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Klebsiella pneumoniae and Its Growing Concern in Healthcare Settings

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Abstract

The increasing clinical incidence of antibiotic-resistant bacteria is a major global health care issue. Among MDR pathogens, *Klebsiella pneumoniae* (KP) is one of the world's most dangerous superbugs; and becoming resistant to virtually every antibiotic available today. Published articles cited majorly from three sources were browsed using selected keywords. Screening technique was done based on article relevance, topic match and English language match. Duplication of findings was avoided. Prevalence of KP among isolates was determined in different study places and the most alarming figure was seen in study conducted in Nigeria (64.2%) followed by India (33.9%) and Denmark (17.4%). Based on our pooled data from a number of studies conducted at different part of the globe, antibiotic resistances among KP isolates were found to be 100% for Cephradin, 87.5% for Cefeclor, 84% for Tobramycin, 82.5% for Cefotaxime, and 80.4% for Norfloxacin. Whereas, *K. pneumonia* was found to be more sensitive to Impenem (92.5%), Meropenem (92.5%), Amoxicillin/Clavulanic acid (87.5%), Gatifloxacin (85%), Moxifloxacin (75%); and chloraphenicol (62.8%). Carbapenems have been regarded as the treatment of choice for serious infections caused by extended-spectrum βeta-lactamase (ESBL)-producers. The combination therapy of fosfomycin+colistin demonstrated synergistic and bactericidal effect against one metallobetalactamase producing KP strains that were resistant to fosfomycin. Some of the factors that are responsible for the decline in number of newly discovered antibiotic include reduced financial grant from funding agencies, closure of many major pharmaceutical and large biotech companies; and the lack of financial reward for large pharmaceutical companies to develop new ambitious projects. In conclusion, MDR bacteria are emerging worldwide causing many public health problems and challenges to healthcare. Based on the result from our pooled data, we can conclude that currently we have only few antibiotics that are effective to treat KP.

Keywords: Nosocomial; *Klebsiella pneumoniae* (KP); Multidrug-resistant (MDR); Antimicrobial resistance (AMR); *K. pneumoniae* carbapenemase (KPC)

Abbreviations

AMR: Antimicrobial Resistance; CHβL: Carbapenem Hydrolyzing β-Lactamase; ESBL: Extended Spectrum β-Lactamase; KP: *Klebsiella pneumoniae*; KPC: *K. pneumoniae* Carbapenemase; MAR: Multiple Antibiotic Resistances; MBL: Metallo-Beta-Lactamase; MDR: Multidrug Resistant; MIC: Minimum Inhibitory Concentration; MLST: Multi-Locus Sequence Typing; OPD: Outpatient Department; OXA: Oxacillinase; PBRT: PCR-Based Replica Typing; PFGE: Pulsed-Field Gel Electrophoresis; PMQRs: Plasmid-Mediated Quinolone Resistance Genes; RMTase: RNA Methyltransferase; ST: Sequence Type; Sp.: Species; UTI: Urinary Tract Infection

Background

The increasing clinical incidence of antibiotic-resistant bacteria is a major global health care issue [1]. Especially this is true when the infections with multidrug-resistant (MDR) pathogens impose a significant and increasing burden on both patients and healthcare providers [2]. Among MDR pathogens, *Klebsiella pneumoniae (K. pneumonia or KP)* is one of the world's most dangerous superbugs; and becoming resistant to virtually every antibiotic available today [3]. The bacterium is non-motile, rod-shaped, Gram-negative, opportunistic, and gammaproteobacterium of the family Enterobacteriaceae; and it is a close relative of many familiar genera, such as Citrobacter, Escherichia, Enterobacter, and Salmonella [1].

Klebsiella has becomes an important pathogen in a hospital settings causing nosocomial infections with outbreaks of 20%, where the problem of antibiotic resistance is typically magnified [4,5]. The bacterium is normally found in the human intestines causing no disease [6], uncommon to found it in the oropharynx of immunocompetent persons (where the carrier prevalence rate is only 1-6%) [7]. Hence, immunocompetent people do not get Klebsiella infections[6] unless they are critically sick and become on mechanical ventilators (breathing machines) or intravenous catheters (IVC), and/or unless they are taking long courses of broad spectrum antibiotics[6].

