Scientific Research Publishing

Open Journal of Pediatrics, 2023, 13, 450-458
https://www.scirp.org/journal/ojped
ISSN Online: 2160-8776
ISSN Print: 2160-8741

Nosocomial *Klebsiella variicola* Infection in Neonatal Intensive Care: A New Emerging Pathogen

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How to cite this paper: Hani, S., Lalaoui, A., Bennaoui, F., Soraa, N., El Idrissi Slitine, N. and Maoulainine, F.M.R. (2023) Nosocomial *Klebsiella variicola* Infection in Neonatal Intensive Care: A New Emerging Pathogen. *Open Journal of Pediatrics*, **13**, 450-458.
https://doi.org/10.4236/ojped.2023.133050

Received: April 20, 2023
Accepted: May 27, 2023
Published: May 30, 2023

Abstract

Klebsiella variicola is a human pathogen that has been misidentified as *K. pneumoniae*. This misidentification has led to a lack of understanding of important clinical and biological aspects of this bacterial species. It is responsible for serious and potentially fatal infections, with a prevalence of multi-resistance to routine antibiotics. We present through three clinical observations, the case of three newborns having been hospitalized in the neonatal intensive care unit and whose evolution was complicated by the occurrence of a nosocomial infection in front of which a blood culture was done on blood agar, with a manual antibiogram on antibiotic disks, isolated the germ *Klebsiella variicola*. The management of the newborns was initially centered on non-invasive ventilation with a bi-antibiotic therapy based on carbapenem and amikacin for two newborns and switched to colymicin for the third case. Newborn follow-up was based on assessment of general condition, clinical signs of infection, as well as a biological control made of a blood count, a c-reactive protein, a complete ionogram, and a blood culture, every four days or if signs of clinical call. The evolution was favorable for two cases with good clinical and biological improvement, and complicated by death due to alveolar hemorrhage in the third case. Given the high pathogenicity of this germ, and the frequency of misidentification, it is crucial to know the clinical spectrum of *Klebsiella variicola* infections in neonatal intensive care units, in order to adapt the antibiotic therapy and to mitigate the fulminant evolution of this germ.

Keywords

Newborn, Nosocomial Infection, *Klebsiella variicola*, Neonatal Resuscitation,

Antibiotic Therapy

1. Introduction

Klebsiella species are a group of heterogeneous pathogenic bacteria from the intestinal flora, associated with community and nosocomial infections in humans and endophytic colonization of plants.

This pathogen is a Gram-negative bacillus, mainly recovered from plants, unlike *Klebsiella pneumoniae* which is mainly isolated from humans.

This pathogen is becoming a public health concern not only for the infections it can cause but also because of its potential to acquire antimicrobial and virulence genes, thus complicating the clinical management of infections produced by *K. variicola*.

We present through these three observations, the case of two newborns having had a nosocomial infection with *Klebsiella variicola*, hospitalized in the neonatal intensive care unit of the Mohammed VI University Hospital of Marrakech during the year 2022.

2. Objective

We report through our work, the clinical, paraclinical and evolutionary profile of three neonates infected with *Klebsiella variicola*, an unusual germ in the neonatal intensive care unit, frequently isolated in a wide range of plant ecosystems.

3. Cases

3.1. Clinical Case 1

Male neonate admitted the first day of his life, from a 25 year old mother with 3 parities and 3 gestations with no particular pathological history.

The pregnancy was monofetal, estimated at 35 SA + 2 days according to the date of the last menstrual period. The newborn was premature, in whom the mother had a premature rupture of the membranes 42 hours before delivery, with a fetid and tinted amniotic fluid. He was admitted to the intensive care unit for neonatal respiratory distress secondary to a neonatal pulmonary infection. On the respiratory level, the newborn was polypneic at 72 cycles per minute, with a low SaO_2 at 86%, signs of respiratory struggle of moderate intensity such as intercostal pulling, thoraco-abdominal swaying and nasal flapping rated 5/10ème according to Silvermann's score.

The initial chest X-ray showed an alveolar syndrome involving both lung fields with thoracic distension.

The infectious workup on admission was negative, especially the blood culture, and the newborn was put on non-invasive ventilation (CPAP CNO type).

