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Analysis of the Incidence of Klebsiella Pneumoniae in Respiratory Infections

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Annotation: Although occurrences of hypervirulent Klebsiella pneumoniae (hvKp) strains are becoming more frequent, they are still thought to be rather uncommon in the US. Between 2020 and 2022, we prospectively and serially gathered clinical isolates of K. pneumoniae found in respiratory specimens at a Western Pennsylvania health system. The string test for a hypermucoid phenotype and multiplex PCR were used to identify isolates expressing the cardinal virulence genes rmpA, rmpA2, iutA, and iro in a total of 273 K. pneumoniae isolates from 216 distinct patients. Thirteen (4.8%) of the 273 isolates, including 11 nonduplicate K. pneumoniae isolates, tested positive by the string test. Two of these isolates (0.7%) tested positive by PCR for the virulence genes rmpA, rmpA2, iutA, and iro. The second two probable hvKp strains were obtained from community-associated infections in people without known travel histories and belonged to sequence types ST23-K1 and ST86-SLV-K2. They carried pLVPK-like plasmids. Human serum did not kill the probable hvKp strains or the two other bacteria that tested positive in the string test.

animals infected by oropharyngeal aspiration developed substantial pneumonia due to the hvKp strains; animals infected with the KL1 (ST23) strain had a significantly larger bacterial burden in their lungs and a significantly higher weight loss than mice infected with the KL2 (ST86-SLV) strain. Additionally, we found that mice infected with the KL1 strain had a lower survival rate than those infected with the KL2 strain. These results contribute to the increasing amount of data indicating that hvKp strains that were previously thought to be endemic to Asia may now be spreading throughout North America.

Keywords: K. pneumoniae, Haemophilus influenzae type b, etiological fraction, genomic and phenotypic characteristics, nosocomial bacterial infections.

Introduction. Although lower respiratory tract infections (LRTIs), also known as childhood pneumonia, have significantly decreased in frequency and severity over the past ten years, they continue to be a leading cause of death for children under five, especially in low- and middle-income countries (LMICs) (GBD Lower Respiratory Infections Collaborators, 2018). The burden of pneumonia has decreased and the etiological spectrum has changed as a result of socioeconomic development, HIV pandemic control, and improved child health interventions, particularly conjugate vaccinations (pneumococcal conjugate [PCV] and *Haemophilus influenzae type b* [Hib] vaccines). Other bacteria and viruses have been linked to an increased etiological fraction of pneumonia since the widespread adoption of PCV and Hib vaccinations, with coinfections occurring particularly in cases of severe illness. Leukocytosis is usually detected by laboratory analysis, however this cannot help the clinician identify the organism that caused a patient's pneumonia. However, chest radiographs can help the doctor narrow down their differential diagnosis to include K. *pneumoniae* as a possible cause of the patient's illness. The posterior part of the right upper lung usually experiences a lobar infiltration when *K. pneumoniae* develops pneumonia [1-4]. Although *K. pneumoniae* infections are frequently linked to empyema, they seldom result in lung abscesses in patients who have pneumonia. The bulging fissure sign is another non-specific indication of *K. pneumoniae* on a chest radiograph. This has to do with how many infections and inflammations the organism may induce. One of the main causes of infections linked to healthcare, such as nosocomial pneumonia, bacteremia, and urinary tract infections, is *Klebsiella pneumoniae*. *K. pneumoniae* is now regarded as one of the most troublesome gram-negative bacteria in the healthcare setting due to its growing antibiotic resistance. However, initially in East Asia and then in other regions of the world, *K. pneumoniae* has also been identified as a community-associated pathogen that causes invasive infections such endogenous endophthalmitis, pyogenic liver abscess, and severe community-acquired pneumonia. Usually, hypervirulent strains from other lineages—specifically, those with capsular serotypes K1 and K2, which correspond to sequence types (ST) 23 and ST65/66/86, respectively—cause these community-associated illnesses [5-10]. Aerobactin siderophore biosynthesis (iuc), salmochelin biosynthesis (iro), metabolic transporter, and mucoid phenotypic regulators (rmpA/rmpA2) are among the genes frequently found in hypervirulent *K. pneumoniae* (hvKp) strains. Although hvKp strains are thought to be somewhat uncommon in the US, more

and more cases are being recorded. Four hvKp strains, belonging to ST23, ST66, and ST380, were discovered through systematic sequencing of 104 distinct *K. pneumoniae* bloodstream infection samples obtained from a hospital in the Chicago region between 2015 and 2017. Although the transmission of hvKp poses a possible public health risk, the majority of investigations conducted in the US to date have examined blood isolates that have been stored. Although *K. pneumoniae* is a common cause of pneumonia in both clinical and community settings, it is still unknown how common hvKp is and how it develops in relation to respiratory tract infections. Therefore, in order to determine the incidence of hvKp and look into their genomic and phenotypic characteristics, we screened a series of *K. pneumoniae* clinical strains that were isolated from respiratory specimens at a Pennsylvania university hospital system between 2020 and 2022 [11-17].

