WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Rising Threat of Klebsiella Pneumoniae on Public Health: A Review

Sura A. Abdulateef

Department of Applied Sciences, University of Technology-Iraq

A B S T R A C T

Klebsiella pneumoniae is a significant pathogen responsible for a variety of diseases, including urinary tract infections and pneumonia, which can result in sepsis and death. Furthermore, the hyper virulent K. pneumoniae causes fatal invasive illnesses including liver abscesses. The emergence of antimicrobial resistance genes, such as those producing extended-spectrum -lactamases and carbapenemases, decreases the effectiveness of conventional antibiotics. The most clinically significant K. pneumoniae strains are carbapenem-resistant. K. pneumoniae is thought to be a major spreader of antibiotic resistance genes. Effective antibiotics are frequently limited, and therapy may rely on few antibiotics as the last option. These possibilities are compromised by K. pneumoniae's outstanding resistance, which allows pathogenic strains to be familiar to hospital setting. It is evident that any potential achievement in addressing K. pneumoniae infections would need a greater understanding of the pathogen's molecular pathophysiology and antibiotic resistance. This will assist in locating different therapeutic choices that are desperately needed.

Keywords: Klebsiella pneumoniae, pathogenicity, virulence factors, antibiotic resistance.

1. Introduction

Klebsiella pneumoniae is the second most pathogenic Enterobacteriaceae pathogen after E. coli. It may infect a healthy person, and it is regarded as a major cause pathogen of nosocomial infection, particularly in patients who are immunocompromised or using immunosuppressive medicines. Klebsiella pneumoniae has a multitude of virulence factors, including capsular polysaccharides, which function as adhesion determinants and are also exploited for immune evasion during infection and bacterial survival. Other virulence factors, including as siderophores and fimbriae type 1 and 3, are crucial in the severity of K. pneumoniae infection (Ganem et al., 2021).

K. pneumoniae has developed antibiotic resistance mechanisms, making it a challenging disease to eradicate. Reduced membrane permeability caused by changes in the total number of pores or in relative activity limits antibiotic penetration into the cell, biofilm formation which acts as a diffusion barrier that reduces antibiotic entry into the bacterial cell's, and different -lactamase enzyme production (Navon-Venezia et al., 2017) are the main mechanisms for antibiotic resistance in K. pneumoniae.

2. Traits and Features of Klebsiella pneumoniae

Klebsiella pneumoniae is an opportunistic, gram-negative, facultative anaerobic rod-shaped bacteria that measures (0.3-1m) in diameter and (0.6-6m) in length and can be found individually, in pairs, or in short chains. K. pneumoniae is lactose fermenting, non-motile, and non-spore forming, with a conspicuous polysaccharide capsule of substantial thickness that gives colonies on agar plates a mucoid look (Brunsn et al., 2019). Upper respiratory tract infection, pneumonia, urinary tract infection (UTI), and septicemia are all resulted by K. pneumoniae. In general, K. pneumoniae is a concern and causes serious infections in persons who have a compromised immune system or are taking immunosuppressive medicines and get treatment in an intensive care unit (ICV) (Bengeochea and Sapessoa, 2019).

3. Prevalence and Distribution

Humans are the principal reservoirs for K.pneumoniae, and in the general population, (5-38%) of people have the organisms in their stool and (1-6%) had it in their nasopharynx. The gastrointestinal system and hospital workers' hands are the most common causes of infection. It has the potential to produce nosocomial eruption (Majeed et al., 2020). It is believed that (3-5%) of all pneumonia population infections in Western culture are caused by K. pneumoniae, whereas it is around 15% of all pneumonia cases in poor nations such as Africa. K.pneumoniae accounts for approximately 11.8% of all pneumonia cases treated in hospitals globally (Hasan et al., 2021). K. pneumoniae causes between 8 and 12 percent of deaths in persons on ventilators, but only 7% in those who do not, while mortality ranges from 50 to 100 percent in patients with alcoholism and septicemia (Munoz-Price et al., 2013). Carriers at levels of up to 75% in the stool of people hospitalized can be observed and felt to be compatible with the doses of antibiotics administered in a single sample. Klebsiella most likely shares two settings in nature: the ecosystem in which they live and their colonized mucosal regions of humans,

horses, or swine of surface waters, sewage, soil, and plants. In this way, the Klebsiella genus is similar to Enterobacter and Citrobacter, but it differs from Shigella spp. and E. coli, which are abundant in persons but not in the environment (Nordmann et al., 2009).

4. Klebsiella pneumoniae Pathogenicity

A. Hospital and community acquired pneumonia

The spread of hospital-acquired pneumonia (HAPs) is greater than that of community-acquired pneumonia. The primary etiology of 11.7% of hospital-acquired is a K. pneumoniae isolate. These hospital-acquired arise among non-ventilated and ventilated individuals, with K. pneumoniae acting as the primary cause in 7% and (8-12%) of these cases, respectively. (Cotoia et al., 2020). This bacterium can induce inflammation, haemorrhage, cell death, and necrosis in patients with chronic lung illness and immune-compromised individuals, resulting in bloody, mucoid, and thick sputum.

