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Review Article

Hypervirulent Klebseilla Pneumoniae is a New Threat

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Abstract

Hypervirulent K. pneumoniae (hvKp) is a pathogenic strain of K. pneumoniae that is more virulent than classical K. pneumoniae (cKp). hvKp typically infects people in the community who are otherwise healthy. Infections are more common in the Asian Pacific Rim, but they occur worldwide. hvKp infection frequently manifests at various places or metastatically spreads, necessitating source control. Hypervirulent K. pneumoniae has a greater proclivity to produce central nervous system infection and endophthalmitis, both of which necessitate prompt diagnosis and site-specific treatment. K. pneumoniae has become a growing global problem in recent decades, owing to its increased resistance and lately concentrated hypervirulence. Despite the fact that SH 1V-1 -lactamase is encoded on the chromosome and is inherent resistance, K. pneumoniae can counteract antimicrobials by a variety of mechanisms, including hydrolyzing enzymes, missing porins, efflux overexpression, topoisomerase, and lipopolysaccharide (LPS) modification. Carbapenem-resistant K. pneumoniae (CR-KP) has reached an alarming rate of more than 30.0% among K. pneumoniae strains, posing serious hurdles in clinical practice. The World Health Organization (WHO) published a list of the most "critical" bacteria with an urgent need for novel therapies in 2016, with carbapenem-resistant Enterobacteriaceae (CRE) being designated as a critical priority organism

Key words: Hypervirulent K. pneumoniae, nosocomial infections, antibiotic resistance.

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Introduction:

Klebsiella pneumoniae differs from other Enterobacterales members in the speed and tenacity of its dissemination. The genus Klebsiella contains gram-negative, fermentative, non-motile bacteria that are extremely common microorganisms. They also naturally exist in the gut microbiomes of healthy humans and animals. There is a rising global public health issue since K. pneumoniae is one of the bacterial species in the genus most frequently linked to nosocomial infections. (1)

Hypervirulent K. pneumoniae first identified as a distinct clinical pathogen in Taiwan in the 1980s, is more virulent than classical K. pneumoniae (cKP) according to animal lethality tests (on mice and wax moth larvae), neutrophil assays, and other methods. (2) While HvKP frequ-ently results in infections in otherwise healthy individuals, such as pyogenic liver abscess (PLA), lung abscess, and endophthalmitis, cKP frequently causes nosocomial infections in individuals at the extremes of age or with underlying immunodeficiency, such as pneumonia, urinary tract infection (UTI), and bacteremia. In areas where HvKP is endemic, the prevalence of the disease ranges from 12% to 45%. Recent research has discovered a CR-KP and HvKP convergence tendency that calls for more investigation. (3)

Virulence factors:

Many differences in virulence factors between Hypervirulent K and classical k.pneumoniae as it is demonstrated in figure.(1)

1-Hypercapsule

The absence of the capsule, a polysaccharide covering affixed to the surface protein of K. pneumoniae, results in K. pneumoniae becoming significantly less virulent or nonvirulent. 79 distinct serotypes of K. pneumoniae are currently known. The ability of HvKP, as opposed to cKP, to create a hypercapsule promotes hypervirulence. (4)

