Novel Research in Microbiology Journal (2023), 7(1): 1857-1872
Review Article

(Print) (ISSN 2537-0286)
(Online) (ISSN 2537-0294)
https://nrmj.journals.ekb.eg/
DOI: 10.21608/nrmj.2023.287177

Hypervirulent *Klebsiella pneumoniae*: Epidemiology, virulence factors, and antibiotic resistance

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Received: 28 January, 2023; Accepted: 22 February, 2023; Published online: 24 February, 2023

Abstract

Human infections induced by *Klebsiella pneumoniae* (*K. pneumoniae*) include pneumonia; urinary tract infections, liver abscesses, bacteremia, and others. The introduction and spread of the hypervirulent *K. pneumoniae* (hvKp) strains have raised the number of persons who are already susceptible to infections, including those who are healthy or immune-compromised. Infections can occur worldwide; however, they are particularly prevalent in the Asia-Pacific area. Virulence plasmids as well as other conjugal components contain the genetic material that gives hvKp its hypervirulence phenotype. Although the vast majority of hvKp isolates are antibiotic-susceptible, the incidence of virulent as well as resistant isolates, such as carbapenem-resistant hvKp isolates, is continuously growing. Multidrug resistance (MDR) and increased virulence of these strains may be the cause of the subsequent clinical crisis. This study aimed to review and analyse the epidemiology, the factors associated with hypervirulence, and the mechanisms of antibiotic resistance of the hvKp strains in order to provide a better understanding of the basic biology of these strains.

Keywords: Hypervirulent *Klebsiella pneumoniae*, Hypermucoviscosity, Aerobactin, Virulence plasmids

1. Introduction

The Gram-negative bacterium known as *Klebsiella pneumoniae* (*K. pneumoniae*) can impose serious community-acquired diseases, and causes major infections in the immune-compromised individuals (Paczosa and Mecsas, 2016). *K. pneumoniae* is receiving more attention due to the surge in infections that it causes, in addition to the significant number of strains that are resistant to antibiotic therapy. *K. pneumoniae* is currently considered as one of the most widespread bacterial causes of pyogenic liver abscesses, a significant clinical problem concerning *K. pneumoniae* appears to

exist. According to the several studies conducted by the US institutions, *K. pneumoniae* has lately eclipsed *Escherichia coli* (*E. coli*) as the main cause of liver abscess (Shon *et al*., 2013). A previous study reported by Al Kaabi, (2019) that *K. pneumoniae* species that cause these intrusive infections are generally known as hypervirulent *K. pneumoniae* (hvKp); however, when grown on agar plates, they have a hypermucoviscous phenotype. This could be attributed to the overabundance of capsule polysaccharides in this bacterium. A relationship has also been discovered between the carriage of virulence plasmids and the hypervirulence phenotype (Tang *et al*., 2010).

2. Comparison between hypervirulent and classical *K. pneumoniae*

The ability of *K. pneumoniae* to acquire more genetic material is a critical characteristic that has allowed it to evolve. According to Shon *et al*., (2013), there are two circulating forms of *K. pneumoniae*: the hvKp and the classical strain of *K. pneumoniae* (cKp), both of which provide unique challenges to the clinicians. Throughout the past three decades, although the predominance of hvKp infections has steadily grown in the Asia Pacific Rim nations, however these pathotypes remain global bugs (Chang *et al*., 2012).

Despite the reality that hvKp infections are growing more widespread outside of Asia; however, cKp has long been considered as the most typical source of sickness in the Western countries (Fazili *et al*., 2016). All clinicians are aware that cKp is an aggressive pathogen that affects the immune-compromised patients, patients who experience a barrier breach in the healthcare settings, and who also have several comorbidities, including intravascular devices, an endotracheal tube, or a surgical wound. The hvKp is best classified as a pathogen that has high virulence (Rossi *et al*., 2018).

