Successful Infection Control of an Extended-Spectrum Beta-Lactamase-Producing Klebsiella pneumoniae ST307 Outbreak in a Neonatal Intensive Care Unit

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Abstract
Background: We experienced an outbreak of extended-spectrum-beta-lactamase-producing Klebsiella pneumoniae (ESBL-KPN) bacteremia in a neonatal intensive care unit (NICU) starting in August 2017. We implemented an active countermeasure to control the outbreak of ESBL-KPN successfully.

Methods: The incidence of ESBL-KPN based on clinical specimens and healthcare-associated infection (HAI) rate were evaluated before and after the initiation of enhanced infection control (IC) practices initiated in January, 2018. Surveillance cultures were carried out for neonates, medical personnel, and NICU environmental samples. Molecular analyses, including pulse-field gel electrophoresis (PFGE), sequence typing, and ESBL genotyping, were performed for the isolated KPN strains. Results: The incidence of ESBL-KPN in clinical specimens decreased from 2.84 to 0.49 per 1,000 patient-days and the HAI rate decreased from 2.43 to 0.0 per 1,000 patient-days after the implementation of enhanced IC procedures. Eleven neonates (11/15, 73.3%), one (1/41, 2.4%) of the medical personnel, and six (6/181, 3.3%) samples from the surroundings and medical devices were positive for ESBL-KPN in the surveillance cultures. All isolates demonstrated the same antibiotic resistance pattern and similar PFGE patterns and were identified as ST307 containing CTX-M-15. Conclusions: Contaminated neonate surroundings and medical devices as well as spreading by medical personnel appeared to be the source of the outbreak of ESBL-KPN. We used an enhanced IC strategy for 3 months and successfully resolved the clonal outbreak of CTX-M-15-producing KPN. ST307 has emerged as an important bacteremia-causing pathogen in the NICU and should be monitored carefully.

Background
Neonates who require intensive care have high mortality and morbidity rates due to healthcare-associated infections (HAI) because they have low immunity. Klebsiella pneumoniae (KPN) is a major reservoir in the neonatal intestines [1] and is more transmissible than Escherichia coli [2]. As KPN is a normal component of the flora in stool specimens, it may easily contaminate a neonate’s surroundings and thereby cause a nosocomial outbreak. It is difficult to control outbreaks due to continuous shedding. ESBL-KPN spreads by person-to-person contact or via environmental sources [3, 4]. Patients are the primary reservoirs, followed by health-care workers and contaminated sinks based
on a systemic review of studies of ESBL-KPN outbreaks [3].

Outbreaks of KPN require enhanced infection control (IC) measures [5-7]. As KPN has the potential to survive in neonatal intensive care units (NICUs) for long durations [4] and can re-emerge despite IC measures [2], eradication in the NICU is challenging.

Extended-spectrum $\beta$-lactamase (ESBL) is involved in the hydrolysis of third-generation cephalosporins as well as aztreonam. Infections with ESBL-producing KPN are associated with higher mortality and morbidity rates as well as increased lengths of stay and medical costs compared to those caused by ESBL non-producers [8]. The prevalence of ESBL-producing KPN is around 20-50% in Korea [9, 10].

The ST307 strain has emerged as an important causal pathogen in outbreaks of carbapenem-resistant Enterobacteriaceae [11, 12]. In this study, we characterized the STs of KPN from a recent outbreak in a NICU in Korea. We performed pulsed-field gel electrophoresis (PFGE) to further evaluate genetic relatedness. Importantly, we successfully eradicated the outbreak by the implementation of enhanced IC measures.

Methods

NICU setting

The ESBL-KPN outbreak occurred in the 17-bed NICU of a university-affiliated hospital. The NICU is staffed by three pediatricians and 35 nurses. Approximately 250 newborns are admitted to the NICU each year and there is one isolation room with two beds. The nurse-to-patient ratio was between 1:3 and 1:4. The infection control team (ICT) of our institute collaborated closely with the NICU team.

Incidence and outbreak

A neonate who tested positive for ESBL-KPN from any specimen and was admitted to the NICU for $\geq 48$ h was defined as a positive case. The incidence was calculated as new cases per 1,000 patient-days. If the incidence exceeded the upper limit of control (mean $+2$ SD), it was defined as an outbreak. HAI was defined according to CDC/NHSN definitions [13].

