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Hypervirulent strains of Klebsiella pneumoniae (hvKp) and development of antibiotic resistance in them: A serious threat to human health.

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ABSTRACT- Klebsiella pneumoniae can be categorized among the most dangerous pathogens discovered till date. It's infection results in many fatal diseases including abdominal diseases, thorasic diseases, endopthalmitis, central nervous system (CNS) diseases, mucoskeletal diseases, soft tissue infection, bacteremia or endovascular infection, genitourinary infection and many more. Hence it is pretty clear that this bacterium is a major health concern moreover emergence of a new strain of it is more dangerous threat to our health. Hypervirulent strain of Klebsiella pneumoniae (i.e. hvKp) is more potential infecting agent than the classical strain (i.e. cKp). It can infect the host more efficiently and cause the disease more critically. But this is not the end of the story; recently many reports are coming from several literatures that those hvKp strains also develop antibiotic resistance in them. And hence it becomes a serious health issue day by day. Here in this review emergence of hvKp along with its more advanced virulence factors are described. Generation of antibiotic resistance and possible way of treatment in terms of immunotherapy are also discussed here. This review summarizes the current status of research regarding hvKp and will help investigators to investigate further in this arena.

Key words- hvKp, cKp, antibiotic resistance, immunotherapy.

I. INTRODUCTION:

Infection caused by the pathogenic bacteria or by other microorganisms is always being a matter of concern for the researchers. Among the list of world's top most pathogenic bacteria, the name of Klebsiella pneumoniae is included in bold. It is a well known pathogen that infects human and can cause many fatal diseases. Moreover a new strain of this bacterium emerges known as hypervirulent strain i.e. hvKp. There a number of factors like special capsular serotype, rmpA gene, magA gene, a virulence plasmid are present in hvKp that makes it more virulent. But still treatment with some broad spectrum antibiotics is there. But recent development of antibiotic resistance in them makes the researchers to think more deeply about it. hvKp becomes resistance to almost all recently available antibiotics including β-lactum, carbapenem, colistin etc. As a result of this infection by this particular bacterium becomes much more fatal. Scientists are investigating new possible ways of treatment in terms of immunotherapy because the infection slowly spreads in many portions of the world map, including Asia and America. Antibody based treatments, many vaccines like live attenuated vaccines, CPS based vaccines, inactivated vaccines, O antigen based vaccines etc. are under investigation. Many scientists are working on phage therapy as a way of treating Klebsiella pneumoniae. Undoubtedly it is a very serious challenge to health but many of the researchers accept the challenge and are doing vigorous research in finding new ways of treatment.

Brief history of emergence of hypervirulent Klebsiella pneumoniae (hvKp):

In the year of 1986, seven cases were reported of Klebsiella pneumoniae infection associated with liver abscess. But each individual out those seven had no biliary duct infection or any septic endopthalmitis **(Liu YC et al., 1986)**. This was the first probable report that brings the infection by hypervirulent strains in the forefront. Some of the characteristics of the patients were distinctive and were features of hvKp. First, those patients were all young and well immune-active but still four out of seven had diabetes. Secondly, metastatic spread had been observed in those infected individuals **(Russo TA et al., 2019).**

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Again in the year of 2004 a study revealed that Klebsiella pneumoniae associated with liver abscess in patients in Taiwan shows more hypermucoviscosity than non invasive strains **(Fang CT et al., 2004)**. These hypermucoviscosity of those isolates was defined by the formation of viscous strings of length greater than 5mm.when the inoculating loop used to stretch into the colony on agar plates. This is the primary test of identification known as string test **(Fang CT et al., 2004)**. Eventually the designation of hypervirulent strains of Klebsiella pneumoniae is framed (**36**). Another report also revealed pathotype that causes majority of the infections caused by Klebsiella pneumoniae is generally termed as classical strains i.e. cKp **(Pomakova DK et al., 2012)**. This distinction between cKp and hvKp frames the genotypic and phenotypic differences between these pathotypes **(Catalan-Najera JC et al., 2017)**.