On the 3th day of hospitalization, our patient presented an increase in oxygen requirements, a febrile peak at 39.7˚, alteration of the general condition with ge-

neralized mottling, axial and peripheral hypotonia, septic complexion in favor of bacteremia, which required a repeat of the biological check-up:

The blood count showed leukoneutropenia, white blood cells at 6789/mm^3, neutrophils at 1097/mm^3, platelets at 189,000.

A c-reactive protein at 58 mg/l.

The blood culture was done on blood agar, with a manual antibiogram on antibiotic disks, which isolated a gram-negative bacillus, the identification objectified *Klebsiella variicola* sensitive to cephalosporin 3ème generation, trimethoprim sulfametoxazole, imipenem, and colistin, and resistant to amoxicillin, carboxypenicillin and cephalosporin 1ère generation.

The neonate was put on bi-antibiotic therapy with imipenem at a dose of 20 mg/kg/12h and amikacin at a dose of 15 mg/kg/d during four days.

A biological check-up was performed after four days of evolution, showing an increase of the c-reactive protein to 151 mg/l. The neonate was treated with colymicin at a dose of 10,000 IU/24h in 2 doses during 10 days.

The evolution of the newborn was favorable with good clinical improvement and negativation of the infectious balance. The newborn was declared out of our training on the 17ème day of life.

3.2. Clinical Case 2

Male neonate admitted at 3 days of life, from a 34 year old mother with 3 parities and 3 gestations with no particular pathological history.

The pregnancy was twin, estimated at 33 weeks according to the date of the last menstrual period. The newborn was premature, and the mother had a premature rupture of the membranes 27 hours before delivery. The newborn was admitted to the intensive care unit for neonatal respiratory distress secondary to stage 2 hyaline membrane disease on a premature basis. The clinical examination revealed a hypotrophic newborn, with axial and peripheral hypotonia. The newborn was polypneic at 69 cycles per minute, with a low SaO_2 of 84%, signs of respiratory struggle of moderate intensity such as intercostal and supra-sternal pulling, xiphoid funneling and nasal flaring rated 6/10ème according to the Silvermann score.

The initial chest X-ray showed an alveolar syndrome involving both lung fields with effacement of the right edge of the heart with thoracic distension.

The infectious workup on admission showed leukopenia with white blood cells at 6179/mm^3, thrombocytopenia with platelets at 49,000, c-reactive protein at 11.76 mg/l.

The neonate was put under non-invasive ventilation (CPAP CNO type), and under bi-antibiotherapy based on cephalosporin 3th generation and aminoside during four days.

On the 4th day of hospitalization, our patient presented generalized mottling with episodes of tachycardia, associated with infectious pulmonary disease on the control chest X-ray, which motivated the re-doing of the infectious work-up which objectified a rise in the c-reactive protein to 68 mg/l. The blood culture of

control was done on blood agar, with a manual antibiogram on antibiotic disks, which isolated a gram negative bacillus, the identification has objectified *Klebsiella variicola* sensitive to cephalosporin 3ème generation, aminoglycoside, imipenem, and colistin, and resistant to amoxicillin, carboxypenicillin and cephalosporin 1ère generation

The neonate was put on bi-antibiotic therapy with imipenem at a dose of 20 mg/kg/12h and amikacin at a dose of 15 mg/kg/d during 10 days.

The evolution of the newborn was favorable with good clinical improvement and negativation of the infectious balance. The newborn was declared out of our training on the 13ème day of life.

3.3. Clinical Case 3

Male neonate admitted at one day of life, from a 36-year-old mother with parity and gestation with a history of gestational diabetes on diet, with gravidic hypertension on L-Methyldopa, with notion of infertility for 6 years.

The pregnancy was monofetal, estimated at 37 SA + 1 d according to the ultrasound of the first trimester, the newborn was admitted to the intensive care unit for neonatal respiratory distress secondary to a neonatal infection with pulmonary localization. The clinical examination revealed a hypotrophic newborn, with axial and peripheral hypotonia. On the respiratory level, the newborn was polypneic at 49 cycles per minute, with a low SaO_2 at 86%, signs of respiratory struggle of moderate intensity such as intercostal and sub-costal pulling, thoraco-abdominal swaying rated 3/10ème according to the Silvermann score.

The initial chest X-ray showed an alveolar syndrome involving both lung fields with thoracic distension.

