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Review

Overview of *Klebsiella Pneumoniae* as a Nosocomial Pathogen and ESBL Producing Strains in Iran

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Abstract: *Klebsiella pneumoniae* is one of the most important human bacterial pathogens with an extensive range of community and hospital acquired infections that may lead to morbidity and mortality. Evaluating the prevalence and epidemic sources of infections and the pathogenicity mechanism of bacteria can be investigated by various typing methods. The emergence of multi-drug resistant strains and extended-spectrum ß-lactamase (ESBL) producing isolates has already become a great challenge in nosocomial infection incidence. There are several reports on ESBL isolates of *K. pneumoniae* in Iran. However, our aim is a comprehensive analysis on ESBL isolates *K. pneumoniae* from different parts of Iran which has not yet been performed.

Keywords: *Klebsiella Pneumonia*, Nosocomial, Infection, ESBL

Introduction

Klebsiella pneumoniae is one of the most abundant species of the Klebsiella genus that causes complications such as urinary tract infections, Ventilator-Associated Pneumonia (VAP), sepsis and endophthalmitis in Asia and America. Emergence of multi-drug resistant strains has already become a great challenge in nosocomial infection incidence (Pokra *et al*., 2016; Kashani and Eliott, 2013). In 1883, Friedlander, the German microbiologist and pathologist, isolated the encapsulated bacilli from a patient with pneumonia. The bacterium was initially called Friedlander's bacillus but was renamed Klebsiella due to Edwin Klebs. Currently, the Klebsiella genus is classified among the five predominant common gram negative pathogens that could lead to nosocomial infections (Horan *et al*., 1988). *Klebsiella oxytoca, Klebsiella rhinoscleromatis* and *Klebsiella ozaenae* are the main subspecies of *K. pneumoniae* based on nucleic acid hybridization (Sakazaki *et al*., 1989). In addition, *Klebsiella terrigena*, *Klebsiella ornithinolytica*, *Klebsiella planticola* and *Klebsiella aerogenes* are known other species (Izard *et al*., 1981; Gavini *et al*., 1986; Iyer *et al*., 2017). Nowadays, more than 50% of these strains are isolated from wound, respiratory and urinary tract infections (Podschun and Ullmann, 1994). There are several reports on ESBL isolates of *K. pneumoniae* in Iran. However, a comprehensive analysis of ESBL isolates of *K. pneumoniae* from different parts of Iran has not yet been performed. The searches were done according to several English and Persian databases including PubMed, Scopus, Isi, Iranmedex and SID to identify studies addressing ESBL isolates of *K. pneumoniae* in Iran during the past decade.

Genomic Structure

In Holt and colleagues' study, more than 300 isolates of *Klebsiella pneumoniae* strains were investigated based on whole-genome sequencing method that lead to KpI (*K. pneumoniae*), KpII (*K. quasipneumoniae*) and KpIII (K. variicola) as the three main distinct species, of which *K. pneumoniae* is the most significant one in human infections (Fig. 1). The most important gene clusters are associated with various virulence factors, regulators of mucoid phenotype (*rmpA*, *rmpA*2), siderophore systems, the ferric uptake operon *kfuABC*, the two-component regulator *kvgAS* and an allantoinase gene cluster. The three chromosomal core genes are classified as LEN β-lactamases, SHV and OKP. On the other hand both *FosA* and *oqxAB* that associate in resistance to fosfomycin and quinolones have been transferred horizontally from *Escherichia coli* (Holt *et al*., 2015; Chen *et al*., 2014).

Cell Structure, Metabolism and Natural Habitat

The most vital metabolic pathways of *K. pneumoniae* are recapitulated as glycolysis, tricarboxylic acid, oxidation of fatty acids and creatine phosphate (Dong *et al*., 2012). Moreover *K. pneumoniae* is able to produce 2-butanone from glucose in 2-3 butanediol synthesis process (Chen *et al*., 2015).

