Virulence factors and drug resistance in *Klebsiella pneumoniae*; an emerging superbug

Faiza Liaqat¹, Wajeeha Naeem¹, Muhammad Shafee², Muhammad Anwar³, Haleema Sadia⁴, Daud Ghilzai⁵ and Ali Akbar¹*

1. Department of Microbiology, University of Balochistan Quetta 87300, Balochistan-Pakistan
2. Center of Advance Studies in Vaccinology and Biotechnology (CASFAB) University of Balochistan Quetta 87300, Balochistan-Pakistan
3. Institute of Biochemistry, University of Balochistan Quetta 87300, Balochistan-Pakistan
4. Department of Biotechnology Balochistan University of Information Technology, Engineering and Management Sciences, Quetta Balochistan-Pakistan
5. Department of Gastroenterology Bolan Medical College Hospital Quetta Balochistan-Pakistan

*Corresponding author’s email: aliakbar_uob@gmail.com

Citation

Received: 01/01/2019 Revised: 29/03/2019 Accepted: 10/04/2019 Online First: 19/04/2019

Abstract
*Klebsiella pneumoniae* is a nosocomial pathogen usually concerned in hospital out-breaks with a propensity for antibiotic resistance (ABR) to support β-lactam antibiotics and several other antimicrobial classes. The effective feast, spread and infection of the Gram-negative bacterium can be credited to an innumerable of influences comprising host, environmental, virulence factors and a vast diversity of ABR mechanisms. The poor handling consequences and insufficient treatment options are significances of the effective pathogenesis and spread of ABR in the increasingly common in *Klebsiella pneumoniae* bacterium which producing β-lactamase. This is a comprehensive literature review on Klebsiella exploring all the drug resistance and pathogenicity related issues associated with this bug, it will provide a roadmap to the researcher for further research extension in this field.

Keywords: Antibiotics; Public health; Pathogenicity; Superbugs; Virulence factor

Introduction
*Klebsiella* genus belongs to Enterobacteriaceae family, frequently rod in shape, grams negative, expanded, lysine decarboxylase but not ornithine decarboxylase producers, and commonly positive in the Voges-Proskauer test [1]. These bacteria are permeating in the environment, and is commonly perceived a diversity of ecological sorts including soil, aquatic, vegetation and sewage due to colonization in nasopharynx and gastrointestinal tract it can act as an opportunistic pathogen in human [2]. It has also been seeming in insects [3] and various mammals.

Clinical importance spp. of Klebsiella is *Klebsiella pneumoniae* which is the maximum significant pathogen in Klebsiella genus, existence responsible for 86% of
infections. Moreover, *Klebsiella oxytoca* is the second most prevalent *Klebsiella* spp. and it’s responsible for 26% of infections [4]. Klebsiella are known as important pathogenic agents in nosocomial infections, which causes several infections in urinary tract and affect the wound, soft tissues and causes septicemia [1].

*Klebsiella* spp. infections may predispose to several host characteristics such as, cardiac diabetes, or pulmonary chronic diseases, extremes of age, renal, as well as oncologic problems [5, 6]. Colonization rates of *Klebsiella* spp. in the hospital environment rise and related to antibiotic therapy. The nature and numeral of virulence factors causing the alterations in medical feature of infections. It has the possibility to causing many infection in urinary, blood, respiratory and wound and liver abscess syndrome reported recently in Asian countries [7]. A plasmid- borne gene (rmpA) and K1-specific gene (magA) are subsequent high virulence strains that is related with hypermucoviscosity (HMV) phenotype [8]. The infection of *Klebsiella pneumoniae* is impaired by its high probable of dispersal in the care units and it can acquire multidrug resistance (MDR). The initiation of *Klebsiella pneumoniae* with plasmid-encoded extended spectrum of beta lactamase (ESBL) action is subsequent in significant illness and death, due to handling failure and consequent septicemia [9].

1. Virulence factors and gene

There are several virulence factors that have been related to the pathogenesis of *Klebsiella* spp. has the capability to use allantoin as a font of N2 [13]. All S gene that is present at the 22 kb region of *Klebsiella pneumoniae* has been linked to liver infection. Additionally, intra gastric infection in the strain of wild type show a virulence as linked to mutant. Another recognized factor is urease which is responsible for pathogens; it causes an extensive sort of pathologies including peptic ulcers, pyelonephritis and urolithiasis [14], ureA mutant in *Klebsiella pneumoniae* have a weekend ability to colonize [15]. ureA mutants in *Klebsiella pneumoniae* have an attenuated the mouse intestine. The nosocomial infection that is produced by *Klebsiella pneumonia*, are usually led by gastrointestinal colonization although of the infection localization, so this
ability to increasing colonization in that tract make a urease as a factor for virulence [15]. Siderophore are highly affinity extra cellular ferric cheletor which are secreted by bacterial cells they have a serious role in microbial virulence. Klebsiella ferric iron uptake (kfu) is a virulence factor responsible for iron uptake this factor allows Klebsiella to get iron if there is limited iron condition is availe through the human host [16]. Virulence gene encoded siderophores are (entB, iutA, irp-1, irp-2, ybtS, and fyuA) [1].

