Genomics, population dynamics, immune evasion and resistance determinants foster the global dissemination of *Klebsiella pneumoniae* (#117348)

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Genomics, population dynamics, immune evasion and resistance determinants foster the global dissemination of *Klebsiella pneumoniae*

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Background: According to the World Health Organization (WHO) *K. pneumoniae* is a critical public health concern and an established ESKAPE pathogen. Mounting incidence of MDR *K. pneumoniae* is worrisome across the globe. *K. pneumoniae* is an established ubiquitous pathogen and associated with various infections in a wide range of the hosts.
Methods: The Peer reviewed findings with given problem statements were thoroughly studied through literature review technique. Multiple antibiotic-resistance genes and virulence genes across various Klebsiella species were studied to explore their evolutionary dynamics and genetic diversity.
Results: Population dynamics revealed that the clonal group (CG) 258 and CG 14 are considered as global disseminated clones. The genome size (5.7 Mbps) of *K. pneumoniae* is reported to be larger than the other Enterobacteriaceae which allows *K. pneumoniae* to survive in diverse geo-graphical niches. It has adequate resistome and virulence machinery to evade the host immune system and establish the infection. Due to the emergence of resistant variants *K. pneumoniae* needs appropriate alternative control measures.
Conclusion: The current review described the characteristics features of *K. pneumoniae* which are the key players in making this organism as a credential pathogen. Additionally, it would be instructive and underpin the molecular insights that may aid in restraining this pathogen.

Genomic, Population Dynamics, Immune Evasion and Resistance Determinants foster the competence and global dissemination of *Klebsiella pneumoniae*

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Abstract

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Conclusion: The current review described the characteristics features of K. *pneumoniae* which are the key players in making this organism a credential pathogen. Additionally, it would be instructive and underpin the molecular insights that may aid in restraining this pathogen.

1. Introduction

The "golden era" of modern medicine in which antibiotics saved innumerable lives is eroded with the emergence of antibiotic resistance. *Klebsiella pneumoniae* is a recognized ESKAPE (*Enterococcus, Staphylococcus, Klebsiella, Acinetobacter, Pseudomonas, Enterobacter*) pathogen, a common cause of antibiotic-resistant hospital-acquired infections (HAIs) and community-acquired infections. It is a notorious pathogen associated with various types of severe infections and has inadequate treatment options. According to the World Health Organization (WHO), *K. pneumoniae* falls among critical public health threats (Wyres & Holt, 2018) *K. pneumoniae* is a well-known resistant pathogen for its diversity and high incidence of antibiotic resistance genes (ARGs).

K. pneumoniae is not only a substantial health concern, but it is also known as the origin and disseminator of various ARGs like bla_{KPC}, blaNDM-1, and blaOXA-48. From a resistance perspective, a resistant strain must have the ability to disseminate ARGs, it may be achieved through vertical transmission of ARGs or via horizontal transmission through mobile genetic elements (MGEs) like plasmids, integrons, insertion sequences (IS) and transposons (S. Navon-Venezia et al., 2017). Such discrete clinical apprehensions have transformed the research interests in K. pneumoniae (Aslam et al., 2022; Wyres & Holt, 2018)

During the last decade, *K. pneumoniae* has emerged as a substantial health concern due to the increasing incidence of MDR *K. pneumoniae* infections across the globe. Some *K. pneumoniae* strains known as hypervirulent (hypermucovisous) variants present an additional agitating mechanism of hyper-virulence due to the acquired virulence factors, first reported in Asia in the 1990s and now has been reported all over the world. The share of *K. pneumoniae* in the crisis of antibiotic resistance is incalculable; the existing data advocates that it has a greater ecological range, significantly diverse composition of DNA, ARG diversity, and plasmid liability than the other Gram-negative bacilli (GNB) (Aslam, Khurshid, et al., 2021; K. L. Wyres et al., 2020).

K. pneumoniae infections need controlling measures such as prompt diagnosis, detection and containment of resistant variants, improved vaccine production, and use of alternative treatment approaches like phage or immunotherapy (Aslam, Arshad, et al., 2021; Aslam et al., 2018; K. L. Wyres et al., 2020; Xiao et al., 2016). However, all the above-mentioned containment measures still failed due to the diverse nature of *K. pneumoniae*.

Therefore, there is an urgent need for appropriate novel therapeutic and controlling measures. In this script, we present the taxonomic and genomic characteristic features of *K. pneumoniae*, which are the key players in making *K. pneumoniae* a credential pathogen. Further, we highlight the transmission mechanism, infection Biology, and Immune Evasion of *K. pneumoniae*.

2. Rational

Antimicrobial resistance (AMR) is a pressing health threat across the globe and multi-drug-resistant pathogens challenged the global health system and modern medicine. Underline mechanisms that make bacteria resistant superbugs are crucial and essential to comprehend, which may play a vital role to address this global challenge. As an ESKAPE member *K. pneumoniae* pose a substantial health and economic burden worldwide. It has complex molecular mechanisms associated with resistance, virulence and immune evasion. A comprehensive and thorough recounting of these insights is critical to finding out the viable solution to this global health concern. Keeping in view the importance of the subject, the current script is set down for the scientific audience associated with medicine and researchers in the field of molecular biology and microbiology.

3. Search Methodology:

The Peer reviewed findings with given problem statements were thoroughly studied through literature review technique. Owing to this approach explicit insights, research gaps and future perspectives regarding the pathogen were identified and narrated in the script accordingly. The Electronic Databases (EDs) like Web of Science, ScienceDirect, Scopus, PubMed and Google Scholar etc. were navigated extensively to retrieve the relevant dataset with numerous keywords, for instance, *Klebsiella pneumoniae*, *population genomics*, *multi-drug-resistant K. pneumoniae* etc. All the listed EDs were navigated because of their scientific reputation and wide-ranging subject coverage. The meticulous scheme of study was not just assured the relevancy and articulacy but enhanced the precision of this chronicle.

4. Taxonomy

The genus Klebsiella is designated after the name of a German microbiologist named Edwin Klebs in 1885, who later described the species Klebsiella pneumoniae in 1887 (Martínez et al., 2004). The causative agent of opportunistic infections belongs to the family Enterobacteriaceae (Partridge et al., 2018). Historically, Friedlander identified a pathogen from the patient's lungs that died due to pneumonia (Ashurst & Dawson, 2018; Friedländer, 1882). Later in that decade

two scientists came up with descriptions for the Friedlander bacterium and named it *Hyalococcus pneumoniae* (Ashurst & Dawson, 2018). Klebsiella was first described by a patient suffering from rhino scleroma later this organism was named "Klebsiella rhinoscleromatis. In the post-antibiotic era, the most prominent and widely cited efforts were made by different scientists such as Cowan in 1960, Bascomb in 1971, Buchanan and Gibbons in 1974, Brenner 1977, Woodward 1979, Izard1981, Bagley 1981 and Naemura in 1979 discovering and arguing the taxonomic position of previously discovered species, concluded different groups within the genus as, (i) *K.* pneumoniae including K. ozaena and K. rhinoscleromatis from clinical origin. (ii) *K. oxytoca* from environmental and clinical origin. (iii) *K. terrigena* and (iv) *K. planticola* from soil and botanical origin, respectively (Trevisan, 1887).

The phylogenetic analysis based on the 16SRNA subunit conducted in 2003, the Generic division of Klebsiella contains closely linked clusters. Klebsiella are much more related to each other than the neighboring bacterial clusters such as Serratia and Citrobacter (Boye & Hansen, 2003). Based on the whole genome and gyrA sequences of *K. pneumoniae* clinical isolates, it split into three distinct species, *K. pneumoniae* (KpI), *K. quasipneumoniae* (KpII), and *K. variicola* (KpIII). Further, it has been demonstrated that K. *pneumoniae* (KpI) is mostly related to human infection (Holt et al., 2015). Substantial genetic divergence among the species, as indicated by the numerical values on the branches such as 8.89, 0.46, and 9.03, which measure the genetic distances or evolutionary changes. Species like *K. pneumoniae* and *K. oxytoca* are shown to cluster closely, suggesting a more recent common ancestry compared to more genetically distant species such as *K. variicola* and *K. mitogenesis*. This clustering indicates not only the evolutionary pathways of these bacteria but also their adaptation strategies to different environments or hosts (Fig 1A).

The WGS revealed that KpI and KpII are equally virulent as both species have acquired the *K. pneumoniae* carbapenemase (KPC) gene and the New Delhi metal-lo-beta-lactamase-1 (NDM-1) gene (Long et al., 2017) (Figure 1B). With genome-wide average nucleotide identity (≥3%) these closely related phylogenetic species are collectively designated as K. pneumoniae species complex (KpsC) (Suzanne Bialek Davenet et al., 2014). Other KpsC included *K. quasipneumoniae subsp. similipneumoniae* (Kp4), *K. variicola subsp. Tropica* (Kp5) (Barbier et al., 2020), *K. quasivariicola* (Kp6), *K. africana* (Kp7) (Long et al., 2017). Like *K. pneumoniae, K. variicola* and *K. quasipneumoniae* are also commonly found bacteria in nosocomial infections

(Potter et al., 2018). These KpsC are emerging threats to hospitalized patients as they can acquire resistance plasmids from *K. pneumoniae* (Mathers et al., 2019; Rodríguez-Medina et al., 2019). The ‘‘Kp’’ term is usually used to describe seven phylogroups of the KpsC, while ‘‘K. pneumoniae’ is designated for phylogroup Kp1 such as K. pneumoniae sensu stricto (Barbier et al., 2020). Phenomena for evolution “descent with modification” allows microbes of a population to adapt and survive within the vast range of habitat in exposure to selective or environmental pressure and severe use of antibiotics-induced selective pressure, which resulted in the geographical distribution of mutated clones (Pitout & Finn, 2020).

5. Population dynamics

Different mechanisms have been reported for subtyping the *K. pneumoniae*, MLST is the most widely used method which employs sequencing of seven core genes named rpoB, gapA, mdh, pgi, phoE, infB, and tonB to check variation within these genes and given numerical numbers to each different sequence alleles set the sequence type (ST) (Brisse et al., 2009). The closely related sequence types whose gene sequence differences occurred by point mutation and have a similarity of 90-98% are combined to form a clonal complex (CC) by using the eBURST program (Turner et al., 2007). Further, these CCs have been arranged into subsets called clonal groups (CGs) containing central genotypes along their single-locus variants (SLVs). The CGs are termed according to the central ST, which was selected for the definition like CG258 is named due to its central genotype i.e. ST258 (S Breurec et al., 2013). These clones are the main source of antibiotic resistance and are referred to as High-risk (HiR) clonal groups with the ability to transfer the resistance genes (Baker & Thomson, 2018). *K. pneumoniae* clonal group CG 258 (ST258, ST11, 83 ST512) and CG14 (ST14 and ST15) are considered global disseminated health threats (S Breurec et al., 2013) (Figure 2). Recent reports have indicated that *K. pneumoniae* ST307 and ST147 are emerging global clones (Peirano et al., 2020), first reported in the USA with blaKPC-2 (Castanheira et al., 2013) and in Pakistan blaCTX-M-15 (Castanheira et al., 2013) and later appeared with blaOXA-48 (Ruiz-Garbajosa et al., 2016). After 2016 the recombination of hypervirulent (HvKP), carbapenem-resistant *K. pneumoniae* isolates produced a superbug of epidemic potential (Chen et al., 2004). Among these CG 23 contains K1-type hypervirulent isolates, whereas K2 type is scattered among various clonal groups immensely (Baker & Thomson, 2018). However, both K1 and K2 types are the most common HvKP with epi-demic potential (Brisse et al., 2009).

Other hypervirulent *K. pneumoniae* K-types included K5, K20, K54, and K57 (Yawei Zhang et al., 2016). All isolates within GC 23 are hypervirulent among these ST23, ST26, ST57, and ST163 are of epidemic potential (Yawei Zhang et al., 2016). Whereas the hypervirulence associated genes were generally encoded by MGEs, including the integrative conjugative element (ICE) (M. M. C. Lam et al., 2018). Two large resistance plasmids pLVPK from CG43 (Peirano & Chen, 2020) and pK2044 from K1 types (Wu et al., 2009) contain hypervirulence signature genes, including rmpA and/or rmpA2 (regulators of the mucoid Phenotype), iro (salmochelin) and iuc (Aerobactin) siderophores (Wu et al., 2009).

Several plasmids are prevalent in different clonal groups like CG23, CG86, CG65, CG66, and CG380 (M. M. C. Lam et al., 2018). *K. pneumoniae* carbapenemases genes like blaKPC, blaNDM, and blaOXA and their dissemination within STs and various GCs is a substantial concern. Populations of CG 258 are considered a main vehicle for the pandemic expansion of blaKPC-harboring K. pneumoniae (Munoz-Price et al., 2013) and blaNDM is frequently associated with ST11, ST14, ST147, ST149 and ST231 (Tängdén & Giske, 2015). While global dissemination of blaOXA-48-harboring *K. pneumoniae* is associated with mobile element Tn1999 (Poirel et al., 2012) and frequently prevalent in several STs e.g. ST11 and ST405, etc. (Fang et al., 2007). Isolates belonging to GC258 and ST258 & ST512 are the common cause of HAIs (Poirel et al., 2012), whereas isolates from GC 23, CG65, and CG86 are associated with invasive community-acquired infections (CAIs) (Decré et al., 2011; Munoz-Price et al., 2013). A detailed description of various CGs along with their STs and virulence determinants etc. is given in Table 1.

6. Genome composition

K. pneumoniae genomes are vast in distribution (Holt et al., 2015), and the phylogenetic lineages of these organisms vary from each other by ~0.5% nucleotide divergence (Suzanne Bialek-Davenet et al., 2014). Most of the ecological and metabolic activities for the survival of K. pneumoniae are governed by ~2000 ‘core’ (shared) genes, which are usually restrained by each strain. In addition to core genes 3500 accessory genes vary among different strains collected from a large pool of > 30,000 genes (Holt et al., 2015). Studies on pan-genome (core and accessory) revealed that genes encode an essential protein, 100,000 coding sequences with functions (Vernikos et al., 2015; Kelly L Wyres et al., 2020).

Overall, 13% of genes are associated with membrane transport, 19% of genes are related to carbohydrate metabolism and about 18% of genes play a role during metabolic pathways. The higher rate of diversity results in variable metabolic capacity (Blin et al., 2017). The genome size of *K. pneumoniae* is reported to be larger than the other Enterobacteriaceae which allows *K. pneumoniae* to survive in diverse geographical niches. Comparatively, the genome of *K. pneumoniae* is 5.7 Mbps in size, with 5455 protein coding genes that are larger than the *E. coli* genome ranging from 5.1 Mbp – 4915 genes, while the genome size of *E. cloacae* ranges from 5.0 Mbps and 4680 genes (Figure 1B). DNA base composition remarkably plays an important role in assigning the taxa and species (Mann & Chen, 2010). Based on the G+C content ratio it has been estimated that *K. pneumoniae* core genes have a 58% GC ratio, because accessory genes originated from dis-tinct ancestors and GC content ranges between 20% to >70% (Holt et al., 2015; Kelly L Wyres et al., 2020). *K. pneumoniae* genome is reported to be more variable than other species like *E. coli,* it is suggested that it acquired its DNA from horizontal gene transfer (HGT) (McInerney et al., 2017). While performing the lowest common ancestor analysis, *K. pneumoniae* accessory genes have occupied >20 diverse genera acquired from donor organisms, that include members of the Enterobacteriaceae and bacteria from a diverse group, including *Acinetobacter, Burkholderia, Streptomyces, Vibrio, Xanthomonas, and Xylella* (Holt et al., 2015). Evidenced from different studies have shown HGT patterns of *K. pneumoniae*, which revealed the presence of similar plasmids as identified in *E. coli, E. cloacae*, *Enterobacter asburiae*, and *Citrobacter freundii* (Conlan et al., 2016; Martin et al., 2017; Sheppard et al., 2016).

7. Virulence factors

Capsule polysaccharide (CPS) is a pivotal physiological feature of *K. pneumoniae*, specifically tissue-invasive and hypermucovisous (hypervirulent) strains that provide protection against the immune system and thus help in the survival of the pathogen (Li et al., 2014). The thick capsular layer on *K. pneumoniae* surface protects it from opsonization, phagocytosis, and the action of neutrophils, macrophages, epithelial cells, and dendritic cells (Cortés, Borrell, et al., 2002; Evrard et al., 2010; Pan et al., 2011; Sahly et al., 2000). An increasing level of CPS material in *K. pneumoniae* serotypes like well-known hypervirulent strains K1 and K2 provide a steady escape from the neutrophil-mediated intracellular killing of the bacterium, resulting in abscess formation in the liver (Wu et al., 2010). The K1 serotype belongs to ST57 and ST23, which are

placed together in CG23 (Brisse et al., 2009). The STs with the K2 serotype are distributed mostly in CG375, CG380, and CG86 (Suzanne Bialek-Davenet et al., 2014).

The presence of RmpA regulator and aerobactin is a characteristic feature of hvKp, both are encoded by virulence harboring plasmids. In addition, yersiniabactin, which is an iron acquisition system is associated with specific hvKp strains as well. It is encoded by ICEKp1 (integrative conjugative element Kp1). It is demonstrated that hypermucoviscosity has some association with antibiotic resistance as well. Hypermucoviscosity is more common in strains harboring blaSHV and blaTEM (Dong et al., 2022).

