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(REVIEW ARTICLE)

Hypervirulent Klebsiella pneumoniae: Characteristic and clinical perspective

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Abstract

Background: *Hypervirulent K. pneumoniae* (hvKP). A virulent pathogen that has the ability to infect individuals in various age, has multiple ports of entry and cause infectious syndromes. Therefore urges an increase awareness and perspective on the characteristics and clinical feature of hvKP, to better understanding and providing appropriate treatment in cases of infection caused by hvKP.

Main Text: *Hypervirulent K. pneumoniae* (hvKP) was first reported in Taiwan in 1986. This bacteria was responsible for liver abscess with septic endophthalmitis, of these cases some of patient have extrahepatic complications such as meningitis pneumonia, prostate abscess and pyogenic ophthalmia. There are several virulence factors hvKP such as, capsule as the main defensive factor, aerobactin provide iron supply and Colibactin can suppressing the activity of regulatory T lymphocyte cells, could improve survival hvKP by avoid the process of phagocytosis, complement, antimicrobial peptides and specific antibodies. The pathophysiology and clinical factors of hvKP showed similar symptom to conventional cKP except liver access and infectious syndrom.

Conclusion: The threat of *Hypervirulent K. pneumoniae* (hvKP) increases worldwide due the virulence factors more vary compared to conventional cKP. Consequently, special measures such as vaccine need to be develop in order to eradicate this pathogen particularly among pediatric patient.

Keywords: *Hypervirulent K. pneumoniae*; Liver Abscess; *Hypermucoviscous*; Capsular polysaccharides; hvKP

1. Introduction

Klebsiella pneumoniae is a gram-negative bacterium, family of *Enterobacteriaceae* that causes nosocomial infections, such as pneumonia, meningitis and hospital-acquired urinary tract infections in the United States [1,2]. These bacteria are also responsible in intensive care units in Africa and Singapore [3]. There are some unusual cases such as those that occurred in Taiwan around 1980, where cases liver abscess along with endophthalmitis is a result of hereinafter known as *hypervirulent K. pneumoniae* (hvKP) [4]. Nowadays hvKP is regarded have high pathogenic and mortality rates [5].

Hypervirulent K. pneumoniae (hvKP) has the ability to resist to neutrophil-mediated phagocytosis when compared with *classic K. pneumoniae* (cKP), it is strongly related to *hypermucoviscous* phenotype [6,7]. *Hypermucoviscous* being one of the main characteristics of hvKP based on string test in agar plates [8]. Related with these characteristics, several studies also found that some hvKP isolates have capsular serotypes K1 and K2, as well several genes that play a role in virulence such as regulators of mucoid phenotype A and A2 (rmpA), mucoviscosity-associated gene a (magA) and also encoding

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GDP-fucose synthetase (wcaG) [9,10]. The phenotypes hvKP are thought to be influenced by virulent plasmids such as pK2044 and pLVPK [11]. Nowadays hvKP is described as a virulent pathogen that has the ability to infect individuals in various age ranges and has multiple ports of entry that can attack multisystem organs and cause infectious syndromes such as non-hepatic abscesses, pneumonia, necrotizing fasciitis, endophthalmitis, and meningitis [12]. Consequently, awareness and perspective on the characteristics and clinical feature of hvKP, are urgently required to get better understanding and providing appropriate treatment in cases of infection caused by hvKP.

2. Overview *Hypervirulent K. pneumoniae*

2.1. History

Based on the genomic analysis 328 isolates *K. pneumoniae* are divided into 3 species, namely *K. pneumoniae*, *K. quasipneumoniae* and *K. variicola*, however only *K. pneumoniae* that are responsible for the majority of human infections, and the hvKP strain is part of the *K. pneumoniae* [13].

Study in Taiwan in 1986 reported as many as 7 clinical cases of liver abscess with septic endophthalmitis caused by *K. pneumoniae*, of these cases some of them have extrahepatic complications such as meningitis pneumonia, prostate abscess and pyogenic ophthalmia [4]. Among 7 individuals 4 of them showed a history of diabetes mellitus, and others were individuals who had no comorbid history. This case became the first reported clinical case that *K. pneumoniae* could to infect multi-system organs with a wide spread of bacteremia.

At the same year, research conducted by Nassif and Sansonetti (1986) found that there are 7 strains of very high virulence *K. pneumoniae* shown by the results of Lethal dose rate of 50% in rats of $<10^3$ CFU [14]. Furthermore, in the study also demonstrated that only *K. pneumoniae* serotypes K1 and K2 demonstrated *hypermucoviscous* phenotypes. This characteristic is proven to be mediated by the capsular polysaccharide regulator RmpA, in addition to plasmids containing genes that can produce aerobactin [15].