2. Antibiotic-resistance mechanisms in Klebsiella pneumoniae

Inborn antimicrobials predisposition could be impacted by adaptive responses, causing variations in gene expression and functioning of cell, which remain influenced in reaction to the pathogen’s natural ecological pressures on host [17, 18, 19]. The ABR mechanisms which are existing in Klebsiella pneumonia, include (1) modification of drug or enzymatic inactivation (2) Antibiotics (AB) mark modification or reduced amount of AB inside cells and (3) greater activity of efflux [20, 21]. These are determined either inherently or learned over mutation and resistance gene attainment [17, 21].

Antimicrobials not only responsible for adaptive responses but it’s also due to environmental pressure that contain: (i) end of growth, (ii) resistance determinants attainment which produce stress, (iii) Altered target sites (iv) Change the roles of membrane barrier, (v) stimulation of resistance-conferring mutations [17, 20]. Atypically, some defensive reactions triggered an importance to begin stress by AB can cause resistance to a very similar antimicrobial drug [18, 19]. Modifications in membrane absorptivity and flux of AB can be predisposed by inconstant appearance and regulation of the efflux pump [20]. An important bacterial efflux pump family is the resistance nodulation division (RND) [22, 21, 23]. The active appearance of the chromosomal native AcrAB-TolC efflux pump of the RND family gives to fluoroquinolones resistance in Klebsiella spp, E. coli and Enterobacter spp. [22, 23, 24]. Alternately, the change in protein of outer membrane of both Klebsiella pneumoniae and E. coli, owed to mutations or porins deletion, may bound influx of AB agents or consecutively rise efflux [21]. Moreover, the main OmpK 35 and 36 porins, the other OmpK 37 porins can be uttered by Klebsiella pneumonia.

The role of these porins in ABR not studied carefully then is assumed to be significant in the absence of OmpK 35 and 36 [25]. Modification or destruction of the OmpK 35 to 36 porin proteins can distress resistance in numerous conducts also important to raised (MICs) or resistance to carbapenem and extended spectrum cephalosporins, reduced fluoroquinolones exposure, or it might infrequently consult extra cross-resistance to quinolone, aminoglycosides and cotrimoxazole within broad-spectrum beta lactamase or ESBL-producers [26, 27, 18, 19].

A further alteration to the outer membrane assisting in resistance, other than porin loss, is the up ruling of capsule polysaccharide production in Klebsiella pneumoniae [22, 28]. Bacteriological cells can occur as particular cells, the planktonic form, or in societies worn together by an own made bio polymer medium and devoted to an external [29, 19, 30, 31]. Genetic elements consulting latent resistance genes are simply conveyed parallel both inter and intra classes owed to the near genetic similarity among bacteria of the Enterobacteriaceae family [17, 20].

The reduced AB drug effect in contrast to bacterial residents in a biofilm is mostly indistinct but might be as a consequence of numerous mechanisms acting in conjunction, such as: (i) poor compound diffusion, (ii) the gentler development and uptake of AB by the bacteria in settled biofilm (>24 hours old),
(iii) the making of AB disabling enzymes, (iv) broad strain reactions, (v) appearance of efflux pump (vi) existence of persisted cells [17, 29, 19, 30, 31, 32]. Formation of biofilm in *Klebsiella pneumoniae* is inclined by cell concentration reliant on minimum recognizing gesturing by the non-specific bacterial type-2 QS controlling molecules, AI-2 auto inducers [33]. Mannose-resistant *Klebsiella*-like (MR/K) haemagglutinin are determined in mrk gene ABCDF in an operon and procedure extent fimbriae 3 type that is significant to arbitrating biofilm formation in *Klebsiella pneumoniae* [34]. ABR can rise to 1000-fold for bacterial cells present in the biofilm [30, 35].

Further reasons on show too ESBL making comprise hyper production of cases of ESBL cases owed to organizer active regulation subsequently through mutation, implanted transposable components in nearby nearness toward the organizer and the capacity to this coproduce additional than one ESBL [27] (Figure 1 & Table 1).

**Figure 1. Common mechanism of drug resistance in *Klebsiella* spp.**

Enzyme mediated resistance to β-lactam AB was revealed firstly in *E. coli* then has later feast to a huge numeral species of bacteria in the form of concluded 890 inimitable β-lactam [36]. Moreover Bush-Jacoby-Medeiros efficient groups established on hydrolysis and reserve appearances or protein constructed 4 classes of Ambler molecular, bush-jacoby-medeiros categorized the β-lactam into 3 groups and sixteen subclasses [22, 36-38]. Few of these gene which have resistance, achieved over many genetic but portable components, which include transposons, insertion sequence elements and plasmids [39, 40].