Most hvKp infections are community-acquired. The ability of hvKp to infect healthy persons of any age, as well as those infected patients in several locations and\ or later metastatic spread; all are attributed to hvKp infection, which is distinct from that of the other members of the *Enterobacteriaceae*. In the absence of a biliary tract illness, the most common clinical affection induced by hvKp infection is a hepatic abscess. On the other hand, hvKp can infect almost all of the body's organs. Non-hepatic abscesses; pneumonia, necrotizing fasciitis, endophthalmitis, and meningitis, are few examples of the infectious disorders (Russo and Marr, 2019).

Initially, it has been thought that hvKp strains may be more specific and sensitive to the positive string test for such a hypermucoviscous phenotype (Fang *et al*., 2004). Later, this has been discovered to be erroneous, because not all hvKp strains are hypermucoviscous, and some cKp strains exhibit this feature as well (Catalan-Najera *et al*., 2017; Russo *et al*., 2018).

HvKp isolates better grow and survive after being introduced into the body than the cKp isolates. Infection can not usually result from simple entering, the bacteria must be able to persist and grow in the presence of host defences. The host's state, the innate virulence of the bacterial strain, and the infecting inoculum, all collaborate to accomplish this invasion. Infection with the virulent strains is possible if its inoculum is high or when the host is injured. In contrast, hvKp has been classified as a specialized pathogen due to its pathogenicity and attacks on the healthy hosts, thus a small inoculum of this pathogen can cause a disease. The capacity of these hvKp species to withstand the bactericidal effects of antimicrobial medicines; complements, and phagocytes in the absence of antibodies is a harmful property (Pomakova *et al*., 2012).

3. Virulence

The hypermucoviscosity or hypermucoviscous phenotype of hvKp is often attributed to an increase in the capsular polysaccharide production, and the presence of specific virulence genes, such as *rmpA* (Paczosa and Mecsas, 2016). The 'string test' is

typically used to determine the hypermucoviscosity trait. A positive string test is observed when the bacterial colonies growing on an agar plate at 37°C become stretched, and develop a mucoviscous string of > 5mm (Lee *et al*., 2017).

The genes implicated in virulence have been investigated as possible molecular indicators for hvKp detection (Russo *et al*., 2018). *Peg-344* (metabolic transporter), *iuc* (biosynthetic genes for such siderophore aerobactin), *rmpA*, and *rmpA2* (regulators that promote the capsule formation), are the most well-known virulence factors with an experimental evidence for conferring the hypervirulent phenotype (Russo *et al*., 2015; Bulger *et al*., 2017).

4. Factors linked to hvKp hypervirulence

Many hypervirulence-related features are present in the hvKp strains, including the virulence plasmid, a pathogenicity island, sequence types, multiple virulence factors, and capsular serotypes.

4.1. KPHP1208 pathogenicity island and pLVPK virulence plasmid

Due to the importance of hvKp isolates in the human infections; especially in people without underlying a disease or an immunodeficiency, it is necessary to use an appropriate laboratory method to obtain an accurate diagnosis of these isolates.

According to Struve *et al*., (2015), a big virulence plasmid has been detected across all the hvKp clonal lineages, which has its entire genome being sequenced (*pLVPK* and *pK2044*-like plasmid). Aerobactin, salmochelin, and *rmpA* that exist only in the hvKp isolates, are encoded by this plasmid. Lin *et al*., (2011) observed that a CC23 clonal complex strain missing *pLVPK* has a considerably reduced virulence, indicating that this plasmid plays a critical function in hvKp. Through genomic research, a new pathogenicity island variation (KPHP1208) has been also discovered that is linked to CC23 clonal complex (Struve *et al*., 2015).

4.2. The mucoid phenotypic regulator A gene (*rmpA*)

The *rmpA* (mucoid phenotypic regulator A gene) promotes capsule synthesis, resulting in hypermucoviscosity and pathogenicity of *K. pneumoniae* (Lin *et al*., 2020). Two large plasmids carry genes (*p-rmpA* and *p-rmpA2*) that are located on the virulence plasmid (*pLVPK*), in addition to a third gene (*c-rmpA*) that is carried on the bacterial chromosome, have been discovered in hvKp strains (Hsu *et al*., 2011). After whole genome sequencing, about 30 hvKp strains that have been recovered from various geographic origins, are positive for *rmpA* (Struve *et al*., 2015). Numerous Chinese researchers have discovered that about 92-100 % of the tested hvKp samples are positive for *rmpA* (Sun *et al*., 2016; Wu *et al*., 2017). Regardless of the investigated infection site, most of the hvKp isolates appear to have the *rmpA* gene (Guo *et al*., 2016; Wu *et al*., 2017; Zhan *et al*., 2017). Although both of hvKp and *rmpA* have a substantial correlation; however, certain *rmpA*-positive isolates have not shown the hypermucoviscosity phenotype (Yu *et al*., 2006).

