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Colistin- and Carbapenem-Resistant *Klebsiella pneumoniae* Isolated from Blood Cultures among Neonates in a Regional Hospital in Turkey

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Abstract

K. pneumoniae is a cause for concern due to its ability to produce carbapenemases and carry multiple resistance genes, characteristics that define it as a 'difficult-to-treat' pathogen. This study aimed to perform a microbiological analysis of colistin- and carbapenem-resistant Klebsiella pneumoniae strains isolated from blood cultures of neonates in our hospital. Between January 2022 and December 2022, patients with bloodstream infections in the neonatal intensive care units (NICUs) at Van Training and Research Hospital were monitored. All isolates were identified using the Vitek II automated microbiological identification system and conventional biochemical tests. Antibiotic susceptibility and minimum inhibitory concentrations (MICs) were determined using the broth microdilution method. Polymerase chain reaction (PCR) was used to identify the resistance mechanisms of *K. pneumoniae* isolates. Pulsed-Field Gel Electrophoresis (PFGE) and multilocus sequence typing (MLST) were employed to determine clonal relatedness. Of the 27 neonates diagnosed with bloodstream infections, 10 were preterm and 17 were full-term infants. Confirmation using the Vitek II system identified all 27 samples as positive for *K. pneumoniae* isolates. Among the environmental samples, the presence of multidrug-resistant *K. pneumoniae* was detected in the filtered incubator water sample. Antibiotic susceptibility testing results revealed that all isolates, including the environmental one, with the exception of a single isolate, were resistant to first-generation cephalosporins, aminoglycosides, carbapenems, and colistin. K. pneumoniae strains were found to carry various resistance genes. The prioritized detection of such high-risk clones of multidrug-resistant strains, surveillance practices, and appropriate infection control programs are crucial for preventing infections and limiting their further spread into the community.

Keywords: Carbapenem resistance, Colistin resistance, *K. pneumoniae*

Introduction

Klebsiella pneumoniae is a Gram-negative bacterium belonging to the Enterobacteriaceae family. This pathogen raises concerns due to its ability to produce carbapenemases and carry multiple resistance genes. In particular, the emergence and rapid spread of carbapenem-resistant *K. pneumoniae* (CRKP) is considered a significant global problem, as it leads to high mortality and morbidity, especially among hospitalized and immunocompromised patients (1, 2). These characteristics define it as a 'difficult-to-treat' pathogen. Hospital outbreaks caused by resistant *K. pneumoniae* strains are reported worldwide. The emergence of hospital-acquired multidrug-resistant *K. pneumoniae* infections can be attributed to the acquisition and evolution of new resistance genes, the use of invasive devices, immunosuppression, the inappropriate use of antibiotics, and inadequate surveillance systems (3). Transmission may occur via the hands of healthcare personnel or through patient-to-patient contact. Neonatal sepsis is a leading cause of mortality and morbidity among hospitalized neonates (4). In neonatal intensive care units (NICUs), bloodstream infections are recognized as one of the most frequent hospital-acquired infections. Neonatal sepsis, often associated with a

high prevalence of *K. pneumoniae*, constitutes 28% to 50% of these infection cases (6). According to a recent study, the identification of colistin-resistant carbapenemase-producing *K. pneumoniae* isolates, belonging to different sequence types, was reported among 14 neonates admitted to the NICU of a tertiary care hospital in India (6). Limited research exists in Turkey regarding bloodstream infections associated with multidrug-resistant *K. pneumoniae* among neonates. The aim of this study was to characterize *K. pneumoniae* strains obtained from patients in the Neonatal Intensive Care Unit (NICU) of a regional hospital in Turkey. Pathogenic *K. pneumoniae* isolates were isolated from neonates over a one-year period. Furthermore, potential sources of transmission were investigated, and *K. pneumoniae* strains were isolated from the environment. The study also describes the infection control measures implemented to manage potential outbreaks and infections.

Material And Method

This study investigated *K. pneumoniae* strains causing bloodstream infections among patients admitted to the 25-bed Neonatal Intensive Care Unit (NICU) at Van Training and Research Hospital, a 1000-bed tertiary care referral hospital in eastern Turkey. Patients were monitored between January 2022 and December 2022.

Evaluation of Bacterial Strains

Blood samples from neonates were transported to the laboratory for standard bacterial culture and susceptibility testing. A total of 27 multidrug-resistant *K. pneumoniae* strains were obtained. All isolates were identified using the Vitek II automated microbiological identification system and conventional biochemical tests.

