HIGH PREVALENCE OF MULTI-DRUG RESISTANT *KLEBSIELLA PNEUMONIAE* IN A TERTIARY TEACHING HOSPITAL IN WESTERN KENYA

Ogalo Edith Apondi[1], Owuor Chrispine Oduor[2], Boor Kipyego Gye[3], Mutai Kennedy Kipkoech[4]

[1]Department of Child Health and Pediatrics, Moi Teaching and Referral Hospital, Eldoret. Kenya.[2]Department of Internal Medicine, Moi University, Eldoret, Kenya (drowuorchris@gmail.com). [3]Department of Medical Microbiology and Parasitology, Moi University, Eldoret, Kenya (kkmutai@gmail.com). [4]Kenya Medical Research Institute-Center for Global Health Research, HIV Implementation Science and Services, Kisumu, Kenya (gyeboor@gmail.com)

Corresponding author *Email: edithapondi@gmail.com

Abstract

Introduction: *Klebsiella pneumoniae* is a gram negative *enterobacteriaciae* commonly associated with nosocomial infections. Multi-drug resistant strains are increasingly being reported with corresponding increase in morbidity and mortality. The study outlines the epidemiology and antibiotic resistance pattern of *K. pneumonia* over a 10 year period in Moi Teaching and Referral Hospital, Eldoret, Kenya.

Methodology and Study Design: This is a retrospective analysis of all the blood culture results for *K. pneumoniae* isolates in the hospital for the period 2002-2013.

Results: *K. pneumoniae* accounted for 23% of the hospital isolates (231/1356) during the study period; of these, 82.6% were from the New Born Unit. Most of the isolates were multi drug resistant with highest resistance of over 80% to Penicillins, Cephalosporins, Macrolides, Tetracyclines, Sulphonamides, Lincosamides and Chloramphenicol. Aminoglycoside and Quinolone resistance was also high at 49.2% and 41.3% respectively. The lowest resistance rates were documented for Carbapenems (23.2%). For specific antibiotics, there was high resistance to commonly used antibiotics (over 80% for Ceftriaxone, Cefipime, Gentamycin and Ceftazidime). The antibiotics with least resistance were Amikacin and Meropenem (21% and 7 % respectively).

Conclusion: There was a high prevalence of multidrug resistant *K. pneumoniae* isolates in the hospital, the majority originated from the New Born Unit. Resistance to third generation Cephalosporins and Gentamycin was high while Meropenem and Amikacin had the least resistance.

Key words: *Klebsiella pneumoniae*; Antibiotic resistance; Multi drug resistance; Nosocomial infections

Introduction

Klebsiella pneumoniae is a gram negative, rod shaped bacterium belonging to the family *Enterobacteriaceae*. It has in recent years become an important pathogen in nosocomial infections worldwide. Increasingly, many strains that are extended-spectrum β-lactamase (ESBL) producing as well as Carbapenem resistant are being reported as causing outbreaks in hospitals and particularly in intensive care units (ICUs) and New Born Units (NBUs) where there is great antibiotic pressure (Centers for Disease Control and Prevention, 2003; George AJ et al., 2005). The spread of these nosocomial infections occur from patient to patient, healthcare workers to patients and vice versa as well as contaminated hospital environment and equipment. Most of the infections occur in neonates, in immunocompromised patients such as critically ill patients in ICU, patients with malignancies, patients on chemotherapy, HIV infected patients and diabetic patients (Adamski J et al., 2008; Richards MJ et al., 1999; Winokur PL et al., 2001).

Treatment options for multi-drug resistant *K. pneumonia* (MDR KP) are limited; more so in resource constrained settings. Most studies on MDR KP are from developed countries with scanty data from resource limited settings. The study objective was to describe the epidemiology and antibiotic resistance pattern and trends for *K. pneumoniae* at Moi Teaching and Referral Hospital (MTRH) in Eldoret, Kenya.

Materials and Methods

Moi Teaching and Referral Hospital (MTRH) is the second largest public hospital in Kenya. It hosts Moi University School of Medicine and serves a catchment with population of about 16 million people. It has a microbiology laboratory that handles the culture and sensitivity specimen in the hospital. Blood specimens were cultured in BACTEC 9120 and BACTEC 9050 (Becton-Dickinson, New Jersey, USA) automated systems. Antibiotic sensitivity at the facility was performed by disc diffusion method and susceptibility reported based on Clinical and Laboratory Standards Institute (CLSI) susceptibility criteria. The laboratory is International Organization for

Standardization (ISO 15189) certified and has internal quality management systems in place. The culture results are manually documented in a microbiology register provided by the Kenya Ministry of Health.