The infectious workup on admission was negative. The neonate was put on non-invasive ventilation (CPAP CNO type). On the 4th day of hospitalization, our patient presented with deep desaturations, with generalized mottling with alveolar hemorrhage. The neonate was intubated and sedated, and an infectious workup was performed, showing leukopenia with white blood cells at 3360/mm^3, thrombocytopenia with platelets at 9000, and a c-reactive protein at 145 mg/l. The control blood culture was done on blood agar, with a manual antibiogram on antibiotic disks, which isolated a gram-negative bacillus, the identification showed *Klebsiella variicola* sensitive to cephalosporin 3ème generation, Ceftazidim, imipenem, and colistin, and resistant to amoxicillin, carboxypenicillin and cephalosporin 1ère generation.

The neonate was put on bi-antibiotic therapy with imipenem at a dose of 20 mg/kg/12h and amikacin at a dose of 15 mg/kg/d during two days.

The neonate became clinically worse with septic shock. A new blood culture was done isolating *K. variicola* resistant to imipenem and aminoglycoside. The newborn was put on colistin at a dose of 10,000 IU/24h in two doses during 2 days.

The newborn died at 8ème days of life due to lightning alveolar hemorrhage complicated by a cardio-respiratory arrest.

4. Discussion

Klebsiella variicola is a Gram-negative bacterium of the Enterobacteriaceae family that was first identified in 2004 by Hauben *et al.* as a distinct species of *Klebsiella pneumoniae*. Initially considered a subspecies of *K. pneumoniae*, subsequent studies have revealed *K. variicola* to be a distinct species with significant differences in its biology and epidemiology [1].

K. variicola is a gram-negative, non-motile, non-spore forming, facultative anaerobic bacterium [2]. It has a polysaccharide capsule that contributes to its virulence and resistance to opsonization by antibodies. Like other Klebsiella species, *K. variicola* is catalase positive, oxidase negative and reduces nitrate to nitrite. It ferments glucose, lactose and starch, but does not produce indole.

Genetically, *K. variicola* shares many similarities with *K. pneumoniae*, but recent studies have identified significant differences in its genome. *K. variicola* has a smaller and less complex genome than *K. pneumoniae*, with fewer antibiotic resistance genes and virulence genes. Some strains of *K. variicola* are also known to possess a type VI secretion system, which is involved in bacterial competition and virulence [3].

K. variicola has been mainly isolated from environmental samples, such as soils, plants and roots [1] [4], as well as from animals, including insects and birds. However, recent studies have also identified *K. variicola* as an opportunistic pathogen in humans, primarily associated with nosocomial infections especially in neonatal resuscitation settings.

Immune immaturity in preterm neonates is one of the major risk factors [5]. In addition, prolonged hospitalization, frequent use of medical devices such as venous catheters, nasogastric tubes, and artificial respirators are also important risk factors. Prior antibiotic therapy also increases the risk of nosocomial infection by disrupting the balance of microbial flora in newborns, thereby promoting the growth of antibiotic-resistant bacteria, including *Klebsiella variicola*.

Cross-transmission of *Klebsiella variicola* from one neonate to another can occur through the hands of healthcare workers, contaminated medical equipment, surfaces in the healthcare environment or through the air [4] [6].

The symptomatology of *Klebsiella variicola* infections in neonates varies depending on the location of the infection. This pathogen can cause infectious pneumonitis [7] [8], meningitis, urinary tract infections, and neonatal sepsis [9] [10] [11].

Nosocomial *Klebsiella variicola* infections in neonates are a serious concern in neonatal resuscitation, as they can result in significant morbidity and mortality. Identification of *K. variicola* is not routinely sought in clinical microbiology laboratories, and misidentification of *K. variicola* as *K. pneumoniae* was documented several years ago [12] [13].

Automated systems such as Vitek 2XL, Phoenix and MicroScan are widely used in microbiology and clinical laboratories for the identification of gram-negative and gram-positive bacteria. These microbiological methods are based on

colorimetric changes in miniaturized substrates. Because the automated systems rely on the general biochemical characteristics of the *K. pneumoniae* complex, it is not possible to differentiate *K. variicola* or any other species in the complex, therefore, the automated systems will identify all isolates as *K. pneumoniae* [1].

Currently, molecular, genomic and proteomic methods are now available to ensure the identification of new bacterial species and subspecies within the K. pneumonia complex, including *K. variicola*. The use of MALDI-TOF mass spectrometry with updated databases, molecular biology techniques such as PCR and DNA sequencing, as well as *Klebsiella variicola* specific genetic markers, have been widely used to isolate this bacterium from clinical or environmental samples. In addition, the use of specific selective culture media can also facilitate the isolation of *Klebsiella variicola* from complex mixtures of bacteria [14] [15] [16].