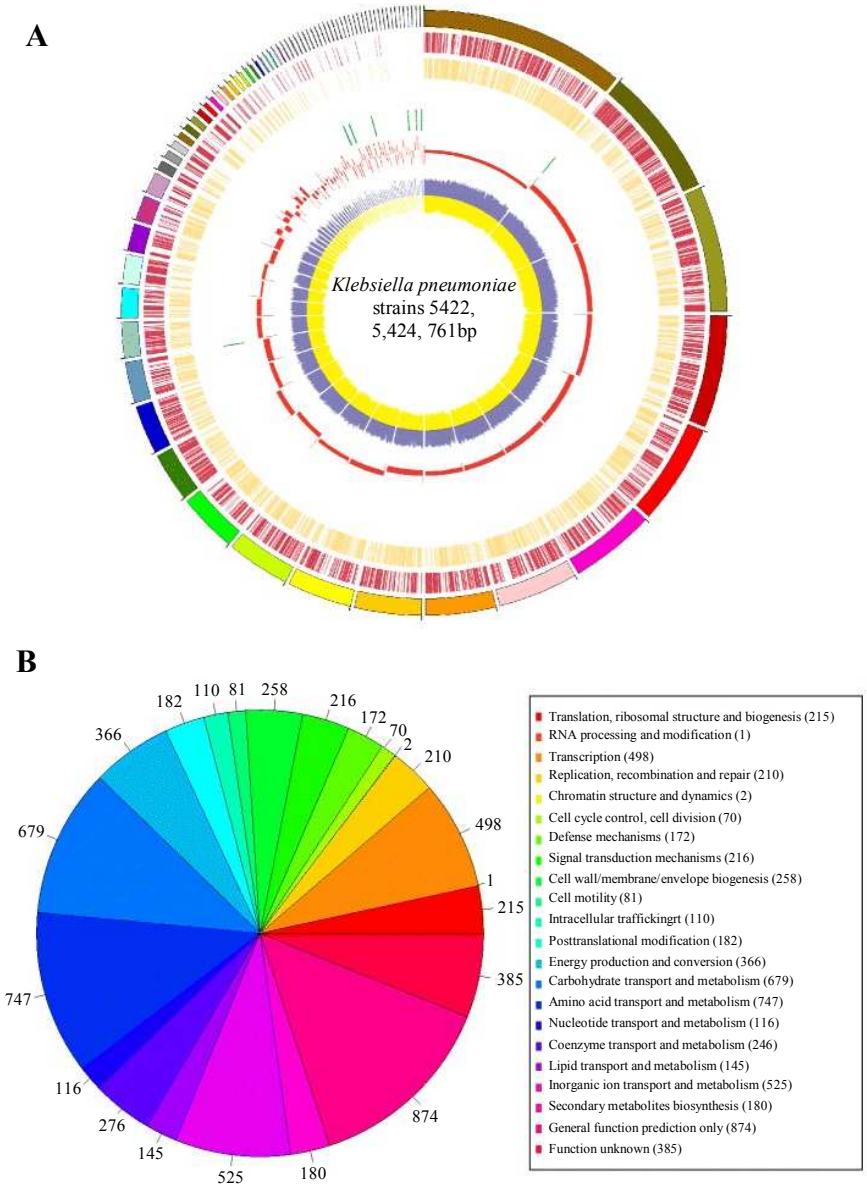

Fig. 1: The examples of *K. pneumoniae* sequencing strains (Zheng *et al*., 2014)

K. pneumoniae isolates from different sources such as environmental specimens, wastewater, soil, plants and mammalian mucosa, can also be found in the intestinal tract, nasopharynx and membrane surfaces as a saprophytic pathogen. It should be noted that indiscriminate antibiotic treatment is leading to the emergence of multidrug resistant strains (Tullus *et al*., 1988).

Microbiology and Epidemiology

K. pneumoniae belonging to the family Enterobacteriaceae is a Gram-negative, non-motile, encapsulated, lactose fermenting, facultative anaerobic, rod-shaped bacterium that can grow in potassium cyanide citrate with no growth at 10°C (Goetz *et al*., 1995). The main source of clinical infections is gastrointestinal tract infection and also hospital staff's hands, though the most outbreaks are found on neonatal wards (Montgomerie, 1979).