The Klebsiella species are known to cause a number of infections in humans including: pneumonia, septicaemia, meningitis, rhinoscleroma, ozaena, sinusitis, otitis, enteritis, appendicitis and cholycystitis [6,8]. The prevalence of extended-spectrum βeta-lactamase (ESBL)-producing bacteria, such as *E. coli* and KP species that are resistant to many penicillin and cephalosporin antibiotics; are increasing globally and becoming a major clinical concern. Hence, the current review study is aimed to examine the prevalence of *K. pnemoniae* in healthcare settings, its antibiotic resistance pattern and the available treatment options.

Methods

Design and technique

Published articles cited majorly from three sources were browsed using keywords *'Klebsiella pneumoniae,'* '*Klebsiella pneumoniae +antibiotic resistance*', '*Klebsiella pneumoniae+inpatients,' 'Klebsiella pneumoniae+hospitals,' 'prevalence+Klebsiella pneumoniae,' and 'Klebsiella pneumoniae+resistance'*. Three hundred twenty one articles were browsed from Google Scholar, 288 articles from PubMed and 10 articles were obtained from HINARY (Table 1).

Screening technique was done based on article relevance, topic match and English language; duplication was avoided. Year of publication was not considered as criteria but the authors have tried their best to make majority of the articles within the last five years. Similarly study place and study design were not used as a criteria but more powerful study designs and studies from developing countries given priority and lastly a total of …….articles were collected (Table 1).

Total articles downloaded using keywords for this review					
Citations Sources	**Google Scholar 321**	**PubMed 688**	**HINARY 10**	**Total 1019**	**Remarks**
Excluded Articles through Screening technique	306	650	9	965	
Selected Articles	15	38	1	54	

Table 1: Method of article selection.

Specimen sources

Anatomic sites of cultures were compared among the different articles and urine was by far the most commonly used in 1654 (51.2%) specimen source followed respiratory tract in 706 (21.9%), and blood in 438 (13.6%) (Table 2).

Studies	Urine	Blood	Respiratory Secretions	Pus	Stool	Other Sources/ Unknown	Total
Study 1	43	37	0	0	12	0	92
Study 2	937	183	564	0	62	0	1746
Study 3	36	12	11	0	0	0	59
Study 4	0	0	0	0	0	120	120
Study 5	88	44	20	84	0	48	284
Study 6	550	162	111	0	81	24	928
Total	1654 (51.2%)	438 (13.6%)	706 (21.9%)	84 (2.6%)	155 (4.8%)	192 (5.9%)	3229

Table 2: Specimen sources for selected articles based on anatomic sites.

Risk factors, prevalence and antimicrobial resistance

A number of potential risk factors were reported in different articles including age, sex, race, and origin of patient at the time of hospital admission, also hospital location, and duration of hospital stay prior to identification of the isolate [9]. Environmental hygiene, personal hygiene and immunity were very determinant for acquiring KP infections. Some study also reported travelling to some developing countries were a risk by itself [10].

Antibiotics are an essential part of modern medicine [11], they have saved millions of lives since their introduction into medicine in 1941. They have substantially reduced the threat posed by infectious diseases [12-14]. The use of these wonder drugs, combined with improvements in sanitation, housing, and nutrition, and the advent of widespread immunization programmes, has led to a dramatic drop in deaths from diseases that were previously widespread, untreatable, and frequently fatal [14]. Unfortunately, after more than 50 years of success, the pharmaceutical industries are now producing too few antibiotics, particularly against Gram-negative organisms, to replace antibiotics that are no longer effective for many types of infection [11].

Prevalence of *K. pneumoniae* among isolates was determined in different study places and the most alarming figure was seen in study conducted in Nigeria (64.2%) followed by India (33.9%) and Denmark (17.4%) (Table 3).

It seems virtually all of the easily discovered novel antibiotics were found between 1929 and 1962 GC, because only few antibiotics were found since then, such as oxazolidinones [15] and the cyclic lipopeptides [16]. This is due to the emergence of antimicrobial resistance (AMR) among previously sensitive microorganisms. Now the problem reached the level that places future patients in real danger [17-19].