Community-acquired pneumonia (CAPs) is a reasonably common illness that can advance quickly and result in being hospitalized, prolonged ICU resides, and elevated incidences of mortality and morbidity (Ciellóniz et al., 2020). K. pneumoniae CAPs are frequently associated with signs of acute pneumonia, such as fever, leukocytosis, cough, and chest discomfort. These infections may also exhibit a K. pneumoniae sputum characteristic that is the formation of mucus with a blood tint as a result of excessive amounts of necrosis and inflammation in the lungs (Ticona et al., 2021).

B. Bacteremia

Bacteremia is described as the existence of active bacteria in the circulation, and it may induce moderate to potentially fatal infections by activating a series of pro-inflammatory and anti-inflammatory cascades, eventually disrupting physiological stability. The prevalence of bacterimia, whether acquired in the community or in a hospital, has significantly increased (Liu et al., 2014). K. pneumoniae is the second most common cause of community-associated and nosocomial bacteremia among gram negative bacteria, behind E.coli. The increased risk of death is associated with several factors, including Individuals referred to ICUs that are over 65 years old, have an associated cancer, have pneumonia, require catheters for urination or ventilator assistance, and those who are alcoholic (Zammiet et al., 2014).

C. Meningitis

Meningitis is an infection that causes an irritation of the meninges. It can be caused by a number of pathogenic organisms, including parasites, bacteria, fungi and viruses, also noncommunicable processes. Although viral meningitis is the most frequent kind of illness, bacterial meningitis can be fatal (Hasbun et al., 2017). Patients (particularly those with nervous system cancer) are more vulnerable to hospital infections during treatment as a result of being subjected to multiple risk variables (such as catheters and tubes, neurological deterioration, multiple injuries, and immune system damage) (Tsitsopoulos et al., 2016). Invading microorganisms circumvent complex host defensive systems for neurological therapies, notably in the ICU, and cause infections with high morbidity and mortality (Sun et al., 2021). Meningitis caused by K. pneumoniae is uncommon throughout the majority of the world. Patients who arrive to the emergency room with meningitis and have risk factors for meningitis, such as alcoholic cirrhosis, should be suspected of having K.pneumoniae-related sequelae (Sun et al., 2021).

D. Urinary tract infections

Pathogen colonization anywhere in the urinary system, including the bladder, kidney, ureter, and urethra, is characterized as urinary tract infection (UTI). UTIs are among the most serious forms of bacterial infections in the globe (Al-Naqshbandi et al., 2019). While curable, UTIs are becoming more difficult to control due to widespread antibiotic resistance among uropathogens, particularly those in the Enterobacteriaceae family. Pathogenic K. pneumoniae is thought to be the 2nd or 3rd most prevalent reason of urinary tract infection, after E. coli. These infections, however, cause increased frequency of dysuria, hematuria, and desire to urinate (Keller and Gluser, 2020).

E. Dermatological and subcutaneous infections

K. pneumoniae also can be responsible for infections of the skin and soft tissues (Cellulitis, Myositis, and Necrotizing Fasciitis), as well as Endophthalmitis and abscesses in other tissues such as the lungs, kidneys, and throat (Mairamraj et al., 2020).

F. Bacterial liver abscesses

Unlike secondary or polymicrobial liver abscesses, primary K.pneumoniae liver abscesses frequently arise in persons with no underlying liver illness. Liver abscesses are associated with an elevated risk of hematogenous spread to other organs such as the eye and lung, as well as relatively high rates of morbidity and death (4-8%) (Cheong et al., 2017).

5. Factors Contribute to the Virulence of Klebsiella Pneumoniae

A. Pili

Pili are made up of globular polymeric protein subunits (pilin) with molecular masses ranging from 15 to 26KDa. These structures may be up to 10m long and 1-11nm in diameter. Pili or fimbrial adherence factor required for attachment to host epithelial cell, K. pneumoniae adhesion to mammalian tissue is mediated by two forms of non-flagellar bacterial pili, type 1 and type 3 (Huynh et al., 2017). Type 1 fimbriae are thin, sticky, stiff, thread-like surface appendages on the outer membrane, with fim H situated near the tip. This fimbriae of K. pneumoniae are often seen in enterobacterial species;

they grow beyond the capsule and use the adhesin fim H to mediate bacterial adherence to mannose-containing structures on host cells or extracellular matrix (Schroll et al., 2010).

K. pneumoniae type 3 fimbriae are (0.5-2m) long and (2-4nm) broad appendages distinguished by their affinity for a range of mammalian cells, including bladder epithelial cells, endothelial cells, and uroepithelial cells. Carbohydrates, glycolipids, and specific proteins are among the components recognized by pathogenic bacteria on the epithelial cell surface (Alcántan-Curiel et al., 2013).