Capsule may play a significant role both outside and within the host, it helps to avoid desiccation in the atmosphere, prevents complement-mediated lysis or phagocytosis, and antibodies neutralization via releasing the capsular content (Clements et al., 2008; Cortés, Borrell, et al., 2002). In *K. pneumoniae* about 80 types have been reported based on antigenic diversity in capsules (Pan et al., 2008; Shon et al., 2013), K1 and K2 types are found to be resistant to phagocytes (Shon et al., 2013). These specified types may also have a crucial role in virulence as the K2 capsular type has often been detected in clinical iso-lates of urinary tract infections, pneumonia, and septicemia (De Jesus et al., 2015; Hennequin et al., 2012; Turton et al., 2008).

The kfu (Iron acquisition system) and PTS (Phosphoenolpyruvate sugar phosphotransferase system) serve as security pathways for the iron supply which is critically important in pathology associated with tissue-invasive *K. pneumoniae* (M. S. Lawlor et al., 2007). The siderophores including yersiniabactin, aerobactin, enterobactin, and salmochelin are iron chelators, these elements provide strength to *K. pneumoniae* against iron deficiency (Bachman et al., 2011). Aerobactin may serve as a virulence enhancer (Matthew S Lawlor et al., 2007) and has been reported to be responsible for more than 90% of the siderophore activities in hypermucovisous K. *pneumoniae*. Yersiniabactin has shown the ability to confer and maintain pneumonia and respiratory infection (Bachman et al., 2011).

Fimbriae is another significant virulence factor associated with infection and biofilm production, i.e., type 1, type 3, Kpc, and KPF-28 adhesins. Type 1 fimbriae serve as an initial factor in urinary tract infections (UTIs). However, it was reported that fimbriae have no role in the colonization of *K. pneumoniae* in the lungs or intestine (Struve et al., 2009). Type 3 fimbriae have a crucial role in biofilm but have no part in intestine or pulmonary infections. The types 1 and 3 fimbriae both worked in a compensating way and have a significant role in the

colonization of *K. pneumoniae* and its biofilm-associated UTI (Struve et al., 2009). The fimbrial adhesins are frequently associated with hypermucoviscosity in *K. pneumoniae* and play a contributing role in biofilm production (Wu et al., 2010). The KPF-28 adhesins facilitate K. pneumoniae colonization in the mammalian intestine (Di Martino et al., 1996). It has been demonstrated that CF29K protein is prevalent in the CC23 and could be either directly associated with pyogenic liver abscess pathogenesis or related to a different virulence factor on that plasmid.

Outer membrane protein A (OmpA) is vital for pathogenesis and has also a major role in the immune evasion mechanism exhibited by *K. pneumoniae* in vitro and in vivo (March et al., 2011). The OmpA enables the *K. pneumoniae* for host invasion, serum resistance, and protection from lung collections (Sukumaran et al., 2003). However, OmpA is a target of neutrophil elastases and serum amyloid protein A, which are the components of the innate immune system of the host, leading to cell lysis and enhancing phagocytosis (Belaaouaj et al., 2000; Hari-Dass et al., 2005).

Lipopolysaccharide (LPS) is essential for the formation of the outer monolayer of the membrane in Gram-negative bacterial pathogen, lipid A moiety modification helps *K. pneumoniae* in the evasion from the innate immune system of the host. There may be some association between lipid A modification and antibiotic resistance in Klebsiella species (Llobet et al., 2015), however, more studies are needed to corroborate this hypothesis. For instance, Colistin causes the disruption of the outer membrane by interacting with lipid A. Primarily LPS modification followed by the addition of 4-amino-4-deoxy-L-arabinose to lipid A are the causes of colistin resistance in *K. pneumoniae*. This change is linked with operon pbgPE regulated by PmrAB/PhoPQ, which is determined through the insertional activation of the PhoQ/PhoP MgrB regulators.

Hospital and other health centers acquired infections due to *K. pneumoniae* led the investigators to figure out the contribution of different virulence factors in the progression of disease (De Jesus et al., 2015). These contributors are the fimbrial and non-fimbrial adhesins, a capsule, siderophores (particularly enterobactin), urease, lipopolysaccharide (LPS), serum resistance as well and biofilm formation (Clements et al., 2008; De Jesus et al., 2015; El Fertas-Aissani et al., 2013; Fuursted et al., 2012; Hennequin et al., 2012). On the other hand, enhancement of the features increasing invasion comprises other siderophores (Aerobactin and yersiniabactin),

catechol receptor, mucoid factor, and hypermucoviscosity (De Jesus et al., 2015; El Fertas-Aissani et al., 2013; Russo et al., 2011; Struve et al., 2008). *K. pneumoniae* shows a variety of fimbrial and non-fimbrial adhesins having the ability to recognize various cell receptors which in turn can enable it to attach the target cell surfaces (Struve et al., 2008). Fimbrial adhesins comprised of mannose-sensitive type 1 fimbria, type 3 fimbriae, and plasmid-encoded fimbriae designated as KPF-28, whereas CF29K is a non-fimbrial adhesins (Podschun & Ullmann, 1998; Schroll et al., 2010; Struve et al., 2008). Type 1 and type 3 fimbriae have frequently been reported in *K. pneumoniae* species, and cause UTIs and biofilm formation (El Fertas-Aissani et al., 2013; Schroll et al., 2010). Fimbrial adhesins are useful as these enhance the adherence capabilities of the pathogen. On the other hand, it can be disadvantageous in the way that it may trigger the immune system of the host indicating the opportunistic nature of *K. pneumoniae* (De Jesus et al., 2015).

The hypervirulent strain of *K. pneumoniae* contains high quantities of siderophores (Shon et al., 2013), which are encoded by genes including entB (enterobactin), iutA (Aerobactin), irp1-irp2-ybtS-fyuA (yersiniabactin) and iroN (ferric catecholates receptor) (Turton et al., 2008). Most investigated virulent genes include [redacted] (encoding uridine diphosphate galacturonate 4-epimerase), wabG (involved in the biosynthesis of the outer core lipopolysaccharide), ureA (related to the urease operon), magA (microviscosity-associated gene A), mrkD (type 3 fimbriae adhesion), allS (activator of the allantois regulon), kfuBC (iron-uptake system), rpmA (regulator of mucoid phenotype) and fimH (fimbrial gene encoding type 1 fimbrial adhesion) (Brisse et al., 2009; Gao et al., 2014). Additionally, acquired β-lactamase encoding genes increase the pathogenicity of *K. pneumoniae*; however, active infection is primarily dependent on a variety of host-dependent factors (El Fertas-Aissani et al., 2013).

8. Naturally occurring resistance determinants

All the genes that can confer antibiotic resistance when grouped are as resistors (Fig-ure 2) (Wright, 2007). One of the schemes used for the classification of β-lactamases is molecular classification, based on the amino acid sequences and dividing them into class A, C, and D enzymes that utilize serine, whereas class B metallo- β lactamases require zinc for hydrolysis (Bush & Jacoby, 2010). Formerly, *K. pneumoniae* was the lone Gram-negative enteric bacterium that harbored a chromosome-encoded penicillinase (Arakawa et al., 1986). *K. pneumoniae* exhibits species-specific class A chromosome encoded β-lactamases which cause resistance

against ampicillin, carbenicillin amoxicillin, and ticarcillin (Lee et al., 2006). Overall, three different families including SHV, LEN, and OKP have been identified as the source of chromosome-based β-lactamases in *K. pneumoniae*, steer intrinsic resistance to ampicillin via the production of class A β-lactamase e.g. SHV, encoded by a core gene blaSHV (Holt et al., 2015). Two core locus OqxAB (efflux pump) and fosA (glutathione S-transferase) have also been detected in the *K. pneumoniae* chromosome using MGEs and distributed to other bacterial species. The wild-type gene expression of both loci is associated with resistance against fosfomycin i.e. fosA and quinolones i.e. OqxAB (Li et al., 2019).

In the mid-20th century, the use of Aminoglycosides was replaced by third-generation cephalosporins, carbapenems, and Fluoroquinolones (Doi et al., 2016), which resulted in a reduction of novel resistance mechanisms against aminoglycosides. However, the evolution of 16S RNA Methylase (Poulikakos & Falagas, 2013) extended the resistance spectrum against all aminoglycosides (Srinivasan & Rajamohan, 2013). Whereas kpnEF (SMR-type efflux pump) developed strong resistance against tobramycin and spectinomycin (Naeem et al., 2016). Resistance to tobramycin, streptomycin, and spectinomycin is considered linked directly with the loss of KpnO porins. Mutations in rrs or rpsL, result in target modification augment the resistance patterns (Redgrave et al., 2014). Extensive use of fluoroquinolones after their discovery in the 1980s has directed quinolone resistance mechanisms (Ward-McQuaid et al., 1963). Right after the first use of nalidixic acid (Guerra et al., 1983) and norfloxacin (Guerra et al., 1983), K. pneumoniae developed a vast variety of resistance mechanisms against quinolones including target modification i.e. gyrA-gyrB subunits and parC-parE subunits of DNA gyrase topoisomerase IV (Martinez-Martinez et al., 1996), (Guillard et al., 2016). Other mechanisms include the expression of efflux pumps acrAB gene (Wong et al., 2015) and OmpK36 porins deficiency (Ping et al., 2007).

Polymyxins which perturbs bacterial membrane via cations (Ca+2/Mg+2) dislocation are considered as one of the last resort antibiotics against Enterobacteriaceae (Antoniadou et al., 2007). Resistance to colistin was initially reported in 2004 from Greece (Marchaim et al., 2011). Resistance against colistin mainly occurs due to mutation in lpxM and its regulator ramA, responsible for the maturation of lipid A (Marchaim et al., 2011), while the addition of amino arabinose results in neutralization of lipid A. Lipid A modification through TupA-like/glycosyltransferase and CrrAB is also an important resistance mechanism (Srinivasan et al.,

2012). Upregulated efflux expression via positive regulation of AcrAB-TolC and KpnEF (C.R. Lee et al., 2016) by the RarA transcription regulator is imperative. Most commonly the resistance to colistin develops via mgrB gene inactivation or point mutations in phoPQ, pmrAB, or crrAB (two-component regulator systems) (C.-R. Lee et al., 2016).

Additionally, resistance against first approved glycylcyclines i.e. Tigecycline has also been reported (Nielsen et al., 2014) through modification in the 30S and the 16S ribosomal units and cell permeability (Villa et al., 2014). Other mechanisms include up-regulation of efflux pumps such as KpgABC (Ahn et al., 2016). The first mutation was detected in S10 (ribosomal protein) encoded by rpsJ, which reduces susceptibility, but their role in tigecycline resistance is unclear (Pitout et al., 2015).

9. Plasmid-mediated antibiotic resistance

In *K. pneumoniae* ARGs attained through horizontal gene transfer play a significant role in the acquisition of resistance as compared to chromosomal mutations. Such accessory genes are often plasmid-mediated; however, these may be incorporated into the bacterial chromosome. For instance, a strong promoter enables the mobile genetic variant of blaSHV with some point mutations to perform ESBL activity, which causes resistance against cephalosporins and even carbapenems (Liakopoulos et al., 2016). Accordingly, a few K. pneumoniae strains cart replicas of blaSHV, one core chromosomal gene, and other acquired plasmid variants directed by a robust IS26 promoter (Hammond et al., 2005).

K. pneumoniae can acquire resistance genes reside on plasmids and mobile elements (Bush & Jacoby, 2010; Calbo & Garau, 2015), like blaOXA (Evans & Amyes, 2014), blaPER, blaTLA and blaVEB (Philippon et al., 2016), rare genes blaGES and blaSFO (Ramirez et al., 2019; Yigit et al., 2001). During the 1960s two β-lactamase blaSHV-1 and blaTEM-1 were described in *K. pneumoniae* for the first time which conferred resistance to penicillin (Datta & Kontomichalou, 1965). Later, the acquisition of blaTEM-3 unveiled resistance against mono-bactams and cephalosporins (Sirot et al., 1987).

In the early 2000's plasmid, plasmid-mediated blaCTX-M shifted the trends of *K. pneumoniae* infections to major hospital-acquired acute infections. It was documentation that metallo-enzyme named blaIMP-1 identified in *K. pneumoniae* displayed resistance to carbapenems. Among other carbapenemases acquired by *K. pneumoniae* including blaNDM-1, blaOXA-48 and blaKPC are

the most common and immensely disseminated resistance determinants in every continent (Naas et al., 2012).

Aminoglycosides on the other hand were frequently used during the early 1940s to late 1960 which were then replaced by β-lactams such as cephalosporins and carbapenems as plasmid-mediated resistance determinants like aph, ant, and aac genes were identified against these antibiotics (Novan,.2017). Unfortunately, Plasmid-mediated aminoglycoside-resistant gene armA is identified, which encodes 16S rRNA methylase enzyme confers resistance to all classes of aminoglycoside. While other 16S rRNA methylase genes belong to the NpmA and Rmt family (Shen et al., 2020).

The very first plasmid-mediated quinolone resistance in *K. pneumoniae* described that qnrA encodes a pentapeptide repeat protein that is responsible for the resistance. Overall, the acquisition of plasmid-mediated resistant genes (PMQR) is associated with resistance to quinolones. These genes include aac (6´)-Ibcr (Bado et al., 2016; Fàbrega et al., 2009; Ruiz et al., 2012) which modifies quinolones in *K. pneumoniae* and qnrA genes whose product protects DNA gyrase and topoisomerase IV from quinolone inhibition in *K. pneumoniae*. PMQR genes modify quinolones in *K. pneumoniae* and pose a narrow spectrum of resistance but their presence augments resistance of *K. pneumoniae* harboring ESBL genes (Tóth et al., 2014). It has been observed in the clonal groups ST11, ST15, and ST147 (Antoniadou et al., 2007).

Plasmid-mediated polymyxin resistance in *K. pneumoniae* strains is also reported in China after the identification of the mcr-1 harboring strains (Zowawi et al., 2015), which modifies lipid A through phosphoethanolamine transferase enzyme activity. Further-more, the recent emergence of hypervirulent colistin resistance *K. pneumoniae* is a major public health concern worldwide keeping in view the colistin as a last resort antibiotic against carbapenem resistance hvKp. However, it is worth mentioning here that mcr-1 is not solely associated with colistin resistance. Other determinants including mcr-2 to 7 and more recently mcr-8 gene are also associated with colistin resistance in *K. pneumoniae.* Additionally, mcr-7.1 which has 70 % amino acid similarity with mcr-3 and mcr-8.1 on a plasmid having IncFIA has been reported as a novel mobile genetic element from various parts of the world (Mmatli et al., 2022).

The CG 258 harboring *K. pneumoniae* carbapenemase (KPC) was first re-ported from the USA, and blaKPC genes reside in a unique Tn4401 transposon (Naas et al., 2012). Most *K. pneumoniae* plasmids cannot be typed by PCR-assisted replicon typing methods (Osborn et al.,

2000). However, many of these novel plasmids are considered to belong to the IncF plasmid family. Based on sequencing data FII replicons of large plasmid family IncFII can be characterized as FIIs, FIIy, and FIIk specific groups (Kaplan et al., 2015). Plasmids also produce an ability to bypass the incompatibility effect where two in-compatible plasmids can reside in the same cell (Chen et al., 2013). This phenomenon is achieved when plasmids replicate using alternative replicons. K. pneumoniae strains undergo the recombination of homologous regions of FIIk replicons. Whereas ST258 was isolated from the USA in 2000 has blaKPC-2 along with blaKPC-3 encoded by IncFIIk and PKpQIL plasmids.

Phylogenetic studies of CG 258 have demonstrated that plasmids belonging to IncI2 are only present in clade II and pKpQIL were found in both clades I and II (Miriagou et al., 2010). Rearrangements of IncFIIk plasmids portions with IncR or IncN plasmids merged in a multi-replicon status have also been seen. Some other diverse plasmids have been described to have resistance genes like NDM metallo-lactamases (MBL), GES, and the carbapenem-hydrolyzing class D OXA β-lactamases (CHDL) and are disseminated in geologically distant *K. pneumoniae* strains. In Greece, plasmids carrying IncN1 blaVIM-1 were identified from different Klebsiella strains isolated from numerous hospitals containing distinct regions having several transposons and integrons (Poirel et al., 2013). The plasmid IncX3 is highly disseminated in *K. pneumoniae* as it acquires resistance genes including blaNDM-5, (Figure 2). It has been described that blaCTX-M genes are mostly associated with IncFII plasmids which are related to IncFII of *E. coli* and highly like plasmid IncFII having FIA replicon and the phage P1, adept of extra chromosomal replication by the IncY replicon and diverge from those carrying blaKPC (Dolejska et al., 2013). Plasmids including IncI1, IncR, and IncN are reported as of animal origin while they also acquired CTX-M-15 and CTX-M-1 (Zhu et al., 2009). The data suggests that ESBL-encoding plasmids are highly disseminated within Klebsiella and other Enterobacteriaceae. Interestingly, Strains of K. pneumoniae isolated from China were carrying pCTX-M-3 plasmid lacking ArmA (Zhu et al., 2009). Overall, taking into consideration IncFIIk plasmids, IncHI, IncI2, and IncN2 alongside novel replicons identified, resistance plasmids of *K. pneumoniae* are distinctive and differ from those which are identified in other members of the Enterobacteriaceae family (Shiri Navon-Venezia et al., 2017).