Study year	# of isolates	# of *K.pneumonia* identified	Prevalence of *K.pneumonia* (%)	Study place
2015	92	13	14.1	Singapore[15]
2013	1746	152	17.4	Denmark [13]
2011	59	20	33.9	India [8]
2011	120	77	64.2	Nigeria [16]
2009	200	40	5	Pakistian[17]
2009	928	121	13	USA[9]

Table 3: Prevalence of *K. pneumonia* in different study places.

AMR has followed the rate of the consumption and the development of new antibiotics [20]. Infections due to these pathogens are associated with high therapeutic failure [20,21] As a result, it is causing higher treatment costs, longer hospital stays, and increased mortality rates [12]. The prevailing hypothesis of AMR mechanism is that these bacteria acquire MDR through horizontal transfer of antimicrobial resistance genes mediated by mobile genetic elements such as integrons [22].

The prevalence of Antimicrobial resistance (AMR) by *K. pneumoniae* approaches 50% in some countries, with particularly high rates in Eastern Europe and Latin America [4]. The incidence of ESBL producing strains among clinical Klebsiella isolates has steadily increased over the years and account for 6 to 17% of all nosocomial urinary tract infections [23].

On the basis of degree of resistance to antibiotic, the microbial strain can be categorized as susceptible, moderately susceptible (intermediate) and resistant to antimicrobials [8]. On the basis of prevalence of antimicrobial resistance genes it can be further classified as extended spectrum β-lactamase (ESBLs) [24], plasmid-mediated quinolone resistance (PMQR) genes [25], and 16S rRNA methylase (16S-RMTase) genes [26,27]. The PMQR, especially involving Qnr proteins and the aminoglycoside acetyltransferase variant determinant (AAC(6′)-Ib-cr), has emerged and is now described worldwide [28].

K. pneumoniae can harbor both ESBL and carbapenem-hydrolyzing β-lactamases (CHβLs) and frequently ESBL-producing *K. pneumoniae* has been resistance to other antibiotics, including fluoroquinolones, aminoglycosides, trimethoprim, and sulfamethoxazoles. Patients who are infected with these resistance bacteria have only a few therapeutic options, among these the carbapenems are the last line class of antibiotics. Unfortunately, Klebsiella bacteria have still developed resistance to this last option class of antibiotics, becoming CHβLs and *K. pneumoniae* carbapenemase (KPC) [6].

CHβLs has rapidly emerged in recent years, with *K. pneumoniae* being the most common organism associated with KPC resistance determinants [20,29]. The increasing incidence of KPCs is a significant public health challenge [20] because as already mentioned these organisms can confer resistance to multiple different antimicrobial classes, including all available β-lactams, fluoroquinolones, and aminoglycosides [20,30]. *K pnemoniae* also exhibit simultaneous resistance to the structurally unrelated antibiotics such as nalidixic acid, trimethoprim and chloramphenicol [31].

ESBL producing isolates are most commonly *Klebsiella* Sp. predominantly *K. pneumonia,* and *E. coli* [6,32]. Study showed that 4% of patients admitted to intensive care units (ICU) were found to be infected with strains of MDR *K. pneumoniae* [33] and these resistance patterns was due to either to new and significant DNA sequence data on *K. pneumoniae* strains and also in whole-genome sequencing characterization as discussed above [1].

Based on our pooled data from a number of studies conducted at different part of the globe, antibiotic resistances among *K. pneumoniae* isolates were found to be 100% for in case of Cephradin, 87.5% for Cefeclor, 84% for Tobramycin, 82.5% for Cefotaxime, and 80.4% for Norfloxacin. Whereas *K. pneumonia* was found to be more sensitive to Impenem (92.5%), Meropenem (92.5%), Amoxicillin/clavulanic acid (87.5%), Gatifloxacin (85%), and Moxifloxacin (75%) and chloraphenicol (62.8%) (Figure 1).