Ethical approval was sought from the MTRH/ Moi University Ethics and Review Board and from the Director of MTRH before the study was conducted. The data was anonymized through unique study numbers and no patient identifiable information was collected.

This was a retrospective analysis of *K. pneumoniae* isolates in patients of MTRH for the period 2002 to 2013. Data is analyzed using SAS version 9.3 (SAS Institute Inc., Cary, NC). Normality test is conducted using Shapiro and Wilks normality test. Categorical variables are presented as frequencies and percentages while continuous variables are expressed as mean and standard deviation. Bar charts and line graphs are used to present the pictorial distribution of organisms.

Results

Majority of the study samples were from female patients (64.8%). The median age was 5 days with interquartile range of 3-15 days (Table i). *K pneumoniae* accounted for 23 % of the total isolates during the study period (281/1231). It was the most prevalent pathogenic isolate. It constituted 65.5% of NBU growths (205/313) and 50% of ICU growths (5/10). It constituted 17%, 15% and 14 % of the growths in the pediatric wards (22/130), medical wards (13/88) and obstetrics/gynecology wards (1/7) respectively. There was no *K. pneumoniae* isolated from the surgical wards (Fig i).The NBU *K. pneumoniae* isolates contributed 83% of all the hospital KP isolates (205/281). The pediatric and medical wards contributed 8% and 5% of the hospital *K. pneumoniae* isolates respectively (Fig i). *K. pneumoniae* was constantly a significant growth in the hospital over the 11 year period (Fig ii).

Table i: Demographic characteristics of patients with *K. pneumoniae* isolates at MTRH 2002-2013

| Characteristics	n (%)N=281
Age, yrs; mean(std)	4.8 (11.5)
Gender	
Male	99 (35.2)
Female	182 (64.8)
Wards*	
Adults	13 (5)
Pediatric	22 (8)
NBU	205 (83)
Obstetrics/Gynecology	1 (0)
ICU	5 (2)
Others	6 (2)

NBU-New born unit; ICU- Intensive care unit

* Percentages reflect distribution of *K. pneumoniae* among the wards. 83% of the *K. pneumoniae* isolates originated from the NBU.

Table ii: *K. pneumoniae* resistance to antibiotic groups at MTRH 2002-2013

ANTIBIOTIC GROUP	RESISTANT n (%)	SENSITIVE n (%)	INTERMEDIATE n (%)	TOTAL NO TESTED
Penicillin	226 (84.6)	37 (13.9)	4 (1.5)	267
Cephalosporins	511 (81.8)	90 (14.4)	24 (3.8)	625
Aminoglycosides	204 (49.2)	161 (38.8)	50 (12)	415
Macrolides	20 (87)	3 (13)	0 (0)	23
Carbapenems	44 (23.2)	143 (75.3)	3 (1.6)	190
Tetracyclins	38 (95)	2 (5)	0 (0)	40
Sulphonamides	79 (88.8)	9 (10.1)	1 (1.1)	89
Quinolones	50 (41.3)	71 (58.7)	0 (0)	121
Lincosamides	4 (80)	1 (20)	0 (0)	5
Vancomycin	29 (87.9)	4 (12.1)	0 (0)	33
Oxazolidinones	18 (75)	6 (25)	0 (0)	24
Minocycline	2 (40)	1 (20)	2 (40)	5
Chloramphenicol	46 (93.9)	3 (6.1)	0 (0)	49

Table iii: *K. pneumoniae* resistance pattern to specific antibiotics at MTRH 2002-2013

