and mortality.

Outbreaks of ESßL-producing *K pneumoniae* (ST39) causing neonatal sepsis have been previously reported in Gambia [2]. In our study site, a previous study that utilized whole genome sequencing for ESßL producing isolates from various clinical specimens documented two ESßL-producing *K. pneumoniae* (ST14) strains as causing neonatal sepsis (not an outbreak) [23]. Although most isolates of *K. pneumoniae* from this study had similar susceptibility pattern with the *K. pneumoniae* (ST14) in that study, further molecular test would be required to establish sequence type and genetic relatedness between species. Also, the enzyme (ESßL) inactivates the third generation cephalosporins and is associated with resistance to other classes of antimicrobials [23]. This may explain the resistance pattern of the *K. pneumoniae* isolates.

Infection prevention and control interventions that were embarked upon summarily included strict adherence to the WHO five moments of hand hygiene, emphasis on the use of alcohol based hand rubs, health education by IPC nurses to mothers and patient relatives, thorough disinfection of the sink drains using 0.5% sodium hypochlorite till repeated cultures became negative, as well as ensuring availability of disinfectants in the unit. These interventions summarily led to the decline in prevalence of *K. pneumoniae* as had been observed in previous studies [2, 22].

This study was limited by inability to utilize molecular techniques such as whole genome sequencing, expanded multi-locus sequence typing (eMLST), random amplified polymorphic DNA analysis and pulse field gel electrophoresis to aid our epidemiological investigations in determining sequence types, clonal relatedness and species differentiation in order to track and define the outbreak in incontrovertible terms. This was due to resource constraints, however, the isolates from this study were archived.

Conclusion

The study details a sequential outbreak of neonatal sepsis caused by Bcc and *K. pneumoniae* in our neonatal unit in UBTH, Nigeria. The study summarily highlights key markers that medical laboratory scientists, microbiologists and clinicians could be on the look for in having a high index of suspicion of an outbreak. It details investigative steps and IPC measures that could be undertaken in resource-limited settings.

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