Pathogenic Factors

The most important virulence factors are as follows:

- Capsule: *K. pneumoniae* capsule structure which consists of repeating sugar units (4-6) which completely including uronic acid residues. This polysaccharide capsule has ability for attachment and producing biofilm formation, however, has

enough capacity to provide resistance to desiccation, preserves from phagocytosis against polymorphonuclears and granulocytes and also from serum bactericidal effect and activation of the C3b complement (Magill *et al*., 2014; March *et al*., 2013). On the other hand, strains with repetitive sequences of mannose-a-2/3-mannose or l-rhamnose-a-2/3-l-rhamnose have less pathogenicity than others, until now 78 various capsular serotypes were defined (Hsu *et al*., 2013)

- Fimbriae: *K. pneumonia* has type 1 and 3 of pili, in which type 1 pili mediates hemagglutination of guinea pig erythrocytes, has the ability to interact with D-mannose residues of glycoprotein receptors on host cells and salivary and genital membrane surfaces (Gupta *et al*., 2003; Firon *et al*., 1984), whereas type 3 pili has capacity to mannose-resistant agglutination of human erythrocytes which were treated with tannic acid. This type of pilus consists of MrkA (original) and MrkD (adhesion) subunits that depends on mrkABCDF operon and responsible for biofilm formation, binding to tracheal epithelium, renal and lung tissue cells (Babu *et al*., 1986; Ares *et al*., 2017). Ares *et al*. conducted a study that confirms the essential role of H-NS protein in the regulation of type 3 polysaccharide capsule of *K. pneumoniae* (Ares *et al*., 2017)
- Outer Membrane Proteins (OMP): These proteins have a critical function in materials transport and pathogenicity. The role of OmpA as a eukaryotic cell adhesion, serum resistance and protects the bacteria against galectin-3 is noticeable (Ares *et al*., 2016). Moreover, OmpK35 and OmpK36 have been reported as a two main outer membrane porins, which are homologous as OmpF and OmpC. It should be mentioned that both OmpK35 and OmpK36 are related with Extended-spectrum ß-lactamase and associated with carbapenem resistance strains in *K. pneumoniae* respectively (Llobet *et al*., 2009; Tsai *et al*., 2011)
- Phospholipase activity: Lery *et al*. study indicates the role of phospholipase (Dpld1) as a new virulence factor in *K. pneumoniae* (Lery *et al*., 2014)
- Siderophore: these high-affinity iron-chelating compounds which were secreted by many microorganisms are required for bacterial growth, reproduction and spread of infection especially during pneumonia inflammation and bacterial dissemination. This event depends on the activation of the master transcription factor hypoxia inducible factor-1(HIF-1) protein and also inducing cytokine secretion (Holden *et al*., 2016)

Typing Methods

Evaluating the prevalence and epidemic sources of infections and the pathogenicity mechanism of bacteria can be investigated by various typing methods, like PFGE, MLST, RAPD, Rep-PCR and etc:

- Pulsed-field gel electrophoresis (PFGE): is one of the most common techniques for identifying the epidemiological and nosocomial source infections (Holden *et al*., 2016; de Souza Lopes *et al*., 2005)
- Multilocus Sequence Typing (MLST): This molecular technique has designed based on the study of DNA housekeeping genes and their alleles (Cuzon *et al*., 2010)
- RAPD: In this molecular technique the short random sequences of the bacterial genome are amplified by oligonucleotide primers (Holden *et al*., 2016)
- Rep-PCR: In this technique short repetitive sequences of bacteria are analyzed by oligonucleotide primers. This method is based on DNA fingerprinting techniques (Siu *et al*., 2011; Nielsen *et al*., 2011)
- MALDI-TOF Mass Spectrometry: matrix-assisted laser desorption/ionization- time-of-flight mass spectrometer is used for microbial identification, bacterial typing, epidemiological studies and also evaluation of antibiotic resistant strains (Perez *et al*., 2010)
- Conventional methods: serotyping, phage typing and bacteriocin typing are the most common methods and are used as the best typing for this bacteria (Berrazeg *et al*., 2013; Slopek *et al*., 1967; Rennie and Duncan, 1974)