B. Capsular Polysaccharide

The capsule is composed of a polysaccharide structure that envelopes the cell and required for K. pneumoniae pathogenicity and is likely the most extensively studied K. pneumoniae pathogenic component. Serotype K1, serotype K2, serotype K4, and serotype K5 of Klebsiella are more pathogenic than the rest types of capsule (Grimont and Grimont, 2015).

Capsular polysaccharide (CPS) is a critical virulence component of K. pneumoniae that covers the bacterial surface and induces inflammation. A thick capsule on the cell surface protects K. pneumoniae against macrophage opsonization and phagocytosis (Cortès et al., 2002). CPS functions as a barrier against host-derived antimicrobial peptides, and free CPS produced from bacterial cells can trap antimicrobial polypeptides, reducing the quantity of antimicrobial polypeptide reaching the bacterial surface (Zurabov and Zhilenkov, 2021).

C. Biofilm

The increased incidence of antibiotic resistance in dangerous bacteria poses significant risks to the regional, medical, and food industries (Khan et al., 2020). Bacterial biofilm formation is assumed to be one of the mechanisms by which bacteria resist antibiotics, increasing their pathogenicity and making them more dangerous. Bacterial biofilm development has been linked to up to 80% of recurring and chronic microbial infections in humans, according to research (Jamal et al., 2018). Biofilm formation is typically associated with inflammatory illness, periodontal disease, cystic fibrosis, and problems in wound healing. The treated complications may result in a chronic condition.

Bacteria in biofilms are up to 1000 times more resistant to antibiotics and host immunological responses than planktonic cells (Vishwakarma et al., 2021). This is due to the fact that the morphology and physiological activities of bacteria in biofilms differ greatly from those of planktonic bacteria in suspension (Vishwakarma et al., 2021). Woblewska et al. (2015) report that 60-70% of bacteria attached to implant surfaces are associated with persistent nosocomial infections. Simultaneously, the majority of infections are connected to the formation of biofilm on the surface of biomaterials. The most prevalent bacterial strains are Staphylococcus epidermidis, Streptococcus viridans, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa. The creation of layers on cardiac implants is the primary source of S. aureus and S. epidermidis. This bacterium is responsible for 40-50% of cardiovascular infections and 50-70% of catheter infections.

During hospitalization, infections linked with biofilm development account for 80% of all chronic responses of organisms. The colonization of microorganisms near the implant is associated to the production of biofilm. One of the main explanations is infection of the operation site following the use of surgical meshes during hernia surgery (Maciejewska et al., 2016). A biofilm is a challenging structure to recognize, especially in its early phases of production. This one does not allow for the removal of germs prior to gene expression. It is critical for patients (Bi et al., 2021).

D. Lipopolysaccharide

Endotoxin, also known as lipopolysaccharide (LPS), is an essential component of the outer leaflet of every gram-negative bacterium's cell membrane (Shankar-Sinha et al., 2004). Although LPS topologies vary greatly across bacterial species, it is made of three unique sections: a core polysaccharide, Lipid A, and an O-antigen polysaccharide side chain. Clements et al. (2008) discovered that O-antigen inhibits complement protein deposition and complement-associated serum lytic activity. LPS has been identified as a key virulence component in K. pneumoniae, the causative agent of bacteremia and pneumonia (Shankar-Sinha et al., 2004).

E. Siderophores

Siderophores are low-molecular-weight iron chelating molecules that are produced within the bacteria before being released throughout the cell. These substances attach to the iron that's present in surroundings and then transporting iron inside the cell to be used for bacterial growth, replication, and virulence in many gram-negative bacteria. Iron is a crucial component in bacterial development, primarily acting as a redox catalyst in electron transport activities and proteins involved in oxygen transport (Gout, 2018). K. pneumoniae secretes the iron-scavenging molecule enterobactin (Ent), which has involvement in the production of inflammation, bacterial dispersion, and hypoxia activation (Holden et al., 2015).

6. Resistance to Antibiotics

Antimicrobial resistance (AMR) is a major problem in developing countries due to antimicrobial overuse, widespread availability of counterfeit or substandard medications, and inadequate infection control methods (Taitt et al., 2017). Antimicrobial resistance is a severe emergency, and the lack of new antimicrobial medication development has steadily restricted treatment options for bacterial infection illness. Antibiotic resistance bacteria pose a challenge to infection control since pathogenic K.pneumoniae is now resistant to the majority of drugs. As a result, a global public health catastrophe is quickly worsening (Effah et al., 2020). Multidrug-resistant organisms cause significant community-acquired and nosocomial infections, limiting therapy choices by limiting the use of existing antibiotics. However, the worldwide crisis of antibiotic resistance in K. pneumoniae has raised the danger of

antibiotic treatment failure in people. Resistance to cephalosporins, carbapenems, trimethoprim, fluoroquinolones, and aminoglycosides was examined in K. pneumoniae (Sukmawinata et al., 2020).