4.3. The mucoviscosity-associated gene A (*magA*)

The *magA* gene has been identified to be critical for the hypercapsular phenotype in *K. pneumoniae* strains, which have been isolated from intrusive liver abscesses throughout 2004 (Fang *et al*., 2004). Later, a genetic study and bioinformatic analysis have indicated that *magA* is indeed the serotype K1 allele (Yeh *et al*., 2010). *MagA* has been linked to the capsule serotype K1 in numerous previous studies conducted by Yeh *et al*., (2006); Guo *et al*., (2017).

4.4. Aerobactin

Hsieh *et al*., (2008) highlighted that in iron-depleted environments; for example in a human host, *K. pneumoniae* can release some iron-acquiring siderophores (eg. aerobactin, enterobactin, salmochelin, and yersiniabactin). When compared with the cKp strains, hvKp strains have shown a 6 to 10-fold higher action of siderophores (Russo *et al*., 2014).

Over 90 % of the examined enterobacterial isolates have produced enterobactin as a siderophore (Raymond *et al*., 2003). The majority of hvKp isolates contain salmochelin and aerobactin siderophores (Paczosa and Mecsas, 2016). Despite the fact that hvKp secretes four different types of siderophores; however, aerobactin remains responsible for more than 90 % of the siderophores activity (Russo *et al*., 2014). Furthermore, aerobactin rather than salmochelin, enterobactin, or yersiniabactin, is essential for growth and retention of the hvKp strains throughout the human ascites fluid or serum, in addition to the in-vivo mouse infection models, indicating that aerobactin is an important virulence factor of hvKp (Russo *et al*., 2015).

The *iucABCD* operon encodes for aerobactin, while the *iutA* gene encodes for its corresponding receptor (Russo *et al*., 2014). Numerous investigations conducted by Ye *et al*., (2016); Zhang *et al*., (2016); Zhao *et al*., (2016); Wu *et al*., (2017); Zhan *et al*., (2017) have revealed that compared to cKp strains, the hvKp strains have shown a greater frequency of the *iucABCD* and *iutA* genes.

4.5. Capsular serotypes K1 and K2

Encapsulated pathogens such as *K. pneumonia*; use the capsule as a virulence factor. *K. pneumoniae* has about 78 serotypes of capsular polysaccharides as a minimum (Wyres *et al*., 2016). Several studies have found a link between both the K1& K2 serotypes and the hvKp (Paczosa and Mecsas, 2016; Catalán-Nájera *et al*., 2017).

In an *in vivo* mouse model, serotypes K1 and K2 of *K. pneumoniae* isolates have substantially more harmful impact than the non-K1/K2 isolates; with recovery rates of 0 vs. 79.2 %, respectively (Yeh *et al*., 2007). Despite their hypermucoviscosity, both K1 and K2 strains are much more resistant to phagocytosis and to the intracellular death induced by neutrophils and macrophages, compared with the other serotypes (Lee *et al*., 2014; Paczosa and Mecsas, 2016). Many characteristics have been offered to explain why the K1 and K2 strains are more virulent than the other strains. First, the K1 as well as K2 strains, lack certain mannose residue repeats, which are recognized by the host elements, including the macrophage mannose-binding receptor and the lung-secreted surfactant protein A (SP-A) (Sahly *et al*., 2008). Second, the surfaces of K1 & K2 strains contain host-specific monosaccharide (sialic acid), which is known to mimic the host cells and helps in avoidance of the immune cells (Lee *et al*., 2014). Thirdly, the K1 and K2 strains cause the neutrophils to produce fewer reactive oxygen species (ROS) compared with the other serotypes, thus allowing them to live longer in the human tissues (Paczosa and Mecsas, 2016). Fourth, compared with the other K serotype strains, the K1 and K2 strains have more diverse O serotypes, which may help the K1 and K2 viruses to evade the host immune systems (Follador *et al*., 2016). The non-K1 or K2 serotypes are found in some strains of hvKp (Fang *et al*., 2007; Shon *et al*., 2013). Beside the K1 and K2, the other capsular serotypes detected in hvKp, include K5, K16, K20, K28, K54, K57, K63, and KN1 (Guo *et al*., 2017).