Factors present in hvKp that makes it more virulent:

The main difference between hypervirulent stain (hvKp) and classic strain (cKp) of Klebsiella pneumoniae is based on mucoviscosity. The hvKp strain is more hypermucoviscous than cKp strain **(Siu et al., 2011).** This hypermucoviscosity is mainly occurs due to the presence of a particular virulence gene named rmpA and over production of the capsular polysaccharide **(Paczosa and Mecsus 2016)**. Not only that there are many other factors present that makes hvKp more invasive and those factors are mainly responsible for emerging resistance in them. These are discussed below-

- **Capsular serotypes**- Klebsiella pneumoniae is an encapsulated bacteria in which capsule is made up of polysaccharide. There are at least 78 serotypes present in the bacterium like K1, K2, K16, K28, K26, K54, K57 etc **(Pan et al., 2008)**. But the thing of interest is that, in hvKp two capsular serotypes are prevalent i.e. K1 and K2. These two serotypes increase the virulence of hvKp in following manner **(Chang-Ro Lee et al., 2017)**. Firstly, mannose residue repeats are absent in these two serotypes. That will eventually prevent macrophages to destroy the pathogen, because macrophages have mannose binding receptors. Secondly, sialic acid is present on the surface of these capsular forms. Due to presence of the sialic acid the bacterium can mimic the body cell. **(Lee et al., 2014)** this strategy is very much helpful in invasion of host defense. Thirdly, these two serotypes have the ability to induce the neutrophils in such a way so that it can release little amount of reactive oxygen species **(Paczosa and Mecsus 2016).** At last among all other serotypes, these two specially have most diverse range of O antigens **(Follador et al., 2016)** this helps them to evade host defense barrier more efficiently.

There are many repots also that shows ckp having these two capsular serotypes **(Chang-Ro Lee et al., 2017).** And due to presence of those two serotypes respective cKp isolates are also showing more virulence property than most of cKp isolates that lacks K1and K2 serotypes. In this way capsular serotypes increases the virulence of hvKp.

- **Sequence types**- Recent study emphasizes that sequence type 23 (ST23) and clonal complex 23 (CC23) mainly associated with K1 serotypes shows more reports of liver abscesses and invasive infections **(Struve et al., 2015).** 85.1% of serotypes among 47 different isolates are ST23 **(Chang-Ro Lee et al., 2017)** but the reason why ST23 associated with K1 is more prevalent is yet not clear till date. In other hand K2 serotypes have more diverse range of ST variations, among them ST65 is more prevalent **(Lin et al., 2014).** Whole genome sequencing analysis shows high expansion of CC23 in different geographical regions throughout the world. It indicates the global transmission of hvKp is higher than local transmission **(Struve et al., 2015).** This particular clonal group shows more hypervirulance and fitness **(Chang-Ro Lee et al., 2017).**
- **Presence of a virulence plasmid**- Plasmid is a self-replicative DNA, in most of the cases it provides some charades to the respective individual organism, that give them some extra level of advantage or fitness. HvkP strain of Klebsiella pneumoniae bears a plasmid pLVPK. This is high virulence plasmid and it is found in almost all whole genome sequenced isolates **(Struve et al., 2015).** An CC23 isolate that has no pLVPK was significantly found less virulent it gives a strong indication toward the important role that the plasmid plays for hypervirulence **(Lin et al., 2011, 2012).** The plasmid contains a number of genes RmpA, aerobactin and salmochelin. These all gene products are restricted to only hvKp. Hence definitely they contribute to high invasiveness of hvKp.

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- **Pathogenecity island in genome-** In the genome of hvKp a distinct pathogenicity island is present, i.e. KPHP1208. A number of genes are present in the island encoding products like colibactin, microsin, E492 and yersiniabactin. All these have tremendous effects in hypervirulence of hvKp **(Chang-Ro Lee et al., 2017).** Among all these products colibactin draws special attention. It is a polyketide-peptide genotoxin and it has the ability to damage eukaryotic DNA **(Lai et al., 2014)**. A recent study also revealed that colibactin is essential for promoting meningeal tropism **(Lu et al., 2017).**

