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ASSESSMENT OF THE PREVALENCE OF MULTI-DRUG RESISTANCE ISOLATES OF *KLEBSIELLA PNEUMONIAE* AMONG THE PATIENTS AT NORTHERN AREA ARMED FORCES HOSPITAL (NAAFH) OF THE EASTERN REGION OF SAUDI ARABIA

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Abstract:

The objective of this study was to assess the prevalence of multi-drug resistance isolates of Klebsiella pneumoniae among the patients at Northern Area Armed Forces Hospital (NAAFH) of the Eastern region of Saudi Arabia. This retrospective, chart review observational study was conducted from February 1, 2016 to February 29, 2016 at Northern Area Armed Forces Hospital (NAAFH), a 330-bed community general hospital located in the Eastern region of Saudi Arabia. A total of 870 isolates were identified in 298 patients (3 isolates per patient involving multiple sites). It was observed that the risk of females being infected or colonized with K. pneumoniae was higher than males; the K. pneumoniae was more frequently encountered in hospitalized patient compared to outpatients; a greater number of isolates were obtained from medical service; and the K. pneumoniae was more likely to be isolated from the genitourinary system. Prevalence of multi-drug resistance of K. pneumoniae to antibacterial agents showed that 41% isolates were resistant to third generation cephalosporin primarily due to production of ESBLs, but this was considered statistically insignificant (RR 1.18; 95% CI, 0.96 to 1.47; p = 0.131). The K. pneumoniae producing carbapenemase (KPC) were significantly prominent in this series (RR 0.32; 95%CI, 0.23 to 0.43; p < 0.001). The rapid growth of the K. pneumoniae species that are resistant to carbapenem, a class of drugs considered the last-line of defense, is a matter of concern.

Kew Words: *Prevalence, multi-drug resistance isolates, Klebsiella pneumoniae, Saudi Arabia.*

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INTRODUCTION:

Infections caused by *Klebsiella pneumoniae* have become endemic in health care systems [1]. This organism can be found as normal flora in the mouth, skin, and intestinal tract, where it initially does not cause disease [2]. Although found in these organ systems as normal flora, *K. pneumoniae* can progress into severe bacterial infections leading to pneumonia, bloodstream infections, wound infections, urinary tract infections, and meningitis. Patients who require equipment such as catheters or ventilators are at high risk for infections. Also, a patient administered a course of broad-spectrum antibiotic treatment is at an even higher risk due to the disruption of the normal flora of the bacteria in the body, deeming it more susceptible to pathogens [2]. The principal pathogenic reservoirs for transmission of *Klebsiella* are the gastrointestinal tract and the hands of hospital personnel. Because of their ability to spread rapidly in the hospital environment, these bacteria tend to cause nosocomial outbreaks [3]. Hospital outbreaks of multidrug-resistant *Klebsiella spp.*, especially those in neonatal wards, are often caused by new types of strains, the so-called extended-spectrum-beta-lactamase (ESBL) producers [4]. What is of major concern clinically is the current onslaught of multi-drug resistant *K. pneumoniae* species that have also become resistant to carbapenems [1, 3-6]. Reports from elsewhere highlight the challenges faced by infectious disease specialists and healthcare systems management of treating these isolates owing to the limited formulary antibacterial armament [1-6]. To the best of our knowledge studies related to the assessment of the prevalence of multi-drug resistance isolates of *Klebsiella pneumoniae* among the patients in some regions of Saudi Arabia has not been carried out. Accordingly, the objective of this study was to assess the prevalence of multi-drug resistance isolates of Klebsiella *pneumoniae* among the visitor at Northern Area Armed Forces Hospital (NAAFH) of the Eastern region of Saudi Arabia.