10. Infection Biology and Immune Evasion

K. pneumoniae prevents the triggering of the host defense mechanism by covering its PAMPs from PRRs, immune globulins, and complement proteins. It prevents binding to both cells of innate and adaptive immunity (Paczosa & Mecsas, 2016). Activation of complement proteins by *K. pneumoniae* occurs in antibodies independent manner as it binds directly to Cq1 (Albertí et al., 1996; Alberti et al., 1993). Although *K. pneumoniae* also activates the complement classical pathway by binding of LPS to complement protein. However, this mechanism of activation was reported as less efficient as compared to Outer membrane proteins (Alberti et al., 1993). The complement system plays a crucial role in phagocytosis and clearance of *K. pneumoniae* by lung epithelial cells facilitated by the C3b complement protein (de Astorza et al., 2004). Mutation of capsular polysaccharides ultimately increases the C3b deposition which results in string bactericidal activity complement proteins. While to avoid increased deposition of C3b O antigen and LPS of outer membrane work as shielding factor (Merino et al., 1992). Other than LPs and O antigen CPS also inhibits complement deposition (Álvarez et al., 2000) and inhibits binding of lung collectins SPA and SP-D to LPS. Studies conducted on mouse models strongly fortify the argument that CPS plays a crucial role in K. pneumoniae virulence (Willsey et al., 2018) by inhibiting the binding of Polymyxins and CAMP therefore, it has been stated that resistance to Polymyxins is directly proportional to the amount of CPS produced by *K. pneumoniae* (Campos et al., 2004). Another mechanism to invade CAMPs and Polymyxins includes modification in Lipid A structure (Llobet et al., 2008). The absence of palpitate, 4-amino-4-deoxy-L-arabinose, phospho-ethanolamine, and 2-hydroxy myristate from Lipid A structure results in loss of virulence in mouse models (Kidd et al., 2017; Llobet et al., 2011; Mills et al., 2017). But something worth mentioning here is that the role of CPS in virulence is indirect as level CPS depends upon 2-hydroxylation and switches on the status of late acyltransferases lpxM and lpxL respectively (Llobet et al., 2011).

It has been reported that *K. pneumoniae* invades the effect of antibiotics and the immune system by penetrating epithelial cells (Clements et al., 2007). However, further research on this phenomenon revealed that the engulfment of *K. pneumoniae* by host epithelial cells is a defense mechanism (Clements et al., 2007). *K. pneumoniae* CPS agonistically activates the TLRs especially the TLR4 function which results in an enhanced inflammatory effect as no. of TLR4 and TLR2 increase in epithelial cells because of *K. pneumoniae* infection (Cortés, Álvarez, et al.,

2002). The host immune system also produces anti-CPS immunoglobulins which activate the secretion of neutrophil extracellular traps (NETs), which upon release kills *K. pneumoniae* in extracellular space (Regueiro et al., 2009). Phosphatidylserine is known as eat me signal for macrophages, however their reduced expression of neutrophils because of their infection ultimately inhibits their phagocytosis (Diago-Navarro et al., 2018) and leads them towards necroptosis and inhibits efferocytosis of neutrophils (Amulic et al., 2012). Subsets of dendritic cells are also activated by *K. pneumoniae* (Jondle et al., 2018). While structures including CPS, LPS, and porins, induce their maturation (Jondle et al., 2018). Inside macrophages *K. pneumoniae* controls the phagosome maturation and 10 h after *K. pneumoniae* infection programmed cell death of macrophages usually occurs (Van Elssen et al., 2010) Interestingly, there is no evidence that CPS augments the *K. pneumoniae* survival inside macrophages, as CPS mutants do not affect intracellular survival patterns, supported by the fact that *K. pneumoniae* inhibits its CPS production once it gets inside the cell (Van Elssen et al., 2010). The plasticity of macrophages allows them to have physiological and phenotypical characteristics. As studies have demonstrated the M2 macrophage presence in mouse infection models, while the elimination of M2 macrophages results in efficient clearance of pathogen (Mills et al., 2017).

High levels of IL-10 during *K. pneumoniae*-triggered pneumoniae result in an anti-inflammatory effect (Fevre et al., 2013). IL-10 cytokines are used to control the activation of cells involved in innate immune response and are secreted by various immune cells (Yoshida et al., 2000). To counter this *K. pneumoniae*-induced anti-inflammatory affect mediated by IL-10 host immune system regulates IFNγ production (Gabryšová et al., 2014). Reports also claim the direct association between CPS and high levels of IL-10 fortifies the pathogenicity of *K. pneumoniae*. While mice infected with mutant CPS do not have high IL-10 concentrations (Gabryšová et al., 2014). NF-κB (transcription factor) upon stimulation of a TLR4/2-MyD88 signaling pathway controls various anti-Klebsiella responses (Yoshida et al., 2001). Here CPS came into play by inhibiting the engulfment of *K. pneumoniae* by epithelial cells resulting in limited NF-κB activation which in turn further sup-presses the production of IL8, ICAM1, and human defensins. In deubiquitinase cylindromatosis (CYLD) negative host cells Klebsiella infection quickly followed by production of IL8 this happens because in (CYLD) positive cells *K. pneumoniae* hijacked the (CYLD) thus inhibits NF-κB signaling (Bengoechea & Sa Pessoa, 2019). Studies have shown CPS mutants are unable to activate the EGFR pathway, while CPS wild strain does

(Bengoechea & Sa Pessoa, 2019). However, their activation is indirect and TLR4-dependent (Moranta Mesquida et al., 2018). *K. pneumoniae* inhibits the production of inflammatory mediators and defensins by inactivating the MAPK-by-MAPK phosphatase-1 (MKP-1). As MAPKs p38, ERK and JNK play important roles in the inflammatory response. The production of (MKP-1) during infection is mediated by activation of NOD1, while inhibition of IL8 from epithelial cells is governed by the synergistic effect of MKP-1 and CYLD (Regueiro et al., 2011). Studies have confirmed the CPS-independent anti-inflammatory role of OmpA during Klebsiella pneumoniae infections (Tomás et al., 2015).

Enterobactin is an iron-binding siderophore secreted by *K. pneumoniae* it competes and binds the iron against host proteins (March et al., 2011). Other iron-binding proteins include aerobactin, salmochelin, and yersiniabactin (Bachman et al., 2012). Importantly, yersiniabactin is associated with invasive infections. During *K. pneumoniae* infection the spread of the pathogen is associated with siderophores as they down-regulate transcription factor HIF-1α responsible for mucosal immunity and cellular intrinsic immunity (Holt et al., 2015) the hypothesis that HIF-1α down-regulation increases the infection rate is usually common in Klebsiella infections (Holden et al., 2016). Overall, the immune evasion strategies of *K. pneumoniae* mechanisms are portrayed in (Figure 4).

11. Prospectives

K. pneumoniae-associated Hospital-acquired infections cannot be easily differentiable from HAIs caused by other clinically important pathogens. Whereas community-acquired infections caused by *K. pneumoniae* show some distinguished characteristics. Conventionally, infection caused by *K. pneumoniae* is designated as community-acquired pneumonia and clinically manifested as sudden onset of high fever, dramatic toxicity, hemoptysis and abnormalities seen in chest radiography such as bulging interlobar cleft and cavitary abscesses (Ashurst & Dawson, 2018; Korvick et al., 1991) Considerable proportion of some ESBL producing clinical isolates of *K. pneumoniae* are sensitive to third generation cephalosporins or aztreonam and therefore it is problematic to detect ESBL's in clinical isolates (Paterson & Bonomo, 2005; Wang et al., 2011). This confusion results in serious health hazards when the same treatment is used against serious infections (Paterson et al., 2001; Paterson & Yu, 1999). Whereas resistance to Ceftazidime is a sufficient marker for the detection of ESBLs (Guideline & Edition).

The Clinical and Laboratory Standards Institute (CLSI) has standardized confirmatory and screening tests for *K. pneumoniae* and *K. oxytoca* for ESBL detection. Production of some important enzymes including extended-spectrum ß-lactamases, cephalosporinases, and carbapenemases and their continuous horizontal gene transfer via plasmids and mobile elements like transposons facilitates the ESBL's associated infection and bacterial survival under the action of ß-lactam drugs (Partridge et al., 2018). As resistance against known antibiotics keeps on increasing and there is a scarcity of new antibiotics, alternative therapeutic and diagnostic strategies may be exploited (Lewis, 2017). Various detection methods for ESBL have been employed in laboratories that include beta-lactamase inhibitors such as clavulanic acid by using double disk diffusion test, Microscan ESBL plus detection system, Vitek ESBL detection card, E test strips containing Ceftazidime or cefotaxime (Singh & Singh, 2014). Additionally, a bacteriophage-based diagnostic approach is also practiced. Recently, studies demonstrated a luminescent bacterio-phage-based detection of *K. pneumoniae* and they suggested that such a diagnostic approach may provide a prompt diagnostic tool to escort the developing subject of phage therapeutics, especially to treat chronic infectious diseases.

While considering novel treatments against drug resistance *K. pneumoniae*, phage therapy is considered a promising therapeutic strategy to fight resistant superbugs. The endolysins that are phage hydrolases and other phage proteins are potential antimicrobials (Aslam, Arshad, et al., 2021; Qurat-ul-Ain et al., 2021). (Zelcbuch et al., 2021). Despite the advancements in this field few challenges still need to be addressed for the general application of phage therapeutics. These shortfalls include target specificity, penetration abilities, immunogenicity, and half-life of the phage product (Karimi et al., 2016).

On the other hand, Immunotherapy is also considered as a rational alternative to manage MDR *K. pneumoniae*, it harnesses the host immune system to elicit the immune response against the pathogen. This method employs various mechanisms to protect the host and avoid the development of resistance, unlike antibiotics. Practically, an all-in-one vaccine having a complete range of CPS or LPS is difficult, though a multivalent vaccine has been developed. It is suggested that a solution to this problem is to identify conserved antigenic regions among various serotypes of *K. pneumoniae* which may be used for the development of a broad-spectrum vaccine (Xiao et al., 2016). In this regard, MrkA is a suitable candidate as it is conserved among various members of the Enterobacteriaceae family is a key element fimbrial (Type III) complex,

and possesses key vital functions like biofilm formation, infection progression, and fimbrial shaft development (Allen et al., 1991). Poly-N-acetyl glucosamine (PNAG) is another possible conserved surface polysaccharide antigen that may also be beneficial to manage *K. pneumoniae* via immunotherapy (Cywes-Bentley et al., 2013; Xiao et al., 2016). Previously, the vaccine was developed from hyper-immune globulins and capsular polysaccharides of *K. pneumoniae,* but the complexity of its production halted further progress (Ahmad, El-Sayed, et al., 2012; Diago-Navarro et al., 2017). In 2017, Diago-Navarro and colleagues isolated Monoclonal antibodies against hyper-mucoid hypervirulent strains which promoted the neutrophil extracellular trap (NET) release and opsonophagocytic killing (Diago-Navarro, Calatayud-Baselga et al. 2017) In preclinical models' immunogenicity of macromolecules like LPS O antigens tends to increase when conjugated covalently with variety of carriers like outer membrane proteins (Ahmad, Haroun, et al., 2012). Recently a humanized anti-body against galactan III O antigen, expressed in about 83% of the Surface polysaccharides, has been reported these sugars are optimal targets for the development of immune prophylactic and therapeutic efforts to counter the emergence of antibiotic-resistant strains, along with the hypervirulent ST258 (Szijártó et al., 2017). E. Di-ago-Navarro et al have also generated murine-based monoclonal antibodies against ST 258 CPS (Diago-Navarro et al., 2018).

Furthermore, the implication of CRISPR-Cas technology to develop sequence-specific antimicrobials is also an emerging field to fight resistant superbugs. In this technique, the guide RNA with nuclease activity is used to target the specific sequences in the desired DNA (Pursey et al., 2018). Guide RNA is delivered proficiently to the target microbial community through phagemid or bacteriophage. The specific DNA targets include polymorphism, virulence determinants, and antibiotic-resistance genes. Use of this approach against *E. coli* and carbapenem-resistant Enterobacteriaceae has been reported in the recent past (Tagliaferri et al., 2020). RNA-guided nucleases (RGNs) are a class of extremely intolerant antimicrobials that put selective pressure into practice at the target DNA to minimize the distribution of unwanted genes, reduce the off-targets, and permit the programmable restoration of microbiota (Citorik et al., 2014).

12. Conclusion

The existing literature recommends that *K. pneumoniae* is a distinctive and credential pathogen among the other ESKAPE Gram-negative bacterial members due to some vital features like

ARGs and virulence genes diversity, genomic configuration, significant plasmid load, etc. Currently, this bacterium represents the incongruity of therapeutic approaches and present research and development (R & D) in the field of antimicrobial resistance. Straightforwardly, there are considerable gaps in our understanding of *K. pneumoniae* pathobiology and population transcriptomics. Hence, to understand the several Achilles heels of *K. pneumoniae* there is an urgent need for cutting-edge research which may be beneficial to cope with this certified pathogen.

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References

Ahmad TA, El-Sayed, LH, Haroun, M, Hussein, AA, & El Sayed, H. (2012). Development of immunization trials against Klebsiella pneumoniae. Vaccine, 30(14), 2411-2420.

Ahmad, TA, Haroun M, Hussein AA, El Ashry ESH, & El-Sayed L H. (2012). Development of a new trend conjugate vaccine for the prevention of Klebsiella pneumoniae. Infectious disease reports, 4(2), 128-133.

Ahn C, Yoon SS, Yong, TS, Jeong, SH, & Lee, K. (2016). The resistance mechanism and clonal distribution of tigecycline-nonsusceptible Klebsiella pneumoniae isolates in Korea. Yonsei medical journal, 57(3), 641.

Albertí S, Alvare D, Merino S, Casado, MT, Vivanco F, Tomás, JM, & Benedí VJ. (1996). Analysis of complement C3 deposition and degradation on Klebsiella pneumoniae. Infection and immunity, 64(11), 4726-4732.

Alberti S, Marqués G, Camprubi S, Merino S, Tomás J, Vivanco F, & Benedi V. (1993). C1q binding and activation of the complement classical pathway by Klebsiella pneumoniae outer membrane proteins. Infection and immunity, 61(3), 852-860.

Allen BL, Gerlach GF, & Clegg, S. (1991). Nucleotide sequence and functions of mrk determinants necessary for expression of type 3 fimbriae in Klebsiella pneumoniae. J Bacteriol, 173(2), 916-920. https://doi.org/10.1128/jb.173.2.916-920.1991

Álvarez D, Merino S, Tomás JM, Benedí VJ, & Albertí S. (2000). Capsular polysaccharide is a major complement resistance factor in lipopolysaccharide O side chain-deficient Klebsiella pneumoniae clinical isolates. Infection and immunity, 68(2), 953-955.

Amulic B, Cazalet C, Hayes GL, Metzler KD, & Zychlinsky A. (2012). Neutrophil function: from mechanisms to disease. Annual review of immunology, 30, 459-489.

Antoniadou A, Kontopidou F, Poulakou G, Koratzanis E, Galani I, Papadomichelakis, E, Kopterides P, Souli M, Armaganidis A, & Giamarellou, H. (2007). Colistin-resistant isolates of Klebsiella pneumoniae emerging in intensive care unit patients: first report of a multiclonal cluster. Journal of Antimicrobial Chemotherapy, 59(4), 786-790.

Arakawa Y, Ohta M, Kido N, Fujii Y, Komatsu T, & Kato N. (1986). Close evolutionary relationship between the chromosomally encoded β lactamase gene of Klebsiella pneumoniae and the TEM β-lactamase gene mediated by R plasmids. FEBS letters, 207(1), 69-74.

Aslam B, Arshad MI, Aslam MA, Muzammil S, Siddique AB, Yasmeen N, Khurshid M, Rasool M, Ahmad M, Rasool MH, Fahim M, Hussain R, Xia X, & Baloch Z. (2021). Bacteriophage Proteome: Insights and Potentials of an Alternate to Antibiotics. Infectious Disease Therapy, 10(3), 1171-1193. https://doi.org/10.1007/s40121-021-00446-2

Aslam B, Chaudhry TH, Arshad MI, Muzammil S, Siddique AB, Yasmeen N, Khurshid M, Amir A, Salman M, Rasool MH, Xia X, & Baloch Z. (2022). Distribution and genetic diversity of multi-drug-resistant Klebsiella pneumoniae at the human-animal-environment interface in Pakistan. Frontiers in Microbiology, 13, 898248. https://doi.org/10.3389/fmicb.2022.898248

Aslam B, Khurshid M, Arshad MI, Muzammil S, Rasool M, Yasmeen N, Shah T, Chaudhry TH, Rasool MH, Shahid A, Xueshan X, & Baloch, Z. (2021). Antibiotic Resistance: One Health One World Outlook. Frontiers in Cellular and Infection Microbiology, 11, 771510. https://doi.org/10.3389/fcimb.2021.771510

Aslam B, Wang W, Arshad MI, Khurshid M, Muzammil S, Rasool MH, Nisar MA, Alvi RF, Aslam MA, Qamar MU, Salamat MKF, & Baloch, Z. (2018). Antibiotic resistance: a rundown of a global crisis. Infection and Drug Resistance, 11, 1645-1658. https://doi.org/10.2147/idr.s173867

Belaaouaj A, Kim KS, & Shapiro SD. (2000). Degradation of outer membrane protein A in Escherichia coli killing by neutrophil elastase. Science, 289(5482), 1185-1187.