Fang's found *K. pneumoniae* that cause cases of liver abscess have *hypermucoviscous* phenotype, which is defined through the string test [16]. All the way to *K. pneumoniae* that have a *hypermucoviscous* phenotype, known as *hypervirulent K. pneumoniae* (hvKP).

2.2. Virulence Factor

There are several factors that affect virulence in hypervirulent *K. pneumoniae*:

2.2.1. Capsules

Based on polysaccharide components hvKP capsules, hvKP are divided into 79 serotypes, of the overall serotype, serotype K1 and K2 are the most commonly encountered in hvKP [17]. Some studies demonstrated serotypes K1 and K2 are highly virulence compared to others because serotypes K1 and K2 do not posses mannose and rhamnose, which are commonly recognized by macrophage leptin receptors in process of phagocytosis [18]. A capsule surrounding the surface of *K. pneumoniae* is a major virulence factor associated with the *hypermucoviscous* phenotype (19). Capsule is the main defensive factor that mediates the occurrence of resistance to bactericidal, thus allowing hvKP to avoid the process of phagocytosis, complement, antimicrobial peptides and specific antibodies [20]. One research showed that hvKP could escape from phagocytosis as well as neutrophil extracellular traps (NETs) due to strong *hypermucoviscous* phenotypes mediated by capsular polysaccharide regulators RmpA [21]. The fact that size of hvKP capsules is thicker > 2 mm when compared to cKP, in addition to the presence of *hypermucoviscous* allows an increase the viability of hvKP capsules as a physical barrier [22,23]. Truly the components of this capsule hvKP to survive against the immune system and increase its ability to resistance to bactericidal compounds.

2.2.2. Siderophore

Iron is a very essential component for metabolic processes with limited availability in microenvironment. In order to survive and thrive bacteria must make the acquisition of iron from the extracellular host cells [24]. Siderophore is a small molecule synthesized by bacteria that serves as a binder of iron around the bacteria and then transport back into the bacteria [25]. There are four types of siderophore molecules expressed hvKP i.e enterobactin, yerseniabactin, salmochelin, and aerobactin, of these four aerobactin has a dominant proportion (90%) of expression by hvKP [20,26]. Another study also stated that the discovered of iucABCD and iutA genes encoding aerobactin synthesis and transport in hvKP virulent plasmids [27]. So that the production of aerobactin can provide iron supply for hvKP to survive.

2.2.3. Colibactin

A recent study found a virulence factor called colibactin, a small genotoxic molecule produced by hvKP [28]. Colibactin in the intestine is able to increase the inflammatory process by suppressing the activity of regulatory T lymphocyte cells, and trigger the formation of hvKP portal of entry to the central nervous system through the vascular [29]. In addition, the production of colibactin by hvKP can mediate the translocation of infection to the meninges of mice [29]. Colibactin has a very influential effect on the ability of hvKP to infect the multiorgan system, through the mechanism of inducing inflammation and colonization.

2.2.4. Plasmid pLVPK

Large virulence plasmids (pLVPK, such as pk2044 plasmid) were detected in all hvKP genomes. This Plasmid encodes aerobactin, salmochelin, and RmpA, which are found in some hvKP isolates. There was a significant decrease virulence in CC23 strains that did not have pLVPK [30]. This suggests an important role of this plasmid in *hypervirulence K. pneumoniae*. In addition, genomic comparisons revealed differences in the pathogenicity variant island (KPHP1208) specifically associated with CC23. Most CC23 isolates contain genes encoding yersiniabactin, colibactin, and microcin E492, in the pathogenicity island of KPHP1208 [31].

2.2.5. Lipopolysaccharide Antigen O and Fimbrae

Antigen O is the endotoxin found in gram negative bacteria including hvKP. antigens O in particular type O1 are thought to contribute to bacterial virulence by a mechanism of reducing macrophage activation and promoting bacteremia [32]. In addition, there are also fimbrae, especially type 3, in fimbrae type 3 is known to mediate the formation of biofilms on the abiotic surface and affect the availability of iron for metabolic processes and hvKP survival [33,34].

3. Pathophysiology and Clinical Feature

3.1. Pathophysiology

3.1.1. Portal of Entry

In early hvKP infection, direct contact route through micro-and macro-aspiration that the formation of colonization in the oropharyngeal can lead to pneumonia. In perineal colonization this occur via the ascending route and can be a urinary tract infection [35]. In some patients, cryptogenic hepatic abscesses due to hvKP associated with colon carcinoma [34]. In other studies show colibactin production by hvKP can help the translocation of infection to the meningen of mice and greatly affect the ability of hvKP translocation to the multiorgan system [36]. However, in most patients who develop hvKP infection, the initial route remains unclear.