ANTIBIOTIC GROUP	RESISTANT n (%)	SENSITIVE n (%)	INTERMEDIATE n (%)	TOTAL NO TESTED
Ceftriaxone	68 (87.2)	9 (11.5)	1 (1.3)	78
Ciprofloxacin	32 (44.4)	40 (55.6)	0 (0.0)	72
Gentamycin	106 (82.8)	19 (14.8)	3 (2.3)	128
Amikacin	48 (21.0)	135 (59.0)	46 (20.1)	229
Meropenem	8 (7.0)	106 (92.2)	1 (0.9)	115
Cefipime	105 (85.4)	12 (9.8)	6 (4.9)	123
Ceftazidime	108 (69.7)	37 (23.9)	10 (6.5)	155
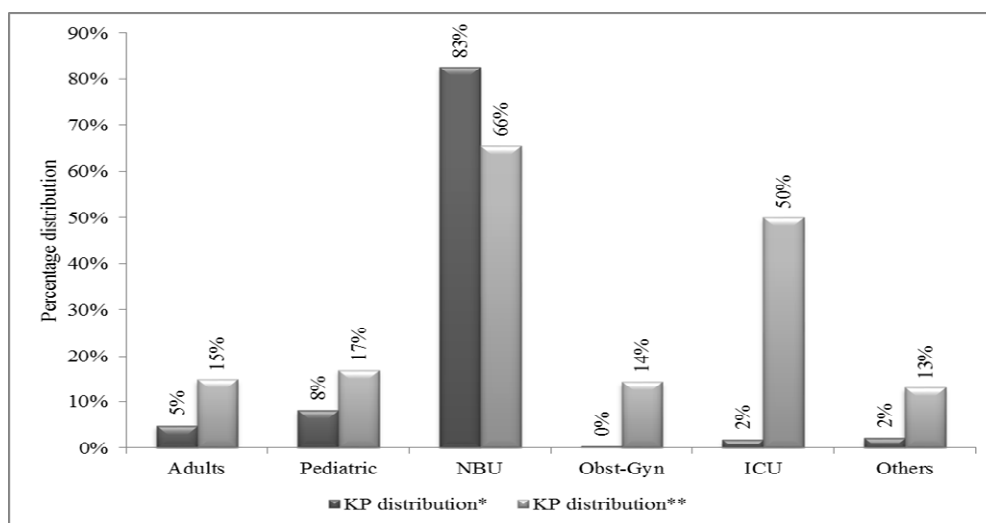
* Ward distribution of *K. pneumoniae* isolates at MTRH. 83% of the isolates originated from the NBU.
** Prevalence of *K. pneumoniae* amongst all isolates within particular wards. *K. pneumoniae* constituted 66% of the NBU isolates and 50% of the ICU isolates.

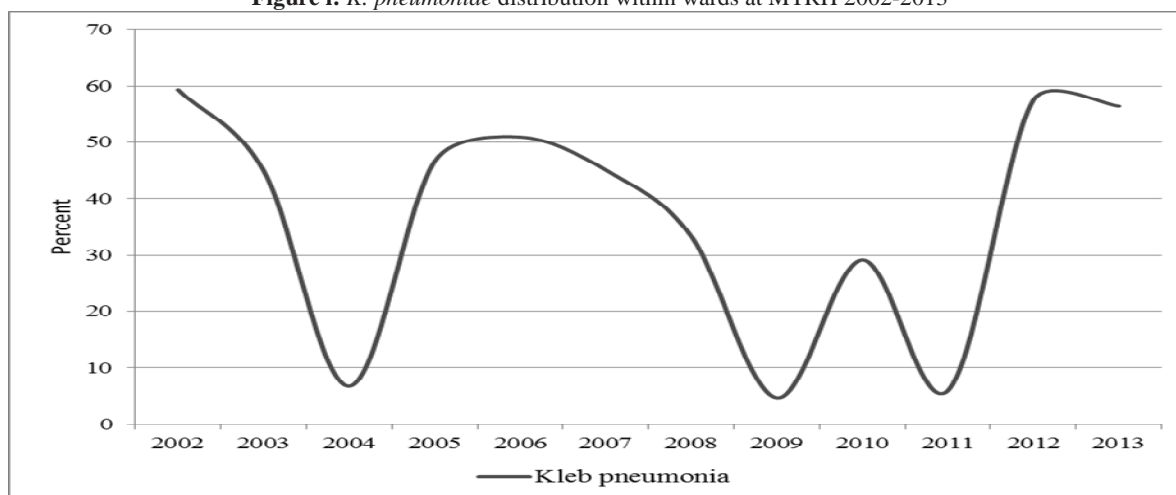**Figure i:** *K. pneumoniae* distribution within wards at MTRH 2002-2013