K. pneumoniae infections are linked to common health-care and community-acquired illnesses such as pneumonia, urinary tract infections, wound infections, and blood infections. However, resistance makes these illnesses more severe (Casey, 2012). Because biofilm can inhibit antibiotic penetration and restrict cell development at the biofilm's center, it can shield K. pneumoniae from antimicrobial medicines (Jafari-Sales et al., 2020). As a result, biofilm shields harmful bacteria from antibiotics and the immune system to a large extent, which may be due to drug penetration decrease, delayed growth, or adaptability and food constraint. Another factor that can increase resistance is quorum sensing, which is density-dependent communication between bacteria that allows gene expression by secreting specific signal molecules and is extremely responsible for the development of pathogenicity in these bacteria strains (Boren et al., 2020). Bacterial resistance can be acquired through both the capacity of a gene in a bacterium to change and the transfer of resistance genes from other bacteria. Bacteria have developed a number of methods to impart antibiotic resistance.

Drug inactivation or modification by the creation of enzymes such as -lactamases, modification of the target site (PBP), modification of a metabolic pathway, or decreased drug accumulation via efflux pump/reduced drug permeability (Garneau-Tsodikova and Labby, 2016). The most common method for antibiotic inactivation is enzymes. Drug inactivation by bacterial enzymes, activation of the drug efflux pump, and suppression of drug uptake in cells are all components of the process by which bacteria transmit antibiotic resistance. Antibiotic resistance in this group of bacteria, which is one of the leading causes of severe infections in humans, has emerged as a major worldwide health concern (Mancuso et al., 2021).

When compared to illnesses associated with susceptible isolates, antibiotic resistance particularly leads in longer hospital admissions, increased exposure of patients to drug-resistant isolates, and, as a result, higher healthcare expenses. -lactam antibiotics are undoubtedly the most important antibiotic family used to treat infections caused by gram negative bacteria. Resistance to -lactam antibiotics has been observed in Gram-negative bacteria (Apanga et al., 2022). Through antibiotic resistance monitoring research, we may learn about present changes in pathogen prevalence and antibiotic resistance mechanisms, the presence of new resistance types, and forecasts for future trends in antibiotic resistance. Monitoring to give the data needed for resistance management must be one of the first actions in combating its emergence, but it is not the only one that can minimize morbidity and death caused by these infections. In order to limit the spread of bacteria in general, and MDR bacteria in particular, within the hospital environment and the greater community, infection control measures must also be applied.

A. Carbapenemase

The World Health Organization (WHO) has included enterobacteria and non-fermenters such as Acinetobacter baumannii and Pseudomonas aeruginosa to its ongoing priority list of antibiotic-resistant bacteria due to the worrisome growth in carbapenem-resistant (CR) Gram-negative infections in recent years. These CR infections can cause greater morbidity and death than their multidrug counterparts (Lodise et al., 2022). Carbapenemases can hydrolyze antibiotics such as carbapenems, oxyimino-cephalosporins, and cephalosporins. Carbapenemases are a kind of -lactamase that is particularly important in Gram-negative bacteria since they are the last-resort therapy for Gram-negative bacteria-caused MDR disease. The carbapenemases are found in each of the four molecular classes of -lactamases. Serratia marcescens enzyme (SME), NMC carbapenemases, imipenemhydrolysing (IMI) -lactamases, and plasmid-mediated Klebsiella pneumoniae carbapenemase (KPC) are examples of molecular class A carbapenemases that produce lactam.

The main carbapenem tolerance mechanisms include the production of -lactamases, alterations that impair the gene expression or function of efflux pumps, penicillin-binding proteins, porins, and carbapenem-hydrolyzing –lactamases (Papp-Wallace et al., 2011). Their high occurrence among members of the Enterobacteriaceae family raises serious concerns. Patients with infections caused by Carbapenem-resistant Enterobacteriaceae (CRE) have few treatment choices, and their fatality rates are substantial. Lactam-producing molecular class A carbapenemases include Serratia marcescens enzyme (SME), NMC carbapenemases, imipenemhydrolysing (IMI) -lactamases, and plasmid-mediated Klebsiella pneumoniae carbapenemase (KPC). Their significant prevalence among Enterobacteriaceae members raises severe concerns. Patients with Carbapenem-resistant Enterobacteriaceae (CRE) infections have few treatment options and a high mortality rate (Giamarellou and Poulakou, 2009).