Bachman MA, Lenio S, Schmidt L, Oyler JE, & Weiser JN. (2012). Interaction of lipocalin 2, transferrin, and siderophores determines the replicative niche of Klebsiella pneumoniae during pneumonia. MBio, 3(6).

Bachman MA, Oyler JE, Burns SH, Caza M, Lépine F, Dozois CM, & Weiser JN. (2011). Klebsiella pneumoniae yersiniabactin promotes respiratory tract infection through evasion of lipocalin 2. Infection and immunity, 79(8), 3309-3316.

Bado I, Gutiérrez C, García-Fulgueiras V, Cordeiro NF, Pirez LA, Seija V, Bazet C, Rieppi G, & Vignoli R. (2016). CTX-M-15 in combination with aac (6′)-Ib-cr is the most prevalent mechanism of resistance both in Escherichia coli and Klebsiella pneumoniae, including K. pneumoniae ST258, in an ICU in Uruguay. Journal of global antimicrobial resistance, 6, 5-9.

Baker S, & Thomson N. (2018). Genomic insights into the emergence and spread of antimicrobial-resistant bacterial pathogens. 360(6390), 733-738. https://doi.org/10.1126/science.aar3777

Barbier E, Rodrigues C, Depret G, Passet V, Gal L, Piveteau P, & Brisse S. (2020). The ZKIR assay, a real-time PCR method for the detection of Klebsiella pneumoniae and closely related species in environmental samples. Applied and environmental microbiology, 86(7).

Bengoechea JA, & Sa Pessoa J. (2019). Klebsiella pneumoniae infection biology: living to counteract host defenses. FEMS Microbiol Review, 43(2), 123-144.

Bialek-Davenet S, Criscuolo A, Ailloud F, Passet V, Jones L, Delannoy-Vieillard AS, Garin B, Le Hello S, Arlet G, & Nicolas-Chanoine MH. (2014). Genomic definition of hypervirulent and multidrug-resistant Klebsiella pneumoniae clonal groups. Emerging infectious diseases, 20(11), 1812.

Bialek-Davenet S, Criscuolo A, Ailloud F, Passet V, Nicolas-Chanoine MH, Decré D, & Brisse S. (2014). Development of a multiplex PCR assay for identification of Klebsiella pneumoniae hypervirulent clones of capsular serotype K2. Journal of Medical Microbiology, 63(Pt12), 1608-1614. https://doi.org/10.1099/jmm.0.081448-0

Blin C, Passet V, Touchon M, Rocha EP, & Brisse S. (2017). Metabolic diversity of the emerging pathogenic lineages of Klebsiella pneumoniae. Environmental microbiology, 19(5), 1881-1898.

Boonyasiri A, Jauneikaite E, Brinkac LM, Greco, C, Lerdlamyong, K, Tangkoskul T, Nguyen K, Thamlikitkul V, & Fouts DE. (2021). Genomic and clinical characterization of multidrug-resistant carbapenemase-producing ST231 and ST16 Klebsiella pneumoniae isolates colonizing patients at Siriraj hospital, Bangkok, Thailand from 2015 to 2017. BMC Infect Dis, 21(1), 142. https://doi.org/10.1186/s12879-021-05790-9

Boye K, & Hansen DS. (2003). Sequencing of 16S rDNA of Klebsiella: taxonomic relations within the genus and to other Enterobacteriaceae. International journal of medical microbiology, 292(7-8), 495-503.

Breurec S, Guessennd N, Timinouni M, Le T, Cao V, Ngandjio A, Randrianirina F, Thiberge J, Kinana A, & Dufougeray A. (2013). Klebsiella pneumoniae resistant to third-generation cephalosporins in five African and two Vietnamese major towns: multiclonal population structure with two major international clonal groups, CG15 and CG258. Clinical Microbiology and Infection, 19(4), 349-355.

Breurec S, Guessennd N, Timinouni M, Le TA, Cao V, Ngandjio A, Randrianirina F, Thiberge JM, Kinana A, Dufougeray A, Perrier-Gros-Claude JD, Boisier P, Garin B, & Brisse S. (2013). Klebsiella pneumoniae resistant to third-generation cephalosporins in five African and two Vietnamese major towns: multiclonal population structure with two major international clonal groups, CG15 and CG258. Clin Microbiol Infect, 19(4), 349-355. https://doi.org/10.1111/j.1469-0691.2012.03805.x

Brisse S, Fevre C, Passet V, Issenhuth-Jeanjean S, Tournebize R, Diancourt L, & Grimont P. (2009). Virulent clones of Klebsiella pneumoniae: identification and evolutionary scenario based on genomic and phenotypic characterization. PLoS One, 4(3), e4982. https://doi.org/10.1371/journal.pone.0004982

Bush K, & Jacoby GA. (2010). Updated functional classification of β-lactamases. Antimicrobial Agents and Chemotherapy, 54(3), 969-976.

Calbo E, & Garau J. (2015). The changing epidemiology of hospital outbreaks due to ESBL-producing Klebsiella pneumoniae: the CTX-M-15 type consolidation. Future microbiology, 10(6), 1063-1075.

Campos MA, Vargas MA, Regueiro V, Lampert CM, Albertí S, & Bengoechea JA. (2004). Capsule polysaccharide mediates bacterial resistance to antimicrobial peptides. Infection and immunity, 72(12), 7107-7114.

Castanheira M, Farrell SE, Wanger A, Rolston KV, Jones RN, & Mendes RE. (2013). Rapid expansion of KPC-2-producing Klebsiella pneumoniae isolates in two Texas hospitals due to clonal spread of ST258 and ST307 lineages. Microbial Drug Resistance, 19(4), 295-297. https://doi.org/10.1089/mdr.2012.0238

Chen L, Chavda KD, Al Laham N, Melano RG, Jacobs MR, Bonomo RA, & Kreiswirth BN. (2013). Complete nucleotide sequence of a blaKPC-harboring IncI2 plasmid and its dissemination in New Jersey and New York hospitals. Antimicrobial Agents and Chemotherapy, 57(10), 5019-5025.

Chen L, Mathema B, Pitout JDD, DeLeo FR, & Kreiswirth BN. (2014). Epidemic Klebsiella ST258 is a Hybrid Strain. MBio, 5(3), e01355-01314. https://doi.org/10.1128/mBio.01355-14

Chen YT, Chang HY, Lai YC, Pan CC, Tsai SF, & Peng HL. (2004). Sequencing and analysis of the large virulence plasmid pLVPK of Klebsiella pneumoniae CG43. Gene, 337, 189-198. https://doi.org/10.1016/j.gene.2004.05.008

Citorik RJ, Mimee M, & Lu TK. (2014). Sequence-specific antimicrobials using efficiently delivered RNA-guided nucleases. Nature Biotechnology, 32(11), 1141-1145. https://doi.org/10.1038/nbt.3011

Clements A, Gaboriaud F, Duval JF, Farn JL, Jenney AW, Lithgow T, Wijburg OL, Hartland EL, & Strugnell RA (2008). The major surface-associated saccharides of Klebsiella pneumoniae contribute to host cell association. PloS one, 3(11), e3817.

Clements A, Tull D, Jenney AW, Farn JL, Kim SH, Bishop RE, McPhee JB, Hancock RE, Hartland EL, & Pearse MJ. (2007). Secondary acylation of Klebsiella pneumoniae lipopolysaccharide contributes to sensitivity to antibacterial peptides. Journal of Biological Chemistry, 282(21), 15569-15577.

Conlan S, Park M, Deming C, Thomas PJ, Young AC, Coleman H, Sison C, Weingarten RA, Lau AF, & Dekker JP. (2016). Plasmid dynamics in KPC-positive Klebsiella pneumoniae during long-term patient colonization. MBio, 7(3).

741 Cortés G, Álvarez D, Saus C, & Albertí S. (2002). Role of lung epithelial cells in defense against
742 Klebsiella pneumoniae pneumonia. Infection and immunity, 70(3), 1075-1080.
743 Cortés G, Borrell N, de Astorza B, Gómez C, Sauleda J, & Albertí S. (2002). Molecular analysis
744 of the contribution of the capsular polysaccharide and the lipopolysaccharide O side
745 chain to the virulence of Klebsiella pneumoniae in a murine model of pneumonia.
746 Infection and immunity, 70(5), 2583-2590.
747 Cywes-Bentley C, Skurnik D, Zaidi T, Roux D, Deoliveira RB, Garrett WS, Lu X, O'Malley J,
748 Kinzel K, Zaidi T, Rey A, Perrin C, Fichorova RN, Kayatani AK, Maira-Litràn T,
749 Gening ML, Tsvetkov YE, Nifantiev NE, Bakaletz L, Pier GB. (2013). Antibody to a
750 conserved antigenic target is protective against diverse prokaryotic and eukaryotic
751 pathogens. Proceeding of National Academy of Science USA, 110(24), E2209-2218.
752 https://doi.org/10.1073/pnas.1303573110
753 Datta N, & Kontomichalou P. (1965). Penicillinase synthesis controlled by infectious R factors
754 in Enterobacteriaceae. Nature, 208(5007), 239-241.
755 de Astorza, B, Cortés G, Crespí C, Saus C, Rojo JM, & Albertí S. (2004). C3 promotes clearance
756 of Klebsiella pneumoniae by A549 epithelial cells. Infection and immunity, 72(3), 1767-
757 1774.
758 De Jesus MB, Ehlers MM, Dos Santos RF, & Kock MM. (2015). Understanding β-lactamase
759 producing Klebsiella pneumoniae. Antimicrobial Resistance: An Open Challenge, 51.
760 Decré D, Verdet C, Emirian A, Le Gourrierec T, Petit JC, Offenstadt G, Maury E, Brisse S, &
761 Arlet G. (2011). Emerging severe and fatal infections due to Klebsiella pneumoniae in
762 two university hospitals in France. J Clin Microbiol, 49(8), 3012-3014.
763 https://doi.org/10.1128/jcm.00676-11
764 Di Martino P, Livrelli V, Sirot D, Joly B, & Darfeuille-Michaud A. (1996). A new fimbrial
765 antigen harbored by CAZ-5/SHV-4-producing Klebsiella pneumoniae strains involved in
766 nosocomial infections. Infection and immunity, 64(6), 2266-2273.
767 Diago-Navarro E, Calatayud-Baselga I, Sun D, Khairallah C, Mann I, Ulacia-Hernando A,
768 Sheridan B, Shi M, & Fries BC. (2017). Antibody-based immunotherapy to treat and
769 prevent infection with hypervirulent Klebsiella pneumoniae. Clinical and Vaccine
770 Immunology, 24(1).
771 Diago-Navarro E, Motley MP, Ruiz-Peréz G, Yu W, Austin J, Seco BM, Xiao G, Chikhalya A,
772 Seeberger PH, & Fries BC. (2018). Novel, broadly reactive anticapsular antibodies
773 against carbapenem-resistant Klebsiella pneumoniae protect from infection. MBio, 9(2).
774 Doi Y, Wachino J, & Arakawa Y. (2016). Aminoglycoside resistance: the emergence of acquired
775 16S ribosomal RNA methyltransferases. Infectious Disease Clinics, 30(2), 523-537.
776 Dolejska M, Villa L, Dobiasova H, Fortini D, Feudi C, & Carattoli A. (2013). Plasmid content of
777 a clinically relevant Klebsiella pneumoniae clone from the Czech Republic producing
778 CTX-M-15 and QnrB1. Antimicrobial Agents and Chemotherapy, 57(2), 1073-1076.

779 Dong N, Yang X, Chan EW, Zhang R, & Chen S. (2022). Klebsiella species: Taxonomy,
780 hypervirulence and multidrug resistance. EBioMedicine, 79, 103998.
781 https://doi.org/10.1016/j.ebiom.2022.103998
782 El Fertas-Aissani R, Messai Y, Alouache S, & Bakour R. (2013). Virulence profiles and
783 antibiotic susceptibility patterns of Klebsiella pneumoniae strains isolated from different
784 clinical specimens. Pathologie Biologie, 61(5), 209-216.
785 Evans BA, & Amyes SG. (2014). OXA β-lactamases. Clinical microbiology reviews, 27(2), 241-
786 263.
787 Evrard B, Balestrino D, Dosgilbert A, Bouya-Gachancard JL, Charbonnel N, Forestier C, &
788 Tridon A. (2010). Roles of capsule and lipopolysaccharide O antigen in interactions of
789 human monocyte-derived dendritic cells and Klebsiella pneumoniae. Infection and
790 immunity, 78(1), 210-219.
791 Fàbrega A, Madurga S, Giralt E, & Vila J. (2009). Mechanism of action of and resistance to
792 quinolones. Microbial biotechnology, 2(1), 40-61.
793 Falcone M, Giordano C, Barnini S, Tiseo G, Leonildi A, Malacarne P, Menichetti F, & Carattoli
794 A. (2020). Extremely drug-resistant NDM-9-producing ST147 Klebsiella pneumoniae
795 causing infections in Italy, May 2020. Euro Surveillance, 25(48).
796 https://doi.org/10.2807/1560-7917.es.2020.25.48.2001779
797 Fang CT, Lai SY, Yi WC, Hsueh PR, Liu KL, & Chang SC. (2007). Klebsiella pneumoniae
798 genotype K1: an emerging pathogen that causes septic ocular or central nervous system
799 complications from pyogenic liver abscess. Clin Infect Dis, 45(3), 284-293.
800 https://doi.org/10.1086/519262
801 Fasciana T, Gentile B, Aquilina M, Ciammaruconi A, Mascarella C, Anselmo A, Fortunato A,
802 Fillo S, Petralito G, Lista F, & Giammanco A. (2019). Co-existence of virulence factors
803 and antibiotic resistance in new Klebsiella pneumoniae clones emerging in south of Italy.
804 BMC Infectious Diseases, 19(1), 928. https://doi.org/10.1186/s12879-019-4565-3
805 Fevre C, Almeida AS, Taront S, Pedron T, Huerre M, Prevost MC, Kieusseian A, Cumano A,
806 Brisse S, & Sansonetti PJ. (2013). A novel murine model of rhinoscleroma identifies
807 Mikulicz cells, the disease signature, as IL-10 dependent derivatives of inflammatory
808 monocytes. EMBO molecular medicine, 5(4), 516-530.
809 Francisco GR, Bueno MFC, Cerdeira L, Lincopan N, Ienne S, Souza TA, & de Oliveira Garcia
810 D. (2019). Draft genome sequences of KPC-2-and CTX-M-15-producing Klebsiella
811 pneumoniae ST437 isolated from a clinical sample and urban rivers in Sao Paulo, Brazil.
812 Journal of global antimicrobial resistance, 16, 74-75.
813 Friedländer C. (1882). Ueber die Schizomyceten bei der acuten fibrösen Pneumonie. Archiv für
814 pathologische Anatomie und Physiologie und für klinische Medicin, 87(2), 319-324.
815 Fuster B, Salvador C, Tormo N, García-González N, Gimeno C, & González-Candelas F. (2020).
816 Molecular epidemiology and drug-resistance mechanisms in carbapenem-resistant
817 Klebsiella pneumoniae isolated in patients from a tertiary hospital in Valencia, Spain.

Journal of Global Antimicrobial Resistance, 22, 718-725. https://doi.org/10.1016/j.jgar.2020.05.002

Fuursted K, Schøler L, Hansen F, Dam K, Bojer MS, Hammerum AM, Dagnæs-Hansen F, Olsen A, Jasemian Y, & Struve C. (2012). Virulence of a Klebsiella pneumoniae strain carrying the New Delhi metallo-beta-lactamase-1 (NDM-1). Microbes and infection, 14(2), 155-158.

Gabryšová L, Howes A, Saraiva M, & O'Garra A. (2014). The regulation of IL-10 expression. Interleukin-10 in Health and Disease, 157-190.

Gao L, Jiang X, Fu S, & Gong H. (2014). In silico identification of potential virulence genes in 1, 3-propanediol producer Klebsiella pneumonia. Journal of biotechnology, 189, 9-14.

Guerra J, Falconi E, Palomino J, Benavente L, & de Mayolo EA. (1983). Clinical evaluation of norfloxacin versus cotrimoxazole in urinary tract infections. European journal of clinical microbiology, 2(3), 260-265.

Guillard T, de Jong A, Limelette A, Lebreil A, Madoux J, De Champs C, & Group CS. (2016). Characterization of quinolone resistance mechanisms in Enterobacteriaceae recovered from diseased companion animals in Europe. Veterinary microbiology, 194, 23-29.