Figure ii: Prevalence of *K. pneumoniae* by year at MTRH 2002-2013 as a percentage of the total hospital blood culture isolates.
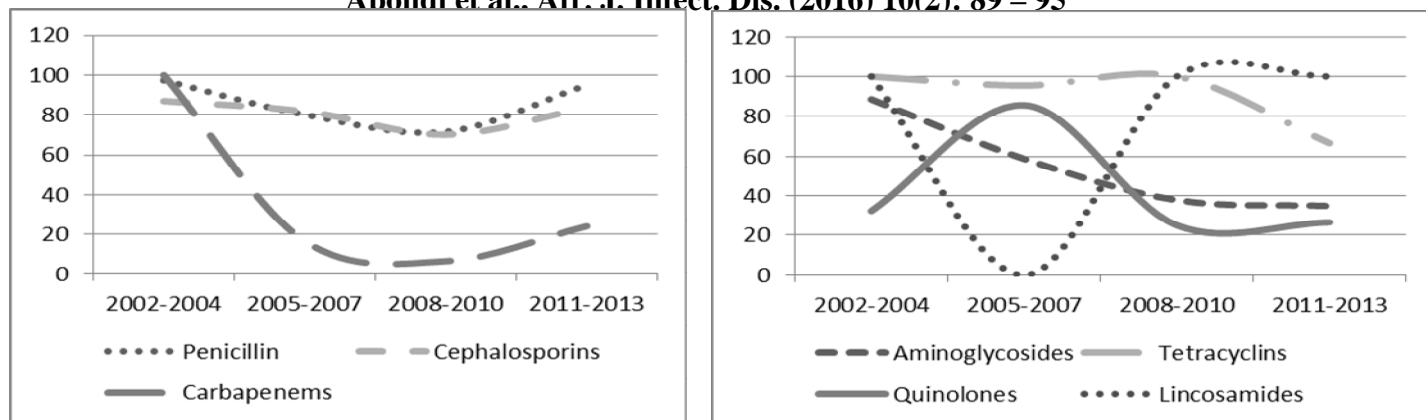
Figure iii: *K. pneumoniae* resistance pattern to antibiotic groups over time at MTRH 2002-2013. Left pane showing trend for *Penicilin*, *Cephalosporins*, and *Carbapenems*; Right pane showing trend for *Aminoglycosides*, *Tetracyclins* and *Quinolones* and *Lincosamides* antibiotic groups
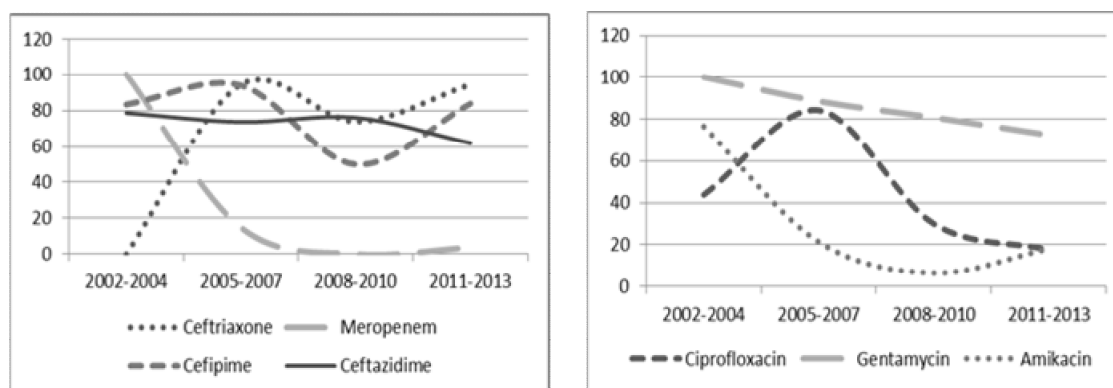

Figure iv: *K. pneumoniae* resistance pattern to individual antibiotics over time at MTRH 2002-2013. Left pane showing trend for *Ceftriaxone*, *Meropenem*, *Cefipime* and *Ceftazidimine*; Right pane showing trend for *Ciprofloxacin*, *Gentamycin* and *Amikacin* antibiotics.

Most of the isolates were multidrug resistant with highest resistance of over 80% to Penicillins, Cephalosporins, Macrolides, Tetracyclines, Sulphonamides, Lincosamides and Chloramphenicol (Table ii). Aminoglycoside and quinolone resistance was at 49.2% and 41.3% respectively. The lowest resistance rates were documented for Carbapenems (23.2 %). An analysis of the resistance levels to individual commonly prescribed antibiotics indicated resistance of over 80% to Ceftriaxone, Cefipime, and Gentamycin (Table iii). Amikacin and Meropenem had least resistance (21% and 7 % respectively).

We assessed for resistance pattern over the 11 year period for possible trends. Antibiotic class resistance pattern analysis showed persistent high resistance (>70%) to Cephalosporins and Penicillins throughout the study period. Quinolone resistance was below 40% for the study period except for 2005-2007 when it peaked to above 80%. Cephalosporin resistance declined from 100% in the year 2002-2004 to below 10% for the next 6 years followed by an increase to 20% in the period 2011-2013 (Fig iii).