- **rmpA gene-** It is already told that the main phenotypic difference between the classic strain i.e. cKp and the hypervirulence stain i.e. hvKp is hypermucoviscosity. Regulator of mucoid phenotype A (rmpA) gene activates the capsule production thus showing hypermucoviscosity **(Cheng et al., 2010)**. Almost all hvKp strains have this gene in their genome **(Guo et al., 2016).** There are three forms of the gene are identified i.e. rmpA, rmpA2 and crmpA. Among these three forms former two are found in the plasmid pLVPK and the last one is found in the chromosome of the bacterium **(Hsu et al., 2011)**. Some investigation revealed that inspite of the presence of rmpA genes some isolates were showing less hypermucoviscosity, probable explanation of this is the gene present in those isolates were mutated thus were unable to perform their function properly **(Yu et al., 2015).**
- **magA gene-** In the year of 2004, a new gene was discovered in the genome of Klebsiella pneumoniae. This gene function is important to express hypermucoviscosity **(Fang et al., 2004).** A report in Taiwan revealed that 83% of the isolates are magA positive and they all are isolated from liver abscess **(Chuang et al., 2006).** Not only that, a recent study in 2017 established that magA gene is more prevalent in specially K1 serotype (All 83% in Taiwan magA positive isolates are K1 serotypes.) than in non K1 serotypes **(Guo et al., 2017)**. All these results of different studies suggest that magA gene is responsible in capsular expression in K1 serotypes **(Chang-Ro Lee et al., 2017).**
- **Siderophores-** In progression of Klebsiella pneumoniae infection iron plays a vital role **(Russo et al., 2014).** Four types of siderophores are reported in K. pneumoniae **(Chang-Ro Lee et al., 2017)** these are aerobactin, salmochelin, enterobactin and yersiniabactin. It has already been found that hvKp strains have 6 to 10 fold more expression of siderophores than cKp **(Russo et al., 2011)**. Genes encoding for aerobactin and salmochelin are present in the plasmid pLVPK, which is absent in cKp. Genes encoding for yersiniabactin are found in genome of yersinia, it seems that hvKp strain acquire the gene from yersinia by horizontal gene transfer **(Bach et al., 2000)**. Among these four siderophores, aerobactin accounts more than 90% **(Chang-Ro Lee et al., 2017).** A recent study suggests that in course of infection aerobactin, enterobaction, yersiniabactin but not salmochelin plays essential role in survival of Klebsiella pneumoniae in human serum and in vivo mouse infection model **(Russo et al., 2015)**

Development of antibiotic resistance in hvKp:

Emergence of hvKp from cKp is a thing of great medical concern but in the first decade of the emergence of hypervirulent strains it was observed that hvKp was susceptible to maximum number antibiotics **(J. E. Choby et al., 2020).** Reports of early investigation shows that 5% of hvKp was resistance to ESBL **(Ko WC et al., 2002)** and 2% of them are resistance to single used antibiotics **(Fang CT et al., 2006).** In the year of 2016 in a study in China results that 57% of the hvKp isolates that were causing blood stream infection has the capacity to produce carbapenemase **(Li J et al., 2016)**. This investigation points out the alarming threat of developing resistance in hypervirulent strains also. After that ESBL producing isolates of hvKp were also found **(Li W et al., 2014)**. In this way several reports are coming out from then and it fells a great impact on clinicians globally **(J. E. Choby et al., 2020).**

- **Resistance to β-lactams-** These are a broad class of antibiotics that includes penicillins, cephalosporins, carrbapenem, monobactums etc. These are most frequently use antibiotics **(C. Hennequin et al., 2016).** The most common resistance mechanisms are production of β-lactamase enzyme that inhibits β-lactams which occurs either by the alteration of membrane permeability **(Chen J-H et al., 2010)** or by the extrusion from the efflux pumps **(Bialek S et al., 2010).**