Haller S, Kramer R, Becker K, Bohnert JA, Eckmanns T, Hans JB, Hecht J, Heidecke CD, Hübner NO, Kramer A, Klaper K, Littmann M, Marlinghaus L, Neumann B, Pfeifer Y, Pfennigwerth N, Rogge S, Schaufler K, Thürmer A, Gatermann S. (2019). Extensively drug-resistant Klebsiella pneumoniae ST307 outbreak, north-eastern Germany, June to October 2019. Euro Surveill, 24(50). https://doi.org/10.2807/1560-7917.es.2019.24.50.1900734

Hammond DS, Schooneveldt JM, Nimmo GR, Huygens F, & Giffard PM. (2005). bla(SHV) Genes in Klebsiella pneumoniae: different allele distributions are associated with different promoters within individual isolates. Antimicrobial Agents Chemotherapy, 49(1), 256-263. https://doi.org/10.1128/aac.49.1.256-263.2005

Hari-Dass R, Shah C, Meyer DJ, & Raynes JG. (2005). Serum amyloid A protein binds to outer membrane protein A of gram-negative bacteria. Journal of Biological Chemistry, 280(19), 18562-18567.

Hennequin C, Aumeran C, Robin F, Traore O, & Forestier C. (2012). Antibiotic resistance and plasmid transfer capacity in biofilm formed with a CTX-M-15-producing Klebsiella pneumoniae isolate. Journal of Antimicrobial Chemotherapy, 67(9), 2123-2130.

Holden VI, Breen P, Houle S, Dozois CM, & Bachman MA. (2016). Klebsiella pneumoniae siderophores induce inflammation, bacterial dissemination, and HIF-1α stabilization during pneumonia. MBio, 7(5).

Holt KE, Wertheim H, Zadoks RN, Baker S, Whitehouse CA, Dance D, Jenney A, Connor TR, Hsu LY, & Severin J. (2015). Genomic analysis of diversity, population structure, virulence, and antimicrobial resistance in Klebsiella pneumoniae, an urgent threat to public health. Proceedings of the National Academy of Sciences, 112(27), E3574-E3581.

857 Jondle CN, Gupta K, Mishra BB, & Sharma J. (2018). Klebsiella pneumoniae infection of
858 murine neutrophils impairs their efferocytosis clearance by modulating cell death
859 machinery. PLoS pathogens, 14(10), e1007338.
860 Kaplan E, Sela N, Doron-Faigenboim A, Navon-Venezia S, Jurkevitch E, & Cytryn E. (2015).
861 Genomic and functional characterization of qnr-encoding plasmids from municipal
862 wastewater biosolid Klebsiella pneumoniae isolates. Front Microbiol, 6, 1354.
863 Karimi M, Mirshekari H, Moosavi Basri SM, Bahrami S, Moghoofei M, & Hamblin M. R.
864 (2016). Bacteriophages and phage-inspired nanocarriers for targeted delivery of
865 therapeutic cargos. Adv Drug Deliv Rev, 106(Pt A), 45-62.
866 https://doi.org/10.1016/j.addr.2016.03.003
867 Kidd TJ, Mills G, Sá-Pessoa J, Dumigan A, Frank CG, Insua JL, Ingram R, Hobley L, &
868 Bengoechea JA. (2017). A Klebsiella pneumoniae antibiotic resistance mechanism that
869 subdues host defenses and promotes virulence. EMBO molecular medicine, 9(4), 430-
870 447.
871 Kitchel B, Rasheed JK, Patel JB, Srinivasan A, Navon-Venezia S, Carmeli Y, Brolund A, &
872 Giske CG. (2009). Molecular epidemiology of KPC-producing Klebsiella pneumoniae
873 isolates in the United States: clonal expansion of multilocus sequence type 258.
874 Antimicrobial Agents Chemotherapy, 53(8), 3365-3370.
875 https://doi.org/10.1128/aac.00126-09
876 Korvick JA, Hackett AK, Yu VL, & Muder R. (1991). Klebsiella pneumonia in the modern era:
877 clinicoradiographic correlations. Southern medical journal, 84(2), 200-204.
878 Lam MM, Wyres KL, Judd LM, Wick RR, Jenney A, Brisse S, & Holt KE. (2018). Tracking key
879 virulence loci encoding aerobactin and salmochelin siderophore synthesis in Klebsiella
880 pneumoniae. Genome medicine, 10(1), 1-15.
881 Lam MM, Wick RR, Wyres KL, Gorrie CL, Judd LM, Jenney AWJ, Brisse S, & Holt KE.
882 (2018). Genetic diversity, mobilization and spread of the yersiniabactin-encoding mobile
883 element ICEKp in Klebsiella pneumoniae populations. Microbial Genome, 4(9).
884 https://doi.org/10.1099/mgen.0.000196
885 Lawlor MS, O'Connor C, & Miller VL. (2007). Yersiniabactin is a virulence factor for Klebsiella
886 pneumoniae during pulmonary infection. Infection and Immunity, 75(3), 1463-1472.
887 https://doi.org/10.1128/iai.00372-06
888 Lawlor MS, O'connor C, & Miller VL. (2007). Yersiniabactin is a virulence factor for Klebsiella
889 pneumoniae during pulmonary infection. Infection and immunity, 75(3), 1463-1472.
890 Lee CR, Lee JH, Park KS, Kim YB, Jeong BC, & Lee SH. (2016). Global dissemination of
891 carbapenemase-producing Klebsiella pneumoniae: epidemiology, genetic context,
892 treatment options, and detection methods. Frontiers in Microbiology, 7, 895.
893 Lee CR, Lee JH, Park KS, Kim YB, Jeong BC, & Lee SH. (2016). Global Dissemination of
894 Carbapenemase-Producing Klebsiella pneumoniae: Epidemiology, Genetic Context,
895 Treatment Options, and Detection Methods. Frontiers in Microbiology, 7, 895.
896 https://doi.org/10.3389/fmicb.2016.00895

Lee YH, Cho B, Bae IK, Chang CL, & Jeong SH. (2006). Klebsiella pneumoniae strains carrying the chromosomal SHV-11 β-lactamase gene produce the plasmid-mediated SHV-12 extended-spectrum β-lactamase more frequently than those carrying the chromosomal SHV-1 β-lactamase gene. Journal of Antimicrobial Chemotherapy, 57(6), 1259-1261.

Lewis K. (2017). New approaches to antimicrobial discovery. Biochemical pharmacology, 134, 87-98.

Li B, Zhao Y, Liu C, Chen Z, & Zhou D. (2014). Molecular pathogenesis of Klebsiella pneumoniae. Future microbiology, 9(9), 1071-1081.

Li J, Zhang H, Ning J, Sajid A, Cheng G, Yuan Z, & Hao H. (2019). The nature and epidemiology of OqxAB, a multidrug efflux pump. Antimicrob Resist Infect Control, 8, 44. https://doi.org/10.1186/s13756-019-0489-3

Liakopoulos A, Mevius D, & Ceccarelli D. (2016). A Review of SHV Extended-Spectrum β-Lactamases: Neglected Yet Ubiquitous. Frontiers in Microbiology, 7, 1374. https://doi.org/10.3389/fmicb.2016.01374

Livermore DM, Nicolau DP, Hopkins KL, & Meunier D. (2020). Carbapenem-Resistant Enterobacterales, Carbapenem Resistant Organisms, Carbapenemase-Producing Enterobacterales, and Carbapenemase-Producing Organisms: Terminology Past its "Sell-By Date" in an Era of New Antibiotics and Regional Carbapenemase Epidemiology. Clin Infect Dis, 71(7), 1776-1782. https://doi.org/10.1093/cid/ciaa122

Llobet E, Campos MA, Giménez P, Moranta D, & Bengoechea JA. (2011). Analysis of the networks controlling the antimicrobial-peptide-dependent induction of Klebsiella pneumoniae virulence factors. Infection and immunity, 79(9), 3718-3732.

Llobet E, Martínez-Moliner V, Moranta D, Dahlström KM, Regueiro V, Tomás A, Cano V, Pérez-Gutiérrez C, Frank CG, & Fernández-Carrasco H. (2015). Deciphering tissue-induced Klebsiella pneumoniae lipid A structure. Proceedings of the National Academy of Sciences, 112(46), E6369-E6378.

Llobet E, Tomas JM, & Bengoechea JA. (2008). Capsule polysaccharide is a bacterial decoy for antimicrobial peptides. Microbiology, 154(12), 3877-3886.

Loconsole D, Accogli M, De Robertis AL, Capozzi L, Bianco A, Morea A, Mallamaci R, Quarto M, Parisi A, & Chironna M. (2020). Emerging high-risk ST101 and ST307 carbapenem-resistant Klebsiella pneumoniae clones from bloodstream infections in Southern Italy. 19(1), 24. https://doi.org/10.1186/s12941-020-00366-y

Long SW, Olsen RJ, Eagar TN, Beres SB, Zhao P, Davis JJ, Brettin T, Xia F, & Musser JM. (2017). Population genomic analysis of 1,777 extended-spectrum beta-lactamase-producing Klebsiella pneumoniae isolates, Houston, Texas: unexpected abundance of clonal group 307. MBio, 8(3).

Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, & Monnet DL. (2012). Multidrug-resistant, extensively drug-resistant and pan drug-resistant bacteria: an international expert

proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect, 18(3), 268-281. https://doi.org/10.1111/j.1469-0691.2011.03570.x

Mann S, & Chen YPP. (2010). Bacterial genomic G+ C composition-eliciting environmental adaptation. Genomics, 95(1), 7-15.

March C, Moranta D, Regueiro V, Llobet E, Tomás A, Garmendia J, & Bengoechea JA. (2011). Klebsiella pneumoniae outer membrane protein A is required to prevent the activation of airway epithelial cells. Journal of Biological Chemistry, 286(12), 9956-9967.

Marchaim D, Chopra T, Pogue JM, Perez F, Hujer AM, Rudin S, Endimiani A, Navon-Venezia, S., Hothi, J., & Slim, J. (2011). Outbreak of colistin-resistant, carbapenem-resistant Klebsiella pneumoniae in metropolitan Detroit, Michigan. Antimicrobial Agents and Chemotherapy, 55(2), 593-599.

Martin J, Phan HT, Findlay J, Stoesser N, Pankhurst L, Navickaite I, De Maio N, Eyre DW, Toogood G, & Orsi NM. (2017). Covert dissemination of carbapenemase-producing Klebsiella pneumoniae (KPC) in a successfully controlled outbreak: long-and short-read whole-genome sequencing demonstrate multiple genetic modes of transmission. Journal of Antimicrobial Chemotherapy, 72(11), 3025-3034.

Martinez-Martinez L, Hernández-Allés S, Albertí S, Tomás JM, Benedi VJ, & Jacoby GA. (1996). In vivo selection of porin-deficient mutants of Klebsiella pneumoniae with increased resistance to cefoxitin and expanded-spectrum-cephalosporins. Antimicrobial Agents and Chemotherapy, 40(2), 342-348.

Martínez J, Martínez L, Rosenblueth M, Silva J, & Martínez-Romero E. (2004). How are gene sequences analyses modifying bacterial taxonomy? The case of Klebsiella. International Microbiology, 7(4), 261-268.

Martins WMBS, Nicolas MF, Yu Y, Li M, Dantas P, Sands K, Portal E, Almeida LGP, Vasconcelos ATR, Medeiros EA, Toleman MA, Walsh TR, Gales AC, & Andrey DO. (2020). Clinical and Molecular Description of a High-Copy IncQ1 KPC-2 Plasmid Harbored by the International ST15 Klebsiella pneumoniae Clone. mSphere, 5(5), e00756-00720. https://doi.org/10.1128/mSphere.00756-20

Mathers AJ, Crook D, Vaughan A, Barry KE, Vegesana K, & Stoesser N. (2019). Klebsiella quasipneumoniae Provides a Window into Carbapenemase Gene Transfer, Plasmid Rearrangements, and Patient Interactions with the Hospital Environment. 63(6). https://doi.org/10.1128/aac.02513-18

McInerney JO, McNally A, & O'connell MJ. (2017). Why prokaryotes have pangenomes. Nature microbiology, 2(4), 1-5.

Merino S, Camprubí S, Albertí S, Benedí VJ, & Tomás JM. (1992). Mechanisms of Klebsiella pneumoniae resistance to complement-mediated killing. Infection and immunity, 60(6), 2529-2535.

Mills G, Dumigan A, Kidd T, Hobley L, & Bengoechea JA. (2017). Identification and characterization of two Klebsiella pneumoniae lpxL lipid A late acyltransferases and their role in virulence. Infection and immunity, 85(9).

Miriagou V, Papagiannitsis C, Kotsakis S, Loli A, Tzelepi E, Legakis N, & Tzouvelekis L. (2010). Sequence of pNL194, a 79.3-kilobase IncN plasmid carrying the blaVIM-1 metallo-β-lactamase gene in Klebsiella pneumoniae. Antimicrobial Agents and Chemotherapy, 54(10), 4497-4502.

Mmatli M, Mbelle NM, & Osei Sekyere J. (2022). Global epidemiology, genetic environment, risk factors and therapeutic prospects of mcr genes: A current and emerging update. Front Cell Infect Microbiol, 12, 941358. https://doi.org/10.3389/fcimb.2022.941358

Moranta Mesquida D, Regueiro V, March C, Llobet E, Margareto J, Larrarte E, Garmendia J, & Bengoechea JA. (2018). Klebsiella pneumoniae capsule polysaccharide impedes the expression of beta-defensins by airway epithelial cells. Infection and Immunity, 2010, vol. 78, num. 3, p. 1135-1146.

Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, Cornaglia G, Garau J, Gniadkowski M, Hayden MK, Kumarasamy K, Livermore DM, Maya JJ, Nordmann P, Patel JB, Paterson DL, Pitout J, Villegas MV, Wang H, Quinn JP. (2013). Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. Lancet Infect Dis, 13(9), 785-796. https://doi.org/10.1016/s1473-3099(13)70190-7

Naas T, Cuzon G, Truong HV, & Nordmann P. (2012). Role of ISKpn7 and deletions in blaKPC gene expression. Antimicrobial Agents and Chemotherapy, 56(9), 4753-4759.

Naeem A, Badshah SL, Muska M, Ahmad N, & Khan K. (2016). The current case of quinolones: synthetic approaches and antibacterial activity. Molecules, 21(4), 268.

Navon-Venezia, S., Kondratyeva, K., & Carattoli, A. (2017). Klebsiella pneumoniae: a major worldwide source and shuttle for antibiotic resistance. FEMS microbiology reviews, 41(3), 252-275.

Navon-Venezia S, Kondratyeva K, & Carattoli A. (2017). Klebsiella pneumoniae: a major worldwide source and shuttle for antibiotic resistance. FEMS Microbiol Rev, 41(3), 252-275. https://doi.org/10.1093/femsre/fux013

Nguyen TNT, Nguyen PLN, Le NTQ, Nguyen LPH, Duong TB, Ho NDT, Nguyen QPN, Pham TD, Tran AT, & The HC. (2021). Emerging carbapenem-resistant Klebsiella pneumoniae sequence type 16 causing multiple outbreaks in a tertiary hospital in southern Vietnam. Microb Genome, 000519.

Nguyen TNT, Nguyen PLN, Le NTQ, Nguyen LPH, Duong TB, Ho NDT, Nguyen QPN, Pham TD, Tran AT, The HC, Nguyen HH, Nguyen CVV, Thwaites GE, Rabaa MA, & Pham DT. (2021). Emerging carbapenem-resistant Klebsiella pneumoniae sequence type 16 causing multiple outbreaks in a tertiary hospital in southern Vietnam. Microb Genome. https://doi.org/10.1099/mgen.0.000519

Nielsen LE, Snesrud EC, Onmus-Leone F, Kwak YI, Avilés R, Steele ED, Sutter DE, Waterman PE, & Lesho EP. (2014). IS5 element integration, a novel mechanism for rapid in vivo emergence of tigecycline nonsusceptibility in Klebsiella pneumoniae. Antimicrobial Agents and Chemotherapy, 58(10), 6151-6156.

Ojdana D, Kochanowicz J, Sacha P, Sieńko A, Wieczorek P, Majewski P, Hauschild T, Mariak Z, & Tryniszewska E. (2020). Infection caused by Klebsiella pneumoniae ST11 in a patient after craniectomy. Folia Microbiologica, 65(1), 205-209. https://doi.org/10.1007/s12223-019-00718-y

Osborn AM, da Silva Tatley FM, Steyn LM, Pickup RW, & Saunders JR. (2000). Mosaic plasmids and mosaic replicons: evolutionary lessons from the analysis of genetic diversity in IncFII-related replicons. The EMBL accession numbers for the sequences reported in this paper are AJ009980 (pGSH500 alpha replicon) and AJ009981 (pLV1402 alpha replicon). Microbiology, 146(9), 2267-2275.

Paczosa MK, & Mecsas J. (2016). Klebsiella pneumoniae: going on the offense with a strong defense. Microbiology and Molecular Biology Reviews, 80(3), 629-661.

Pan YJ, Fang HC, Yang HC, Lin TL, Hsieh PF, Tsai FC, Keynan Y, & Wang JT. (2008). Capsular polysaccharide synthesis regions in Klebsiella pneumoniae serotype K57 and a new capsular serotype. J Clin Microbiol, 46(7), 2231-2240.

Pan YJ, Lin TL, Hsu CR, & Wang JT. (2011). Use of a Dictyostelium model for isolation of genetic loci associated with phagocytosis and virulence in Klebsiella pneumoniae. Infection and immunity, 79(3), 997-1006.