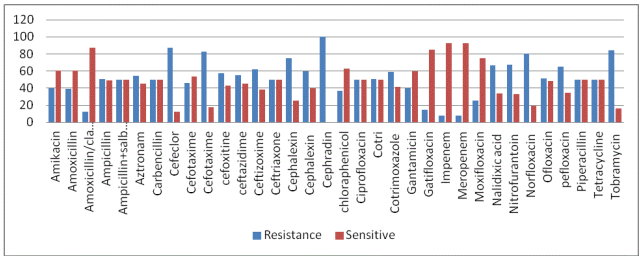

Figure 1: Pattern of antibiotic resistance of *Klebsiella pneumoniae* isolates [pooled data].

Some of the factors that are responsible for the decline in number of newly discovered antibiotic include reduced financial grant from funding agencies [34], closure of many major pharmaceutical and large biotech companies[35,36]; and also the lack of financial reward for large pharmaceutical companies to develop ambitious new projects [11].

Some studies reported that *K. pneumoniae* producing novel KPC variant was resistant to most of the antibiotics, such as carbapenem (imipenem, ertapenem and meropenem), aztreonam, cephalosporin (cefazolin, cefotaxime and ceftazidime), but susceptible to amikacin and colistine [37] in which we were unable to show with our pooled data analysis. Definitive monotherapy with a β-lactam/β-lactamase inhibitor (BLBLI) was done and 95.8% were sensitive to piperacillin-tazobactam [38].

Similar studies showed that *K. pneumoniae* strains from clinical cases were found highly susceptible to quinolones and aminoglycoside,

amikacin and gentamycin [20]. Among the β-lactam antibiotics, penicillin resistance rate was the highest and amoxicillin combined with clavulanic acid showed improved susptablity [39]. At the same time over 60% strains were found resistant to Chloramphenicol and Gentamicin [20]. In the face of this rapidly changing epidemiology, there is a pressing need to reduce carbapenem overuse. One strategy could be re-evaluating existing agents which have previously been considered ineffective or lack clinical data to support their use [40].

Review of current treatment approaches

This section focuses on current well-tested strategies of selection of compounds from natural and non-natural sources and modifying agents. The current methods have concentrated on compounds that target logarithmic multiplying bacteria [11]. The traditional answer to MDR has also been to introduce new antibiotics that kill the resistant mutants [11]. Traditional practices in infection control, antibiotic stewardship, and new antibiotic development are cornerstones of society's approach to combating resistance and must be continued [41].

Initial selection of antimicrobial therapy is nearly always empirical, which is the initiation of antimicrobials sometimes prior to documentation of the presence of infection and before the offending organism is identified [42]. When selecting antimicrobial regimens, local susceptibility data should be considered whenever possible rather than information published by other institutions or national compilations [43]. Therefore, the overall goal of antimicrobial therapy should be to cure the patient's infection; limit harm by minimizing patient risk for adverse effects, including secondary infections; and limit societal risk from antimicrobial-resistant bacteria (Figure 2).

As already mentioned, among the β-lactams tested the most effective antibiotics were carbapenems (meropenem and imipenem) which have similar spectrum of activities. The ESBL-producing strain had 1.5 to 2-fold higher MIC values for ertapenem, meropenem and doripenem compared with the native strain, whereas the MIC for imipenem did not differ [10,20].

Cephalosporins have been widely used as monotherapy and in combination with aminoglycosides for the treatment of Klebsiella infection [20]. For example Ceftriaxone, the most commonly prescribed antibiotic in developing countries, have minimal activity, same as to the other cephalosporins such as cefpirome, ceftazidime, cefeclor.

The traditional first-line available options for treating serious infections caused by enterobacteria include penicillins, cephalosporins, monobactams, carbapenems, fluorquinolones, and in certain situations, aminoglycosides [44] (Table 4).

β-lactam antibiotics such as cefotaxime, ceftazidime, and cefoxitin are most commonly prescribed however recent test result showed they are poorly responding to MDRE.

One of the most prevalent and concerning β-lactamases found around the world are known as ESBL which deactivate extended spectrum cephalosporins. As β-lactam antibiotics continue to be a widely used treatment, the natural environment has become a reservoir for antimicrobial resistant *Klebsiella* Sp. [45].

Carbapenems have been also regarded as the treatment of choice for serious infections caused by ESBL-producers. However, the increasing worldwide incidence of ESBL-related infections is driving increased use of carbapenems, leading to selection pressure for carbapenem resistance [38].