METHODS:

This retrospective, chart review observational study was conducted from February 1, 2016 to February 29, 2016 at Northern Area Armed Forces Hospital (NAAFH), a 330-bed community general hospital located in the Eastern region of Saudi Arabia. The hospital has 40 intensive care unit beds (12 adult, 21 neonatal and 6 pediatric) with approximately 4,716 admissions per year. In addition, the hospital operates about 8 peripheral health care centers (clinics) that offer primary care (ambulatory) services to the community. The outpatient and central pharmacy are located in the hospital proper adjacent to the medical laboratory (central pharmacy). Each peripheral clinic has a pharmacy which is limited to a primary health care formulary.

Data Collection

Data were collected on all patients within NAAFH (inpatient and outpatient) in whom *K. pneumoniae* was isolated by the microbiology laboratory. This study was approved by Northern Area Armed Forces Hospital Ethics Committee (February 16, 2016). Clinical patient information was collected from the patients' antibiogram, missing patient data was accessed through the computerized physician order entry (CPOE) by the investigator. Data collected included demographic information, patient location, type of service or sub-specialty where applicable, anatomical site of the isolate. Patients treated with at least one of the following were analyzed; cefazolin, cefuroxime, ceftriaxone, cefotaxime, ceftazidime, imipenem-cilastatin, piperacillin-tazobactam, ciprofloxacin, levofloxacin, cefepime, amikacin, gentamicin, tobramycin and trimethoprim/sulfamethoxazole (TMP/SMX) in whom *K. pneumoniae* was confirmed using the CDC definitions [7] for infection. The initial *K. pneumoniae* isolate was considered the baseline isolate. Baseline resistance was defined as resistance of baseline isolate to any of the study antibacterials and multi-drug resistance was defined as resistance to any 3 of these antibacterials. Microbiologic outcomes were categorized as "susceptible", "baseline resistance", "multi-drug resistant", "extended-spectrum beta-lactamases (ESBL) producers" and "carbapenem-resistance enterobacteriaceae (CRE)". These outcomes were compared between services, between community-acquired versus hospital-acquired (nosocomial) infection.

The minimal inhibitory concentrations used to determine susceptibility thresholds for the different antibacterials aimed at *K. pneumoniae* were, according to the NAAFH guidelines ($\leq$ 8 for cefazolin, $\leq$ 4 for cefuroxime $\leq$ 8 µg/mL for piperacillin-tazobactam, < 8 µg/mL for cefepime, < 1 µg/mL for ceftazidime, $\leq$ 4 for ceftriaxone, $\leq$ 2 for cefotaxime, < 4µg/mL for imipenem-cilastatin, $\leq$ 2 µg/mL for levofloxacin, $\leq$ 1µg/mL for ciprofloxacin, < 1 for gentamicin, TMP/SMX $\leq$ 0.5/9.5 and < 2 for tobramycin). Isolates with intermediate susceptibility were considered resistant. At NAAFH, MICs for meropenem and aztreonam are not routinely performed. All collected data were entered into an Excel® spreadsheet (Microsft Corporation, Redmond. Wash.).

Data analysis

Descriptive statistics were used to summarize data. Demographic data and all other categorical variables were analyzed using the χ^2 statistic and Fischer's exact test between genders. Continuous variables such as age were analyzed using Student t-test or Mann-Whitney U-test for nonparametric data. Comparisons between the frequency of isolating *K. pneumoniae* in hospitalized patients (nosocomial) versus isolates from the community as well as the frequency of susceptible isolates compared to resistant ones were quantified using the relative risk. Multivariate regression was performed to establish correlations between variables and the Pearson's product-moment correlation coefficient (r^2) was used. Alternatively, either Kendall's tau correlation or Spearman rho correlation was used for ordinal variables where applicable. Multiple regression statistics were employed in the case of multiple variances. Data were analyzed using Stata (Version 12; StataCorp, College Station, TX, USA) statistical software. Statistical significance was defined with a p value of less than 0.05.