Partridge SR, Kwong SM, Firth N, & Jensen SO. (2018). Mobile genetic elements associated with antimicrobial resistance. Clinical microbiology reviews, 31(4).

Paterson DL, & Bonomo RA. (2005). Extended-spectrum β-lactamases: a clinical update. Clinical microbiology reviews, 18(4), 657-686.

Paterson DL, Ko WC, Von Gottberg A, Casellas JM, Mulazimoglu L, Klugman KP, Bonomo RA, Rice LB, McCormack JG., & Victor LY. (2001). Outcome of cephalosporin treatment for serious infections due to apparently susceptible organisms producing extended-spectrum β-lactamases: implications for the clinical microbiology laboratory. J Clin Microbiol, 39(6), 2206-2212.

Paterson DL, & Yu VL. (1999). Editorial response: extended-spectrum β-lactamases: a call for improved detection and control. Clinical Infectious Diseases, 29(6), 1419-1422.

Peirano G, & Chen L. (2020). Emerging Antimicrobial-Resistant High-Risk Klebsiella pneumoniae Clones ST307 and ST147. 64(10). https://doi.org/10.1128/aac.01148-20

Peirano G, Chen L, Kreiswirth BN, & Pitout JD. (2020). Emerging antimicrobial-resistant high-risk Klebsiella pneumoniae clones ST307 and ST147. Antimicrobial Agents and Chemotherapy, 64(10).

Philippon A, Slama P, Dény P, & Labia R. (2016). A structure-based classification of class A β-lactamases, a broadly diverse family of enzymes. Clinical microbiology reviews, 29(1), 29-57.

Pillonel T, Nordmann P, Bertelli C, Prod' Hom G, Poirel L, & Greub G. (2018). Resistome Analysis of a Carbapenemase (OXA-48)-Producing and Colistin-Resistant Klebsiella pneumoniae Strain. Antimicrobial Agents Chemotherapy, 62(5). https://doi.org/10.1128/aac.00076-18

Ping Y, Ogawa W, Kuroda T, & Tsuchiya T. (2007). Gene cloning and characterization of KdeA, a multidrug efflux pump from Klebsiella pneumoniae. Biological and Pharmaceutical Bulletin, 30(10), 1962-1964.

Pitout JD, & Finn TJ. (2020). The evolutionary puzzle of Escherichia coli ST131. Infection, Genetics and Evolution, 81, 104265.

Pitout JD, Nordmann P, & Poirel L. (2015). Carbapenemase-producing Klebsiella pneumoniae, a key pathogen set for global nosocomial dominance. Antimicrobial Agents and Chemotherapy, 59(10), 5873-5884.

Podschun R, & Ullmann U. (1998). Klebsiella spp. as nosocomial pathogens: epidemiology, taxonomy, typing methods, and pathogenicity factors. Clinical microbiology reviews, 11(4), 589-603.

Poirel L, Nordmann P, Ducroz S, Boulouis HJ, Arné P, & Millemann Y. (2013). Extended-spectrum β-lactamase CTX-M-15-producing Klebsiella pneumoniae of sequence type ST274 in companion animals. Antimicrobial Agents and Chemotherapy, 57(5), 2372-2375.

Poirel L, Potron A, & Nordmann P. (2012). OXA-48-like carbapenemases: the phantom menace. Journal of Antimicrobial Chemotherapy, 67(7), 1597-1606. https://doi.org/10.1093/jac/dks121

Potron A, Rondinaud E, Poirel L, Belmonte O, Boyer S, Camiade S, & Nordmann P. (2013). Genetic and biochemical characterization of OXA-232, a carbapenem-hydrolyzing class D β-lactamase from Enterobacteriaceae. Int J Antimicrob Agents, 41(4), 325-329. https://doi.org/10.1016/j.ijantimicag.2012.11.007

Potter RF, Lainhart W, Twentyman J, Wallace MA, Wang B, Burnham CAD, Rosen D. A., & Dantas, G. (2018). Population structure, antibiotic resistance, and uropathogenicity of Klebsiella variicola. MBio, 9(6).

Poulikakos P, & Falagas ME. (2013). Aminoglycoside therapy in infectious diseases. Expert opinion on pharmacotherapy, 14(12), 1585-1597.

Pursey E, Sünderhauf D, Gaze WH, Westra ER, & van Houte S. (2018). CRISPR-Cas antimicrobials: Challenges and prospects. PLoS Pathogen, 14(6), e1006990. https://doi.org/10.1371/journal.ppat.1006990

Qurat-ul-Ain H, Ijaz M, Siddique AB, Muzammil S, Shafique M, Rasool MH, Almatroudi A, Khurshid M, Chaudhry TH, & Aslam B. (2021). Efficacy of Phage-Antibiotic Combinations Against Multidrug-Resistant Klebsiella pneumoniae Clinical Isolates [Research Article]. Jundishapur J Microbiol, 14(1), e111926. https://doi.org/10.5812/jjm.111926

1093 Ramirez MS, Iriarte A, Reyes-Lamothe R, Sherratt DJ, & Tolmasky ME. (2019). Small
1094 Klebsiella pneumoniae plasmids: neglected contributors to antibiotic resistance. Front
1095 Microbiol, 10, 2182.
1096 Redgrave LS, Sutton SB, Webber MA, & Piddock LJ. (2014). Fluoroquinolone resistance:
1097 mechanisms, impact on bacteria, and role in evolutionary success. Trends in
1098 microbiology, 22(8), 438-445.
1099 Regueiro V, Moranta D, Campos MA, Margareto J, Garmendia J, & Bengoechea JA. (2009).
1100 Klebsiella pneumoniae increases the levels of Toll-like receptors 2 and 4 in human
1101 airway epithelial cells. Infection and immunity, 77(2), 714-724.
1102 Regueiro V, Moranta D, Frank CG, Larrarte E, Margareto J, March C, Garmendia J, &
1103 Bengoechea JA. (2011). Klebsiella pneumoniae subverts the activation of inflammatory
1104 responses in a NOD1-dependent manner. Cellular microbiology, 13(1), 135-153.
1105 Rodríguez-Medina N, Barrios-Camacho H, Duran-Bedolla J, & Garza-Ramos U. (2019).
1106 Klebsiella variicola: an emerging pathogen in humans. Emerging microbes & infections,
1107 8(1), 973-988.
1108 Ruiz-Garbajosa P, Hernández-García M, Beatobe L, Tato M, Méndez MI, Grandal M, Aranzábal
1109 L, Alonso S, López M, Astray J, & Cantón R. (2016). A single-day point-prevalence
1110 study of fecal carriers in long-term care hospitals in Madrid (Spain) depicts a complex
1111 clonal and polyclonal dissemination of carbapenemase-producing Enterobacteriaceae.
1112 Journal of Antimicrobial Chemotherapy, 71(2), 348-352.
1113 https://doi.org/10.1093/jac/dkv355
1114 Ruiz E, Sáenz Y, Zarazaga M, Rocha-Gracia R, Martínez-Martínez L, Arlet G, & Torres C.
1115 (2012). qnr, aac (6′)-Ib-cr and qepA genes in Escherichia coli and Klebsiella spp.: genetic
1116 environments and plasmid and chromosomal location. Journal of Antimicrobial
1117 Chemotherapy, 67(4), 886-897.
1118 Russo TA, Shon AS, Beanan JM, Olson R, MacDonald U, Pomakov AO, & Visitacion MP.
1119 (2011). Hypervirulent K. pneumoniae secretes more and more active iron-acquisition
1120 molecules than “classical” K. pneumoniae thereby enhancing its virulence. PloS one,
1121 6(10), e26734.
1122 Sahly H, Podschun R, Oelschlaeger TA, Greiwe M, Parolis H, Hasty D, Kekow J, Ullmann U,
1123 Ofek I, & Sela S. (2000). Capsule impedes adhesion to and invasion of epithelial cells by
1124 Klebsiella pneumoniae. Infection and immunity, 68(12), 6744-6749.
1125 Samuelsen Ø, Toleman MA, Hasseltvedt V, Fuursted K, Leegaard TM, Walsh TR, Sundsfjord A,
1126 & Giske CG. (2011). Molecular characterization of VIM-producing Klebsiella
1127 pneumoniae from Scandinavia reveals genetic relatedness with international clonal
1128 complexes encoding transferable multidrug resistance. Clin Microbiol Infect, 17(12),
1129 1811-1816. https://doi.org/10.1111/j.1469-0691.2011.03532.x
1130 Schroll C, Barken KB, Krogfelt KA, & Struve C. (2010). Role of type 1 and type 3 fimbriae in
1131 Klebsiella pneumoniae biofilm formation. BMC microbiology, 10(1), 1-10.

1132 Shankar C, Jacob JJ, Vasudevan K, Biswas R, Manesh A, Sethuvel DPM, Varughese S, Biswas
1133 I, & Veeraraghavan B. (2020). Emergence of Multidrug Resistant Hypervirulent ST23
1134 Klebsiella pneumoniae: Multidrug Resistant Plasmid Acquisition Drives Evolution. Front
1135 Cell Infect Microbiol, 10, 575289. https://doi.org/10.3389/fcimb.2020.575289
1136 Shen X, Liu L, Yu J, Ai W, Cao X, Zhan Q, Guo Y, Wang L, & Yu F. (2020). High Prevalence
1137 of 16S rRNA Methyltransferase Genes in Carbapenem-Resistant Klebsiella pneumoniae
1138 Clinical Isolates Associated with Bloodstream Infections in 11 Chinese Teaching
1139 Hospitals. Infect Drug Resist, 13, 2189-2197. https://doi.org/10.2147/idr.s254479
1140 Sheppard AE, Stoesser N, Wilson DJ, Sebra R, Kasarskis A, Anson LW, Giess A, Pankhurst LJ,
1141 Vaughan A, & Grim CJ. (2016). Nested Russian doll-like genetic mobility drives rapid
1142 dissemination of the carbapenem resistance gene blaKPC. Antimicrobial Agents and
1143 Chemotherapy, 60(6), 3767-3778.
1144 Shon AS, Bajwa RP, & Russo TA. (2013). Hypervirulent (hypermucovisous) Klebsiella
1145 pneumoniae: a new and dangerous breed. Virulence, 4(2), 107-118.
1146 Singh RM, & Singh HL. (2014). Comparative evaluation of six phenotypic methods for detecting
1147 extended-spectrum beta-lactamase-producing Enterobacteriaceae. The Journal of
1148 Infection in Developing Countries, 8(04), 408-415.
1149 Sirot D, Sirot J, Labia R, Morand A, Courvalin P, Darfeuille-Michaud A, Perroux R, & Cluzel R.
1150 (1987). Transferable resistance to third-generation cephalosporins in clinical isolates of
1151 Klebsiella pneumoniae: identification of CTX-1, a novel β-lactamase. Journal of
1152 Antimicrobial Chemotherapy, 20(3), 323-334.
1153 Srinivasan VB, & Rajamohan G. (2013). KpnEF, a new member of the Klebsiella pneumoniae
1154 cell envelope stress response regulon, is an SMR-type efflux pump involved in broad-
1155 spectrum antimicrobial resistance. Antimicrobial Agents and Chemotherapy, 57(9), 4449-
1156 4462.
1157 Srinivasan VB, Venkataramaiah M, Mondal A, Vaidyanathan V, Govil T, & Rajamohan G.
1158 (2012). Functional characterization of a novel outer membrane porin KpnO, regulated by
1159 PhoBR two-component system in Klebsiella pneumoniae NTUH-K2044. PloS one, 7(7),
1160 e41505.
1161 Struve C, Bojer M, & Krogfelt KA. (2008). Characterization of Klebsiella pneumoniae type 1
1162 fimbriae by detection of phase variation during colonization and infection and impact on
1163 virulence. Infection and immunity, 76(9), 4055-4065.
1164 Struve C, Bojer M, & Krogfelt KA. (2009). Identification of a conserved chromosomal region
1165 encoding Klebsiella pneumoniae type 1 and type 3 fimbriae and assessment of the role of
1166 fimbriae in pathogenicity. Infection and immunity, 77(11), 5016-5024.
1167 Sukumaran SK, Shimada H, & Prasadarao NV. (2003). Entry and intracellular replication of
1168 Escherichia coli K1 in macrophages require expression of outer membrane protein A.
1169 Infection and Immunity, 71(10), 5951-5961. https://doi.org/10.1128/iai.71.10.5951-
1170 5961.2003

Surgers L, Boyd A, Girard PM, Arlet G, & Decré D. (2016). ESBL-Producing Strain of Hypervirulent Klebsiella pneumoniae K2, France. Emerging Infectious Diseases, 22(9), 1687-1688. https://doi.org/10.3201/eid2209.160681

Szijártó V, Guachalla LM, Hartl K, Varga C, Badarau A, Mirkina I, Visram ZC, Stulik L, Power CA, & Nagy E. (2017). Endotoxin neutralization by an O-antigen specific monoclonal antibody: a potential novel therapeutic approach against Klebsiella pneumoniae ST258. Virulence, 8(7), 1203-1215.

Tagliaferri TL, Guimarães NR, Pereira MPM, Vilela LFF, Horz HP, Dos Santos SG, & Mendes TAO. (2020). Exploring the Potential of CRISPR-Cas9 Under Challenging Conditions: Facing High-Copy Plasmids and Counteracting Beta-Lactam Resistance in Clinical Strains of Enterobacteriaceae. Frontiers in Microbiology, 11, 578. https://doi.org/10.3389/fmicb.2020.00578

Tängdén T, & Giske CG. (2015). Global dissemination of extensively drug-resistant carbapenemase-producing Enterobacteriaceae: clinical perspectives on detection, treatment and infection control. J Intern Med, 277(5), 501-512. https://doi.org/10.1111/joim.12342

Tomás A, Lery L, Regueiro V, Pérez-Gutiérrez C, Martínez V, Moranta D, Llobet E, González-Nicolau M, Insua JL, & Tomas JM. (2015). Functional genomic screen identifies Klebsiella pneumoniae factors implicated in blocking nuclear factor κB (NF-κB) signaling. Journal of Biological Chemistry, 290(27), 16678-16697.

Tóth, Á., Kocsis, B., Damjanova, I., Kristóf, K., Jánvári, L., Pászti, J., Csercsik, R., Topf, J., Szabó, D., & Hamar, P. (2014). Fitness cost associated with resistance to fluoroquinolones is diverse across clones of Klebsiella pneumoniae and may select for CTX-M-15 type extended-spectrum β-lactamase. European journal of clinical microbiology & infectious diseases, 33(5), 837-843.

Trevisan V. (1887). Sul micrococco della rabbia e sulla possibilità di riconoscere durante il periode d'incubazione, dall'esame del sangue della persona moricata, se ha contratta l'infezione rabbica. Rend Ist Lombardo Accad Sci Lett Sez (ser. 2), 20, 88-105.

Turner KM, Hanage WP, Fraser C, Connor TR, & Spratt BG. (2007). Assessing the reliability of eBURST using simulated populations with known ancestry. BMC microbiology, 7(1), 1-14.

Turton JF, Baklan H, Siu L, Kaufmann ME, & Pitt TL. (2008). Evaluation of a multiplex PCR for detection of serotypes K1, K2 and K5 in Klebsiella sp. and comparison of isolates within these serotypes. FEMS microbiology letters, 284(2), 247-252.

Van Elssen CH, Vanderlocht J, Frings PW, Senden-Gijsbers BL, Schnijderberg MC, van Gelder M, Meek B, Libon C, Ferlazzo G, & Germeraad WT. (2010). Klebsiella pneumoniae-triggered DC recruit human NK cells in a CCR5-dependent manner leading to increased CCL19-responsiveness and activation of NK cells. European journal of immunology, 40(11), 3138-3149.

Vernikos G, Medini D, Riley DR, & Tettelin H. (2015). Ten years of pan-genome analyses. Curr Opin Microbiol, 23, 148-154.

Villa L, Feudi C, Fortini D, Brisse S, Passet V, Bonura C, Endimiani A, Mammina C, Ocampo AM, Jimenez JN, Doumith M, Woodford N, Hopkins K, & Carattoli A. (2017). Diversity, virulence, and antimicrobial resistance of the KPC-producing Klebsiella pneumoniae ST307 clone. Microb Genome, 3(4), e000110. https://doi.org/10.1099/mgen.0.000110

Villa L, Feudi C, Fortini D, García-Fernández A, & Carattoli A. (2014). Genomics of KPC-producing Klebsiella pneumoniae sequence type 512 clone highlights the role of RamR and ribosomal S10 protein mutations in conferring tigecycline resistance. Antimicrobial Agents and Chemotherapy, 58(3), 1707-1712.

Villa L, Feudi C, Fortini D, Iacono M, Bonura C, Endimiani A, Mammina C, & Carattoli A. (2016). Complete Genome Sequence of KPC-3- and CTX-M-15-Producing Klebsiella pneumoniae Sequence Type 307. Genome Announcements, 4(2). https://doi.org/10.1128/genomeA.00213-16

Wang P, Hu F, Xiong Z, Ye X, Zhu D, Wang YF, & Wang M. (2011). Susceptibility of extended-spectrum-β-lactamase-producing Enterobacteriaceae according to the new CLSI breakpoints. J Clin Microbiol, 49(9), 3127-3131.