A previous study reported by Yu *et al*., (2008) has assessed the prevalence and importance of *K. pneumoniae* virulence determinants in the liver abscesses; among samples with capsular K1\K2 serotypes and samples without the-K1\K2 serotypes. Results have shown that *K. pneumoniae* isolates with the hypermucoviscosity phenotype in addition to the existence of the *rmpA*, *iucABCD*, and *iutA* genes, have demonstrated significant virulence and lethality for the mouse model; irrespective of the capsular serotypes (Yu *et al*., 2008).

K. pneumoniae isolates of serotypes K1 and K2 have displayed considerably higher phagocytic resistance and virulence compared with the non-K1\K2 bacteria, demonstrating that the existence of the K1\K2 serotypes is responsible for the enhanced virulence. These findings imply that the presence of K1\K2 serotypes contributes to the hypervirulence of hvKp strains, and their combination with the other hypervirulence-associated characteristics may also

increase the *K. pneumoniae* virulence (Yeh *et al*., 2007).

4.6. The hvKp strains and creation of a biofilm

A bacterial biofilm is a clump of cells that can exist on a surface and is coated with layers of polysaccharides; proteins, and DNA. The ability of bacteria to form a biofilm increases their resistance to the host defence elements and to the antimicrobials, and is well-recognized as a key virulence trait (Thornton *et al*., 2012). Biofilm production has been proven to be a key factor in the closed-space infections even when there is no foreign body exists (Yamanaka *et al*., 2011). A slimy extracellular matrix that is made up of extracellular polymeric molecules (EPS) surrounds the adhering cells in a biofilm. The hvKp strains make much more biofilm than the cKp strains, indicating that biofilm formation may play a role in the hvKp pathogenesis (Wu *et al*., 2011).

5. Antibiotic resistance in *K. pneumoniae*

There are two forms of antibiotic resistance observed in *K. pneumoniae*. Production of extended-spectrum β-lactamases (ESBLs) is a technique that renders the bacteria resistant to cephalosporins and monobactams. The development of carbapenemases by *K. pneumoniae* represents a more dangerous route of antibiotic resistance, which renders this bacterium resistant to practically all known ß-lactams, including the carbapenems.

5.1. Extended-spectrum β-lactamases

K. pneumoniae resistance to ampicillin as well as to carbenicillin is attributed to the manufacture of SHV-1-β-lactamase, which is encoded on the chromosome. The development of extended-spectrum β-lactamases (ESBLs) is the primary cause of the third-generation cephalosporin resistance. Penicillins, first, second, and third-generation cephalosporins, in addition to aztreonam, are hydrolyzed mainly by these plasmid-mediated enzymes. ESBLs producing *K. pneumoniae* are resistant to cefoxitin and carbapenems, however they're susceptible to β-lactamase inhibitors. Resistance to cotrimoxazole, fluoroquinolones, and aminoglycosides, are among the other resistance mechanisms that are encoded by ESBLs-carrying plasmids (Hennequin and Robin, 2016).

The ESBL enzymes *SHV-1* and *TEM-2* genetic variants have been discovered in most ESBL-producing *K. pneumonia*. The widespread use of gene sequencing to locate the lactamase genes in the clinical isolates has led to the discovery of several variations of the common TEM and SHV enzymes. Recently, about 243 TEM and 228 SHV variants have been discovered; however not all of them exhibit the ESBL phenotype (Castanheira *et al*., 2021). In the 1990s, a new ESBL family known as the *CTX-M* has been introduced. The CTX-M enzymes have emerged as the most popular types of ESBL; with CTX-M-15 being the most common in *K. pneumoniae* (Calbo and Garau, 2015). In *K. pneumoniae*, the development of β-lactamase is the earliest mechanism of resistance to β-lactams, followed by the permeability changes and the efflux pump extrusion (Mejía-Zambrano, 2022).