Gram-negative, encapsulate, and non-motile, *Klebsiella pneumoniae* is a member of the Enterobacteriaceae family. Numerous factors contribute to the bacterium's virulence, which can result in infection and drug resistance. The most significant virulence feature of the organism is its polysaccharide capsule, which enables the bacteria to avoid the host organism's opsonophagocytosis and serum death. There are currently 77 varieties of capsular bacteria that have been investigated, and the less virulent Klebsiella species that do not have a capsule are generally less common. Gram-negative bacteria's outer surface is coated in lipopolysaccharides, which are a second virulence factor. One of the main causes of the sequelae in sepsis and septic shock is the host organism's inflammatory cascade, which is triggered by the detection of lipopolysaccharides [1-4]. Fimbriae, another virulence component, enable the bacterium to adhere to host cells. Another virulence component required by the organism to infect hosts is siderophores. In order for the infecting organism to spread, siderophores must obtain iron from the host. Due to changes in the organism's basic DNA, *Klebsiella pneumoniae* is one of a few bacteria that are currently exhibiting a high rate of antibiotic resistance. The organism's enhanced synthesis of ESBL enzymes, changes to the outer membrane, and up-regulation of efflux pumps have all been connected to carbapenem resistance [5-10].

The main reservoir for *K. pneumoniae* is humans. The organism is present in the nasopharynx in 1% to 6% of people and in the stool in 5% to 38% of people in the general population. The gastrointestinal system of the patient and hospital staff members' hands are the primary sources of infection. It may cause a nosocomial infection. However, people of Chinese origin and those who suffer from chronic alcoholism have been found to have greater rates of colonization [3,4,6,9]. The carrier rate for *K. pneumoniae* is significantly greater in hospitalized patients than in the general population. According to one study, hospitalized patients' stool contains carrier rates of up to 77%, which are correlated with the quantity of antibiotics administered. There are two types of pneumonia brought on by *K. pneumoniae*: hospital-acquired pneumonia and community-acquired pneumonia. Infection with *K. pneumoniae* is rare, although community-acquired pneumonia is a reasonably common diagnosis. *K. pneumoniae* infections are thought to be responsible for between 3% and 5% of all community-acquired pneumonia in Western culture, but they can account for up to 15% of all pneumonia cases in developing nations like Africa. Approximately 11.8% of all hospital-acquired pneumonia worldwide is caused by *K. pneumoniae*. *K. pneumoniae* is responsible for 8% to 12% of pneumonia cases in patients who are on a ventilator, compared to 7% in people who are not. The mortality rate for people with septicemia and alcoholism varies from 50% to 100% [2,5,7,8].

All of the infants in the intense follow-up cohort were used to create the case-control dataset. The selection of cases was based on the presence of a matched control, a valid NP at the time of LRTI, and an LRTI episode during the first year of life. In order to compare with cases, controls were chosen from among age-matched children in the cohort who had received NP swab collection twice a week and who had a valid NP result at the relevant time point. By age of presentation and birth date (within two weeks), controls and cases were matched 1:1. Since lower respiratory tract samples from healthy controls could not be obtained, NPs were utilized to

identify possible infections in order to facilitate a case-control analysis [1,2,3,14]. LRTI episodes were divided into two categories: KP-LRTI, where the swab obtained at LRTI was positive for *K. pneumoniae* and linked to LRTI, and non-KP-LRTI, where the swab was negative but positive for other organisms. The controls (KP controls or non-KP controls) were also categorized according to whether the swab tested positive or negative for *K. pneumoniae*. Births before 37 weeks gestation were considered preterm, and those between 34 and 37 weeks gestation were considered late preterm. Fenton's growth standards were used to calculate weight-for-age Z-scores at birth (Fenton and Kim, 2013), and the WHO child growth standards were used to calculate weight-for-age Z-scores after delivery [17,18,19].

Antibiotic susceptibility test. *K. pneumoniae* isolates were incubated initially on the nutrient agar media (at 4°C) and their positive colonies were transferred to the Mueller– Hinton agar (Merck, Germany). Antimicrobial susceptibility was performed on Mueller-Hinton agar by the standard disk diffusion method recommended by the Clinical and Laboratory Standards Institute. This was done by dipping a sterile swab stick in to overnight nutrient broth and carefully swabbing the entire surface of Mueller–Hinton agar plates [11-14]. The antibiotic disk (Oxoid, UK) was used to determine the susceptibility of *K. pneumoniae* strains to the following: tetracycline (30 µg/disk), ceftazidime (30 µg/disk), ciprofloxacin (5 µg/disk), sulfamethoxazol (25 µg/disk), ampicillin (10 u/disk), trimethoprim (5 µg/disk), gentamycin (10 µg/disk), ceftriaxone (30 u/disk), amikacin (10 µg/disk), imipenem (30 µg/disk), erythromycin (15 µg/disk), and amoxicillin/clavulanic acid (20/10 µg/disc). For 18 to 24 hours, plates were incubated at 37^0C. In order to determine whether an isolate was sensitive or resistant, the diameter of the zone of inhibition was measured in millimeters and compared to the values suggested by standard charts. When determining antimicrobial susceptibility, *K. pneumoniae* ATCC 43816 was employed as a quality control organism [15-19].