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- **Resistance to carbapenem-** Carbapenem are the last line agents of treatment in the infection caused by Klebsiella pneumoniae, development of resistance against this group of antibiotics is the worst thing. Three genes bla_{KPC}, $bla_{NDM,}$ and bla_{OXA} are mainly responsible for encoding the enzyme carbapenemase that inhibits the carbapenem **(Lascols C et al., 2013)**. These genes are most often carried by plasmids and jumping DNAs (transposons) therefore K. pneumoniae can easily acquire these through horizontal gene transfer **(Yi-Chyi Lai et al., 2019)**. A study shows that 100 different STs carrying KPC genes **(Cubero M et al., 2015)**. CG 258 was mainly associated with the outbreak of KPC resistance strains in UK **(Meatherall BL et al., 209)**. But in India, Sweden different STs like ST 11, 14, 147, 149 and 231 are distributed as NDM resistance isolates **(Giske CG et al., 2012).** Similar to NDM, OXA resistance isolates are also associated with various STs including ST 11, 14, 15, 101, 147, 235 etc. **(Potron A et al., 2013)**. Development of carbapenem resistance in various sequence types and clonal groups are mot leading thing of medical concern in recent days.
- **Resistance to fluoroquinolones-** In Klebsiella pneumoniae resistance to fluoroquinolones can be developed in three ways (**Mazzariol A et al., 2002**). Firstly mutation in gyrA and parC genes in bacterial chromosome. Secondly, plasmids can also contribute in developing resistance by altering membrane permeability i.e. porin loss. Thirdly, efflux over expression can also cause lower uptake of quinolones. There is a strong link between fluoroquinolone resistance and fitness of the organism **(Tóth A et al., 2014)**. A study firmly indicates that the role of efflux over expression in developing fluoroquinolone resistance is more prevalent than mutation in chromosomal genes **(C. Hennequin et al., 2016).**
- **Resistance to colistin-** These antibiotics are detrimental for gram negative bacterium specially. They interact with lipid A of the outer membrane and thereby causing membrane disruption **(Ah Y-M et al., 2014).** 4-amino-4-deoxy-L-arabinose is added to lipid A to modify the outer membrane thus making Klebsiella pneumoniae resistance to colistin. This modification of outer membrane is mainly regulated by the genes pmrAB and phoPQ present in the pbgPE operon **(Cannatelli A et al., 2013).** Resistance to colistin is related to mutation in three different genes also. These are mgrB, phoQ, and ccrAB **(C. Hennequin et al., 2016).**. A recent study indicates that a plasmid encoded enzyme phosphoethanolamine transferase MCR-1, have significant role in conferring resistance to colistin. But this enzyme is rare in Klebsiella pneumoniae and its proper contribution in virulence is yet to clarify **(Liu Y-Y et al., 2015).**

II. DISCUSSION:

Klebsiella pneumoniae is really a serious threat to human health moreover two things makes it more dangerous. First one is the emergence of new pathotype i.e. hypervirulent strains hvKp. And second one is the development of resistance against many antibiotics in them. These two led the challenge more hard to overcome. But some recent advancement in treatment of hvKp infection shows little way further.

Passive immunization- interest in antibody based treatment is gradually increasing due the development of multi drug resistance (MDR) strains and consequently due to failure of the current available antibiotics **(Diago-Navarro E et al., 2017)**. The approach to treat Klebsiella infection using monoclonal antibody (MAb) against the K1 capsule **(Diago-Navarro E et al., 2017)** and O antigen **(Hsieh PF et al., 2012)** present in hypervirulent strains of Klebsiella had achieved success **(Diago-Navarro E et al., 2017)**. But antigenic diversity on the capsule is the challenge that has to overcome while treating the patients through passive immunization **(Follador R et al., 2016).** Capsular serotypes are more diverse than the O antigens present in hvKp strains. But point-of-care test can identify capsular antigens and O antigens rapidly of the infecting strain **(Diago-Navarro E et al., 2017).** This will eventually helps incase of passive immunization of patients.

Phage therapy- this arena of research is still at its infancy but it developing fast. Already specific bacteriophage viruses that can bind with none but K1 capsular serotype is identified **(Lin TL et al., 2014).** not only that bactericidal activity of this particular virus gives positive response against the hvKp stain NTUH-K2044 **(Lin TL et al., 2014).** Another bactriophage virus that attaches with K5 capsular serotype was also identified and isolated **(Hsieh PF et al., 2017)**. Eastern Europe and former Soviet Union already implied successfully this therapy **(Wittebole X et al., 2014)** but rest of the globe are yet to apply this therapy in

practical. The thing that is most challenging, if no such phage virus are found that can recognize all the capsular serotype of hvKp then like passive immunization point-of-care test will have to apply **(Diago-Navarro E et al., 2017).**

III. CONCLUSION:

Hence it can be concluded that in course of evolution new hypervirulent strain is emerged from the classical strain. And due indispensible use of antibiotics it becomes resistance to antibiotics. But new hopes are coming out in form of various immunological treatment techniques. Immune therapies are deals with the immune system of the patient hence there is a very little chance of side effects, apart from that no question of resistance will arise while we are using immunology based methods for treatment. But still much more focus is needed to overcome this serious threat of hvKp infection.

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