Collection of Demographic and Clinical Data

All demographic information and clinical data for the patients were collected using the hospital's information system.

Antimicrobial Susceptibility Testing Methods

Antibiotic susceptibility and minimum inhibitory concentrations (MICs) were determined using the broth microdilution method. Results were interpreted according to Clinical and Laboratory Standards Institute (CLSI) guidelines (8), except for colistin, for which European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (7) were applied.

Investigation of Resistance Mechanisms

Polymerase chain reaction (PCR) was used to detect genes encoding carbapenemases (blaNDM, blaKPC, blaOXA-48, blaIMP, blaVIM), ESBLs (blaCTX-M), other Class A β-lactamases (blaSHV, blaTEM), and colistin resistance (mcr-1, mcr-2, and mcr-3) in the 27 *K. pneumoniae* strains (9, 10). The following isolates obtained from our previous studies were included as positive controls: *K. pneumoniae* CRkp22 and CRkp23 (10) were used for blaOXA-48, blaNDM, blaIMP, blaCTX-M, blaVIM, blaTEM, blaKPC, and blaSHV, while *K. pneumoniae* CRL3 was used for the mcr gene (9). *E. coli* DH5α was used as a negative control.

Analysis of Clonal Relatedness

Clonal relatedness of the 27 clinical and 2 environmental *K. pneumoniae* isolates was analyzed by Pulsed-Field Gel Electrophoresis (PFGE) using XbaI-digested DNA (Invitrogen Inc., USA), following a previously described method (11). The results were interpreted according to the criteria defined by Tenover et al. (12). Banding patterns were identified, and a dendrogram was constructed using BioNumerics software version 7.6 (Applied-Maths, Sint-Martens-Latem, Belgium).

Multilocus sequence typing (MLST) of the 27 *K. pneumoniae* isolates was performed as previously described (13). Seven housekeeping genes were amplified and sequenced. The sequence type (ST) was assigned by determining the allelic number for each housekeeping gene using the database provided by the Pasteur Institute at http://bigsdb.pasteur.fr/klebsiella/klebsiella.html/.

Environmental Microbiological Analysis

Screening cultures (swabs) were obtained from various surfaces and items within the NICU, including the room entrance, IV stands, incubators, oxygen connectors, normal saline, 10% dextrose, reverse osmosis water, and lactated Ringer's solution. Samples were inoculated onto Blood agar and MacConkey agar for microbiological analysis and incubated aerobically for 16-18 hours. Samples were also inoculated into Robertson cooked meat broth and incubated for 16-18 hours. After 48 hours, subcultures were performed from positive Blood agar and MacConkey agar plates. Additionally, air samples were collected using an air sampler to monitor the environmental bioburden.

Implementation of Infection Control Measures

A hospital infection control committee, composed of physicians, microbiologists, pharmacists, nurses, hospital administrators, technical personnel, and cleaning staff, operates to control hospital-acquired infections and outbreaks. During hospital-acquired infection incidents, we implemented effective infection control measures consisting of the following components: a) temporarily evacuating the affected intensive care unit and transferring all patients to a different unit; b) performing fogging of the evacuated intensive care unit and cleaning it with sodium hypochlorite; c) discontinued the shared use of medical equipment; d) provided in-service training on cleaning procedures for sanitation staff, established a cleaning protocol requiring sodium hypochlorite solution to be stored in closed containers to prevent evaporation, implemented the use of single-use cloths for each area, and ensured cloths were changed every 24 hours; e) Infection control physicians and nurses enhanced surveillance of hand hygiene practices among resident physicians and nursing staff and provided training on implemented control measures and hand hygiene procedures; f) surveillance screening of bacterial cultures obtained from various body sites and hands of healthcare personnel continued.

In addition to the NICU and its personnel, infection control measures were also implemented in other hospital areas, primarily other intensive care and critical care units. Compliance with infection control measures in the NICU was approximately 70% prior to the infections; however, it was raised to 100% to control the infection and maintained for the following year to prevent subsequent infections.