5.2. Carbapenems

In the late 1980s, carbapenems have been introduced to the hospitals, and proved to be particularly successful in treating *K. pneumoniae* infections that produce ESBLs (Paterson *et al*., 2004). The carbapenem resistant *Enterobacteriaceae* (CRE) produces MBL IMP-1, which is a carbapenem-hydrolyzing enzyme that is encoded on plasmids, and can be transmitted from one species to another. Verona integron-encoded metallo-β-lactamase (VIM-1) has been identified in the *Enterobacteriaceae* family of bacteria (Bahmani, 2019). In 1996, a carbapenem-resistant *K. pneumoniae* strain has been discovered in the United States, and this strain has developed *K. pneumoniae* carbapenemase (KPC) as a new carbapenemase (Yigit *et al*., 2001). This plasmid-encoded KPC gene is capable of efficiently hydrolyzing both the oxyimino-cephalosporins and the carbapenems. *K. pneumoniae* bacterium that causes KPC has spread throughout the United States and in

many other countries, thus generating outbreaks and endemicity in these areas (Munoz-Price *et al*., 2013). OXA-48 is a new group of carbapenemases, which has appeared in the early 2000s and spreads mostly to *K. pneumoniae* in the Mediterranean nations; coinciding with the rise in KPC inside the United States and across the world (Mlynarcik *et al*., 2020).

NDM (New Delhi metallolactamase) has been detected in carbapenem-resistant *K. pneumoniae* as well as in *E. coli* in a patient who has been relocated in 2009 from India (Yong *et al*., 2009). Later, NDM-1 has rapidly spread throughout South Asia and the rest of the world (Nordmann *et al*., 2011). The most frequent cause of carbapenem resistance in Gram-negative bacteria is the production of carbapenemase. Carbapenemase synthesis usually leads to clinically substantial carbapenem resistance (Iovleva and Doi, 2017).

5.3. Antibiotic-resistant hvKp

Except for ampicillin resistance, many hvKp strains are antibiotics sensitive and resistant to the commonly used antimicrobial medications (Paczosa and Mecsas, 2016). Recently, antibiotic-resistant hvKp strains have evolved as a result of the global dissemination of the mobile genetic components, which harbor several antibiotic-resistance genes, including carbapenemases from *K. pneumoniae* (KPC), NDM, and oxacillinases-48 (OXA-48) (Lee *et al*., 2016; Mlynarcik *et al*., 2020).

In 2010, Taiwanese researchers have examined numerous characteristics of *K. pneumoniae* isolates either with or without the hypermucoviscosity trait. Results have revealed that the incidence of ESBL is much greater in the *K. pneumoniae* isolates; even those isolates without the hypermucoviscosity phenotype (Lee *et al*., 2010).

China has uncovered several ESBL-producing hvKp strains that cause bloodstream infections (Liu *et al*., 2014; Yan *et al*., 2016). Another Chinese investigation conducted by Lee *et al*., (2014) has revealed that 17 % of the hvKp strains have ESBL, and that certain hvKp isolates have shown resistance to all the antimicrobials; except for carbapenems and amikacin. According to Zhang *et al*., (2016) study, 12.6 % of the hvKp isolates with invasive infections have generated ESBLs, where the majority have been harboring *blaCTX-M* genes (Zhang *et al*., 2016). In China, the prevalence of hvKp among the carbapenem-resistant *K. pneumoniae* strains has ranged from 7.4 % to 15 % (Guo *et al*., 2017). The *blaKPC-2* gene has been detected in the majority of the carbapenem-resistant hvKp isolates (Guo *et al*., 2017).