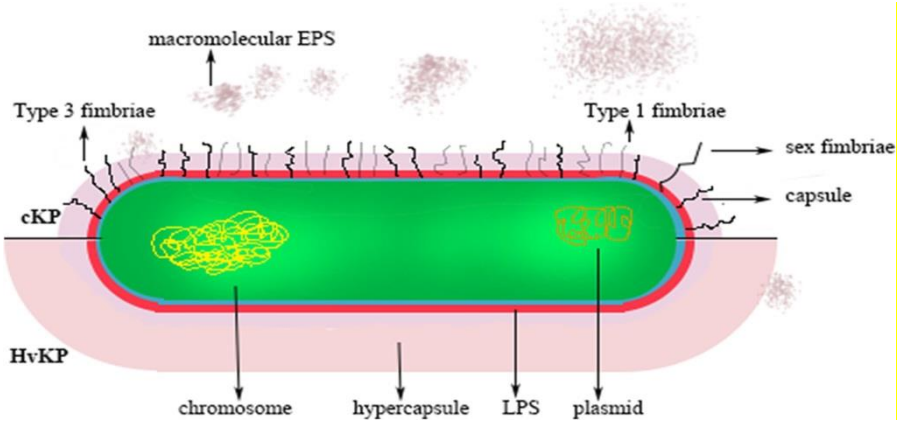

Fig 1. The schematic diagram of *Klebsiella pneumoniae* and the difference between classical Klebseilla Pneumoniae and Hypervirulent Klebseilla Pneumoniae. [5]

2-Macromolecular exopolysaccharide:

Nutritional immunity is the host's restriction of iron, a component required for bacterial development during infection. The growth of K. pneumoniae and subsequent bacterial count, which is also a significant driver of virulence, may be affected by the availability of iron. Only a tiny amount of iron is loose; the rest is deposited in the host in bound forms like transferrin and ferritin. Therefore, K. pneumoniae needs to absorb iron in order to survive and grow. The siderophores enterobactin, yersiniabactin, salmochelin, and aerobactin, which have stronger affinities than host transport proteins and may be successful in stealing iron from hosts' iron-chelating proteins, may be present in K. pneumoniae. At least one siderophore is present in K. pneumonia. [6]

3-Other virulence factors:

The O antigen, a core oligosaccharide, and lipid A are all present in the body and are the main ingredients of LPS, also known as endotoxin, and are encoded by the wb, waa, and lpx gene clusters, respectively. LPS, which serves as a powerful immunological stimulant, shields K. pneumoniae from humeral defenses.

The generation of cytokines and chemokines, as well as the attraction and activation of neutrophils and macrophages, are all sparked by the strong TLR4 ligand lipid A. Numerous cationic antimicrobial peptides are shielded from K. pneumoniae by lipid A. [7]

LPS, which was also present in HvKP, was able to be masked by K. pneumoniae strains of serotypes K1, K10, and K16. Furthermore, K. pneumoniae may alter its LPS to the point where immune receptors can no longer recognize it. LPS is K. pneumoniae's primary line of defense. [8]

Diseases caused by HVKP:

One of the most important microbes responsible for potentially fatal infections such bacteremia, pneumonia, intra-abdominal infections, and urinary tract infections is Klebsiella pneumoniae. Medical experts and microbiologists have shown the most interest in the K. pneumoniae strains known as classic K. pneumoniae (cKP), which are well known for their ability to generate hospital outbreaks with high rates of morbidity and mortality. A novel strain of K. pneumoniae known as hypervirulent K. pneumoniae (hvKP) has been discovered in Asia over the past 20 years and is currently spreading throughout the world. The hvKP strains stand out because they can result in invasive liver abscess syndrome with or without metastatic effects, such as endophthalmitis or necrotizing fasciitis, especially meningitis.[9]

Risk Factors:

The host's susceptibility to K. pneumoniae infection is influenced by the host's intrinsic (such as genetics, age, and immune status), extrinsic (such as antibiotic use, environmental exposure, nutrition, and alcoholism), and pathogen variables (such as virulence factors and antibiotics resistance) factors.[10]

Because of their undeveloped gastrointestinal tract mucosal barriers and compromised immune systems, newborns are more vulnerable, especially those who are born preterm or in intensive care units. K. pneumoniae, on the other hand, puts older people at the greatest danger of dying. Aspiration of oropharyngeal flora is thought to be primarily responsible for the 30% mortality

incidence among elderly patients hospitalized for K. pneumoniae infection. Studies on patients with mean ages over 60 years revealed that K. pneumoniae was responsible for 6.5-11.6% of all HAPs and 17.2% of all CAPs. Additional risk factors for aging include diabetes, cancer, liver and gallbladder disease, chronic obstructive pulmonary disease, renal failure, and nutritional issues.(11)