Three cases of ESBL-KPN HAI were observed in August and September, 2017. Considering the high
risk of spread in the NICU, a reinforced conventional IC program was initiated in November, 2017. However, three cases of bacteremia occurred in December, 2017. Accordingly, an extended ICT was organized to address this ESBL-KPN outbreak in the NICU.

Survey of the outbreak
When the incidence density rate of HAI increased to 6.0 in December, 2017 (Fig. 1), a survey was initiated immediately. First, neonatal characteristics were determined, including birth week and weight, birth method, route of admission, previous antibiotic use, microbiological data, start date of isolation, location, and presence of HAI. IRB permission was not required from the ethics board of our institute because this was a formal IC activity to resolve the outbreak.
Second, the behavior of medical personnel was monitored, including hand hygiene and contact precaution rates. Rectal swab specimens were obtained from medical personnel (N = 41) to screen carriers as well as from neonates (N = 15).
Third, the disinfection of medical devices and environmental cleaning were promoted. Samples were obtained to rule out transmission via medical devices (N = 71), such as thermometers, stethoscopes, or patient monitoring systems as well as environmental sources (N = 110), such as incubators or surroundings.

Reinforced and enhanced IC program
Improvements in hand hygiene and contact precaution were reinforced for all medical personnel working in the NICU. More frequent and thorough disinfection and cleaning was implemented for medical devices, incubators, and surroundings. Group education and frequent rounding were performed to encourage IC activities and to share the seriousness of the situation.
An enhanced IC program was established, including cohort care of neonates and medical personnel, active surveillance cultures (ASC), and universal gown and glove wearing for medical services, in addition to the reinforced IC program from January to March, 2018. ASC involved the isolation of ESBL-KPN from skin, fecal, or perianal specimens from a neonate who did not have clinical symptoms
or signs of infection. ASC was performed every week for neonates in the NICU until March, 2018.

**Antibiotic susceptibility test and molecular epidemiological study**

Bacteria were identified by MALDI-TOF MS (bioMérieux; Durham, NC, USA) and antibiotic susceptibility tests were performed by the broth microdilution method using the Vitek-2 system (bioMérieux, Marcy l'Etoile, France). Isolates of KPN showing ESBL resistance were analyzed by PFGE and multi-locus sequence typing to understand molecular relatedness. Once the isolates were digested with XbaI (Roche, Basel, Switzerland) enzyme, electrophoresis was performed using CHEF MAPPER (Bio-Rad, Hercules, CA, USA). Agarose gel was stained with SYBR Gold (ThermoFisher Scientific, Waltham, MA, USA) to yield a PFGE pattern. A dendrogram was obtained using BioNumerics (Bio-Rad) to evaluate the relationships between the strains. Seven housekeeping genes (*rpoB, gapA, mdh, pgi, phoE, infB,* and *tonB*) were amplified and sequenced to identify STs as described in Institute Pasteur [http://bigsdb.pasteur.fr/klebsiella/][14].

ESBL was amplified by PCR with known primers targeting the CTX-M-1, CTX-M-2, and CTX-M-9 groups [15, 16]. DNA sequencing was performed using the amplified PCR product and ESBL genotypes were identified using BLAST.

**Statistical analysis**

Chi-square tests were used to compare the incidence of HAI and the compliance rates for hand hygiene and contact precaution before and after enhanced IC measures using SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). A *P* value < 0.05 indicates a significant difference.

**Results**

**Incidence**

The incidence of ESBL-KPN including ASC decreased gradually from 45.0 to 25.5 and 18.5 in January, February, and March, 2018, respectively (*P* = 0.035, Fig. 1).

The HAI incidence of ESBL-KPN decreased from 2.43 to 0.0 after enhanced IC measures (*P* = 0.026).
Compliance with optimal hand hygiene practices increased from 60.8% (96/158) to 75.4% (303/402) after the initiation of enhanced IC measures \((P = 0.004)\). Compliance with contact precaution also improved from 87.5% (42/48) to 98.3% (225/229) \((P < 0.001)\). The number of neonates per nurse decreased from 1:3–1:4 to 1:2–1:3, thereby reducing crowded conditions. No positive clinical specimen or HAI was detected since January, 2018, even after the discontinuation of enhanced IC measures. June 2018 was declared the end of the outbreak.