In several countries; including China, KPC-2 is the most often detected carbapenemase in *K. pneumoniae* (Lee *et al*., 2016). A recent research conducted by Xie *et al*., (2021) has demonstrated that the classic ST23 K1 HvKP strains have acquired plasmids that include different carbapnemase genes, such as *blaKPC-2*, *blaVIM*, or *blaNDM*, which caused them to evolve further and become multidrug-resistant, particularly to carbapenem.

6. Host immune defences

Paczosa and Mecsas, (2016) reported that to induce infection, *K. pneumoniae* should overcome the mechanical barriers, in addition to the cellular and humeral innate immune systems. The mechanical mucociliary elevator, which consists of mucus covering the respiratory system that catches the particles and germs and then shuttles them up and out through the ciliary lining, represents one of the first human defences against the respiratory tract diseases. In addition, the flow of urine through the genitourinary tract exerts strong mechanical stress on *K. pneumonia*.

Accordingly, after passing through these early mechanical hurdles, *K. pneumoniae* must cross the cellular and humeral inherent defences. The antimicrobial factors produced by the immune system have a variety of functions, including those that are opsonic, bactericidal, and bacteriostatic, and they make up the humeral defences. For example, the complement system is a humeral defence that can kill

the bacteria through a variety of methods (Merle *et al*., 2015). For the immunological effector cells, the pro-inflammatory mediators and chemo-attractants are also generated when the complement cascade becomes initiated. Some complement components can also operate as opsonins that facilitate phagocytosis through binding to the pathogens (Clegg and Murphy, 2017).

A previous study by Coya *et al*., (2015) added that two more humeral defences are used to prevent the bacterial infections, such as defensins, which are bactericidal proteins that exist in the lungs and destroy the bacterial membrane, in addition to transferrin, which is a bacteriostatic factor that adsorbs iron; a vital element for growth of bacteria. Both of the surfactants and immunoglobulins can operate as phagocytosis opsonins. Within the lungs, the surfactant protein A (SP-A) and allocation of the SP-B proprotein can enhance the neutrophil enrolment and *K. pneumoniae* killing.

7. **Pathogenesis of infection**

Acquisition, which results in bacterial colonization, is most likely the first step required for eventual endogenous hvKp infection (Shon *et al*., 2013). The infection rates in hvKp-colonized patients are unknown, just as the time interval between acquisition and infection. The gastrointestinal system is much more commonly colonized, whereas the oropharynx and skin are less commonly colonized (Fung *et al*., 2012).

According to a previous study conducted on other *Enterobacteriaceae*, such as *E. coli* and cKp, the food, water, personal transmission, and animal-to-person transmission are all plausible pathways for bacterial acquisition and subsequent colonization by these bacteria (Johnson and Russo, 2005). Although hvKp infection is most common in the ambulatory persons; however, it has been reported also in the healthcare facilities (Lee *et al*., 2006). Furthermore, due to the hvKp's inherent virulence; infection in patients with co-morbidities (e.g. cancer) may lead to a serious disease. As a result, contact with the healthcare workers or inanimate items within the facility may be a cause of infection by hvKp, and thus effective infection control measures should be addressed (Lin *et al*., 2010).

The next essential step in hvKp pathogenesis is the entry into an extra-intestinal organ or location. The cKp as well as other *Enterobacteriaceae* use a variety of invasive mechanisms, including bowel disruption, to allow the bacteria to colonize the gastrointestinal tract in order to invade the peritoneal cavity. In addition, macro- or micro-spiration of the oro-pharyngeal inhabitants to the respiratory tract, in addition to interference with the integrity of the skin barriers, are possible mechanisms of bacterial invasion and infection (Johnson and Russo, 2005). The oropharyngeal colonization and micro- or macro-aspiration often cause pneumonia. Although some hvKp patients appear to have aspiration pneumonia; however this is not always the case (Lin *et al*., 2010).

8. Epidemiology and clinical diseases

Complete understanding of the frequency and scope of hvKp disease is lacking, due to the lack of an objective diagnostic tests. The lack of unambiguous genotypic\ phenotypic markers for hvKp has made it difficult to gain a thorough grasp of the diseases caused by hvKp. Although the best available laboratory-based surrogate measure is the positive "string test," which shows the hypermucoviscous phenotype; however, it is uncertain if all hvKp strains have this characteristic or not. Furthermore, this test is not performed regularly in the clinical laboratories (Wyres *et al*., 2016).

