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Its Alarming, *Klebsiella spp.* towards Multidrug Resistance

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A B S T R A C T

Klebsiella pneumoniae and *Klebsiella oxytoca* are the two most frequently encountered *Klebsiella* species giving rise to infections in humans. *Klebsiella* spp. causes urinary tract infections, ventilator-acquired pneumonias and blood stream infections (sepsis) among other conditions and is proving to be fatal. Klebsiella spp. has been associated with various types of infections and recently one of the most important and alarming aspects of *Klebsiella* spp. is the emergence of multi-drug resistant strains particularly those involved in nosocomial infection. Bacteria producing *Klebsiella* carbapenemases and extended-spectrum β-lactamases(ESBL), are rapidly emerging as a cause of multidrug-resistant infections worldwide. Bacterial isolates harbouring these enzymes are capable of hydrolysing a broad spectrum of β-lactams including the penicillins, cephalosporins, carbapenems and monobactam. Several cases which are almost resistant to all the antibiotic compel us to study its pattern. About hundred clinical isolates were collected from different wards, Icu, Nicu, Picu, postoperative wards of Tertiary care hospital of Jhalawar district. Out of which fifty two confirmed sample of *Klebsiella* spp.were further tested for antimicrobial drug susceptibility. The study is done in period of seven month from sep.2015 to march 2016.

Introduction

During 1883, Friedlander a German Pathologist and Microbiologist isolated a capsulated bacillus from the lungs of patient who died of pneumonia. This was named after him as Friedlander's bacillus. Later on this organism was given the generic name of *Klebsiella*, which is ubiquitously present and reported worldwide. *Klebsiella* is among the five gram-negative pathogens most commonly encountered in hospital-acquired infections (Horan *et al*., 1988), and *Klebsiella pneumoniae* is the most frequently occurring species, accounting for 75 to 86% of *Klebsiella* species reported (Torre *et al*., 1985; Hansen *et al*., 1998). Much more rarely encountered are *Klebsiella ozaenae* and *Klebsiella rhinoscleromatis*, which have been retained as separate species because of their association with specific diseases (Podschun *et al*., 1998). Taxonomically, these two species are regarded as subspecies of *K.*

pneumoniae based on DNA-DNA hybridization data. *Klebsiella oxytoca* is the other well-established species, accounting for 13 to 25% of isolates. Strains of *Klebsiella* are responsible for a wide variety of diseases in humans. These bacteria have become important pathogens in nosocomial infections (Nordamann *et al*., 2009) which have been well documented in United States and India. Epidemic and endemic nosocomial infections caused by *Klebsiella* species are leading causes of morbidity and mortality.

Infections caused by bacteria-producing *Klebsiella pneumoniae* carbapenemases (KPCs) are becoming an increasingly significant problem worldwide since the first detection of these enzymes greater than a decade ago. (Paterson *et al*., 2005)

Resistance to β-lactams is mainly mediated by extended-spectrum β-lactamases, with the TEM, SHV and CTX-M types being predominant. More recently, resistance to carbapenems, mediated by β-lactamases with carbapenem-hydrolysing activity (carbapenemases), has emerged. The most prevalent among these enzymes are the serine carbapenemases KPC and OXA-48, and the metallo-β-lactamases VIM, IMP, and NDM. Carbapenemase-producing *K. pneumoniae* (CPKP) isolates have undergone extensive dissemination in many countries, and continues to spread in new geographical locations, indicating an ongoing dynamic process. Certain types of carbapenemases show geographical associations. KPC-producing *K. pneumoniae* isolates were first found in North Carolina, and subsequently emerged in Europe, Latin America, and China (Gundmann, 2010). In countries such as Greece and Israel, and in the eastern USA, KPC-producing *K. pneumoniae* isolates have become endemic (Bratu *et al*., 2005). The metallo-β-lactamases VIM and IMP are scattered globally, with VIM predominating in southern Europe and IMP in the Far East, and NDM being widespread in India and Pakistan. OXA-48-producing *K. pneumoniae* isolates were first described in Turkey, and subsequently emerged in the Middle East, India, Europe, and North Africa (Poirel *et al*., 2004). CPKP isolates affect mainly hospitalized patients with underlying diseases and poor functional status (Mathers *et al*., 2009). They often exhibit extensive drug resistance phenotypes, complicate therapy, and limit treatment options. These organisms generally have elevated carbapenem MICs, but, for some isolates, routine susceptibility testing may show low MIC values (≤4 mg/L) despite the production of a carbapenemase. It is also necessary to discuss about *Klebsiella oxytoca* which is an opportunistic pathogen involved in antibiotic-associated diarrhoea and in nosocomial infections. The chromosome of wild-type *K. oxytoca* carries a β-lactamase gene. This gene is constitutively expressed at low levels, which usually confers low-level resistance to amino- and carboxy-penicillins but no significant resistance to other β-lactams. The β-lactamases of *K. oxytoca* have been divided into two main groups: bla_{OXY-1} and bla_{OXY-2}. (Fournier, 1997)These two β-lactamases have been placed in functional group 2be in Bush's scheme and in class A of Ambler's classification. These two genes share 87% nucleotide sequence identity. Each β-lactamase group is represented by at least four different forms according to their pI values from 7.1 to 8.8 and 5.2 to 6.8 for OXY-1 and OXY-2, respectively. Two other groups of *K. oxytoca* genes have recently been reported and named bla_{OXY-3} and bla_{OXY-4}.(46) The nucleotide sequence of the bla_{OXY-4} gene is 95% identical to that of the bla_{OXY-1}gene. The bla genes display