**Survey of the outbreak**

There was no correlation between neonate characteristics and positive ESBL-KPN status. In surveillance cultures, KPN was not detected in rectal swab or stool specimens from mothers of neonates \((N = 15)\). In addition, medical equipment and environmental cultures from the operating room and in the delivery room were negative \((N = 28)\).

Although one medical worker (2.4%) was positive in the surveillance culture, ESBL-KPN was continuously positive even after she resigned. Moreover, there was no specific association between neonates and the attending medical personnel who tested positive.

Six (3.3%) isolates from medical devices or incubators and eleven (73.3%) isolates from neonates in ASC were positive, suggesting a strong causal relationship. The mean acquisition duration of ESBL-KPN was 7.5 days (range, 3-50 days). These results suggested that the neonates contracted widespread ESBL-KPN from medical devices or from the environment via medical personnel.

**Antibiotic resistance and molecular epidemiological characteristics**

All isolates were equally resistant to ampicillin, aztreonam, cefazolin, cefepime, ceftazidime, ciprofloxacin, gentamicin, and trimethoprim/sulfamethoxazole but were susceptible to amikacin, cefoxitin, ertapenem, imipenem, piperacillin/tazobactam, and tigecycline.

PFGE revealed that all strains isolated from the blood \((N = 1)\), medical devices \((N = 5)\), and neonate surveillance cultures \((N = 13)\) were closely related (Fig. 2). All isolates were identified as ST307 with
Discussion

Preterm newborns are immunologically immature and often require invasive procedures, rendering them highly susceptible to infections [17, 18]. The risk of infections is associated with a low birth weight, prolonged length of stay, empiric antibiotic treatment, frequent manipulation, and nasopharyngeal or rectal colonization [1, 3, 4, 16, 18, 19]. An age of <12 weeks and previous treatment with third-generation cephalosporins and aminoglycosides are associated with multi-drug resistant KPN colonization and infection observed in Spain [18]. The screening of high-risk patients during outbreaks is recommended to control epidemics [18]. As our study did not include a control group, we could not analyze risk factors. We reduced the number of neonates admitted to the NICU during the outbreak because over-crowding or under-staffing contribute to the outbreak [6, 7].

In the first report of an ESBL-KPN outbreak in a NICU in Korea in 1996, isolates from patients with sepsis showed the same PFGE pattern with ASC isolates from neonates and medical personnel, indicating a clonal outbreak [20]. By implementing cohort care and strict barrier precautions, the outbreak was eliminated. However, environmental cultures were not performed until a second outbreak of ESBL-KPN in the NICU in 2000, at which point ESBL-KPN was not detected [5]. The origin of the outbreak was suspected to be a medical person who transmitted the pathogen to neonates. The reversal of ESBL-KPN was observed when the neonates returned to the community [5]. Although a nurse tested positive at our institute, she was unlikely to be the source of spread because the outbreak continued even after she resigned.

In a large-scale outbreak of ESBL-KPN, samples from 145 patients who were either infected or colonized showed the same clonal type, as determined by PFGE [1]. The carriage of ESBL-KPN in the digestive tract has been identified as the most important risk factor for ESBL-KPN infection or colonization [1]. Therefore, weekly rectal swabs could be used to identify high-risk carriers in the NICU [1, 5]. There is also a significant correlation between the restricted use of oxyimino-β-lactams and trends in ESBL-KPN infection. According to a previous study, a change to piperacillin/tazobactam from extended-spectrum cephalosporins decreases the prevalence of ESBL-KPN [10]. Therefore, the
restriction of extended-spectrum cephalosporin use is needed to control outbreaks of ESBL-KPN [18]. However, we did not apply an antibiotic stewardship program to control the outbreak.

Another large-scale outbreak of ST37 KPN occurred in Haiti in 2014-2015, accounting for 257 cases of sepsis and 191 deaths [21]. After improving clinical management and strengthening infection prevention and control measures, mortality dropped from 100% to 24%.