HvKp infections cause severe morbidity and death. Community-acquired pneumonia with bacteremia and necrotizing fasciitis are both remarkable infections that have high fatality rates (Lin *et al*., 2010). Furthermore, the survivors of hvKp-associated infections in the crucial areas frequently experience severe morbidities, including visual loss and neurologic sequelae (Cheng *et al*., 2012).

9. Common sites of infection by HvKp

9.1. Pyogenic liver abscess (PLA)

The defining symptom that led to the diagnosis of hvKp is the primary pyogenic liver abscess (PLA), which has been observed in the ambulatory patients without biliary illness (Shon *et al*., 2013). HvKp is most likely hematogenously transmitted through the portal or systemic circulation. There are several reports of re-infections at the same or different sites; often by the same strain, months to even more than a year after completion of therapy, which are circumstantial but interesting and require more investigation (Fierer *et al*., 2011; Harada *et al*., 2011). HvKp also causes splenic abscesses that could be attributed to primary or secondary infections (Lee *et al*., 2011).

9.2. Pneumonia

Community acquired pneumonia caused by hvKp with or without primary lung abscesses, has been rarely documented. A recent study has been conducted by Hirai *et al*., (2020), which included a literature review has recorded only 10 reported cases of pneumonia in total; with 5 of these patients having bacteremia and 5 experiencing septic shock. About 50 % of these patient cases have unfortunately died. Among the 10 cases, 4 have had diabetes as a comorbidity. The studies in this review have been all recorded in South America, Japan, and Taiwan (Hirai *et al*., 2020; Fliss *et al*., 2022).

9.3. Endophthalmitis

The PLA patients have a 0.83–11 % chance of having endogenous endophthalmitis (EE), which results from the hematogenous dissemination (Sng *et al*., 2008). EE develops in 4.8 % of individuals suffering from hvKp bacteremia (Lee *et al*., 2006). Even with intensive therapy, the prognosis of EE is miserable with diminished vision and blindness being the most typical outcomes (Serban *et al*., 2021).

9.4. Meningitis

In the absence of neurosurgery or head trauma, *K. pneumoniae* appears to become a frequent source of community-acquired meningitis (Chang *et al*., 2012). In the context of meningitis, subdural empyema; brain abscess, and epidural abscess, all have all been reported and documented either alone or in combination (Doud *et al*., 2009).

9.5. Soft tissue and musculoskeletal system diseases

The hvKp has appeared as a common agent of the necrotizing fasciitis; with an identical number of instances and a higher death rate than group A Streptococcus (Cheng *et al*., 2012), psoas abscess (Mita *et al*., 2012), septic arthritis (Kishibe *et al*., 2016), and osteomyelitis (Chang *et al*., 2001). All these soft tissue and musculoskeletal system infections have been described and may be the source sites of bacterial infection.

9.6. Urinary tract

HvKp bacteremia has been connected to the urinary tract infections (Lee *et al*., 2006). Bacteremic spread towards the kidneys; perinephric area, and prostate that culminates in the formation of an abscess, has been widely documented (Shon *et al*., 2013).

10. Treatment options

The hvKp strains could be the next emerging "superbugs". The necessity to drain abscesses/closed space infections is a key principle of the infectious disease treatment. Because hvKp strains are known to cause abscesses, source control is an important part of the overall therapeutic strategy. Opening surgical drainage is unusual in the today's era of interventional radiology and percutaneous draining of the treatable abscesses. However, the hvKp's physical feature of hypermucoviscosity may make draining of catheter difficult (Shon *et al*., 2013).

