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CLASSICAL, ANTIBIOTIC-RESISTANT, EMERGING, AND HYPERVIRULENT STRAINS

Submitted by

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Klebsiellapneumoniae (*K. pneumoniae*) is a Gram negative, facultative anaerobic bacilli that has great potential for significant morbidity and mortality in acute care settings, particularly in immunocompromised patients (1) .

Moreover, *K. pneumoniae* is one of the most common organisms showing multiple antibiotic resistance worldwide (2) .

These bacteria easily acquire and transfer drug resistance genes through plasmids and transposons . Acquisition of these genes leads to production of β-lactamases of which extended spectrum β-lactamases (ESBLs) are the most common (3) .

ESBLs are capable to hydrolyze extended spectrum penicillins, cephalosporins and monobactams, leaving the carbapenem group of β-lactam antibiotics as the only choice for therapy, hence carbapenem antibiotics are used as a last resort to treat infections caused by these multidrug resistant organisms (4) .

However, there has been emergence of carbapenem resistant *Enterobacteriaceae*, most commonly carbapenem resistant *K. pneumoniae* (CRKP), which have a worldwide prevalence (5), due to high antibiotic use, self-medication by patients and lack of implementation of antibiotic policies in hospitals (6).

Mechanisms described for carbapenem resistance include, production of different classes of carbapenemase, hyperproduction of AmpC β-lactamase with an outer membrane porin mutation, and production of ESBL with a porin mutation or drug efflux. Production of carbapenemases is the most commonly reported mechanism of carbapenem resistance in *K. pneumoniae* (7).

Carbapenemases are β-lactamase enzymes that are capable of hydrolyzing all beta-lactam antibiotics, including monobactams, extended spectrum cephalosporins and carbapenem [8].

The most common carbapenemases include Verona integronmetallo-beta-lactamases types (VIM), imipenemase (IMP) types, *Klebsiellapneumoniae* carbapenemase (KPC), oxacillinase-48 (OXA-48), and New Delhi metallo-beta-lactamase-1 (NDM-1), encoded by carbapenem resistance determining genes *bla*VIM, *bla*IMP, *bla*KPC, *blaOXA-48-like*, and *bla*NDM, respectively (9).

Phenotypic assays are used to identify activity of carbapenemase while molecular assays have developed to identify carbapenemase encoding genes (8) .

Analysis of hospital surveillance data by the Center for Disease Control and Prevention (CDC) suggested that 8% of all *Klebsiella* isolates are carbapenem resistant (10).

Other studies showed that it accounted for 5–24% of *Klebsiella* isolates identified in hospitalized patients (11).

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In Egypt, carbapenem resistance is emerging and alarming, one study reported that carbapenem resistance was detected in 44.3% of *K. pneumoniae* isolates in Suez Canal university hospitals (12).

The detection of carbapenem resistance is essential for the proper choice of antibiotic therapy as well as infection control measures to prevent dissemination of resistant strains in hospital settings (13).

Therefore we set out this study to determine the prevalence of carbapenem resistance and carbapenemase encoding genes among clinical *K. pneumoniae* isolates obtained from patients at intensive care units (ICUs) of Minia university hospitals (MUHs), taking in consideration that carbapenems are frequently used as an empiric therapy in ICUs at our institution(14).

Klebsiellapneumoniae has recently gained notoriety as an infectious agent due to a rise in the number of severe infections and the increasing scarcity of effective treatments (15).

These concerning circumstances have arisen due to the emergence of K. pneumoniae strains that have acquired additional genetic traits and become either hypervirulent (HV) or antibiotic resistant. K. pneumoniae was first isolated in the late 19th century and was initially known as Friedlander's bacterium (16).

It is a Gram-negative, encapsulated, nonmotile bacterium that resides in the environment, including in soil and surface waters and on medical devices (17).

studied in depth and are important in one or more types of infections as well as on additional K. pneumoniae virulence factors that have been identified in recent work. To understand the roles of these factors in the context of K. pneumoniae infections, we first review the different types of K. pneumoniae strains that are now causing significant disease, the types of diseases caused by these K. pneumoniae strains, and the host factors that K. pneumoniae encounters when establishing an infection (18).
Over the last few decades, there has been a concerning rise in the acquisition of resistance to a wide range of antibiotics by strains derived from "classical" K. pneumoniae. As a consequence of this antibiotic resistance, simple infections such as urinary tract infections (UTIs) have become resistant to treatment, and more serious infections such as pneumonias and bacteremias have become increasingly life-threatening (19).

Two major types of antibiotic resistance have been commonly observed in K. pneumoniae One mechanism involves the expression of extendedspectrum lactamases (ESBLs), which render bacteria resistant tocephalosporins and monobactams. The other mechanism of resistance, which is even more troubling, is the expression of carbapenemases by K. pneumoniae, which renders bacteria resistant to almost all available lactams, including the carbapenems (20).

The first case of K. pneumoniae expressing a carbapenemasewas identified in North Carolina in 1996, and thus, this type ofcarbapenemase is called KPC (21).

Additional carbapenemases, such as MBL, NDM-1, IMP, and VIM, have since been found in K. pneumoniae strains (22).

Notably, all of these carbapenemases, including KPC, have been found in other bacteria, and collectively, they contribute to the worldwide occurrence of carbapenem- resistant bacteria (23).

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Regardless of the type of carbapenemase that they carry,carbapenem-resistant K. pneumoniae isolates are termed CRE, forcarbapenem-resistantEnterobacteriaceae. Due to a lack of availableeffective treatments, K. pneumoniae infections caused byESBL-producing and carbapenem-resistant bacteria have significantly higher rates of morbidity and mortality than infections withnonresistant bacteria (24).

Work reported by the CDC in 2013 demonstrates the frequency and severity of infections with these strains based on a 2011 survey of 183 hospitals in the United States ESBL-producing strains caused 23% of nosocomial K. pneumoniae infections, equaling 17,000 infections, and resulted in 1,100 deaths (25).

Meanwhile, carbapenem-resistant K. pneumoniae Typically, classical K. pneumoniae strains cause serious infections, such as pneumonia, bacteremia, or meningitis, when infecting immunocompromised individuals, including people sufferingfrom diabetes or malignancies (26).

The carriage and expression of drug resistance do not enhance the virulence of K. pneumoniae strains despite making them more difficult to treat. However, since the 1980s, strains of K. pneumoniae that can cause serious infections in otherwise healthy individuals have alsogained traction in the human population (27).

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These strains are considered HV compared to classical K. pneumoniae strains due to their ability to infect both healthy and immunocompromised populations and because of the increased tendency of these infections to be invasive; i.e., they can establish infection in the liver (30).

This additional virulence correlates with the acquisitionof a 200- to 220-kb plasmid containing genes that enhance capsuleproduction as well as encode siderophores (31).

These and other bacterial factors that contribute to the hypervirulence of these strains are discussed in detail below (32).

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