Wang X, Li Q, Kang J, Zhang Z, Song Y, Yin D, Guo Q, Song J, Li X, Wang S, & Duan J. (2021). Co-Production of NDM-1, CTX-M-9 Family and mcr-1 in a Klebsiella pneumoniae ST4564 Strain in China. Infect Drug Resist, 14, 449-457. https://doi.org/10.2147/idr.s292820

Ward-McQuaid J, Jichlinski D, & Macis R. (1963). Nalidixic acid in urinary infections. British medical journal, 2(5368), 1311.

Weng X, Shi Q, Wang S, Shi Y, Sun D, & Yu Y. (2020). The Characterization of OXA-232 Carbapenemase-Producing ST437 Klebsiella pneumoniae in China. Canadian Journal of Infectious Diseases and Medical Microbiology, 2020.

Wayne, PA: Clinical and Laboratory Standards Institute; 2008. CLSI document GP34-A.

Wijetunge DS, Karunathilake KH, Chaudhari A, Katani R, Dudley EG, Kapur V, DebRoy C, & Kariyawasam S. (2014). Complete nucleotide sequence of pRS218, a large virulence plasmid, that augments pathogenic potential of meningitis-associated Escherichia coli strain RS218. BMC Microbiology, 14, 203. https://doi.org/10.1186/s12866-014-0203-9

Willsey GG, Ventrone S, Schutz KC, Wallace AM, Ribis JW, Suratt BT, & Wargo M. J. (2018). Pulmonary surfactant promotes virulence gene expression and biofilm formation in Klebsiella pneumoniae. Infection and immunity, 86(7).

Wong MHY, Chan EWC, & Chen S. (2015). Evolution and dissemination of OqxAB-like efflux pumps, an emerging quinolone resistance determinant among members of Enterobacteriaceae. Antimicrobial Agents and Chemotherapy, 59(6), 3290-3297.

Wright GD. (2007). The antibiotic resistome: the nexus of chemical and genetic diversity. Nature Reviews Microbiology, 5(3), 175-186.

Wu CC, Huang YJ, Fung CP, & Peng HL. (2010). Regulation of the Klebsiella pneumoniae Kpc fimbriae by the site-specific recombinase KpcI. Microbiology, 156(7), 1983-1992.

Wu KM, Li LH, Yan JJ, Tsao N, Liao TL, Tsai HC, Fung CP, Chen HJ, Liu YM, Wang JT, Fang CT, Chang SC, Shu HY, Liu TT, Chen YT, Shiau YR, Lauderdale TL, Su IJ, Kirby R, & Tsai SF. (2009). Genome sequencing and comparative analysis of Klebsiella pneumoniae NTUH-K2044, a strain causing liver abscess and meningitis. J Bacteriol, 191(14), 4492-4501. https://doi.org/10.1128/jb.00315-09

Wyres KL, & Holt KE. (2018). Klebsiella pneumoniae as a key trafficker of drug resistance genes from environmental to clinically important bacteria. Curr Opin Microbiol, 45, 131-139. https://doi.org/10.1016/j.mib.2018.04.004

Wyres KL, Lam MM, & Holt KE. (2020). Population genomics of Klebsiella pneumoniae. Nature Reviews Microbiology, 18(6), 344-359.

Wyres KL, Lam MM, & Holt KE. (2020). Population genomics of Klebsiella pneumoniae. Nat Rev Microbiol, 18(6), 344-359. https://doi.org/10.1038/s41579-019-0315-1

Xiao X, Wu H, & Dall'Acqua WF. (2016). Immunotherapies against antibiotics-resistant Klebsiella pneumoniae. Hum Vaccine Immunotherapy, 12(12), 3097-3098. https://doi.org/10.1080/21645515.2016.1210746

Yigit H, Queenan AM, Anderson GJ, Domenech-Sanchez A, Biddle JW, Steward CD, Alberti S, Bush K, & Tenover FC. (2001). Novel carbapenem-hydrolyzing β-lactamase, KPC-1, from a carbapenem-resistant strain of Klebsiella pneumoniae. Antimicrobial Agents and Chemotherapy, 45(4), 1151-1161.

Yoshida K, MATSUMOTO T, TATEDA K, UCHIDA K, TSUJIMOTO S, & YAMAGUCHI K. (2000). Role of bacterial capsule in local and systemic inflammatory responses of mice during pulmonary infection with Klebsiella pneumoniae. Journal of medical microbiology, 49(11), 1003-1010.

Yoshida K, Matsumoto T, Tateda K, Uchida K, Tsujimoto S, & Yamaguchi K. (2001). Induction of interleukin-10 and down-regulation of cytokine production by Klebsiella pneumoniae capsule in mice with pulmonary infection. Journal of medical microbiology, 50(5), 456-461.

Zaman TU, Alrodayyan M, Albladi M, Aldrees M, Siddique MI, Aljohani S, & Balkhy HH. (2018). Clonal diversity and genetic profiling of antibiotic resistance among multidrug/carbapenem-resistant Klebsiella pneumoniae isolates from a tertiary care hospital in Saudi Arabia. BMC Infectious Diseases, 18(1), 205. https://doi.org/10.1186/s12879-018-3114-9

Zelcbuch L, Yitzhaki E, Nissan O, Gidron E, Buchshtab N, Kario E, Kredo-Russo S, Zak NB, & Bassan M. (2021). Luminescent Phage-Based Detection of Klebsiella pneumoniae: From Engineering to Diagnostics. Pharmaceuticals (Basel), 14(4). https://doi.org/10.3390/ph14040347

Zhan L, Wang S, Guo Y, Jin Y, Duan J, Hao Z, Lv J, Qi X, Hu L, Chen L, Kreiswirth BN, Zhang R, Pan J, Wang L, & Yu F. (2017). Outbreak by Hypermucovisous Klebsiella

pneumoniae ST11 Isolates with Carbapenem Resistance in a Tertiary Hospital in China. Front Cell Infect Microbiol, 7, 182. https://doi.org/10.3389/fcimb.2017.00182

Zhang Y, Zhao C, Wang Q, Wang X, Chen H, Li H, Zhang F, Li S, Wang R, & Wang H. (2016). High prevalence of hypervirulent Klebsiella pneumoniae infection in China: geographic distribution, clinical characteristics, and antimicrobial resistance. Antimicrobial Agents and Chemotherapy, 60(10), 6115-6120.

Zhang Y, Zhao C, Wang Q, Wang X, Chen H, Li H, Zhang F, Li S, Wang R, & Wang H. (2016). High Prevalence of Hypervirulent Klebsiella pneumoniae Infection in China: Geographic Distribution, Clinical Characteristics, and Antimicrobial Resistance. Antimicrobial Agents Chemotherapy, 60(10), 6115-6120. https://doi.org/10.1128/aac.01127-16

Zhu WH, Luo L, Wang JY, Zhuang XH, Zhong L, Liao K, Zeng Y, & Lu YJ. (2009). Complete nucleotide sequence of pCTX-M360, an intermediate plasmid between pEL60 and pCTX-M3, from a multidrug-resistant Klebsiella pneumoniae strain isolated in China. Antimicrobial Agents and Chemotherapy, 53(12), 5291-5293.

Zowawi HM, Forde BM, Alfaresi M, Alzarouni A, Farahat Y, Chong TM, Yin WF, Chan KG, Li J, & Schembri MA. (2015). Stepwise evolution of pan drug-resistance in Klebsiella pneumoniae. Scientific reports, 5(1), 1-8.

Figure 1

Taxonomy details

. Taxonomy details (Phyloviz) of *K. pneumoniae*, along with the positioning of different Klebsiella spp.

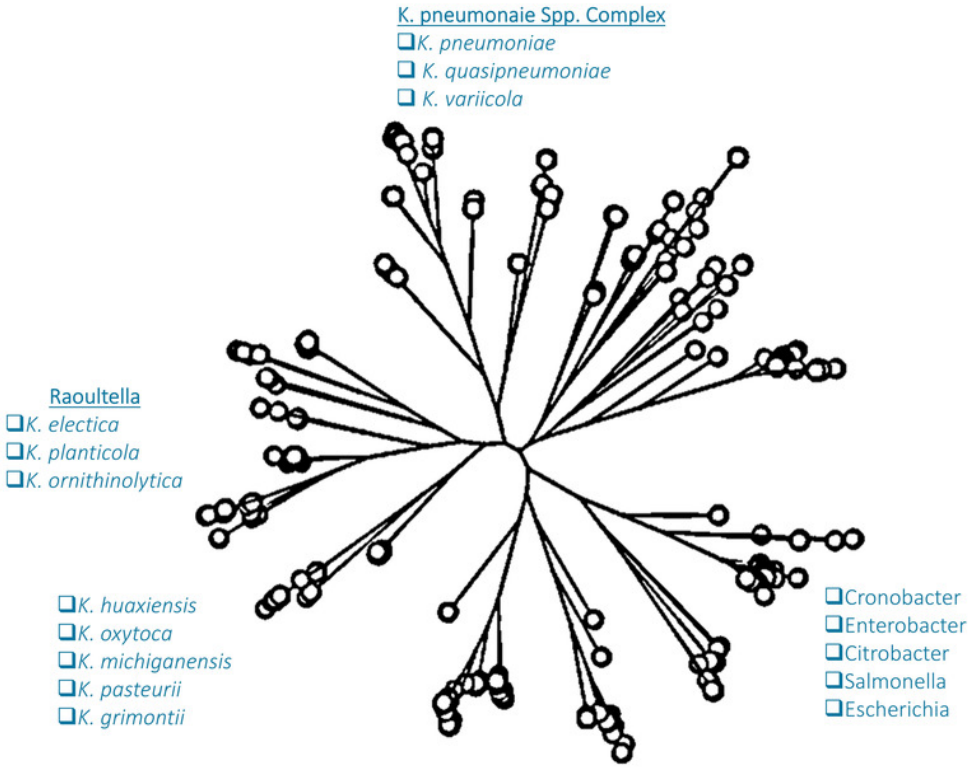

Figure 2

Genomic orchestrate

Circular Genomic orchestrate of *K. pneumoniae*, showing genetic, virulence and resistance determinants

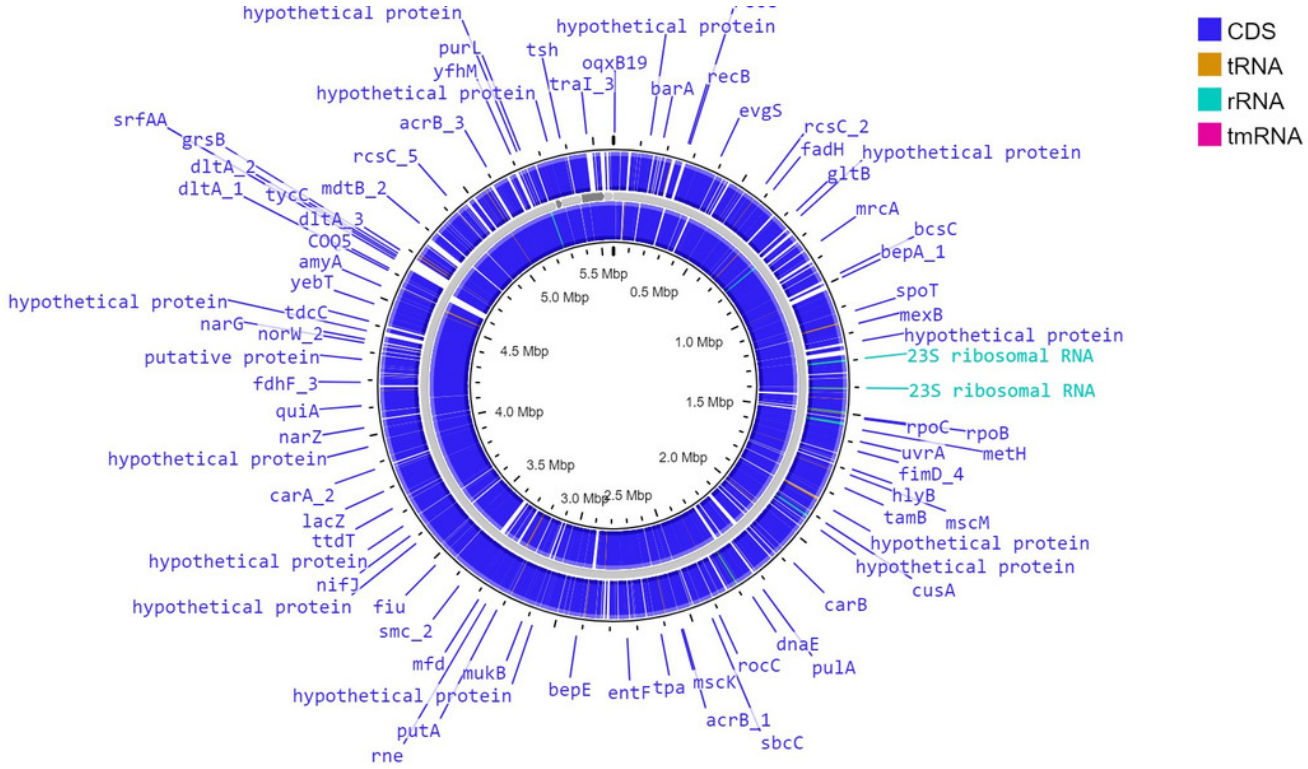

Figure 3

Phylogenetic tree

Phylogenetic tree showing the relative depth of the (CG258) nodes extracted from Kleborate, Pathogenwatch