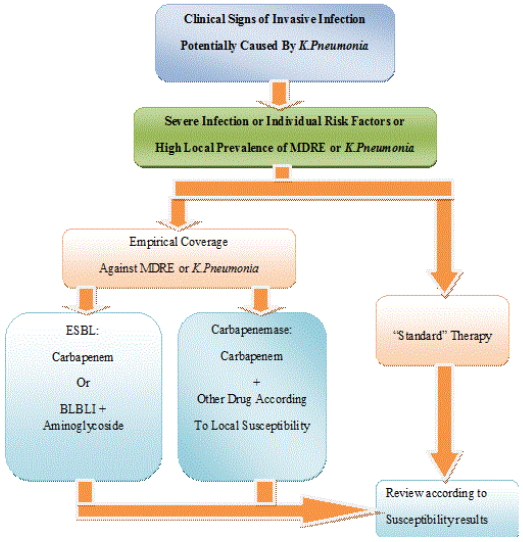

Figure 2: Algorithm for clinical decisions. MDRE, multidrug-resistant enterobacteria; BLBLI, β-lactam/ β -lactamase inhibitor combination; ESBL, extended-spectrum β –lactamase [46].

A recently published meta-analysis of observational studies found that mortality was lower in patients who received empirical or definitive therapy with carbapenem in comparison with other antibiotics, including cephalosporins, fluoroquinolones, and aminoglycosides, with the exception of non-BLBLI combinations [46]. The BLBLI combination antibiotics, such as amoxicillin-clavulanate, ticarcillin-clavulanate and piperacillin-tazobactam, have also a controversial status in the treatment of infections caused by ESBL-producers [40].

Tigecycline has demonstrated excellent spectrum of activity against KPC-producing organisms. However, there are no breakpoints set for tigecycline for Enterobacteriaceae (FDA approved breakpoint for tigecycline is <2 μg/mL). In addition, tigecycline has limited activity against Pseudomonas species [20]. A recent study demonstrated that aminoglycosides, which are active *in vitro,* were associated with a significantly higher rate of microbiologic clearance of KPC in the urine compared to polymyxin B or tigecycline [47].

Polymyxin monotherapy had higher rates of treatment failure compared to polymyxin-based combination therapy (73% vs. 29%; p=0.02). However, polymyxin prescription was the most commonly used against KPC infections in urinary systems [20]. And several recently done studies report support the role of combination therapy for treating KPC infections [48].

Fosfomycin showed high activity against all ESBL-producing strains and *K. pneumonaie* (>80%) [49-51]. Fosfomycin shows an excellent bactericidal activity against Gram-positive cocci, such as methicillin-sensitive *Staphylococcus aureus* (MSSA), cephalosporin- and penicillin-resistant *Streptococcus pneumoniae*, and methicillin-resistant *S. aureus* (MRSA), and Enterococcus species, even in vancomycin-resistant strains [49,52-54]. The combination therapy of

fosfomycin+colistin demonstrated synergistic and bactericidal effect against one metallo-beta-lactamase (MBL) producing KP strains that were resistant to fosfomycin. Fosfomycin+meropenem+colistin showed synergistic effect against all strains and bactericidal effect against 3 of 4 strains. Rifampin+colistin demonstrated synergistic and significant bacterial count reduction after 24 h compared to the starting inoculum against MBL-KP producing strains [10].

Aztreonam+colistin and aztreonam+meropenem+colistin were bactericidal against both specific MBL-KP strains. However, Aztreonam+meropenem did not demonstrate synergetic effect [10].