the STFK and KTG sequences typically found in β-lactamases possessing a serine active site. Clinical isolates of *Klebsiella* spp. including *K. oxytoca*, resistant to broad-spectrum cephalosporins and aztreonam, have been increasingly reported and are due to the acquisition of plasmids encoding extended-spectrum β-lactamases (ESBLs). In addition, *K. oxytoca* isolates that overproduce the chromosomally-encoded β-lactamase have been found to be resistant to broad-spectrum cephalosporins (e.g. cefotaxime and ceftriaxone) and monobactams. Although β-lactamase production is not regulated, some mutations in the promoter region cause its overproduction. Various mutations have been reported in the −35 and −10 promoter regions. Strains that overproduce β-lactamase are resistant to cefuroxime, ceftriaxone and aztreonam. In contrast, these strains are not resistant to ceftazidime, distinguishing β-lactamase overproducers from strains of *K. oxytoca* with plasmid-borne ESBLs. A strain of *K. oxytoca* that produces a chromosomally-encoded β-lactamase conferring resistance to ceftazidime was recently reported (Mammeri *et al*., 2003).

Materials and Methods

Sputum, urine, and pus, blood samples collected from inpatients admitted into clinical wards were sent to Microbiology laboratory within 6 hours of collecting samples. The samples were inoculated on blood agar and mac conkey agar, brain heart infusion broth and incubated according to the sample at 37oC..All the clinical isolates were examined morphologically for colony characteristics on agar media. Those exhibiting mucoid colonies were processed for biochemical testing. Biochemical test employed were urease production, citrate utilization and fermentation of sugars. Sugar fermentation tests performed were sucrose, glucose, mannitol, lactose, adonitol, dulcitol, melibiose and esculin. Indole test and H2S production on TSI agar, oxidase, catalase and nitrate were also carried out. Besides these tests, motility and growth of organism in potassium cyanide were also checked. For biochemical tests standard procedures were used. Antibiotic sensitivity testing was done for all the isolates on Mueller-hinton agar/Nutrient agar by modified Kirby-bauer disc diffusion technique. Antibiotic used were azithromycin (AZM), gentamicin (GM), augmentin(AUG),ceftriaxone (CTR), tobramycin(TOB), ceftazidime (OR), cefixime(CFM), piperacillin-tazobactam (PIT), imipenem(IMP), meropenem (MRO), chloramphanicol (C), ciprofloxacin (CIP), ofloxacin (OF), amikacin (AK), gentamycin (HLG), doxycycline(DO), cefoxitin (CX), norfloxacin (NX), nitrofurantoin (NIT), netilmicin (NIT), cotrimoxazole(COT).

Results and Discussion

Out of 100 samples, 52 were confirmed as *Klebsiella* spp. through microscopy, colony morphology, biochemical reactions. These includes 40 species of *K. pneumoniae* and remaining of *K. oxytoca*. These are differentiated on the basis of biochemical reactions including Indole reaction. *K. pneumoniae* gives negative indole reaction and *K. oxytoca* gives positive. Isolates further tested for antibiotic sensitivity on Mueller-hinton agar/Nutrient agar .In our studies we have found that *Klebsiella* spp. from clinical cases were highly susceptible to Netilimicin, Tobramycin, Azithromycin, Amikacin, Gentamicin Norfloxacin, Nitro-furantoin, Ofloxacin comparatively. Studies also shows that antibiotic such as Augmentin, Ceftazidime, Cefixime are 100 % resistant and Meropenem and imipenem were 11.5 % susceptible which is due to bacteria-producing *Klebsiella pneumoniae*

carbapenemases (KPCs). *Klebsiella* isolates were found to show resistance to cefotaxime, ceftazidime, cefepime, cefoxitin, ceftriaxone.