B. Extended-spectrum beta-lactamases (ESBLs)

Beta-lactam antibiotics are the most often used antibiotics for treating bacterial infections in both clinical and community settings. However, their overuse and misuse are the leading drivers of resistance in Enterobacteriaceae worldwide (Subramaniam and Girish, 2020). They are also associated with significant rates of morbidity and death. Bacteria often acquire resistance to these medications by producing a -lactamase enzyme, which hydrolyzes -lactam antibiotics. SHV, TEM, and Carbapenemases (MBL, KPC, and class Doxacillinases), as well as CTX-M forms generated by Klebsiella pneumoniae and Escherichia coli, are the most common Enterobacteriaceae -lactamases. ESBLs can hydrolyze penicillins, cephalosporins, and aztreonam, but not carbapenems or cephamycins. Clavulanic acid inhibits lactamases and decreases the generation of ESBLs (Mlynarcik et al., 2021). Because carbapenems are the primary therapy for ESBL-PE Enterobacteriaceae infections, the number of Enterobacteriaceae that generate carbapenemase has grown. ESBL-PE and CPE have become increasingly common in a range of settings during the last 10 years (Athanasakopoulou et al., 2022).

The most prevalent way of resistance to gram-negative bacteria (many broad-spectrum beta-lactams) belonging to the family Enterobacteriaceae is the creation of extended spectrum beta-lactamases (ESBLs) (Ahmed, 2022). ESBL enzymes hydrolyze third-generation cephalosporins (3GCs) such as ceftriaxone and cefotaxime effectively but not oxyimino-cephalosporins such as ceftazidime. These antibiotics are not effective against ESBL-producing bacteria (Moremi et al., 2021). The colonization of ESBL-producing gram negative bacteria (ESBL-GNB) raises the chance of developing multidrug resistant (MDR) bacterial disorders such as urinary tract infections, bloodstream infections, or wound infections (Moremi et al., 2021). The rising

incidence of MDR pathogens in this setting, notably the continuous development of Gram-negative Enterobacteriaceae that manufacture extended-spectrum -lactamases (Peeters et al., 2019), poses a severe challenge to cIAI treatment.

MDR bacterial infections are associated with longer hospital admissions, greater healthcare expenses, and increased death rates due to treatment failure and/or restricted therapeutic alternatives. ESBLs are -lactamases that hydrolyze extended-spectrum cephalosporins with an oxyimino side chain. Aztreonam, an oxyimino-monobactam, is one of these cephalosporins, as are Cefotaxime, Ceftriaxone, and Ceftazidime. As a result, oxyimino-lactams and other similar antibiotics are ESBL-resistant. As a result, these enzymes are able to hydrolyze a broader range of beta-lactam antibiotics.

C. AmpC beta-lactamase

Some Gram-negative bacteria have chromosomes that carry genes that make ampC -lactamases, which are key defense mechanisms (Gupta et al., 2014). Because these enzymes work as cephamycin hydrolyzers, beta-lactamase inhibitors do not inhibit them. Except for carbapenem and cefepime, they are resistant to all -lactam antibiotics including atypical extended spectrum -lactamases (ESBLs). The substrate profiles of these enzymes include monobactam, penicillins, and cephalosporins (Castanheira et al., 2021). Wide-spectrum cephalosporin resistance is developed, and ampC-lactamase production increases in response to -lactam antibiotic exposure. Specific genetic mutations cause AmpC beta-lactamase to be overexpressed and generated (Mizrahi et al., 2020).

Pseudomonas aeruginosa and members of the Enterobacteriaceae family, for example, have chromosomes that include ampC beta-lactamases, a type of cephalosporinases with major medicinal uses (cefoxitin). A high majority of hospital and community-acquired illnesses are caused by Gram-negative bacteria that generate ampC-lactamases (Chika et al., 2018). Because ampC -lactamase is resistant to all-lactam antibiotics except carbapenems and cefepime, ampC -lactamase-producing bacterial infections typically result in poor clinical outcomes. Numerous nosocomial outbreaks have been caused by ampC lactamases-producing organisms, many of which go unnoticed. Phenotypic approaches for identification are difficult to characterize. Therapy failure in critically sick patients may occur owing to any sort of ampC producer, which is equally essential (Altun et al., 2013).

7. Conclusion

Perplexity in antibiotic resistance patterns of Klebsiella pneumoniae is on the rise. This phenomenon is influenced by various factors, including the misuse of antibiotics and the proliferation of mobile genetic elements transporting antibiotic resistance genes. The multidrug-resistant K. pneumoniae strains poses a significant public health challenge. These strains exhibit resistance across diverse antibiotic classes, presenting formidable treatment hurdles. K. pneumoniae, a prevalent and potentially pathogenic bacterium, necessitates a comprehensive understanding of its characteristics, features, virulence factors, and antibiotic resistance determinants. Leveraging this knowledge can lead to the development of innovative and more efficacious strategies for the prevention and treatment of K. pneumoniae infections.

REFERENCES

Ahemd, D.A. (2022). Prevalence of Extended- Spectrum and Metallo Beta-lactamases in some gram-negative bacteria. Bulletin of National Institute of Health Sciences, 140 (2): 2005-2017.