Antibiotic Resistance

K. pneumoniae is naturally resistant against several antibiotic agents such as penicillin, ampicillin, amoxicillin, oxacillin, carbenicillin due to frequency of ß-lactamase genes (Ørskov and Ørskov, 1984; da Silva *et al*., 2012; Chambers, 2000). Resistance to ß-lactamase and carbapenem antibiotics is associated through a range of ß-lactamase, such as strains SHV, TEM, CTX-M and carbapenemase respectively (Chaves *et al*., 2001). Strains which are harboring SHV-1 and TEM-1 may be resistant to piperacillin or first-generation cephalosporin (Grundmann *et al*., 2010; Girlich *et al*., 2000; Lemozy *et al*., 1995). Moreover, ESBL producing strains were reported for the first time in Germany that are responsible for resistance to cephalosporins such as cefotaxime, ceftriaxone and ceftazidime and monobactams (aztreonam) (Nicolas-Chanoine, 1997; Knothe *et al*., 1983). Due to this issue the prevalence of antibiotic-resistant A. baumannii strains have increased in Iran and this may cause significant clinical problems. In addition, the AmpC gene was also identified in *K. pneumoniae* strains, albeit in another form called MIR-1, which is 90% similar to Enterobacter cloacae. This gene contains FOX-1, FOX-2, FOX-3, CMY-2, CMY-4, CMY-8, MOX-1, MOX-2, DHA-1, DHA-2, LAT-1, LAT-2 and

ACC-1 (Jacoby and Sutton, 1991; Philippon *et al*., 2002). These strains are resistant to aminopenicillins, carboxypenicillins and ureidopenicillins, while these classes of genes are not well able to hydrolysis with cefepime or a carbapenem. Relevant studies that were performed in different region of Iran are described in Table 1.

Treatment

As shown in Table 1, reported Klebsiella resistance rates in Iran ranged as high as 96%. and as seen in Fig. 2, mean multidrug resistance rates generally increased over time and the last set of isolates collected in Iran were more resistant to all antibiotics (30%). The highest rates of resistance were observed towards β-lactam antibiotics (ceftriaxone, cefotaxime, piperacillin, ceftazidime, cefepime, aztreonam and ampicillin). Also, most of the isolates from all over the country were still sensitive to imipenem, meropenem, tazocin, piperacillin-tazobactam and amikacin and the imipenem is still a effective drug in Iran.

Prevention and Control

According to conducted studies, identifying the risk factors and mechanisms of drug resistance is related to various enzymes that are produced, including ESBLs, MBLs, KPC and Amp-C belonging to Ambler A, B and C groups. Identification of these resistance factors will lead to the pivotal proper treatment. Direct contact limitation between patients and healthy people, following patients under treatment and compliance with individual health are the critical strategies for controlling the outbreak infections.

Table 1: The prevalence of antibiotic-resistant ESBL producing strains in the different regions of Iran