**2.1 β-lactam resistance genes**

Since the 1940s β-lactam antibiotics, was used clinically which are a main
antimicrobial agent class suggested in humanoid treatment. According to Bush and Jacoby [41]. There are dissimilar β-lactam which have developed between enteric pathogens containing Klebsiella pneumoniae, attainment a surprising amount at about (>2000) and diversity [42]. According to Sirot et al., the initial ESBL gene was describe are those gene which show an extended spectrum action against β-lactam (third-generation cephalosporins and monobactams) in France the modified gene blaTEM-3 plasmid-mediated ESBL was reported. During the 1990–2000s, Klebsiella pneumoniae has come to be the most important ESBL-carrying pathogen related in nosocomial outbreaks. During the 1990–2000s, Klebsiella pneumoniae has come to know the major nosocomial outbreak that have ESBL-carrying pathogen. 40% ESBL production were found in hospital isolate [43, 44]. Klebsiella pneumoniae strains frequently TEM and SHV β-lactamases were hid in that period [45]. Resistance to beta-lactam antibiotics is acquired due to the presence of beta-lactamase gene [162]. Hospital outbreaks producing Klebsiella pneumoniae that have an alteration in ESBLs present in them it was due to attainment of plasmids and transposons encoding that causes dominance in strain that producing CTX-M [46]. blaOXA gene a-type of ESBLs were shifted to Klebsiella pneumoniae by horizontal gene transfer [47], and other blaGES in addition blaSFO [48] or blaPER, blaTLA and blaVEB [49]. Furthermore, some gene producing enzymes that subdued by acid tazobactam and clavulanic that gene are inhibitor-resistant β-lactamase [36] WHO [50] reported in different geographical regions the ESBL gene content and prevalence varies and in different part of world the endemic rates of the incidence of Klebsiella pneumoniae that producing ESBL- has got resistance up to 49% and 30% rates of the widespread nature in the public representative.

2.2 Plasmid-mediated AmpC genes
The notable adaptability of Klebsiella pneumoniae to include β-lactam genes onto movable plasmids that permit their feast, provided rise to the appearance and spread of plasmid mediated AmpC-like cephalosporins in this classes [51, 36]. These genes arisen in the 1990s, in equivalent with the explosion of ESBL genes, and they are entirely plasmid-borne in Klebsiella pneumonia. The furthermore abundant blaAmpC gene families in this classes belong to the CMY, DHA, FOX and MOX types, and their Klebsiella pneumoniae strains presentation developed resistance to β-lactam owing to the existence of blaAmpC shared over porin harm, or more efflux, were too described as through the case of blaACT-1. Due to several copies these all genes can expressed on plasmids, or enlarged administrative quality of plasmid genes, and uniform lead to carbapenem resistance [51].

2.3 Carbapenem resistome
The widespread incidence of ESBL-producing Klebsiella pneumoniae in diverse portions of the world was exposed that novel type of ESBL and alleles confined via this species, and in other Enterobacteriaceae, assimilated by transfer of plasmids and transposons that encoding ESBL-horizontally. The Klebsiella pneumoniae strains that producing ESBL have phenotypic characteristics of MDR run to a main rise in carbapenem use, which became the latter alternative AB to treat Klebsiella pneumonia that producing ESBL [52]. The wide practice of carbapenem has caused in the development of plasmid-mediated carbapenemases, all beta lactamase comprising the last-line carbapenem had hydrolyzed by these enzymes [53]. Their presence in enterobacteriaceae run to carbapenem-resistant enterobacteriaceae. In all probability Owed to their sickbay
association of *Klebsiella* spp. Its consider to be major enterobacteriaceae that have to extent global, causing a major community healthiness risk [54], back in 1983 the initial carbapenem AB imipenem was the used to treat infections that cause by *Klebsiella pneumoniae*, and after 2 years the strain that resistant to imipenem were identified. In 1991 in japan the earliest detected carbapenem was imipenem-1 metalloenzyme [55], in 1996, another carbapenem in *Klebsiella pneumoniae*, was arisen in the United States informed which called KPC [56]. While other carbapenem genes blaOXA-48 arisen in *Klebsiella pneumoniae* and were even reported [57], and blaNDM-1 [58], blaKPC gene in carbapenem *Klebsiella pneumoniae* developed the most extensive and vastly impacting. In many countries, the hospital outbreak was mostly prevalent in those strains that exist with these two gene blaKPC-2 and blaKPC-3 [59]. Since it was initially reported in us that the chief powerful force for range of these was and is immobile clonal extension of *Klebsiella pneumoniae* ST258 [60].