Invasive medical procedures like implantation, percutaneous surgery, hypodermic injection, chemotherapy, transplantation, and dialysis are examples of external impacts. Additional external variables include things like individual preferences and prescription medications like glucocorticoids and antibiotics. During several of these procedures, the mucosal barrier at the colonization site is frequently disrupted, allowing the pathogen to escape and cause infections. One such operation that enables germs to enter bodily locations directly is intubation.(12) Invasive medical procedures like implantation, percutaneous surgery, hypodermic injection, chemotherapy, transplantation, and dialysis are examples of external impacts. Additional external variables include things like individual preferences and prescription medications like glucocorticoids and antibiotics. One of the numerous methods that either allows bacteria to enter the body directly or harms the mucosal barrier is intubation.(13)

Diagnosis

1-Testing for antibiotic sensitivity and ESBL production

Amikacin, gentamycin, imipenem, meropenem, cefoxitin, ceftazidime, ceftriaxone, cefepime, aztreonam, ampicillin, amoxicillin-clavulanate, piperacillin-tazobactam, trimethoprim-sulphamethoxazole, ciprofloxacin, and levofloxacin are some examples of clinically used antibiotics in treatment of infection caused by Hypervirulent Klebseilla Pneumoniae.

The Phoenix 100 automated microbiology system was used to test for the development of extended-spectrum -lactamases (ESBLs).(14)

2-The String Test

Stretching bacterial colonies that had grown overnight on a blood agar plate at 37 °C was done using a standard bacteriological loop. The isolate was categorized as hypermucoviscous if a mucoviscous string of at least 5 mm in length emerged following the string test. (14)

3-Biofilm Formation

Biofilm formation was examined by using the semi-quantitative assay in 96-well flat bottom plates.

4-Serum Resistance Assay

After the serum resistance experiment, viable counts (VCs) of bacteria were counted at 3-hour intervals. The responses were rated into one of six categories: highly sensitive (grades 1 and 2), intermediately sensitive (grades 3 and 4), or resistant (grades 5 and 6).

6- Detection of Capsular Serotype-Specific Genes and Virulence-Associated Genes

Genes associated with virulence (rmpA, rmpA2, magA, and iucA) as well as genes particular to each capsular serotype (K1, K2, K5, K20, and K57) were discovered using polymerase chain reaction (PCR). Since these novel strains were first reported in Taiwan, hypervirulent hypermucoviscous K. pneumoniae (hmKP) strains have been widely recognized. In other words, the majority of past studies just evaluated the value of hvKP using string tests. It appears that hmKP and hvKP are two different phenotypes, despite the fact that populations of hypervirulent and hypermucoviscous strains typically overlap.

Numerous studies have used the two genetic markers plasmid-borne rmpA (p-rmpA) and aerobactin synthase gene (iucA), which are widely used to differentiate hvKP from cKP, together to define hvKP strains.(15)

Control Strategies

1-Source Control

Extensive screening, identification, education, and multimodal intervention are needed to control the spread of K. pneumoniae at the source. Exposure avoidance should be practiced by rapidly recognizing the sick individuals and adopting the required precautions, including the use of personal protective equipment such gowns, gloves, and masks. In addition to the typical safety precautions including the wearing of masks, gloves, and gowns, it is important to identify the affected individuals as soon as feasible.(16)

Rules and guidelines should be strictly followed when using antibiotics, especially during the first empirical treatment. Both hvKp and CRKP should follow their specific treatment regimens during

therapy. When possible, reasonable and consistent antibiotic administration procedures should be used. These procedures should include precise indications, an appropriate dose, a long enough course of treatment, cautious antibiotic switching, and other interventions including surgical drainage and implant removal. Additionally, there should be a decrease in the misuse of antibiotics, which happens in the medical field and during the breeding of cattle. Controlling antibiotic usage in non-human circumstances can aid in lowering the source of CRKP.[17]

2-Prevention of Transmission/Block of the Transmission Route

The most significant and practical measure to stop the transmission of disease is hand washing.