Authors	The percentage of ESBL producing strains	Genes	The Highest rate of antibiotic resistance	enrollment time	Type of sample	Province	References
Shahcheraghi *et al*. (2007)	33%	-	Carbenicillin, Piperacilin, Cefotaxime and Ceftriaxone	2006	urine, blood, wounds, sputum, CSF, central venous line and intra-abdominal abscess	Tehran	(Shahcheraghi *et al* 2007)
Aminzadeh *et al*. (2008)	52.5%	-	Ampicillin, Cephalothin, and Ceftazidime	2007	urine	Tehran	(Aminzadeh *et al*., 2008)
Behrooozi *et al*. (2010)	12%	-	Cefazolin, Cephalothin, Ceftazidime, Ampicillin, Carbenicillin and Ceftizoxime	2009	urine	Tehran	(Behrooozi *et al*., 2010)
Nasehi *et al*. (2010)	96%	*blaSHV* (26%), *blaTEM* (18%), blaPER (7.5%)	Ceftazidime, Cefotaxime, and Piperacilin	2006-2007	urine, blood, wound, sputum, CSF, central venous line, intra abdominal abscess, throat, sperm, stool, vaginal swab, trachea, dialysate solution	from different three general and two private hospitals in Iran	(Nasehi *et al*., 2010)
Mansouri *et al*. (2012)	41.3%	*blaCTX-M* (20%), blaCMY (2.6%)	Amoxicillin, Cephalexin, Ceftazidime and Gentamicin	2007-2008	urine, blood and other body	kerman	(Mansouri *et al*., 2012)
Eftekhar *et al*. (2012)	27.45%	*blaSHV* (43.14%), *blaCTX-M* (13.37%), *blaTEM* (35.29%)	Amoxicillin, Nitrofurantoin and Ciprofloxacin	2008	Urine	Tehran	(Eftekhar *et al*., 2012)
Riyahi Zaniani *et al*. (2012)	20%	*blaTEM* (8.77%), *blaSHV* (10.52%)	-	2009-2010	out-patients and hospitalized patients from urine, blood, wound and abscess aspirates, peritonitis and pulmonary secretions	Mashhad	(Riyahi Zaniani *et al*., 2012)
Khosravi *et al*. (2013)	47.27%	*BlaSHV*-1(46.15%) *blaTEM-1*(43.165%), *blaCTX-M*-1(26.92%)	Amoxicillin/clavulanic Acid, Amoxicillin, Ampicillin, and Cefoxitin	2012	-	Ahvaz	(Khosravi *et al*., 2013)
Azimi *et al*. (2014)	-	*BlaOXA*-48(96.47%), blaVIM-4 (3.57%)	Cephalosporins, Carbapenems (imipenem, Ertapenem, meropenem), Trimethoprim-sulfamethoxazole and Quinolones	2011	from patients a burn unit	Teheran	(Azimi *et al*., 2014)
Derakhshan *et al*. (2014)	54.9%	*blaCTX-M* (54.9%)	Cefotaxime	2011	urine, wound, tracheal secretions and other samples (including catheter, eye and etc.).	Teheran	(Derakhshan *et al*., 2014)
Hashemi *et al*. (2014)	57.5%	blaKPC (6%), *blaCTX-M*-15 (62.5%) *blaOXA*-48 (4.1%)	Ampicillin, Cefpodoxime, Cefotaxime and Piperacillin	2012	urine, blood culture, wound, sputum, intra-abdominal, cerebrospinal fluid, and other samples	Tehran	(Hashemi *et al*.. 2014)
Gholipour *et al*. (2014)	38.18%	*blaSHV* (14.28)	Cefotaxime, Ampicillin, Ceftazidime and Ciprofloxacin	2012	urinary tract infections	Isfahan	(Gholipour *et al*., 2014)
Raei *et al*. (2014)	46.9%		Ceftriaxone, Cefotaxime, Piperacillin and Aztreonam	2008-2012	-	Tehran	(Raei *et al*., 2014)
Mansouri *et al*. (2014)	28%	-	Amoxicillin, Cephalexin, Ceftazidime and Gentamicin	2007-2008	blood, urine and body fluids	Kerman	(Mansouri *et al*., 2014)
Izadi *et al*. (2014)	43%	*blaTEM* (87.54%) *blaSHV* (69.64%)	Gentamicin, Trimethoprim-sulfamethoxazol and Meropenem	2011-2012	urine, wound, blood	Mashhad	(Izadi *et al*., 2014)
Saeidi *et al*. (2014)	66.6%	*blaCTX-M* (65%), *blaTEM* (65%)	Ceftazidime, Ampicillin, Gentamicin and	2010- 2011	urine culture	Zabol	(Saeidi *et al*., 2014)
Fazeli *et al*. (2015)	-	*blaNDM-1* (12.2%)	Piperacillin, aztreonam, and ceftazidime	2012- 2013	urine, tracheal aspirate, bronchoalveolar-lavage (BAL) fluid, wound, abscess, cerebrospinal fluid, sputum, catheter and eye	Isfahan	(Fazeli *et al,* 2015)
Rajabnia *et al*. (2015)	30%	*blaVIM-1* (30%)	Imipenem	2015	patients at ICU	Babol	(Rajabnia *et al*., 2015)
Mansury *et al*. (2016)	26.3%	*blaSHV* (22.2%), *blaCTX-M* (19%), *blaTEM* (16%)	Amoxicillin, Trimethoprim-sulfamethoxazol, and Cefpodoxime	2012-2013	from urine, sputum, wound, body fluids, blood, throat and other samples	Shiraz	(Mansury *et al*., 2016)
Maleki *et al*. (2018)	25.5%	*blaCTX-M* (92%) and *blaTEM* (76%)	Cefotaxime and Ceftazidime	2013	urine	Isfahan	(Maleki *et al*., 2018)