Almost 10 isolates were 100% resistant to all antibiotics used which were like a superbug to those patients and eye opener for medical fraternity.

Our study shows that aminoglycosides like netimicin, tobramycin, gentamicin, amikacin are potent antibiotics to some extent with susceptibility of 36.5%, 34.6%, 21.1%, 30.7% which is also not satisfactory and it indicates that *Klebsiella* is getting resistant to them also.

Clinical isolates of *Klebsiella* spp. including *K. oxytoca*, resistant to broad-spectrum cephalosporins and carbapenem, have been increasingly reported and are due to the acquisition of plasmids encoding extended-spectrum β-lactamases (ESBLs) and KPC producing bacteria. In vitro data showed a wide range of beta-lactams, aminoglycosides, quinolones and other antibiotics which are useful for treatment of *Klebsiella* infections. Both Gram positive and Gram negative bacteria have cell walls which is composed of heavily cross-linked peptidoglycan layers which are catalysed by cell-wall transpeptidases also known as penicillin binding protein(PBP). B-lactam antibiotics disturb peptide bond formation by acting as competitive inhibitors to these PBPs. These result in formation of irreversible covalent bonded penicilloyl-enzyme complexes with weak cross-linked peptidoglycans, thus ease bacteria lyses and death (Wilke *et al*., 2005). All the *Klebsiella* isolates were resistant to most of the antibiotics and ten among them were resistant to all the antimicrobial agents tested which is alarming and dangerous. In our studies we found that *Klebsiella* spp. from clinical cases were highly susceptible to Netilimicin, Tobramycin, Azithromycin, Amikacin, Gentamicin Norfloxacin, Nitrofurantoin, Ofloxacin. The emergence of multidrug resistant strains particularly those involved in nosocomial diseases and the alarming rise in resistance to SHV and ESBL producing groups of antibiotics result in high morbidity and mortality. Early identification of agent, therefore, is important for timely management of patients. *Klebsiella* has been associated with different types of infections and one of the important aspects of *Klebsiella* associated infection is the emergence of multi-drug resistant strains particularly those involved in nosocomial diseases. The alarming rise in resistance to SHV and ESBL producing groups of antibiotics result in high morbidity and mortality. TEM- and SHV type ESBL producing *Klebsiella* pneumoniae were extensively reported worldwide after it was first identified in enterobacterial isolates from India. The high prevalence of these drug resistant strains has further necessitated the requirement of a rapid and accurate identification system for K.pneumoniae. We have found that the isolates were highly susceptible to quinolones and the aminoglycosides. Carbapenem-resistant *K. pneumoniae* infection is associated with numerous healthcare-related risk factors and with high mortality. The mortality rate associated with carbapenem-resistant *K. pneumoniae* infection and the limited antimicrobial options for treatment of carbapenem-resistant *K. pneumoniae* infection highlight the need for improved detection of carbapenem-resistant *K. pneumoniae* infection, identification of effective preventive measures, and development of novel agents with reliable clinical efficacy against carbapenem-resistant *K. pneumoniae*. KPC-producing bacteria have emerged in multiple species of Gram-negative bacteria across the world.

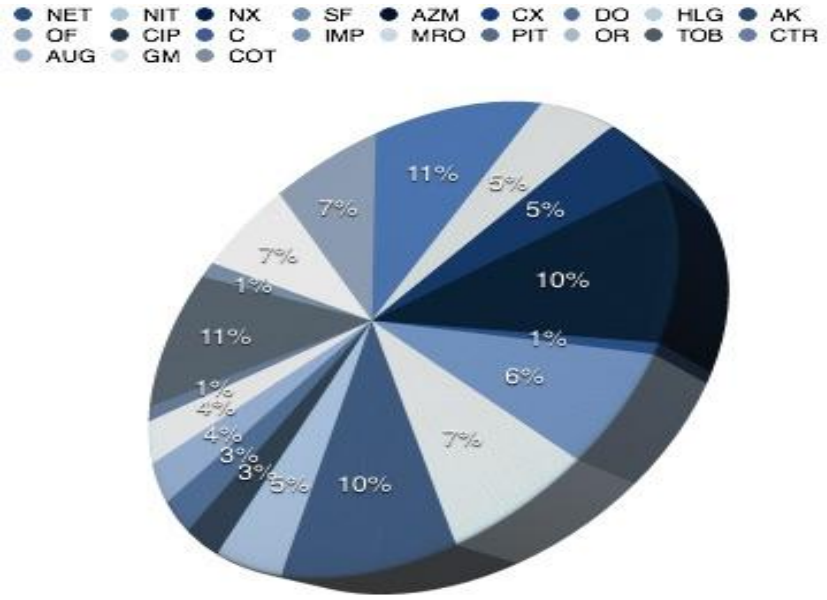
They have created significant clinical challenges for clinicians as they are not consistently identified by routine screening methods and are highly drug-resistant, resulting in delays in effective treatment and a high rate of clinical failures. Effective antibiotics are limited to polymyxins, tigecycline and occasionally aminoglycosides. Hospitals must prepare so that they can identify these organisms early and institute enhanced infection control efforts when necessary. Clinical microbiology laboratories need to recognize the signature of ertapenem resistance as a marker for KPC-producing bacteria, and should alert physicians to assume cross resistance to all carbapenems when it is present.