Among the Cephalosporins, resistance to Ceftriazone showed a steady rise over the study period from no resistance recorded in 2002-2004 to remain constantly above 70% for the remaining period. Resistance to Cefipime and Ceftazidime was high (above 50% and 60% respectively) throughout the study period. For the Aminoglycosides, Gentamycin resistance was constantly above 70% while that of Amikacin dropped from above 70% at the beginning to below 20% in the last 6 years. Likewise, Meropenem resistance steadily reduced from 100% resistance in the first 3 years to below10% in the last 6 years. Ciprofloxacin resistance was at 40% in the first 3 years, peaked during the period 2005-2007 at 84.6% then rapidly declined thereafter.

Discussion

Klebsiella pneumonia is normal human intestinal enterobacteria. It is considered an opportunistic human pathogen and is responsible for severe nosocomial infections in immunocompromised patients, in patients with prolonged hospital stay and in patients with various implants (Adamski J et al., 2008; Mehrgan H et al., 2010; Velasco E et al., 2004) . It has been found to be a significant cause of neonatal sepsis in the developing countries (Mathure NB et al., 2002; Stephen EM et al., 2013; Tiwari DK et al., 2013; Tumaini VM et al., 2012) . In the developed world, multi drug resistant *K. pneumoniae* (MDR KP) has been documented to cause disease outbreaks

leading to significant morbidity and mortality (Lee K et al., 2010; Patricia AB et al., 2004). It was the commonest pathogenic organism isolated in our hospital during the study period and was most prevalent in the New Born Unit (NBU), the pediatric wards and Intensive Care Unit (ICU). Most of the KP isolates were multidrug resistant with high resistance to Cephalosporins, Penicillins and Gentamycin, relatively high resistance to the Quinolones and relatively moderate sensitivity to Carbepenems. Our study suggests a high prevalence of MDRKP in the hospital with possible cross contamination between the wards.

MDR KBP has been found to be resistant to third generation Cephalosporins, Aminoglycosides and Quinolones but often sensitive to Carbapenems (Bradford PA, 2001; Hirsch EB et al., 2010). In our study, resistance to Cephalosporins was very high (>80% resistance) possibly due to widespread use of ceftriaxone especially in our NBU where the largest burden of this organism was present. Ceftriaxone resistance increased rapidly during the study period to remain constantly above 70%. Cefipime and Ceftazidime, although not frequently prescribed in our set up, had very high resistance throughout the study period. Cephalosporin resistance is conferred from β-lactamase production, which is plasmid mediated and transferable to other Cephalosporins and to other gram negative enterobacteriacea such as *E. coli* (Bradford PA, 2001; George AJ et al., 2005). Similar findings were documented in Tanzania where Cefotaxime was the most prescribed antibiotic in the NBU resulting in high overall third generation Cephalosporin resistance (Stephen EM et al., 2013). Data from Korea for the year 2007 showed lower Cephalosporin resistance rates than in our study (Cefotaxime 25%, Cefepime 22%, Ceftazidime 29%, Cefoxitin 21%)) although during an ESBL KP outbreak Ceftazidime resistance rose to 47% (Lee K et al., 2010; Roh KH et al., 2008) .

Development of bacterial resistance to Aminoglycosides has been documented to be slowest amongst the antibiotics (Rennie RP et al., 1977). In Toronto, the first Gentamycin resistance was documented 7 years after first use (Curie K et al., 1978). This resistance was transferrable to other Gram Negatives, particularly *E. coli*. Gentamycin is part of many first line regimens in both developed and developing countries. In our hospital, it is often used as first line antibiotic in neonatal sepsis and has been used in the unit for over 10 years. It recorded a high level of resistance of 83% compared to Amikacin (21% resistance) which is preserved for second-line treatment. In Korea, both Gentamycin and Amikacin had relatively lower resistance of about 30% (Lee K et al., 2010). Data from Tanzania was similar to ours for Gentamycin (77% resistance) and slightly lower for Amikacin (1.45 % resistance) (Tumaini VM et al., 2012). Gentamycin resistant KP species has been found to have higher carriage in the intestinal and urinary tracts and longer durations of shedding than Gentamycin sensitive KP resulting in nosocomial hospital outbreaks (Hart CA et al., 1982).