Has develop widespread in worldwide [61]. blaKPC genes exist in an exclusive Tn4401 transposon T alternatives among by clonal spreading [62] and are implanted into plasmids of several sorts of replicon, which helps the spreading of the gene to another species of bacterial [63]. In US, it was reported that an exciting instance of interspecies transfer blaKPC-3 gene of transposons-encoded from *Klebsiella pneumoniae* to E. coli was. *E. coli* plasmid hiding in isolate of serrata marcescens and this transposon was successively improved from the patients, representative *Klebsiella pneumoniae* as an origin for KPC genes in numerous pathogens [64]. Along by their action in contradiction of all β-lactam AB and high transmission capacity, KPCs frequently keep resistance to communal β-lactamase inhibitors, posturing a medical contest [65]. Raised death was revealed for infections that is formed by *Klebsiella pneumoniae* that is producing KPC [61]. Through the rising repetition of carbapenem to treat *Klebsiella pneumoniae* that making ESBL and origins infections, frequent developments arisen: (i) carbapenem resistance appeared lacking the real bearing of a carbapenem gene as a significance of penetrability variations owed to loss of porin and over appearance of efflux pump. The initial report of this phenomenon was in 1988 [66], and was more established by a mixture of high-level plasmid mediated AmpC blaACT-1 organized through loss of porin; reduced vulnerability to ertapenem by a combination of ESBL and harm of OmpK36 [67], and the influence of AcrAB efflux pump [68]. (ii) The appearance of single ESBL genes by broader range of activity, such as blaGES [53]. The blaGES-4 in *Klebsiella pneumoniae* was recognized in 2002 which was initial GES-type [69].

### 2.4 Multiple β-lactamase-encoding *Klebsiella pneumoniae*

In the identical strain the carriage of multiple β-lactamase genes is a recognized capability of *Klebsiella pneumoniae* and it may give rise of this pathogen. All classes of bla genes were stated in this species [70]. It’s might possibly be to at all (i) carriage of an ABR plasmid encoding an range of antibiotic resistance genes owed to acquisition of transposons comprising diverse bla genes which is present on the same plasmid or (ii) co-carriage of more than one antibiotic resistance plasmid. Distinct strains might transmit many genes of bla similar the report of a strain in NY City which were secluded from a mucus of a hospitalized persistent, carrying at nearly 10 different genes of bla with a FOX-like plasmid mediated, AmpC, blaKPC, blaSHV and inhibitor resistant β-lactamase [71], according to Doi *et al.* [72] another strain containing blaNDM-1 and OXA-232 having 2 variant plasmid on it. The
evolutionary benefit for *Klebsiella pneumoniae* to haven multiple β-lactamase through an overlying catalytic activity is an understudied range. Around are signals that variety of β-lactam might be involved in additional consistent resistance. For example, imipenem, carbapenemase are susceptible first to aztreonam between β-lactam AB, but they frequently hide that slit through the occurrence of ESBL or AmpC β-lactamase [73]. Additional duplicates of genes were too associated to develop resistance level, microbial response to enlarged AB amount [74].

### 2.5 Aminoglycoside resistance genes

Aminoglycosides were vigorously used since mid-1940s to 1980s until they were exchanged with 3rd-generation, cephalosporins, fluoroquinolone and carbapenem [75]. In this era of practice, they get increase level of resistance mechanisms contrary to this drug, due to occurrence of drug alteration in enzymes taking diverse actions. Less usage of aminoglycosides usage reduced the evolution of novel phenomena of resistance active to the finding of 16S rRNA methylase, which relating to the family of armA gene it contains an enzyme which avoid aminoglycosides to joining with their 16S rRNA target [76]. In *Klebsiella pneumoniae* the plasmid is encoded by these genes [77], and although drug altering enzymes have a fine range of action, 16S rRNA methylase consult resistance to almost wholly aminoglycosides, with plazomicin, the furthermore current aminoglycosides composite established [78].

In *Klebsiella pneumoniae* armA gene location on Chromosomal was defined single after [79]. Further recognized plasmid mediated 16S rRNA mt with Rmt family and NpmA were too initiate in *Klebsiella pneumoniae* [75], through no signal of chromosomal position. Resistance phenomena of Chromosomal in contrast to aminoglycosides in *Klebsiella pneumoniae* contain alterations in cell penetrability owed to changes in AcrAB-TolC and KpnEF efflux pump systems, and due to damage of assumed porin, KpnO. Troubles in AcrAB-TolC improved vulnerability to tobramycin and gentamicin [68], while kpnEF mutant displayed strong alteration in resistance to tobramycin and spectinomycin, then pretentious only somewhat resistances to gentamicin and streptomycin. This might recommend changed considerations of the penetrability apparatus to changed aminoglycosides. Through contribution in aminoglycosides resistance was defined in vitro for KpnO porin, which upon harm produced resistances to tobramycin, streptomycin and spectinomycin. Alterations which converse resistance through mark change, like rrs or rpsL which has not present in medical strains of *Klebsiella pneumoniae*. It is probable that rpsL alterations are associated through high capability rate and compact virulence, thus they are fewer choice. Several duplicates of rrs in chromosome of *Klebsiella pneumoniae* might too confound the resistance to be rise owed to transformations in this gene [81, 82].