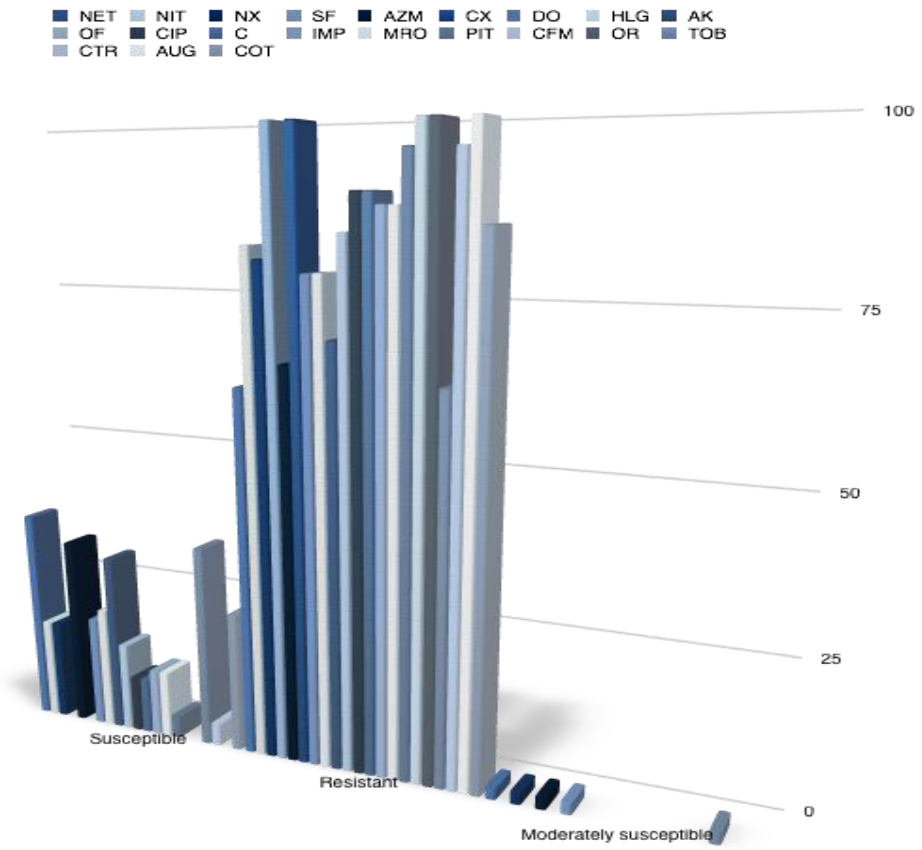
Table 1.

Hospital-acquired bacterial infections caused by *Klebsiella* spp.

Infection	% of infections caused by *Klebsiella*	Rank[a]	References
UTI	6–17	5–7	61,62,63,64
Pneumonia	7–14	2–4	61,65,63
Septicemia	4–15	3–8	66,67,68-70,71, 72,73,74,64,75
Wound infections	2–4	6–11	63,76,64
Nosocomial infections in intensive care unit patients	4–17	4–9	61,63,77,64
Neonatal septicemia	3–20	2–8	78,79,80,81,82, 83

a Ranking of *Klebsiella* compared to all other bacterial pathogens.





Furthermore, clinicians need to appreciate that KPC-production can occur in many Gram-negative bacilli and become familiar with the limited effective antibiotics against KPC-producing bacteria as the frequency of KPC-producing bacteria is expected to continue to increase. Recently, WHO warned society during press release and stated that antibiotics may lose their power to cure disease if action is not taken now against antimicrobial resistance problem. WHO also recommended six ways to overcome multi drug resistant problem, those are:

Committing to a comprehensive, financed national plan with lines of accountability and community engagement;

Strengthening surveillance and laboratory capacity;

Ensuring a regular supply of good-quality medicines;

Regulating and promoting rational use of medicines and proper patient care;

Enhancing infection prevention and control in health settings; and

Fostering innovation, research and development

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