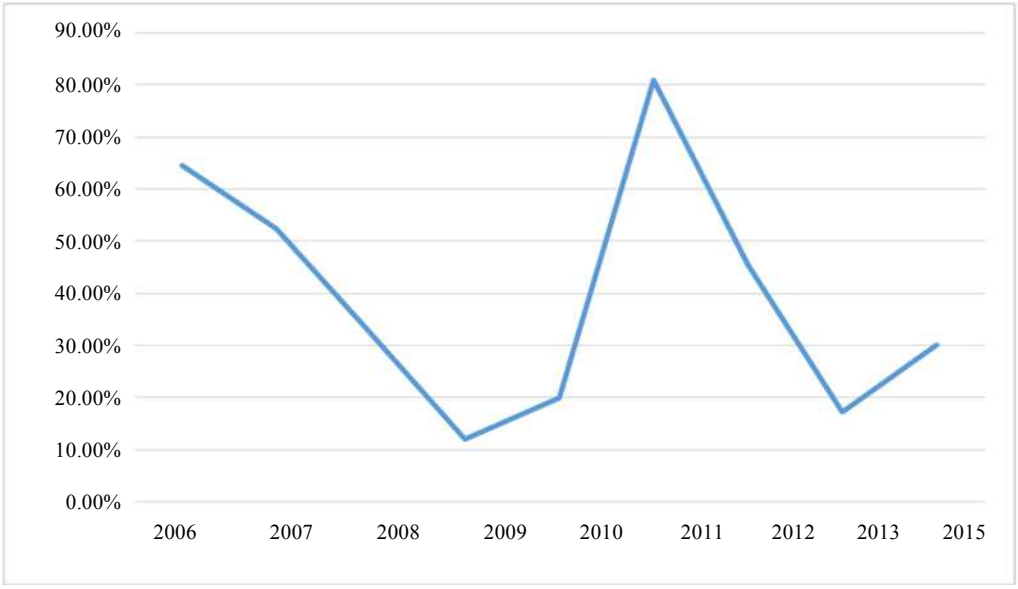

Fig. 2: Percentage of ESBL strains over time in Iran

Loss of this porin may be one of the factors contributing to antimicrobial resistance among ESBL-producing *K. pneumoniae* and may favor the selection of additional mechanisms of resistance. Microbiology laboratories must be able to identify resistant bacteria in a timely suitable manner, especially those that are falsely susceptible in vitro to antibiotics. Bacteriological excellence is needed more than ever (57).

Conclusion

There is a relatively high prevalence of drug resistant *K. pneumoniae* isolates in Iran. This review showed that the prevalence of ESBL-producing *K. pneumoniae* varies in different regions of Iran and the capital city of Iran (Tehran,) has a higher incidence of ESBL compared to northern regions and the western cities. Thus, a high degree of awareness among physicians and microbiologists, active infection control committees, appropriate antimicrobial therapy, improvement of hygiene conditions and monitoring of drug resistant isolates are urgently needed in order to better control the emergence and spread of ESBL *K. pneumonia* isolates in hospital settings.

Ethical Consideration

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely addressed by the authors.

Conflict of Interests

The authors declare that there is no conflict of interests.

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