CTX-M-15 is prevalent in Korean hospitals, even in blood samples [22]. Several studies have reported STs for ESBL-KPN outbreaks. For example, outbreaks have been caused by ST20 in Greece [23], ST199 in Latvia [24], ST14 in Tanzania [25], ST13, ST16, ST35, ST48, and ST101 in France [26], and ST607 in Spain [27]. In each of these studies, the CTX-M-15 ESBL type was reported.

ST307 has not been reported in NICU outbreaks to date. ST307 emerged in the mid-1990s and its distribution has rapidly expanded worldwide. This strain is intimately associated with CTX-M-15 ESBL and sometimes exhibits carbapenem resistance [11, 28]. Therefore, close observation of the spread of ST307 is warranted. There was a clonal spread of ST307 KPN in nearby Busan, Korea in 2015 and the strain carried a self-transferable IncX3-type plasmid harboring bla_KPC-2 [12]. In-depth genetic investigations, such as whole-genome sequencing, are needed to reveal the relationship with this clonal outbreak.

The reinforcement of hand hygiene is the most effective intervention to control outbreaks [3]. Therefore, we monitored the optimal hand hygiene rate as well as the contact precaution rate. Compliance increased significantly after implementing IC measures.

We applied IC measures in two steps. At the onset of the outbreak, reinforced conventional IC measures were initiated. Optimal hand hygiene, contact precaution, and disinfection of medical devices or environmental cleaning were monitored. Mutual collaboration between the ICT and medical personnel in the NICU or delivery room was promoted. Frequent rounding or education was performed by the ICT. After observing three additional bacteremia cases, enhanced IC practices, including cohort care of neonates and attending nurses, the use of disposable gloves and gowns for medical services, and ASC, were implemented, in addition to reinforced IC measures. Enhanced IC practices might be required in outbreaks. Finally, the outbreak was controlled after 3 months of enhanced IC practices.
Molecular epidemiological studies were useful for characterizing the clonal outbreak and mode of transmission. The strain of KPN in the NICU was CTX-M-15-producing ST307. Our results emphasize the potential for ST307 to be an important cause of bacteremia outbreaks in the NICU as well as the importance of careful monitoring and control.

Conclusions
We experienced an outbreak of ESBL-KPN bacteremia in a NICU. Molecular epidemiological analyses showed a clonal outbreak by ST307. We implemented enhanced IC practices and successfully controlled the outbreak of ESBL-KPN.

List Of Abbreviations

**ESBL:** extended-spectrum-beta-lactamase

**KPN:** Klebsiella pneumoniae

**NICU:** Neonatal intensive care unit

**HAI:** Healthcare-associated infection

**IC:** Infection control

**PFGE:** Pulse-field gel electrophoresis

**ICT:** Infection control team

**ASC:** Active surveillance cultures

Declarations

**Ethics approval and consent to participate**

The written consent was waived by the IRB, because the research was a routine part of infection control activities and presented no more than minimal risk of harm to participants.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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design, data collection and interpretation, or the decision to submit the work for publication.

**Authors’ contributions**

EHB, SEK analyzed incidence and had collaborated with NICU team (Drs. HJD and CHP). EHB conveyed a statistical analysis. SL prepared bacterial isolates for molecular analysis. OHC, SIH had worked as infection specialists to advise to control the outbreak. JHS performed MLST and ESBL genotyping. IH and EP performed PFGE. SK wrote the paper and is responsible for the whole study. All authors have read and approved the manuscript.

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**Authors’ information**

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Figures
Incidence of extended-spectrum beta-lactamase (ESBL)-producing Klebsiella pneumoniae (KPN) in the neonatal intensive care unit. HAI, healthcare-associated infections of ESBL-KPN.

IC, infection control. Reinforced IC practice included optimal hand hygiene, contact precaution, disinfection of medical devices, and environmental cleaning. Enhanced IC practices included cohort care of medical personnel and neonates, active surveillance culture, and wearing of disposable gowns and gloves for medical services in addition to reinforced IC practice.
Figure 2

Dendrogram of pulsed field gel electrophoresis (PFGE) results for Klebsiella pneumoniae isolated. All strains except isolated from blood, the environment, and medical staff were obtained from active surveillance culture (ASC) of neonate skin surface, stool, or perianal swab specimens. All isolates showed similar PFGE patterns.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

ESBL KPN_raw data (Supplementary File).xlsx