Mechanism of resistance	Antimicrobial	Comment
ESBL and plasmid AmpC producers	Carbapenems	Drugs of choice for severe infections
	BLBLI	ESBL: alternative to carbapenems if active *in vitro*. Data available mainly for urinary bacteremia due to *Escherichia coli.* AmpCs are not inhibited
	Cephalosporins	ESBL: potentially active for isolates with low MIC. Controversial AmpC: cefepime might be useful
	Temocillin	Potentially useful as definitive therapy
	Fluoroquinolones	Useful if *in vitro* active. Caution in case of isolates showing borderline MIC
	Aminoglycosides	Useful if active mainly for urinary tract infections
	Fosfomycin	Useful for cystitis
KPC, MLB, and OXA producers	Carbapenem	Potentially useful for isolates with low MIC (optimized dose). Probably worse than combination
	Aztreonam, cephalosporins	Aztreonam only for MLB or OXA-48 (without ESBL). Cephalosporins only for OXA-48 without ESBL. Potentially useful. Limited experience
	Colistin	Real efficacy is controversial. Optimized dosing might improve results
	Fosfomycin	Limited experience. To be used in combination
	Tigecycline	Limited experience. To be used in combination. Less efficacy expected in UTI
	Combinations	Better results in observational studies. Carbapenems should probably be included. A third drug may improve the results

ESBL, Extended-Spectrum β-lactamase; KPC, *Klebsiella pneumoniae* Carbapenemase; MIC, Minimum Inhibitory Concentration; MLB, Metallo β-lactamase; OXA, Oxacillinase; UTI, Urinary Tract Infection.

Table 4: Summary of current available treatments for MDRE [46].

Future treatment options

Promising future strategies to combat resistance requires additional societal investment in basic and applied research and policy activities. These interventions include preventing infections from occurring in the first place, encouraging new economic models that spur investment in anti-infective treatments, slowing the spread of resistance in order to prolong the useful lives of antibiotics, discovering new ways to directly attack microbes in a manner that does not drive resistance, and altering host–microbe interactions in order to modify disease without directly attacking microbes [41].

A more innovative form of stewardship is the development of therapies that do not drive resistance and hence the genomic revolution and the use of bacteriophages has been promising in the last one decade studies [55].

The genomics revolution

The complete sequencing of the genomes of many pathogenic bacteria has led to an explosion in knowledge about these organisms. Genomics is used to select potential antibacterial targets and can also be used to provide insights into, for example, pathogenesis and antibiotic resistance [12]. Hence, the genomics route has proven to be target rich, but has not led to the introduction of a marketed antibiotic yet [11].

Bacteriophages

Recently it has been recognized that bacteriophages, the natural predators of bacteria can be used efficiently in modern biotechnology [56]. It is estimated that every 2 days, half of the world's bacterial population is destroyed by bacteriophages [12].Bacteriophages have also been shown to be antibacterial in animals, and may find use in specific infectious diseases [11]. The main advantage of phages is their specificity for target bacteria which reduces the damage to normal flora of the host greatly [55].Synergy has been demonstrated for a multitude of combinations between phage-encoded peptidoglycan hydrolases (PGH) or PGH and other classes of antimicrobials [56].

Marine actinomycetes

Abyssomicin C is produced by a Verrucosispora strain isolated from the Sea of Japan at a depth of 289 M; hence its name, the antibiotic

from the "abyss." This polycyclic polyketide antibiotic acts by inhibiting para-aminobenzoic acid biosynthesis in the folic acid pathway. It and its analogs are being evaluated as candidates for treating drug-resistant gram-positive pathogens [57].

Conclusion

A number of evidences from researches across the globe prove that MDR bacteria are emerging worldwide causing many public health problems and challenges to healthcare. The prevalence of AMR due to KP approaches 50% in some countries, with particularly high rates in Eastern Europe and Latin America. Hence, the problem reached the level where future patients are real danger. Based on the result from our pooled data, we can conclude that currently we have only few antibiotics that are effective to treat KP. Future approaches to treat KP has been promising but different reports suggest that there has been diminished governmental supports for antibiotic related researches and the pharmaceutical sector also focusing manufacturing on more profitable chronic illness medications.

Recommendations

Every attempt should be made to obtain specimens for culture and sensitivity testing prior to initiating antibiotics. Empirical antibiotic therapy should be based on knowledge of likely pathogens for the site of infection, information from patient history (e.g., recent hospitalizations, work-related exposure, travel, and pets), and local susceptibility. All patients receiving antibiotics should be monitored for resolution of infectious signs and symptoms (e.g., decreasing temperature and white blood cell count) and adverse drug events. Clinicians should work towards optimizing antibiotic use through antibiotic stewardship programs and interventions, which help ensure that patients get the right antibiotics at the right time for the right duration.

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