Results

Of the 27 neonates diagnosed with bloodstream infections, 10 were preterm and 17 were full-term infants. Confirmation using the Vitek II system identified all 27 samples as positive for *K. pneumoniae* isolates. Among the environmental samples, the presence of multidrug-resistant *K. pneumoniae* was detected in the filtered incubator water sample. Antibiotic susceptibility testing results revealed that all isolates, including the environmental one, with the exception of a single isolate, were resistant to first-generation cephalosporins, aminoglycosides, carbapenems, and colistin.

Molecular screening for carbapenemase genes revealed that blaNDM-5 was positive in 18 isolates and blaNDM-1 in 9 isolates. The blaOXA-32 gene was detected in 7 isolates, invariably co-occurring with either blaNDM-1 or blaNDM-5. Among other carbapenemases, blaIMP was not detected in any isolate, whereas blaVIM was positive in three isolates. Further screening for β-lactamases determined that the blaSHV gene was positive in all *K. pneumoniae* strains, while blaTEM was positive in 5 strains. Among ESBLs, the blaCTX-M gene was detected concurrently with blaNDM-1 in 3 isolates. Regarding colistin resistance genes, mcr-1 and mcr-2 were observed in seven *K. pneumoniae* isolates, whereas mcr-3 was absent in all isolates. Other variants of the mcr gene and chromosomal mutations conferring colistin resistance were not analyzed. Genetic analysis of the environmental *K. pneumoniae* isolate revealed positivity for blaOXA-232, blaNDM-5, blaSHV, blaCTX-M, and blaTEM, while it tested negative for mcr genes. MLST analysis of the 27 clinical strains identified 10 isolates belonging to ST101, 13 to ST16, and 4 to ST11. The environmental *K. pneumoniae* isolate was found to belong to ST101. Analysis of clonal relatedness by PFGE

demonstrated that three clinical ST101 isolates, the environmental ST101 isolate, and four clinical ST16 isolates were closely related. The three clinical ST101 isolates and the environmental isolate clustered together with >95% similarity, whereas the ST16 isolates exhibited >85% similarity to the ST101 cluster.

To evaluate the impact of infection control measures and the reduction in *K. pneumoniae* prevalence within the NICU, surveillance cultures were repeated from various areas of the unit and hospital personnel. Following 48 hours of aerobic incubation, all collected samples were found to be sterile.

Discussion

Hospital-acquired infections are considered a major cause of prolonged hospital stays and mortality among hospitalized patients. Studies have shown that multidrug-resistant *K. pneumoniae* accounts for 18% to 31% of all hospital-acquired infections. The mortality rate attributed to *K. pneumoniae* in intensive care units (ICUs) has been reported to range from 30% to 54% (14, 15, 16). We report an investigation of a *K. pneumoniae*-associated infection in the Neonatal Intensive Care Unit (NICU) of a tertiary care hospital in Van, one of the most populous cities in Eastern Turkey. The infection involved 27 neonates admitted to the NICU. Upon admission, 10 of the 27 neonates were preterm, while the other 17 presented with portosystemic shunt and ARDS, respectively. Since all patients tested positive more than 48 hours after admission, it is probable that they acquired the *K. pneumoniae* strains within the hospital. Hospital-acquired infections are defined as infections that manifest 48 hours or more after hospital admission (17). Various reports on carbapenem-resistant *K. pneumoniae* infections exist from the USA and Europe, predominantly associated with blaKPC. However, in Asian countries, such infections have been reported to be associated with MBLs (Metallo-β-lactamases) (18). Furthermore, in India, blaNDM, blaOXA-48, and their variants have been identified as common mediators for the rapid dissemination of such isolates (6, 19). In our study, blaNDM-5, blaNDM-1, and blaOXA-232 were frequently detected, often concurrently with blaTEM, blaSHV, and blaCTX-M. Although the isolates exhibited colistin resistance, the plasmid-mediated colistin resistance genes mcr-1 and mcr-2 were identified in only four and three isolates, respectively, while mcr-3 was absent in all isolates. Notably, a previous study reported mutations in the chromosomal mgrB gene in K. pneumoniae ST16 isolates from a healthcare setting (10). Multilocus sequence typing (MLST) results revealed that the 27 *K. pneumoniae* strains belonged to three different sequence types: ST101, ST16, and ST11. The *K. pneumoniae* strain isolated from the incubator water was determined to belong to ST101. PFGE is regarded as a valuable tool for providing crucial information on the molecular epidemiology of bacterial strains. PFGE data, analyzed according to the criteria established by Tenover et al. (12), revealed a close relationship between the clinical and environmental strains identified as ST101, as well as with the clinical strains belonging to ST16. According to the analysis, ST16 belongs to the CG17/20 clonal group, ST101 to CG43, and ST11 to CG258 (20). CG258, comprising ST11, ST258, and ST512, is a clonal group posing a global challenge, responsible for approximately 60% of all global outbreaks (21). ST11 represents a paraphyletic group within CG258, while ST258 likely originated from an ST11-like ancestor following genomic recombination events (20). Studies have reported that ST16 and ST101 belong to sub-lineages of ST258, which are believed to have evolved due to major genomic recombination events (22, 23). Recent research suggests that ST101 is an international clone and a potential candidate for becoming an extremely high-risk multidrug-resistant *K. pneumoniae* in the future (24). According to a study conducted in South India, *K. pneumoniae* ST101 causing bloodstream infections was found to be positive for blaKPC-2 (25). In our study, the absence of the blaKPC gene indicates that the plasmid carrying this gene was not present in any of our strains. *K. pneumoniae* ST16 is an internationally prevalent clone; however, studies have reported significant variation in its antimicrobial resistance