10.1. Antimicrobials

The effective management of hvKp infections demands on combination of sufficient source control and ongoing antibiotic treatment. The length of

treatment varies from two to six weeks; depending on the extent and location of the infection. Drainage of liver abscesses has been linked with a lower risk of metastatic infection and mortality. It is essential to note that all *K. pneumoniae* strains have inherent resistance to ampicillin. No studies have specifically assessed the most effective antibiotics for treating hvKp infections, thus the physicians should consider the local antimicrobial resistance patterns and the site of infection when selecting an empirical antibiotic therapy (Choby *et al*., 2020). There is a lack of data and trials to determine the best antibacterials for treating hvKP infections. Meanwhile, the occurrence of multi drug resistance (MDR) in hvKP is increasing along with health care-associated infections. Recommendations have been made to use newer combinations of antibacterials, including ceftazidime–avibactam, meropenem–vaborbactam, and imipenem–relebactam, for effective treatment of CR-Kp infections. However, these antibacterials are not effective in treating infections caused by class β-carbapenemases, which are a major factor of carbapenem resistance in these isolates; as demonstrated in this study conducted by Banerjee *et al*., (2021), and in other studies from several developing countries. It's vital to remember that due to the low penetration ability of some antibacterials, several hvKp-infected locations pose more therapeutic problems. Based on the susceptibility data, ceftriaxone and meropenem are effective antimicrobial agents for treatment of central nervous system (CNS) infections. Several antibiotics, including trimethoprim-sulfamethoxazole, fluoroquinolones, and\or fosfomycin, can produce therapeutic concentrations in the prostate. However, the ocular infection has been treated with a mixture of systemic and intravitreal medications (e.g., cefazolin, ceftazidime, aminoglycosides, and imipenem). Moreover, the use of intraocular steroid therapy has been reported (Xu *et al*., 2018).

10.2. Passive immunization

The increasing incidence of extensive drug-resistance (XDR) and pan-drug-resistant (PDR) strains, in addition to the increased development and usage of monoclonal antibodies (MAbs) for treating many medical problems, have raised the interest of hvKp antibody-based treatment (Wang-Lin *et al*., 2017). MAbs directed against the K1 bacterial capsule have been used efficiently *in vitro* to treat and\ or prevent hvKp infection (Diago-Navarro *et al*., 2017). Passive immunization must resist the antigenic diversity of the bacterial surface polysaccharides to avoid hvKp infection (Follador *et al*., 2016).

10.3. Phage therapy

The current incidence and inadequate treatment choices for MDR hvKp necessitate finding potential alternative approaches. The use of phages has been well reported and is a proven strategy across the globe to fight MDR pathogens. Bacteriophages are natural predators of bacteria with the self-replicating ability and rigorous specificity to spot and destroy the bacterial host through taking over the cellular machinery (Aslam *et al*., 2021). Different structural components of the bacteriophages are responsible for lysis of the bacterial host, including endolysins, holins, and spanins. These components play a significant part in the assembly and release of the bacteriophages from the host bacteria. The endolysins degrade the peptidoglycans, whereas the holins and spanins disrupt the cell membrane. These specific particles efficiently kill the bacteria without causing any harm to the human microbiota; so unlike the antibiotics, the bacteriophages have no side effects, i.e., antibiotic-associated diarrhea. Additionally, the bacteriophages neither produce any type of toxins nor disseminate antibiotic resistance genes (Aslam *et al*., 2022).

Conclusion

The progressive hvKps diseases have some dangerous traits that are not observed in cKp infections. HvKP infects people who are young or who do not have any co-morbidity. The hvKp strains are mostly associated with the community-associated infections. In addition, hvKp infections have a mortality incidence of 3 to 42 %, and are frequently

linked to deadly disseminated infections. These pathogenic features of hvKp may be primarily involved in its hypervirulence. Many virulence factors, including the K1\K2 serotypes, *RmpA*, and aerobactin, appear to be closely related to hvKp hypervirulence. The precise hvKp's phenotypic and genotypic traits must be defined, and the determinants of hvKp hypervirulence need to be investigated further. These hypervirulence-related parameters of hvKp can be used to develop new therapeutics. HvKp infection management is challenging; therefore the morbidity and death rates will continue to rise. A combination of hypervirulence and multiple or pan-drug resistance in hvKp infection may lead to a "post-antibiotic" situation.

Acknowledgement

None.

Conflict of interest

There have been no documented conflicts of interest by any author about this study.

Funding

No financial support was received for this work.

Ethical approval

Non-applicable.

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