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

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Abstract

Introduction: Klebsiella pneumoniae is a gram negative enterobacteriaceae 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. pneumonia 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 Cefazidime). 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 TESTED | NO |
|------------------|-----------------|-----------------|--------------------|--------------|----|
| 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.
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.
E. coli 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 enterobacteriaceae 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. 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). 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 transferable to other Gram Negatives, particularly E. coli. Gentamicin 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 transferable from person to person 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 enterobacteriaceae 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. In Korea, the first Gentamycin resistance was documented 7 years after first use (Curie K et al., 1978). This resistance was transferable to other Gram Negatives, particularly E. coli. Gentamicin 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).

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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

Mr. Richard Too (Head of the Microbiology Laboratory MTRH) who availed the records of the data and clarifications in an orderly and timely manner. Dr. Wilson Aruasa the Deputy director MTRH, for encouraging and supporting the study. All the people involved in any manner at all stages of this study.

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