profiles, suggesting that different variants of the clone are circulating in various countries (26). A study involving 344 *K. pneumoniae* strains from 8 different healthcare centers in India identified a 3% prevalence of ST16, which exhibited diverse genomic profiles (27). Similarly, in our study, the 13 isolates belonging to ST16 displayed varied resistance profiles, aligning with patterns observed in other studies. To our knowledge, our study is one of the first reports describing the presence of ST11 in Turkey. Initially reported from China and later identified in 1.3% of clinical *K. pneumoniae* strains in a retrospective study across 8 healthcare centers in India, ST11 isolates are known to be highly virulent and have been associated with the spread of KPC, particularly in China and Taiwan (27).

Hospital-acquired infections are a major cause of morbidity and mortality among patients presenting to healthcare facilities. Overcrowded healthcare facilities, particularly in low- and lower-middle-income countries, play a significant role in the emergence and dissemination of multidrug-resistant bacteria. Infections caused by colistin-resistant, carbapenemase-producing Gram-negative bacterial pathogens pose a significant threat due to limited therapeutic options. However, the spread of multidrug-resistant organisms can be controlled through the implementation of strict infection control measures and adherence to appropriate hand hygiene practices. In the context of the present infections, the source of the environmental strain was traced back to jars used for storing equipment water within the NICU. Personnel responsible for autoclaving the jars were informed, and corrective measures were implemented to ensure infection control.

This study investigated infections caused by colistin-resistant, carbapenemase-producing (blaNDM and blaOXA-232) K. pneumoniae among neonates admitted to the Neonatal Intensive Care Unit (NICU) at a large tertiary care hospital in Eastern Turkey. These infections resulted in severe clinical outcomes, contributing to neonatal mortality and prolonged hospital stays. Molecular epidemiology of the clinical isolates revealed the presence of sequence types ST16, ST101, and ST11. However, PFGE patterns indicated a close relationship between the ST16 and ST101 strains. Although carbapenemase-associated ST16 and ST101 are recognized as internationally disseminated clones and have been associated with *K. pneumoniae* infections in various countries, including Turkey, the ST11 clone is not a common sequence type in Turkey. One limitation of our study was the lack of whole-genome analysis of the strains, which would have provided more detailed information regarding resistance profiles and helped elucidate the dissemination patterns of high-risk clones. Furthermore, although the transmissible mcr gene contributes to colistin resistance, chromosomally mediated mutations in genes such as mgrB, phoP/phoQ, pmrA, and pmrB are also implicated; however, these alternative mechanisms were not analyzed, constituting another limitation of our study. Additionally, while the source of the ST101 strains was traced back to the equipment water, the source of ST11 could not be identified. Moreover, despite the observed clonal relatedness between the clinical ST16 isolates and the environmental ST101 isolate, follow-up surveillance failed to isolate ST16 from healthcare personnel or environmental samples, highlighting the need for more rigorous surveillance and environmental screening. However, based on the relatedness of the strains involved in these infections, we believe the equipment water was the likely primary source. Furthermore, the infections were controlled after corrective measures were implemented to ensure proper autoclaving of the jar by the relevant personnel. The prioritized detection of such high-risk clones of multidrug-resistant strains, surveillance practices, and appropriate infection control programs are crucial for preventing infections and limiting their further spread into the community.

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