Klebsiella, Staphylococcus aureus, Clostridium difficile, and other Gram-negative bacteria have been discovered on medical staff. In hospitals, healthcare staff members' hands can become infected through close contact with patients or by touching contaminated objects .[18] Collections from relevant areas, such as skin, urine, sputum, and wound secretions, should be evaluated for the presence of bacterial infections in patients who have indwelling devices. [19]

By consistently tracking contact precautions and specimen culture findings, transmission among patients can be avoided. Any unexpected transmission should be reported to healthcare experts so they can act effectively and without delay. [20]

For the CRKP/HvKp, it's crucial to take contact precautions, especially in groups where the danger of transmission is high or in those who come into touch with infected individuals. High-risk individuals should have their CRKP/HvKp levels frequently checked after admission and throughout their hospital stay. The same contact precautions should be taken by patients with minimal risk of transmission and individuals who have an epidemiological link to CRKP/HvKp patients who are infected or colonized but haven't been diagnosed. While admission monitoring test results are pending, preventive contact measures may be taken, especially for patients admitted from other hospitals who are known to have HvKp/CRE. [21]

3-Host Defense and Protection of the Susceptible Population

The lipopolysaccharides and capsule of Klebsiella pneumoniae are both excellent potential antigens that a vaccine or host immunity can target. Due to the 77 different capsule types and nine different LPS serotypes found in K. pneumonia, it is challenging to develop antibodies and vaccines against capsular polysaccharides. It is essential to identify highly conserved K. pneumoniae antigens in order to create antibodies or vaccines that provide comprehensive defense and long-lasting immunity against all strains. [22, 23]

Another strategy to boost immunity is to lead a healthy lifestyle, which includes getting regular exercise, getting adequate sleep, quitting smoking, and eating a diet high in fruits and vegetables. Alternative treatments should also be investigated in light of the rise in antibiotic resistance. A novel therapeutic approach known as "bacteriophage therapy" can be used in place of or in addition to conventional antibiotics. Phase therapy has been shown to have a number of benefits, including high specificity, high efficacy, little side effects, and cheaper cost. [23]

Treatment:

To determine the appropriate course of antibiotic treatment for K. pneumoniae, bacterial cultures and subsequent tests for antibiotic susceptibility are frequently utilized. Patients with gangrene, an abscess, or empyema should get surgery or other forms of interventional therapy. In community-acquired pneumonia empirical antibiotic therapy should effectively eradicate Hypervirulent Klebseilla Pneumoniae. [24] For at least two weeks, third-generation cephalosporins or quinolones should be given, either alone or in combination with aminoglycosides. Patients with hospital-acquired K. pneumonia should receive the recommended antibiotic regimens, such as imipenem, third-generation cephalosporin, quinolones, or aminoglycosides, for at least 14 days. Quinolones may be administered intravenously if a person reacts quickly. To treat Extended-Spectrum ESBL, colistin, tigecycline, and intravenous fosfomycin should be utilized instead of carbapenems.

Conclusion

The late 19th century saw the first description of Klebsiella pneumoniae, which has since attracted more attention due of its medication resistance and hypervirulence. Despite having many

virulence genes, K. pneumoniae's hypervirulence is mostly dependent on a few number of elements, such as hypercapsules, macromolecular exopolysaccharides, or an abundance of siderophores. Although it still needs work, molecular detection of HvKP is a useful alternative to the conventional labor-intensive lethality assays. The exceptional virulence and treatment resistance of HvKP, particularly Hv-CRKP and CR-HvKP, may in the future pose significant challenges to clinical practice. This procedure might be accelerated by immune system dysfunction (perhaps brought on by CRISPR-Cas and R-M).

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