### 2.6 Quinolone resistance genes

Quinolone target bacterial topoisomerases obstructive bacterial DNA repetition. It’s used in therapeutic field subsequently the 1960s, then their usage improved widely after the overview of the chief fluoroquinolones in the 1980s, which has directed to progress of bacterial quinolone resistance phenomena [83]. *Klebsiella pneumoniae* resistome associations wholly the resistance mechanisms recognized for resistance of quinolone in gram negative bacteria [84], with mark location gene mutations, rise manufacture of MDR efflux pump, altering enzymes or mark defense proteins. Cases of *Klebsiella* treated with nalidixic acid, the initial clinically accepted quinolone [85], and
first fluoroquinolones used by *Klebsiella pneumoniae* was norfloxacin, the [86].

### 2.7 Tigecycline resistance genes

Tigecycline is the initial glycylcycline flung, and this drug has been practicing contrary to *Klebsiella pneumoniae* infections till 2005, afterward it was revealed to escape after the chief resistance mechanisms recognized against tigecycline [87]. It was a probable drug that show an activity of broad-spectrum against those isolate which producing ESBL [88]. Presently when its use primary, an MDR *Klebsiella pneumonia* strain owning reduced tigecycline vulnerability (MIC 4 μg/mL) was secluded at a hospice [89]. Conferring to the presently suggested tigecycline divides, this strain was intermediately resistant to tigecycline [90] though it was report, that in *Klebsiella pneumoniae* isolates tigecycline resistance has been increased.

### 2.8 Tetracycline resistance genes

Tetracycline (TET) has been commonly used for the management of infections, but inappropriately frequent use of this drug has caused in the progress of resistant in most strains. TET resistance in bacteria is arbitrated through 4 mechanisms: enzymatic inactivation, efflux, ribosomal protection, and target modification [91]. It was reported that about genes encoding for efflux pump were 23, not containing the newly defined mosaic TET resistance genes reported [92]. In preceding surveys of clinical, tetB gene was recognized as the greatest widespread TET resistance cause with an extensive host sort since it exists in on extremely transportable hereditary components that freely allocation among unlike genera of bacterial. The gene tetA is found on conjugative plasmids of altered unsuitability groups [93].

### Table 1. Drug resistance genes and mechanisms for selected antibiotics

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Genes conferring resistance</th>
<th>Mechanism of resistance</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>acrB, kpnEF, rpsi, armA, KpnO</td>
<td>Efflux pump, Modification of drug, Porin loss</td>
<td>[80]</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>tetA, tetB</td>
<td>Modification of drug</td>
<td>[93]</td>
</tr>
</tbody>
</table>

### 2.9 Extensively drug-resistant XDR resistome

The rise of several resistances to changed AB groups is commonly originate in hospital-adapted *Klebsiella pneumoniae* isolates owed to the growth of ranges of antibiotic resistance genes that determined on numerous plasmids establishing a ‘super resistome’. A great resistome might include groupings of ESBLs and/or carbapenem
genes with AmG altering enzymes, or suggestion of CTX-Ms or NDM carbapenem with 16S rRNA M as defined in an existing investigation [75]. IncA/C plasmids, for instance, encode carbapenem composed through rmt M, quinolone resistance gene qnrA and AmpC-β-L blaCMY [94]. Additional exciting case of a Klebsiella pneumoniae strain owning a super resistome was exposed carrying 4 changed β-lactam (blaNDM-1, blaCMY-16, qnrA and armA on one plasmid and blaOXA-48 and 15, individually on distinct plasmids), organized by porin absence, additional antibiotic resistance genes and chromosomal mutations in quinolone resistance [95].

3. Klebsiella pneumoniae-resistance to third-generation cephalosporin and to carbapenem

A comprehensive date from published literature has been presented in (Table 2 & 3) regarding the resistance in Klebsiella pneumoniae to cephalosporin (CSN), which have been the typical intravenous management for uncomplicated infection of Klebsiella in hospitals, and to carbapenem, which are the last choice for handling of plain infections when CSN are no prolonged dependable due to a great volume of ESBL-mediated resistance. Data shows that resistance proportions to 3rd generation of CSN were frequently developed in Klebsiella pneumoniae. The high extents of CSN resistance revenue that handling for complete or assumed severe Klebsiella pneumoniae infections in various conditions must rest on carbapenem, uncertainty obtainable. This generally includes developed charges and a hazard of more development of carbapenem-resistant strains. Of level, larger concern is that infections with carbapenem-resistant strains essential to be treated through the last-resort drugs tigecycline or colistin, which are not only a reduced amount of effective then too not widely existing. Thirty studies were involved for 3rd generation CSN-resistant Klebsiella pneumoniae, and 13 for carbapenem resistant Klebsiella pneumoniae.