3.1.2. Colonization

Once hvKP has successfully infected the host, the next stage is colonization. Colibactin aids the colonization process of hvKP, by the mechanism of enhancing the inflammatory process by suppressing the activity of regulatory T lymphocyte cells [36]. Microcin E492 is a bacteriocin that is active against *Enterobacteriaceae*. That activity requires the attachment of salmochelin that facilitate the uptake microcin to the target bacteria. HvKP strains produce a combination of colibactin, microcin E492, and salmochelin, which is thought to be significantly beneficial in the colonization process. Several genes have been identified using signature-tagged mutagenesis, which appear to play a role in some combination of intestinal colonization and/or invasion across the intragastric mucosal barrier in mice [36].

3.1.3. Growth and survival

hvKP strains have been shown to be more resistant to phagocytosis, neutrophil, complement mediated activity, and neutrophil extracellular traps (NETS) than *classical K. pneumoniae* strain [37]. This factor is a major impact on the survival of hvKP from eradication of the immune system. However, an important condition contributing to the hvKP phenotype is the ability to increase the amount of capsular polysaccharides. It is mediated by RmpA and/or RmpA2, which are hvKP-specific factors located in hvKP plasmids [38]. hvKP has the ability to escape from phagocytosis and neutrophil extracellular traps (NETs) which are suspected of strong hypermucoviscous phenotype mediated by capsular polysaccharide regulator RmpA [21]. In studies using hvKP strains, capsular polysaccharides have been shown to protect against phagocytosis and defensin-mediated bactericidal activity, and these attenuate human defensin production in vitro [39]. Moreover, the synthesis of aerobactin molecules by iucABCD and iutA genes on hvKP virulent plasmids [27], also plays a role in improving the ability of hvKP to carry out iron acquisition to survive and increase colonization.

3.1.4. Tissue Damage

hvKP infection often leads to abscess formation. However, until now the explanation is still limited. The most probable factor is colibactin, which has been shown to be genotoxic, causing DNA damage and cell death [40]. However, there are some strains of hvKP that do not produce colibactin (for example, the non-cg23-K1 capsule type) but can also cause abscesses to form. This suggests the possibility that unknown factors may also be contributing to the occurrence of abscesses by hvKP strains. Beside that, the immune response of the host body that is not well regulated also contributes to damage to the body [29].

3.2. Signs and Symptoms

There are several clinical symptoms caused by hvKP infection in puppy as test animals, such neurological disorders, like decreased consciousness to death, swelling of the joints and even decreased body motoric, several other signs, namely septic arthritis or cellulitis [41]. There are also other symptoms in the ocular such as formation of hypopyon and blepharospasm, rise of the body temperature with the highest temperature 40^{o}C. There are also some non-specific symptoms such as polyarthritis, pyothorax, suppurative meningitis and subdural hemorrhage [41].

Studies conducted in Taiwan found that patients who had been infected with hvKP showed several signs and symptoms such as fever, chills, abdominal pain, nausea and vomiting [42]. It was also reported that of 800 patients infected with hvKP with liver abscess one-third of patients had complications to other organs such as endophthalmitis or uveitis, empyema, meningitis, brain and epidural abscess [42, 43, 44].

Table 1 Clinical Feature differentiating *hypervirulent K. pneumoniae* (hvKP) and *classical K. pneumoniae* (cKP) (38)

Nu.	Parameter	hvKP	cKP
1	Location of Infection	Commonly the community	Commonly Hospital acquired
2	Host	All ages, often healthy host	Older with some comorbid
3	Hepatic Abscess	Usually	Usually in the presence of biliary disease
4	Site of Infection	Often Multiple	Usually single
5	Infectious Syndrome	Endophthalmitis, meningitis, brain abscess, necrotizing fasciitis, splenic abscess, epidural abscess	None

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4. Conclusion

First clinical case of *hypervirulent K. pneumoniae* (hvKP) reported in Taiwan 1986 with clinical feature liver abscess with septic endophthalmitis, and some patient have extrahepatic complications such as meningitis pneumonia, prostate abscess and pyogenic ophthalmia. Another study found *K. pneumoniae* cause liver abscess have *hypermucoviscous* phenotype as the main characteristic, which is defined through the string test positive. There are several virulence factor which can support growth and survival rate of hvKP such as capsule polysaccharide, aerobactin, colibactin, plasmid pLVPK, Lipopolysaccharide Antigen O type O1 and Fimbrae type 3. The pathophysiology of hvKP still unclear but there several explanation such as hvKP strains demonstrated resistant to phagocytosis, neutrophil, complement mediated activity, and neutrophil extracellular traps (NETS) because hvKP has ability to increase the amount of capsular polysaccharides. It is mediated by RmpA and/or RmpA2 this factor major impact on the survival of hvKP. This review consequently, awareness and perspective on the characteristics and clinical feature of hvKP, are urgently required to get better understanding and providing appropriate treatment in cases of infection caused by hvKP.

Compliance with ethical standards

Disclosure of Conflict of interest

No conflicts of interest.

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