AlCantan-Curiel, M.D.; Blackburn, D.; Saldaña, Z.; Gayosso-Vázquez, C.; Iovine, N.; De La Cruz, M.A. and Girón, J.A. (2013). Multi-functional analysis of klebseilla pneumoniae fimbria types in adherence and biofilm formation. Virulence, 4(2): 129-138.

Al-Naqshbandi, A.A.; Chawsheen, M.A. and Abdulqader, H.H. (2019). Prevalence and antimicrobial susceptibility of bacterial pathogens isolated from urine specimens received in Rizgary hospital – Erbil. Journal of infection and public health, 12(3): 330-336.

Altun, S., Tufan, Z.K., Yağci, S., Önde, U., et al. (2013). Extended spectrum beta-lactamases, AmpC and metallo beta-lactamases in emerging multi-drug resistant gram-negative bacteria in intensive care unit. Sci. Rep., 2(4): 707.

Apanga, P.A., Ahmed, J., Tanner, W., Starcevich, K., et al. (2022). Carbapenem-resistant Enterobacteriaceae in skin drains of 40 healthcare facilities in Sindh, Pakistan: A cross- Sectional study. PloS One, 17(2):e0263297.

Athanasakopoulou, Z., Diezel, C., Braun, S.D., Sofia, M., et al. (2022). Occurrence and characteristics of ESBL- and Carbapenemase producing Escherichia Coli from Wild and Feral Birds in Greece. Microorganisms, 10(6):1217.

Bengoechea, J.A. and Sapessoa, J. (2019). Klebseilla pneumoniae infection biology: living to counteract host-defenses. FEMS microbiology reviews, 43(2): 123-144.

Bi, Y.; Xia, G.; Shi, C.; Wan, J.; Liu, L.; Chen, y.; Wu, Y.; Zhang, W.; Zhou, M.; He, H.; et al. (2021). Therapeutic strategies against bacterial biofilms. Fundam. Res., 1, 193-212.

Boren, K.; Crown, A. and Carlson, R. (2020). Multidrug and pan-antibiotic resistance-The role of antimicrobial and synergistic essential oils: A review. Natural product communications, 15(10), 1934578-2096595.

Brunson, N.D.; Maldosevic, E.; Velez, A.; Figgins, E. and Ellis, T. (2019). Porin loss in klebseilla pneumoniae clinical isolates impact production of virulence factors and survival within macrophages. Int. J. Med. Microbiol, 309 (3-4): 213-224.

Casey, G. (2012). Antibiotics and the rise of superbugs. Kai Tiaki: Nursing New Zealand, 18(10), 20.

Castanheria, M., Simner, P.J. and Bradford, P.A. (2021). Extended- spectrum β-lactamases: An update on their characteristics, epidemiology and detection. JAC-Antimicrobial Resistance, 3(3): dlabo092.

Cheong, H.S.; Chung, D.R.; Park, M.; Kim, S.H.; KO, K.S.; Ha, Y.E. and Song, J.H. (2017). Emergency of an extended-spectrum β-lactamase-producing serotype K1 klebseilla pneumoniae ST23 strain from Asian countries. Epidemiology and Infection, 145(5), 990-994.

Chika, E., Charles, E., Ifeanyichukwu, I. and Michael, A. (2018). First detection of Fox-1 AmpC β-lactamase gene expression among Escherichia Coli isolated from abattoir samples in Abakaliki, Nigeria. Oman Medical Journal, 33(3): 243.

Cillóniz, C.; Dominedó, C.; Pericás, J.M.; Rodriguez-Hurtado, D. and Torres, A. (2020). Community-acquired pneumonia in critically ill very old patients: a growing problem. European Respiratory Review, 29, 155.

Clements, A.; Gaboriaud, F.; Duval, J.F.; Farn, J.L.; Jenney, A.W.; Lithgow, T.; Wijburg, O.L.C.; Hartland, E.L. and Strugnell, R.A. (2008). The major surface-associated saccharides of klebseilla pneumoniae contribute to host cell association. PLos one, 3(11): 1-10.

Cortès, G.; Borrell, N.; De Astroza, B.; Gómez, C.; Sauleda, J. and Alberti, S. (2002). Molecular analysis of the contribution of the capsular polysaccharide and the lipopolysaccharide O side chain to the virulence of klebseilla pneumoniae in a `murine model of pneumonia. Infect. Immune, 70(5): 2583-2590.

Cotoia, A.; Spadaro, S.; Gambetti, G.; Koulenti, D. and Cinnella, G. (2020). Pathogenesis-Targeted preventive strategies for multidrug resistant ventilator-associated pneumonia: A Narrative Review. Microorganisms, 8(6), 821.

Effah, C.Y.; Sun, T.; Liu, S. and Wu, Y. (2020). Klebseilla pneumoniae: an increasing threat to public health. Annals of clinical microbiology and anti microbials, 19(1): 1-9.