In recent years, *K. variicola* has shown an increasing trend of developing resistance to several classes of antibiotics, including beta-lactams, aminoglycosides, fluoroquinolones, and carbapenems, making the treatment of infections caused by *K. variicola* increasingly complex and difficult [17]. *K. variicola* is inherently resistant to ampicillin due to the presence of the chromosomal β-lactamase LEN; however, it is susceptible to most classes of antibiotics [18]. This profile has largely changed over time by the increasing number of reports of multidrug-resistant *K. variicola* isolates. Similarly, reports of ESBL- and carbapenemase-producing *K. variicola* isolates have increased even though some strains have not been isolated from clinical settings, highlighting the key role of the environment as a reservoir of antimicrobial resistance genes.

In our study, one neonate (1/3) had a favourable evolution with imipenem and amikacin, while two patients (2/3) required the switch to colistin.

Long *et al.* demonstrated that *K. pneumoniae*, *K. quasipneumoniae* and *K. variicola* share chromosomal and mobile genes, which encode virulence factors and antimicrobial resistance genes. In this study clinical isolates were identified as *K. quasipneumoniae* and *K. variicola*.

The *K. variicola* isolates were identified as ESBL-producing or carbapenemase-producing isolates. The ESBLs identified were SHV and CTX-M-15. The carbapenemases identified were KPC-2 and NDM-1. One *K. variicola* isolate contained both CTX-M-15 and NDM-1 genes. The authors reported the presence of KPC-2 and NDM-5 in clinical isolates of *K. variicola*; this report is the first description of *K. variicola* producing the NDM-5 allele. Analysis of the distribution of antimicrobial resistance genes using genomic approaches revealed the presence of an OXA-48-producing isolate from a hospitalized patient in Norway [19].

Lu *et al.* described the first report of hypervirulence associated with colistin resistance. Colistin resistance was mediated by a chromosomal change in a two-component regulatory system (PhoP-PhoQ) [20].

Plasmids play an important role in the spread of antimicrobial resistance and virulence genes [21]. *K. variicola* shares a similar distribution of plasmids with other members of the *K. pneumoniae* complex, suggesting that horizontal gene

transfer between these members occurs and promotes the spread of antimicrobial resistance and virulence genes. In particular, the FIBk, FIIk, and FII replicon types were found primarily in *K. variicola* and *K. quasipneumoniae* isolates [12].

The outcome of neonates infected with *K. variicola* depends on several factors, including the severity of the infection, the gestational age of the neonate, the presence of other comorbidities, the speed of detection of the pathogen, and the treatment deployed [6]. In some cases, *Klebsiella variicola* infections can be effectively treated with appropriate antibiotics. However, in other cases, they can be severe and lead to potentially serious and life-threatening complications, including severe sepsis or severe pneumonia.

The existing methods for identification have not been widely adopted, leading to incorrect classification. *K. variicola* has unique virulence genes that are not fully understood, and further investigation of its virulence factors would contribute to a better understanding of its virulence profile.

Most typing schemes for *K. variicola* are based on data obtained from its closely related species, *K. pneumoniae*. However, due to the distinct characteristics of *K. variicola* compared to the *K. pneumoniae* complex, it would be beneficial to develop specific tools and methods for characterizing and typing *K. variicola*.

K. variicola is widely distributed in the environment and can be used in industrial processes, indicating that it possesses its own molecular typing system. Therefore, it is important to implement methods that can differentiate *K. variicola* from the *K. pneumoniae* complex, both in clinical settings and experimental laboratories.

Accurate identification of *K. variicola* is crucial because differentiating it from other Klebsiella species can have implications for patient outcomes. Understanding the specific microorganism causing an infection can help healthcare professional make informed decisions regarding treatment and management strategies [1].

5. Conclusions

Nosocomial *Klebsiella variicola* infections in the neonatal intensive care unit are a growing concern because of their impact on morbidity and mortality in hospitalized neonates. Management of these infections requires a multidisciplinary approach, including appropriate medical management, infection prevention and control, and education and training of healthcare personnel.

It is important to continue to monitor the evolution of antibiotic resistance in *Klebsiella variicola* species in order to implement effective prevention measures and reduce the prevalence of nosocomial infections with this bacterium in neonatal intensive care.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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