Table 2. Klebsiella pneumoniae: Sleeted literature on resistance to 3rd generation Cephalosporin

<table>
<thead>
<tr>
<th>Countries</th>
<th>Resistance %</th>
<th>Isolates</th>
<th>Samples type</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosnia and Herzegovina</td>
<td>50 (CTX); 60 (CRO); 61.5 (CAZ)</td>
<td></td>
<td>Gynecology</td>
<td>[126]</td>
</tr>
<tr>
<td>Trinidad and Tobago</td>
<td>15,2</td>
<td>403</td>
<td>Clinical isolates</td>
<td>[127]</td>
</tr>
<tr>
<td>Brazil</td>
<td>55.6</td>
<td>81</td>
<td>Blood stool</td>
<td>[128]</td>
</tr>
<tr>
<td>Mexico</td>
<td>37 (CRO); 38 (CAZ)</td>
<td>150</td>
<td>Clinical isolates</td>
<td>[129]</td>
</tr>
<tr>
<td>Iraq</td>
<td>32.3</td>
<td>31</td>
<td>UTI (OP)</td>
<td>[130]</td>
</tr>
<tr>
<td>Iraq</td>
<td>17 (CTX) 43 (CAZ) 50 (CRO)</td>
<td>30</td>
<td>BI (ICU)</td>
<td>[131]</td>
</tr>
<tr>
<td>Kuwait</td>
<td>20 (com) 33 (hosp)</td>
<td>253 (com) 217 (hosp)</td>
<td>Urinary infections; (Com &amp; Hosp. acquired)</td>
<td>[132]</td>
</tr>
<tr>
<td>Lebanon</td>
<td>29 (CTX), 21 (CAZ)</td>
<td>947</td>
<td>Hospital samples</td>
<td>[133]</td>
</tr>
<tr>
<td>Morocco</td>
<td>69.5 (CAZ) 75 (CRO)</td>
<td>39</td>
<td>ICU</td>
<td>[134]</td>
</tr>
<tr>
<td>Morocco</td>
<td>20</td>
<td>40</td>
<td>Urinary isolates</td>
<td>[135]</td>
</tr>
<tr>
<td>Pakistan</td>
<td>47.2 (CAZ) 59.7 (CTZ) 62.5 (CRO)</td>
<td>72</td>
<td>Medical ICU patient</td>
<td>[136]</td>
</tr>
<tr>
<td>Pakistan</td>
<td>20.9 (CTX) 28.6 (CAZ)</td>
<td>77</td>
<td>Vaginal swab</td>
<td>[137]</td>
</tr>
<tr>
<td>Countries</td>
<td>Resistance%</td>
<td>Isolates</td>
<td>Samples type</td>
<td>References</td>
</tr>
<tr>
<td>--------------------</td>
<td>-------------</td>
<td>----------</td>
<td>-----------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Brazil</td>
<td>0 (IMI); 1.6 (ETP)</td>
<td>63</td>
<td>Clinical samples</td>
<td>[154]</td>
</tr>
<tr>
<td>Trinidad and Tobago</td>
<td>0</td>
<td>92</td>
<td>Hospitalized children</td>
<td>[155]</td>
</tr>
<tr>
<td>Iraq</td>
<td>0</td>
<td>30</td>
<td>BI (Neonate ICU)</td>
<td>[131]</td>
</tr>
<tr>
<td>Lebanon</td>
<td>1.8 (DOR); 8.8 (IMI)</td>
<td>57</td>
<td>Hospital samples</td>
<td>[133]</td>
</tr>
<tr>
<td>Pakistan</td>
<td>20.8</td>
<td>72</td>
<td>Medical ICU patients</td>
<td>[136]</td>
</tr>
<tr>
<td>Pakistan</td>
<td>0.4</td>
<td>5016</td>
<td>Hospital samples</td>
<td>[139]</td>
</tr>
<tr>
<td>Israel</td>
<td>7</td>
<td>299</td>
<td>Patient screening</td>
<td>[156]</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>0</td>
<td>45</td>
<td>Blood isolates (neonates)</td>
<td>[146]</td>
</tr>
<tr>
<td>India</td>
<td>39.4 (IMI); 36.5 (MEM)</td>
<td>104</td>
<td>Blood isolates</td>
<td>[157]</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>0.4</td>
<td>285</td>
<td>ICUs</td>
<td>[158]</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>7.8</td>
<td>128</td>
<td>Hospital isolates</td>
<td>[159]</td>
</tr>
<tr>
<td>Turkey</td>
<td>0</td>
<td>18</td>
<td>Burn patients</td>
<td>[160]</td>
</tr>
<tr>
<td>India</td>
<td>18.6</td>
<td>327</td>
<td>UTI (HP)</td>
<td>[161]</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>92.5 (IMI); 92.5 (MEM)</td>
<td>3229</td>
<td>Hospital isolates</td>
<td>[153]</td>
</tr>
</tbody>
</table>

**Note:** MEM= Meropenem; DOR= Doripenem; ETP= Ertapenem; IMI= Imipenem; UTI= Urinary tract Infections, HP= Hospital patients

Table 3. *Klebsiella pneumoniae*: Selected literature on resistance to carbapenem