Ganem, N.A.A., Saleh, B.H., and Aal Owaif, H.A.H. (2021). Bacteriological and molecular study for detection of virulence genes in pseudomonas aeruginosa isolated from Burns and wounds infections. Annals of the Romanian Society for cell Biology, 25(6):159-168.

Garneau-Tsodikova, S. and Labby, K.J. (2016). Mechanisms of resistance to aminoglycoside antibiotics: Overview and perspectives. Med.Chem.Comm, 7(1): 11-27.

Giamarellow, H. and Poulakou, G. (2009). Multidrug- resistant gram-negative infections. Drugs, 69(14): 1879-1901.

Gout, I. (2018). Coenzyme A, protein coAlation and redox regulation in mammalian cells. Biochem. Soc. Trans., 46(3): 721-728.

Grimont, P.A. and Grimont, F. (2015). Klebseilla. Bergey's Manual of systematic of Archeae and Bacteria. EBook. Hoboken. New Jersy, 1-26.

Gupta, G., Tak, V. and Mathur, P. (2014). Detection of AmpC β-Lactamases in gram-negative bacteria. Journal of laboratory physicians, 6(01): 1-6.

Hasan, T.H.; Alasedi, K.K. and Jaloob, A.A. (2021). Proteus Mirabilis virulence factors. International Journal of pharmaceutical Research, 13(1).

Hasbun, R., Rosenthal, N., Balada-Liasat, J.M., Chung, J., Duff, S., Bozzette, S., and Ginocchio, C.C. (2017). Epidemiology of meningitis and encephalitis in the United States, 2011-2014. Clinical infectious diseases, 65(3):359-363.

Holden, V.I. and Bachman. M.A. (2015). Diverging roles of bacterial siderophores during infection. Metallomics, 7(6): 986- 995.

Huynh, D.T.N.; Kim, A.Y. and Kim, Y.R. (2017). Identification of pathogenic factors in klebseilla pneumoniae using Impedimetric sensor Equipped with Biomimetic surfaces. Sensors, 17(6): 1-13.

Jafari-Sales, A.; Soleimani, H. and Moradi, L. (2020). Antibiotic resistance pattern in klebseilla pneumoniae strains isolated from children with urinary tract infections from Tabriz hospitals. Health Biotechnology and Biopharma, 4(1):38-45.

Jamal, M.; Ahmed, W.; Andleeb, S.; Jalil, F.; Imran, M.; Nawaz, M.A.; Hussain, T.; Ali, M.; Rafiq, M. and Kamil, M.A. (2018). Bacterial biofilm and associated infections. J. Chin. Med. Assoc., 81: 7-11.

Keller, L.J. and Gluster, J. (2020). Urinary tract infection updates and recent developments. Current Emergency and Hospital Medicine Reports, 8(2):41-44.

Khan, F.; Pham, D.T.N.; Oloketuyi, S.F. and Kim, Y.M. (2020). Antibiotics application strategies to control biofilm formation in pathogenic bacteria. Curr. Pharm. Biotechnol, 21: 270-286.

Liu, H.; Cheng, Z.; Song, W.; Wu, W. and Zhou, Z. (2014). Immune proteomic to analysis the pathogenicity factors in leukopenia caused by klebseilla pneumoniae bacteremia. PLoS one, 9(10). E110011.

Lodise, T.P., Bassetti, M., Ferrer, R., Naas, T., et al. (2022). All-cause mortality rates in adults with Carbapenem-resistant gram-negative bacterial infections: a comprehensive review of pathogen-focused, prospective, randomized, interventional clinical isolates. Expert Review of Anti-infection Therapy, 20(5):707-719.

Maciejewska, M.; Bauer, M. and Dawgul, M. (2016). Nowoczense metody zwalczania biofilm bakteryjnego. Postspy Mikrobiol, 55: 3-11.

Majeed, H.T.; Hasan, T.H. and Aljanaby, A.A. (2020). Epidemiological study in women infected with toxoplasma gondii, rubella virus, and cytomegalo virus in Al-Najaf Governorate –Iraq. International Journal of pharmaceutical Research, 12: 1442-1447.

Mancuso, G., Midiri, A., Gerace, E. and Biondo, C. (2021). Bacterial antibiotic resistance: the most critical pathogens. Pathogens, 10(10): 1310.

Maramraj, K.K.; M1, K.L.; Dikid, T.; Choudhary, S.; Reddy, S.; Jain, S.K. and Singh, S.K. (2020). An outbreak of acute skin and soft tissue infections including necrotizing Fasciitis in Kalwala village, India, 2018: public health implications for the lymphatic filariasis elimination program. Transactions of the Royal Society of Tropical Medicine and Hygiene, 114(10), 742-750.