K. pneumoniae resistance to Quinolones was 41.3% with Ciprofloxacin resistance being at 44.4 %. Similar findings were reported in India where *K. pneumoniae* resistance to Ciprofloxacin amongst children below ten years was 35.71% (Tiwari DK et al., 2013). In our study, Ciprofloxacin resistance reduced from over 80% in 2005-2007 to below 30% in 2011-2013 possibly due to reduction in prescription in our hospital over that period. Quinolone resistance has been noted to be low in NBU compared to other wards due to contra-indication of their use in newborns (n= 25, 38%, p<0.05) (Stephen EM et al., 2013). However, in our study Quinolone resistance in the medical wards was lower than the over-all resistance (36.6% versus 44.4%). Quinolone resistance is plasmid mediated and transferrable from person to person especially amongst patients with long hospital stay. Aminoglycoside exposure has been associated with Quinolone resistance in *K. pneumoniae* and *Pseudomonas aeruginosa*, suggesting the need for awareness of the potential cross resistance and thus failure of Quinolones in settings where there is widespread use of Aminoglycosides such as in our hospital (Lautenbach E et al., 2001; Masuda N et al., 1992; Strausbaugh LJ et al., 1996).

The resistance to Carbapenems was lowest at 23.2%. Resistance to Meropenem was 7.0%. Carbapenem resistant *K. pneumoniae* is considered the most resistant strain. Carbapenem resistance has been shown to result from changes in membrane permeability, high β lactamase and Cephalosporinase levels and production of carbapenemases. Evidence of carbapenemase production from a unit needs to be handled efficiently as they are associated with β lactamase production resulting in penicillin and cephalosporin resistance (Walsh TR et al., 2012). A prospective study of clinical enterobacteriacea isolates in Morocco found a Carbapenemase production rate of 2.8% (Wartiti MA et al., 2012). Data from several European countries record rates of less than 1% except during outbreaks where rates as high as 17-43% are recorded. (Chetcuti Z et al., 2014; Marina K et al., 2014) .In Kenya only seven Carbapenem resistant *K. pneumoniae* were detected in a two years study at the Aga Khan University Hospital in Nairobi (Nordmann P et al., 2011). Most of the isolates were from urine of adult patients in contrast to our study where the isolates were from blood cultures and significantly from neonates. Our results indicate higher rates of Carbapenem resistance and this should be monitored with possible genomic and epidemiologic studies to curb any further rise. There was 100% resistance to Meropenem in the period 2002-2004 (n=8) and all the samples were from the NBU.

Diagnosis and treatment of MDR KP infections and colonization in our hospital and similar hospitals in the developing countries is complicated. A multidisciplinary approach is necessary with teams including clinicians, pharmacists, and microbiologists with support from the hospital management. Prevention of spread of resistance by proper aseptic procedures such as hand washing, disinfection of equipment, reduction in ward congestion and isolation need to be intensified. Awareness on MDR organisms should be raised. Early detection of MDR KP through routine surveillance with profiling of the resistance pattern should be encouraged to avoid ineffective therapy in order curb the spread of the strain responsible for the outbreak. In one incidence in New York, increased use of Ceftazidime in treatment of Acinetobacter infections resulted in an outbreak of Ceftazidime resistant *K. pneumoniae*, and it was after detection that effective therapy was instituted (Kenneth SM et al., 1993). Attempts to reduce the multi-class resistance should also be made to regain susceptibility to cheaper and more readily available drugs. Antibiotic restriction and rotation are possible options for developing countries where access to newer antibiotics is limited. In the USA, an 80% reduction of hospital consumption of Cephalosporins resulted in a 44.0% reduction in Ceftazidime-resistant *K. pneumoniae* infection and colonization throughout the medical center (*P*<.01), a 70.9% reduction of cephalosporin resistance within all intensive care units (*P*<.001), and an 87.5% reduction within the surgical intensive care unit (*P*<.001) within 1 year of restriction (Rahal JJ et al., 1998).

Conclusion

There was a high prevalence of MDR KBP isolates in our hospital with most of the isolates in the NBU. The isolates were

highly resistant to third generation Cephalosporins and Gentamycin.

Recommendations

Stringent infection prevention control measures need to be instituted especially in the NBU to minimize the nosocomial spread of MDRKP. In case of suspected or confirmed infection with MDRKP; Carbapenems are the drug of choice for treatment. Quinolones and Amikacin may be considered where Carbapenems are unavailable. We also recommend further studies to characterize the molecular genetic composition of MDR and Carbapenem resistant *K. pneumoniae* in our set up.

Acknowledgements

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