<table>
<thead>
<tr>
<th>Countries</th>
<th>Resistance%</th>
<th>Isolates</th>
<th>Samples type</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>0 (IMI); 1.6 (ETP)</td>
<td>63</td>
<td>Clinical samples</td>
<td>[154]</td>
</tr>
<tr>
<td>Trinidad and Tobago</td>
<td>0</td>
<td>92</td>
<td>Hospitalized children</td>
<td>[155]</td>
</tr>
<tr>
<td>Iraq</td>
<td>0</td>
<td>30</td>
<td>BI (Neonate ICU)</td>
<td>[131]</td>
</tr>
<tr>
<td>Lebanon</td>
<td>1.8 (DOR); 8.8 (IMI)</td>
<td>57</td>
<td>Hospital samples</td>
<td>[133]</td>
</tr>
<tr>
<td>Pakistan</td>
<td>20.8</td>
<td>72</td>
<td>Medical ICU patients</td>
<td>[136]</td>
</tr>
<tr>
<td>Pakistan</td>
<td>0.4</td>
<td>5016</td>
<td>Hospital samples</td>
<td>[139]</td>
</tr>
<tr>
<td>Israel</td>
<td>7</td>
<td>299</td>
<td>Patient screening</td>
<td>[156]</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>0</td>
<td>45</td>
<td>Blood isolates (neonates)</td>
<td>[146]</td>
</tr>
<tr>
<td>India</td>
<td>39.4 (IMI); 36.5 (MEM)</td>
<td>104</td>
<td>Blood isolates</td>
<td>[157]</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>0.4</td>
<td>285</td>
<td>ICUs</td>
<td>[158]</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>7.8</td>
<td>128</td>
<td>Hospital isolates</td>
<td>[159]</td>
</tr>
<tr>
<td>Turkey</td>
<td>0</td>
<td>18</td>
<td>Burn patients</td>
<td>[160]</td>
</tr>
<tr>
<td>India</td>
<td>18.6</td>
<td>327</td>
<td>UTI (HP)</td>
<td>[161]</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>92.5 (IMI); 92.5 (MEM)</td>
<td>3229</td>
<td>Hospital isolates</td>
<td>[153]</td>
</tr>
</tbody>
</table>

**Note:** MEM= Meropenem; DOR= Doripenem; ETP= Ertapenem; IMI= Imipenem; UTI= Urinary tract Infections, HP= Hospital patients

---

Liaqat et al.
4. Treatment of *Klebsiella pneumoniae* infections

Suitable health-giving opportunities are frequently determined founded on the AB range, expediency of usage and adequacy of AB, such as 3rd and 4th generation cephalosporin. Aminoglycosides are used in combination therapy with beta-lactam antibiotics. Therefore, it is expected to reveal high rate of resistance to aminoglycosides as well as beta-lactams [163]. The applicable AB treatment is reliant on vulnerability forms of native bacterial and hazard side view of patient, which may eventually control the risk of infection with opportunitistic and possibly ABR infections [96]. MDR bacterial strains, such as *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Pseudomonas aeruginosa* existing a health-giving challenge owed towards their capacity to weaken handling, while too decreasing suitable AB choices existing and producing a deferral in proper dealing due to ineffective experiential treatment [97, 98].

4.1 Treatment of multidrug-resistant *Klebsiella pneumoniae* infections

The worldwide development of MDR Grams negative bacilli is an incomparable problematic, which is impaired by the focus on refining current classes of AB in its place of evolving novel classes of drugs with changed marks resolved the 49 years earlier [99, 100]. The increase amount of MDR microorganisms and the progressively inadequate handling options is established by ever predominant ESBL-producing *Klebsiella pneumoniae* for which carbapenem stood the support treatment but are progressively reduced useless via the infrequent rise of carbapenem-resistant enterobacteriaceae [101-102]. Usual appearances of ESBL-producing members of the enterobacteriaceae family comprise resistance to amino- and carboxypenicillins,2ND and several 3rd and 4th generation of cephalosporins in accumulation to monobactams (such as aztreonam) however about might persist vulnerable to cephamycins [27, 103-105]. ESBL and clavulanate, a βL inhibitor, and might display further resistance to additional AB, such as fluoroquinolones, aminoglycosides, trimethoprim and sulphamethoxa-zoles [20, 103, 106]. Experiential treatment must contest data on pathogens dispersed in the medical location and their predisposition forms thus as to well confirm exact early AB treatment. Late suitable treatment can increase the possibility of expiry [107]. In a retroactive study led through Micek et al., [96] a fine significance was expected to be related by exact initial combination AB treatment when empirically treating gram negative bacteria by mediated sepsis as related to monotherapy. A combination of as ciprofloxacin, or an aminoglycosides with or cefepime, carbapenem (imipenem and MEM), as primary handling for severe gram negative bacterial infections current a widespread range of action. 92 Further reviewing studies additional favor combination cure in CRE infections used for which treatment choices have been compact mostly to colistin, tigecycline about aminoglycosides and fosfomycin (FFC) [99, 102]. While FFC seems lively in vitro, now is small therapeutic knowledge by the AB in addition to information of acceptable combinations for treatment lacking inspiring ABR [99, 108, 109]. TCL has established productivity against MDR enterobacteriaceae and uniform with requiring medicine changes, due to little level of blood, has good medical practices [99, 106, 110]. A disastrous disadvantage to TCL might comprise the collection of gram negative bacteria with efflux pump alterations [100, 106]. Colistin has been suggested for usage first in cases of recognized nosocomial or MDR strains and ICU late sepsis tremor anywhere strains of MDR are assumed [99]. The practice of colistin for a persistent retro (>13 days) of time has been suggested as liable for the rise of colistin resistant or in some
cases of bacterial strain having pandrug-resistant [111-113]. The rise of strains that producing KPC in *Klebsiella pneumoniae* has reduced the resistant to wholly nonetheless unique AB i.e. colistin [114].