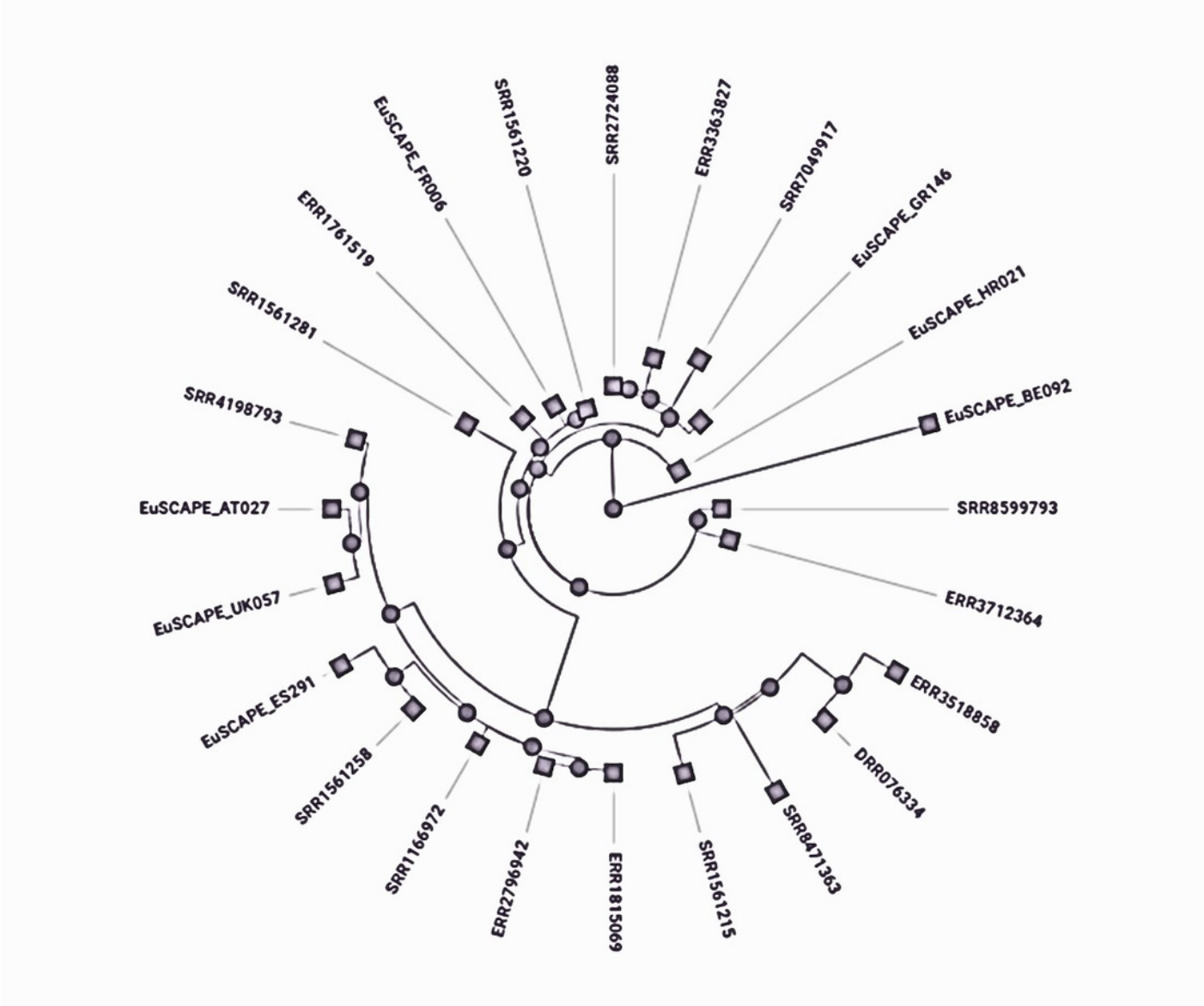

Figure 4

resistance mechanisms

Genetic insights into various resistance mechanisms employed by *K. pneumoniae*

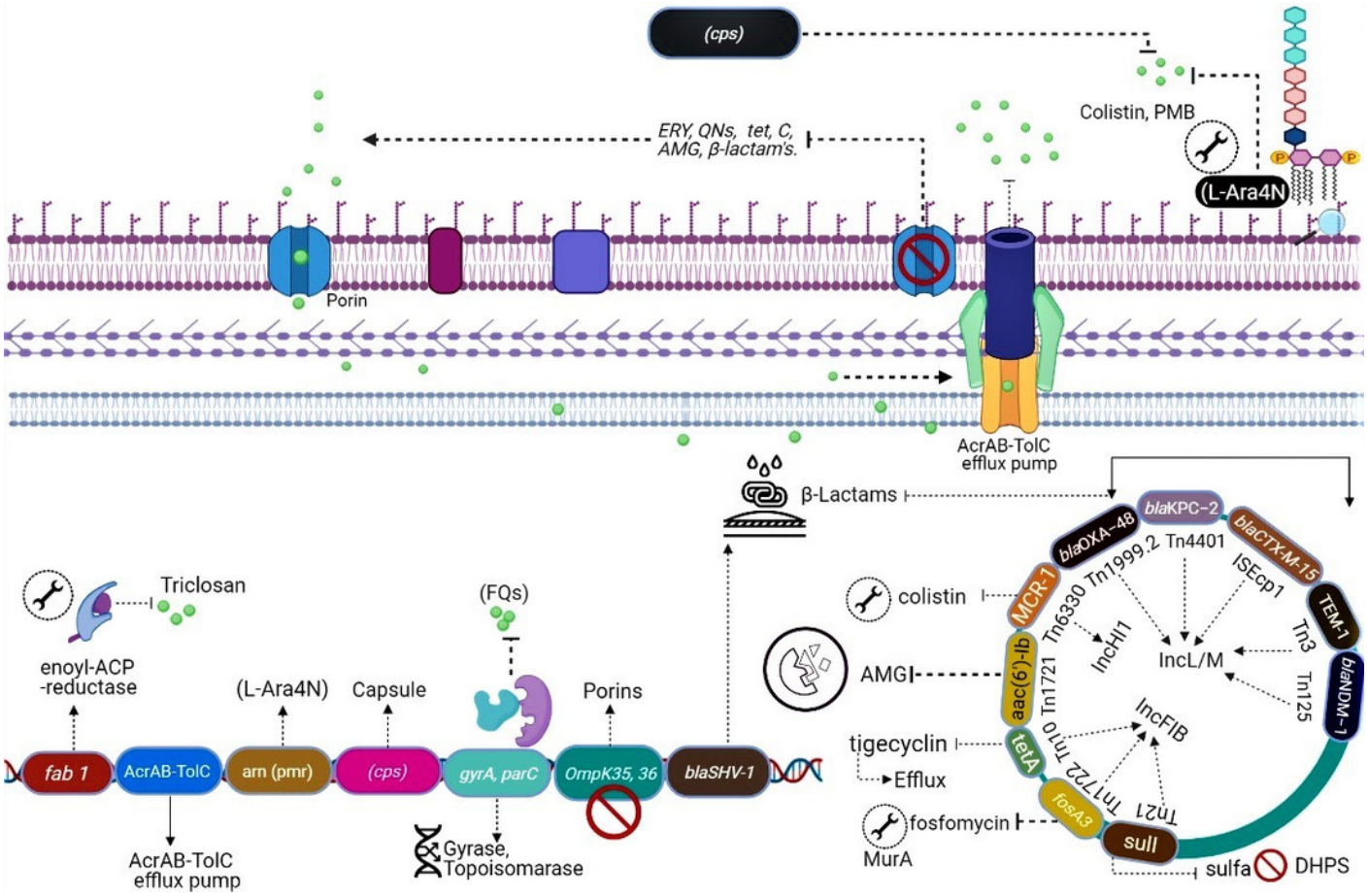

Figure 5

Immune Evasion

Immune Evasion strategies of K. pneumoniae

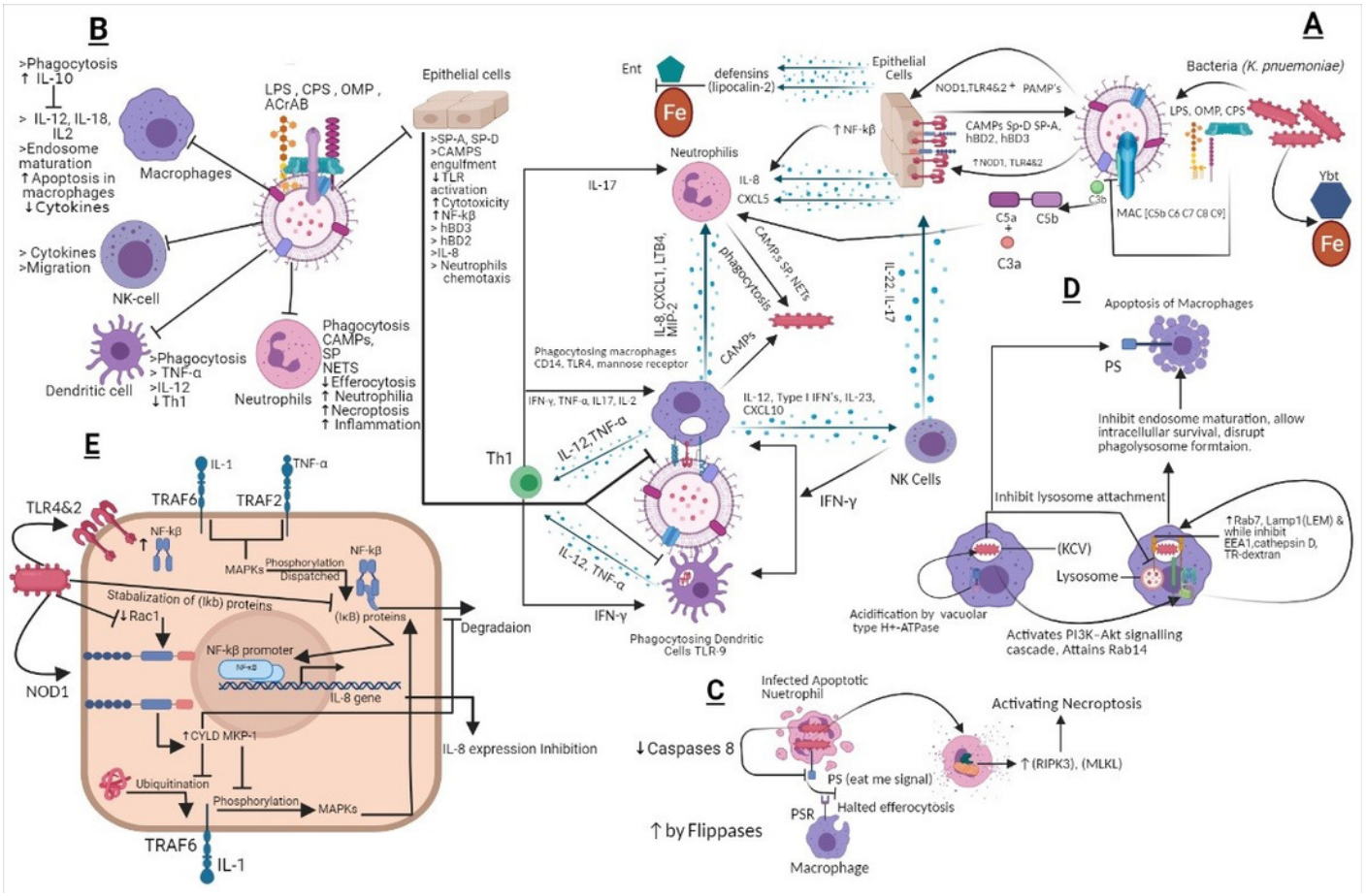

Table 1(on next page)

Clonal disseminatiom

Regional distribution of K. pneumoniae clonal groups

Endemic countries	CGs	STs	Dominant K & O locus	GC Content %	Virulence Determinants.	Resistance Determinants	MGEs	Type of infection	References
Singapore, Vietnam, Russia,	CG23	ST23, ST26, ST57 and ST163	KL1, O1v2	56.6-57.2	ybt 1, clb 2, iuc 1, iro 1, (RmpADC / rmpA2), rmp 1; KpVP-1 / rmpA2, iucABCD-iutA	CTX-M-15 ESBL and *bla*$_{OXA-48}$, Mutations in gyrA or parC, sul1 tetAr	IncA/C$_2$, IncFIB (pQil), IncFIB, IncX$_3$, ColRNAI, and Col440II	Pneumonia, Bacteremia, sepsis, Abdominal infection, Liver abscess and invasive infections	(Brisse et al., 2009), (Livermore et al., 2020), (Shankar et al., 2020), (M. M. Lam et al., 2018)
Madagascar, china.	CG380	ST375	KL2, O1v2	57.1-57.5	ybt 1, ybt 14, iuc 1 iro 1, (RmpADC / rmpA2,	blaKPC-2 blaSHV-11, SHV-1	IncL/M plasmid	Meningitis, liver abscess, severe CAI, Invasive infection in Diabetic patients	(S. Bialek-Davenet et al., 2014) (Zhan et al., 2017) (Magiorakos et al., 2012)
Singapore, Vietnam	CG65	ST65	KL2, O1v2	56.8-57.2	(RmpADC / rmpA2), ybt 17, clb 3, iuc 1, iro, iucABCD-iutA, entB, wabG, uge and ycfM,	blaKPC-2 blaSHV-11, SHV-1, blaKPC-3, *SHV-1*		UTI's pneumonia, Septicemia, liver abscess, Invasive infections, CAI's	(Magiorakos et al., 2012) (Zhan et al., 2017)
Vietnam, New Zealand, Australia	CG86	ST86	KL2, O1v1	56.5-57.5	ybtS, iucABCD-iutA, rmpA and entB	SHV-1	IncL/M plasmid	Invasive Infection, Sepsis, Liver abscess, CAI's	(Y. Zhang et al., 2016) (Surgers et al., 2016) (Magiorakos et al., 2012)
United Kingdoms, United states of America, Vietnam	CG25	ST25, ST277,ST326, ST309	KL2, O1v2	57.1-57.4	ybt 2, ybt 16, ybt 9, ybt 6, 3, iro 3, iucABCD-iutA	SHV-1 CTX-M 15 OXA-48	IncFII IncFIB ColKP3	UTI's septicemia, pneumonia, Liver Abscess	(S. Breurec et al., 2013) (Potron et al., 2013) (Shiri Navon-Venezia et al., 2017)

United Kingdoms, United states, Netherlands	CG37	ST37	KL15, KL12, KL38. O2v2 O3b, O4, OL103	56.7-57.4	ybt 3, ybt 5, ybt 9, ybt 14 (RmpADC / rmpA2),	OXA-48 TEM-1, SHV-11 OXA-48, KPC-2 KPC-3, OXA, NDM, CTX-M15	pKPN-704 pKPN-332	UTI's, RI's, Septicemia,	(Zaman et al., 2018) (Wijetunge et al., 2014) (Shiri Navon-Venezia et al., 2017) {Li, 2017 #52}
United Kingdoms, Serbia, Romania Netherlands, Italy	CG101	ST101	KL17, O1v1	56.3-56.9	ybt 9, (RmpADC / rmpA2), clb 3, iro1	blaKPC−2, KPC-2 KPC-3,OXA-48,NDM,CTX-M-15, OmpK35/OmpK36	Tn1721 transposon, IncFII(K), IncR, IncFIB, IncFII, IncQ1, and Col440II	Blood Stream Infections, HAI's, UTI's,	(S. Breurec et al., 2013) (Loconsole et al., 2020) {Roe, 2019 #53}
United Kingdoms, United states, Thailand, Russia, Oman, Netherlands, Pakistan	CG147	ST147,ST392	KL19, KL64, O2v1, O3/O3a	56.4-57.4	ybt 9, ybt 16, (RmpADC / rmpA2),	NDM-1, NDM-9, ARMA, AADA1, AAC(6')-IB, APH(3')-VI, APH(3')-1A, CATB3, DFRA5, MPH(E), MSR(E), QNRS1, SUL1, SUL2, CTX-M-15, OXA-1, OXA-9, TEM-1A	IncF, IncA/C and IncL/M, pKpQIL, pKPN3, pNDM-MAR and IncR IncA/C, ColRNAI	Nosocomial Infections, Abdominal wound Infections, UTI's	(Falcone et al., 2020) (Lee et al., 2016) (Samuelsen et al., 2011) {Ouertani, 2016 #54}
Pakistan, United states, United Kingdoms, Vietnam, Spain, Netherlands, Nepal,	CG15	ST15	KL24, KL112. O1v1	56.6-57.4	ybt 1, ybt 16, ybt 13 iuc 3, clb 3	KPC-2, KPC-3, OXA-48,NDM,CTX-M, aac(3)-IIa, aph(3')-Ia, blaOXA-48, MgrB, tet(A),	IncQ, ColRNAI, IncL, ColpVC, and IncFIB, IncFII	Pediatric Infections, UTI's, Neonatal meningitis	(Lee et al., 2016) (Martins et al., 2020), (Pillonel et al., 2018) {Löhr, 2015 #55}

Germany, China.						catA1,			
United states, Italy, Greece, Germany, Australia, Israel China, Spain, United states, Brazil	CG258	ST11 ,340, 258, 512	ST258 [KL106, KL107, O2v2] ST11 [KL105, KL24, KL15, KL47, KL64. O2v1, O2v2, O3b, O4,OL101]	56.7-57.4 56.9-57.4	ybt 14, ybt 13 ybt 17, clb 3, iucABCD-iutA	blaKPC-2 blaSHV-11, blaKPC-3, bla OXA-9, CTX-M-15, SHV-1, SHV-11, SHV-12), blaOXA-48 frame shift mutation in mgrB, mcr, aph3-Ia	ICEKp258 .1 and ICEKp258 .Tn4401	Neurosurgical Site Infections, urinary tract, bacteremia, Lower respiratory tract Infections, surgical intensive care unit Infections, pneumonia	(Chen et al., 2014) (Kitchel et al., 2009) (Fasciana et al., 2019), (Kelly L Wyres et al., 2020), (Ojdana et al., 2020)
United states, United Kingdoms, Norway, Netherlands, Italy	CG307	ST307	KL102, O2v2	56.6-57.3	(RmpADC / rmpA2), (T4SS), mobA and mobB, ybt, irp1, irp2 and fyuA, π-fimbrial chaperone/usher pathway.	*acc3*, *blaSHV*, *blaCTX-15*, bla_{KPC-3}, bla_{NDM-1}, bla_{OXA-48}, and $bla_{CTX-M-15}$, KPC-3, KPC-2, aac(3)-IIa, aac(6′)Ib-cr, qnrB, tet(A), strAB, sul2, dfrA14 and catB3, SHV-28, oqxAB and fosA	pKPN-307 Tn1721 FIB-M, HIB-M, FIBK, FIIK, pKpQIL, IncN type B, n5403-ΔISKpn6-bla KPC-2–ISKpn7	Sepsis, UTI's, Pneumonia, Neonatal Infections	(Villa et al., 2017) (Villa et al., 2016) . (Haller et al., 2019)
Thailand, United states, Netherland, Australia,	CC16	ST16	KL51, O3b	56.9-57.5	ybt 9, ybt 1, (RmpADC / rmpA2),	qnrS, rmtB, mphA and bla OXA-181, bla OXA-48, arr3, catA, aadA16, rmtB, sulI, mphA, bla	IncFII, ISL3-like insertion sequence, IncL plasmid, ISL3-like element, Col(pHA	Super Infections, VAP, blood stream infections, meningitis, septic shock, sepsis, pneumonia	(To Nguyen Thi Nguyen et al., 2021) (Boonyasiri et al., 2021) (T. N. T. Nguyen et al., 2021)

						TEM-1, bla CTX-M-15, dfrA, qnrS, qnrB, tetA, mutations on gyrA and parC , Disruption mgrB gene by an ISL3-like insertion sequence	D28)/Col440II, Col(IRGK),		
Croatia, Spain	CC 11	ST 437	KL36, O4	57.2-57.5	Ybt 1, rmpA (RmpADC / rmpA2)	KPC-2, blaOXA-232, CTX-M-15, blaNDM, blaCTX-M-55, aph (3')-IIa, aph (3")-Ib, aph (6)-Id, and rmtB), oqxA and oqxB, sul2, (floR), (tetA), OXA-9, TEM-1	Tn4401b, IncN, ISKpn7, ColKP3-type no conjugative plasmid, IncFIB (K), IncR, Col440I, IncFII (K), IncP1.	Community acquired Urinary tract Infections, nosocomial infections.	(Francisco et al., 2019) (Weng et al., 2020) (Fuster et al., 2020)
China	CC1571	ST4564			iucA, iutA, rmpA, rmpA2 and iroN, magA, iutA, fepD, iroE, acrAB, rcsAB, T6SS	blaCTX-M-14, blaCTX-M-17, acrA, acrB, NDM-1 and CTX-M-9, mcr-1, blaNDM, blaTEM, qnrBs, mphA, mrx, sul1, sul2		HAI's	(Wang et al., 2021)

1 **Table 1: Global disseminated Clonal Groups of *K. pneumoniae* with details of genetic determinants**
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