Discussion. According to this birth cohort study, *K. pneumoniae* was linked to community-acquired LRTI in African newborns, particularly in those who had HIV exposure or had been born prematurely. In the setting of a well-immunized newborn population, with Hib and PCV13, virtually no childhood HIV infection, and adequate nutrition, the discovery that KP was linked to LRTI is significant and novel, with potential implications for empirical treatment. Furthermore, at a median age of 3.7 months, KP-LRTI happened after the neonatal era. KP has been identified as a significant contributor of nosocomial pneumonia and newborn sepsis in the past. After separating *Klebsiella pneumoniae* from the lungs of pneumonia victims, Carl Friedlander initially identified the bacteria as an encapsulated bacillus in 1882 [1-5]. The bacteria was first known as Friedlander's bacillus and did not get the name Klebsiella until 1886. Using a case-control design with age-matched controls from the same cohort, we demonstrated that *K. pneumoniae* was significantly linked with LRTI, despite the fact that it may be challenging to differentiate causality from colonization. Using the same PCR technology, the multicenter PERCH study also employed a case-control methodology to determine the etiology from NP sampling of children admitted with severe or very severe pneumonia. Gram-negative, encapsulated, non-motile *Klebsiella pneumoniae* is a common environmental bacterium that has been linked to pneumonia in patients with diabetes mellitus and alcohol use disorders. Human mucosal surfaces of the gastrointestinal (GI) tract and oropharynx are usually colonized by the bacteria [6-10]. The bacteria may exhibit significant levels of pathogenicity and antibiotic resistance once it has entered the host. In the United States, *K. pneumoniae* pneumonia is currently thought to be the most frequent cause of hospital-acquired pneumonia, accounting for 3% to 8% of all nosocomial bacterial infections. An increasingly important Gram-negative bacterial infection that can cause major organ damage and even death is *Klebsiella pneumoniae*. The two pathotypes of *K. pneumoniae* that are currently recognized as classical *K. pneumoniae* (cKp) and hypervirulent *K. pneumoniae* (hvKp) present distinct challenges for medical professionals. Although both pathotypes are widespread throughout the world, the incidence of hvKp infections has steadily increased in the countries that comprise the Asian Pacific Rim

during the last three decades. While cKp has long been the most prevalent offending agent in Western countries, infections caused by hvKp are becoming more well-known outside of Asia [11-15]. The specific combination of siderophores secreted by *K. pneumoniae* during infection can have an impact on tissue localization, systemic dispersion, and host survival. In particular, gene clusters encoding the synthesis of the siderophores aerobactin (iuc) and salmochelin (iro) are commonly observed in hypervirulent *K. pneumoniae* clones that cause severe community-related illnesses such liver abscess and pneumonia, and they are associated with invasive illness. But as worrisome are instances of iuc in MDR strains in a hospital setting [11, 14, 17,18].

Conclusion. Even with proper treatment, the fatality rates from *Klebsiella pneumonia*, a dangerous infection, are still high. An interprofessional healthcare team of a respiratory therapist, pulmonologist, nutritionist, intensivist, pharmacist, nurse, and infectious disease specialist is the most effective way to treat this infection. To stop the organism from spreading, nurses who care for these patients should adhere to stringent infection control procedures. For both tourists and medical staff, hand cleansing is essential. To reduce transmission, nurses should make sure that devices are only used once.

The pharmacist should make sure that an empirical antibiotic prescription is not filled because doing so will simply cause drug resistance to grow. To maximize their calorie intake, a nutritional consultation should be requested because many of these individuals are fragile. Lastly, a physical therapy consultation should be taken into consideration to help with movement and prevent joint stiffness, as many of these patients are bedridden.

Tissue localization, systemic dispersion, and host survival may all be impacted by the specific combination of siderophores secreted by *K. pneumoniae* during infection. In particular, hypervirulent *K. pneumoniae* clones that cause severe community-associated diseases including pneumonia and liver abscess often have gene clusters that encode the synthesis of the siderophores salmochelin (iro) and aerobactin (iuc), which are linked to invasive sickness. On the other hand, findings of iuc in hospital-associated MDR strains are similarly alarming.

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