Mizrahi, A., Delerue, T., Morel, H., Le-Monnier, A., et al. (2020). Infections caused by naturally AmpC producing Enterobacteriaceae: can we use third-generation Cephalosporines? A narrative review. International Journal of antimicrobial agents, 55(2): 105834.

Mlynarcik, P., Chudobova, H., Zdarska, V. and Kolar, M. (2021). In silico Analysis of Extended-Spectrum-β-lactamases in bacteria. Antibiotics, 10(7): 812.

Moremi, N., Silago, V., Mselewa, E.G., Chifeaguzi, A.P., et al. (2021). Extended –Spectrum β-lactamase blaCTX-M-1 group in gram-negative bacteria colonizing patients admitted at Mazimbu hospital and Morogoro Regional hospital in Morogoro, Tanzania. BMC Research Notes, 14(1):1-7.

Munoz-price, L.S.; Poirel, L.; Bonomo, R.A.; et al. (2013). Clinical epidemiology of the global expansion of klebsiella pneumoniae carbapenemases. The Lancet infectious diseases, 13(9): 785-796.

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

Nordmann, P.; Cuzon, G. and Naás, T. (2009). The real threat of klebsiella pneumoniae carbapenemase-producing bacteria. The Lancet infectious diseases, 9(4): 228-36.

Papp-Wallace, K.M., Endimiani, A., Taracila, M.A. and Bonomo, R.A. (2011). Carbapenems: past, present, and future. Antimicrobial Agents And Chemotherapy, 55(11): 4943-4960.

Peeters, P., Ryan, K., Karve, S., Potter, D., et al. (2019). The impact of initial antibiotic treatment failure: real- world insights in patients with complicated, health care-associated intra-abdominal infection. Infection and Drug Resistance, 12: 329.

Schroll, C.; Barken, K.B.; Krogfelt, K.A. and Struve, C. (2010). Role of type 1 and type 3 fimbriae in klebsiella pneumoniae biofilm formation. BMC. Microbiol, 10(1):1-10.

Shankar-Sinha, S.; Valencia, G.A.; Janes, B.K.; Rosenberg, J.K.; Whitfield, C.; Bender, R.A.; Standiford, T.J. and Younger, J.G. (2004). The klebsiella pneumoniae O antigen contributes to bacteremia and lethality during marine pneumonia. Infect. Immune, 72(3): 1423-1430.

Subramaniam, G. and Girish, M. (2020). Antibiotic resistance- a cause for reemergence of infections. The Indian Journal of Pediatrics, 87(11): 937-944.

Sukmawinata, E.; Vemura, R.; Sato, W.; Thuhtun, M. and Sueyoshi, M. (2020). Multidrug- resistant ESBL/ Ampc- producing klebsiella pneumoniae isolated from healthy thoroughbred racehorses in Japan. Animals, 10(3), 369.

Sun, M.; Xiao, W. and Xu, Q. (2021). Whole genome analysis of Kpc-producing klebsiella pneumoniae isolates from hospital acquired post- neurosurgical meningitis. Infection control and hospital epidemiology, 31(4): 414- 417.

Taitt, C.R.; Leski, T.A.; Erwin, D.P.; Odundo, E.A.; Kipkemi, N.C.; Ndonye, J.N.;… and Vora, G.J. (2017). Antimicrobial resistance of klebsiella pneumoniae stool isolates circulating in Kenya. Plos one, 12(6), e0178880.

Ticona, J.H.; Zaccone, V.M. and Mcfarlane, I.M. (2021). Community-acquired pneumonia: A focused review. American Journal of medical Case reports, 9(1), 45.

Tsitsopoulos, P.P.; Losifidis, E.; Antachopoulos, C.; Anesties, D.M.; Karantani, E.; Karyoti, A.; Papaevangelow, G; Kyriazidis, E.; Roilides, E. and Tsonidis, C. (2016). Nosocomial bloodstream infections in neurosurgery: a 10-year analysis in a center with high antimicrobial drug-resistance prevalence. Acta neurochirurgica, 158(9) : 1647-1654.

Vishwakarma, A.; Dang, F.; Ferrell, A.; Barton, H.A. and Joy, A. (2021). Peptide mimetic poly urethanes inhibit bacterial biofilm formation and disrupt surface established biofilm. J. Am. Chem. Soc, 143, 9440-9449.

Wroblewska, M.; Struzycka, I. and Mierzwinska-Nastalska, E. (2015). Significance of biofilms in dentistry. Przegl. Epidemiol, 69, 879-883.

Zammit, S.C.; Azzopardi, N. and Sant, J. (2014). Mortality risk score for klebsiella pneumoniae bacteremia. European journal of internal medicine, 25(6), 571-576.

Zurabov, F. and Zhilenkov, E. (2021). Characterization of four virulent klebsiella pneumoniae bacteriophages, and evaluation of their potential use in complex phage preparation. Virol. J., 18(1): 1-20.