5. Spread, prevention and control

The increase in ABR between bacteria, such as those definite as ‘ESKAPE’ pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa* and *Enterobacter spp*.), has emphasized the vital aimed at new AB owed toward the ‘escape’ after currently promoted AB drugs [115]. The influence of infections by β-lactamase producing bacteria comprise improved rates of death mainly in blood stream infections (BSI), and rise in measurement of expenses in hospitalization and sickbay. Value lakes usually concerned in healthcare related occurrences or extent comprises the patients, the well-being maintenance worker and the surroundings (such as sink drains) [116]. Influences impacting the extent and regulator of MDR bacteria contain feast of plasmids and are compressed via the nutrition chain or worldwide travel [117]. In the journeys, acquirement can arise in the time off healthcare contact otherwise with rest and medicinal tourism [118, 119].

In places of healthcare, overfilling is a significant influence in impairing the faecal oral way of spread through direct or incidental interaction by healthcare staffs [120]. The connection that staff have by patients during uncertain community contacts, such as taking a patient’s blood pressure and the touching of extinct matters in the patient’s atmosphere, could give to level spread of pathogens, particularly when elective hand sterility practices are unnoticed [99, 121]. The application of alcohol built hand scrubs and even instructive programs are so significant phases in regulator actions assumed [121]. Infection control actions assumed can contain: (i) improved barrier safety measures, (ii) separation of sick patients, (iii) suitable AB handling period (iv) epidemiological principles for the management of apparatus and patient lesions [2, 99].

A technique explored aimed at its prospective to decrease irritated infection amounts in medical locations, like ICU, is the consequence of selective digestive tract decontamination (SDD) for the removal of cephalosporin-resistant enterobacteriaceae [122-124]. Numerous key inadequacies have, still, been recognized by the WHO in the conflict contrary to ABR. This problem is conferred below 4 issues which comprise: (i) absence of assurance and data, (ii) unverified AB value and unreasonable usage, (iii) reduced inhibition and control of infections (iv) failing investigation into novel AB apparatuses and agents, comprising analytical trials and AB. The subsequent strategy set suggested through the WHO so initially recommends that administrations assume and economics inclusive state plans with liability and likable public civilization by building community alertness.

Another approval is constructed on refining investigation and test site volumes, whereas the 3rd recommends native administrations to assurance a continuous source of needed, value secure medication. The instruction and raise of the precise use of earlier stated medicine is too highlighted beside with good patient care. Lastly, the last 2 approvals include control though inspiring research, improvement in prevention of infection and improvement of new tools, containing diagnostic tests and AB [125].

**Conclusion**

Bacteria such as *Klebsiella* spp. are adapted to harsh surroundings formed through the usage of antibiotics concluded numerous mechanisms, which comprise the appearance of β-Lactam proficient of hydrolyzing penicillin’s along with another β-lactam antibiotics. ESBL producing *Klebsiella pneumoniae* forms part of the ESBL
producing enterobacteriaceae, together which is recorded as single of 6 hazardous pathogens by the Infectious Disease Society of America collected with ESKAPE (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species)’. Antibiotics resistance is frequently conversed in terms of range and succeeding production of MDR strains or the chromosomes and plasmids which are the components horizontal transmission of genome encoding resistance. A numeral of indications on or after studies crossways the world show that MDR bacteria are evolving global producing numerous community health problems and tasks to healthcare. The incidence of drug resistance owed to Klebsiella pneumoniae approaches 60% in around states, with largely high proportions all around the globe. The misuse of antibiotics is creating superbugs, which is a lethal threat to the community and public health. Search of alternative antibiotics and the redressal to drug resistance against commonly in use antibiotics are the need of day.

Authors’ contributions

Acknowledgement
The study was partially supported by the funds from AIP-PARC-2017 USAID, NRPU-HEC 6470 and UBRF-2017 University of Balochistan Quetta.

References


56. Yigit H, Queenan AM, Anderson GJ, Domenech-Sanchez A, Biddle JW, Steward CD, Alberti S, Bush K & Tenover FC (2001). Novel carbapenem hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of...


123. Oostdijk EA, De Smet AM, Kесесиоглу J, Bonten MJ & Dutch SOD-SDD Trialists Group (2011). The role of intestinal colonisation with Gram-