RESULTS:

A total of 870 isolates of *K. pneumoniae* were recovered from 298 patients (average of 2.9 isolates per patient from multiple sites). The overall average age of our study population was 50.39±28.07. Females, on average, were significantly younger than their male counterparts (46.08 ± 28.23 vs 57.76 ± 27.47; 95%CI, -18.23 to -5.1; p = 0.0006). Females were significantly more likely to be infected or colonized with *K. pneumoniae* than males (63% vs 37%; 95% CI, 0.576 to 0.686). The distribution of *K. pneumoniae* by age range indicates that most of the isolates were recovered from the 71-80 age range (22%, 66). The 31-40 age range was next with 45 isolates (15%) followed by the 21-30 (13%), 0-10 (12%) and the 41-50 (10%) age ranges. In the 51-60 (8%), 61-70 (6%) age ranges, *K. pneumoniae* was not as common as the foregoing age ranges. *K. pneumoniae* was isolated with less frequency in the 81-90 (6%), 91-100 (3%) and in the age range greater than 100 (4%) (Figure 1).

K. pneumoniae was more frequently encountered in hospitalized patients (nosocomial) compared to patients visiting outpatient clinics (80% vs 20%; 95% CI, 0.156 to 0.247). Of the patients who acquired *K. pneumoniae* from the hospital (nosocomial), a greater number were isolated from the medical service (44%) followed very closely by intensive care units (41%) [adult intensive care unit (ICU) 74%, pediatric (ICU) 19% and neonatal (ICU) 7%] (Figure 2). The *K. pneumoniae* was more likely to be isolated from the genitourinary system (46%) followed by the respiratory (25%), others (25%), and wound (18%) and less frequently encountered were *K. pneumoniae* isolated from the bloodstream (4%). These findings were found to be statistically insignificant (p = 0.878).

Prevalence of multi-drug resistance of *K. pneumoniae* (Table 1) to anti-bacterial showed that 41% isolates were resistant to third generation cephalosporin primarily due to production of ESBLs, but this was considered statistically insignificant (RR 1.18; 95% CI, 0.96 to 1.47; p = 0.131). However, resistance of *K. pneumoniae* to cephalosporin as a class (including 1st and 2nd generation cephaolosporin) was statistically significant (RR = 1.27; 95% CI, 1.14 to1.41; p < 0.001). The *Klebsiella pneumoniae* producing carbapenemase (KPC) were significantly prominent in this series (RR 0.32; 95% CI, 0.23 to 0.43; p < 0.001). All other resistance patterns of *K. pneumoniae* to formulary antibacterial were statistically non-significant.

DISCUSSION:

The prevalence of multi-drug resistant *K. pneumoniae* due to ESBL production was identified in 121 (41%) patients in this study. ESBL producing *K. pneumoniae* poses a unique challenge in the treatment and eradication of this organism given limited formulary options available. Currently, to treat ESBL-producing *K. pneumoniae* clinicians have to use carbapenem. Carbapenem are stable in the presence of hydrolytic effects of ESBLs, which may explain the consistent finding that 98% of ESBL-producing organisms retain susceptibility to either imipenem or meropenem [11-13]. These reports are consistent with our findings in that in the current study, all ESBL-producing isolates were susceptible to imipenem or meropenem, but 38% were resistant to piperacillin-tazobactam, 31% were resistant to aminoglycosides, and 37% were resistant to ciprofloxacin (Figure 2). Other reports have suggested that the inferior outcome associated with apparently active cephalosporin and β-lactam / β-lactamase inhibitors, compared with that for other antibiotic classes, could be explained by the inoculum effect [14]. This effect (in which MICs of a drug increase up to 100-fold in the presence of increased inocula) is consistently observed with cefotaxime, ceftriaxone, and cefepime against ESBL-producing organisms [14]. An inoculum effect is least frequently observed with carbapenem; piperacillin-tazobactam has an inoculum effect intermediate between those of carbapenem and cephalosporin [14]. Apart from the inoculum effect, an alternative explanation for failure of β-lactam

antibiotics is failure to achieve pharmacodynamic targets. Quinolones are not prone to substantially increase their MICs against ESBL-producing strains as the inoculum increases. The relatively poor outcome for patients treated with quinolones in this study is possibly the result of under dosing [15].

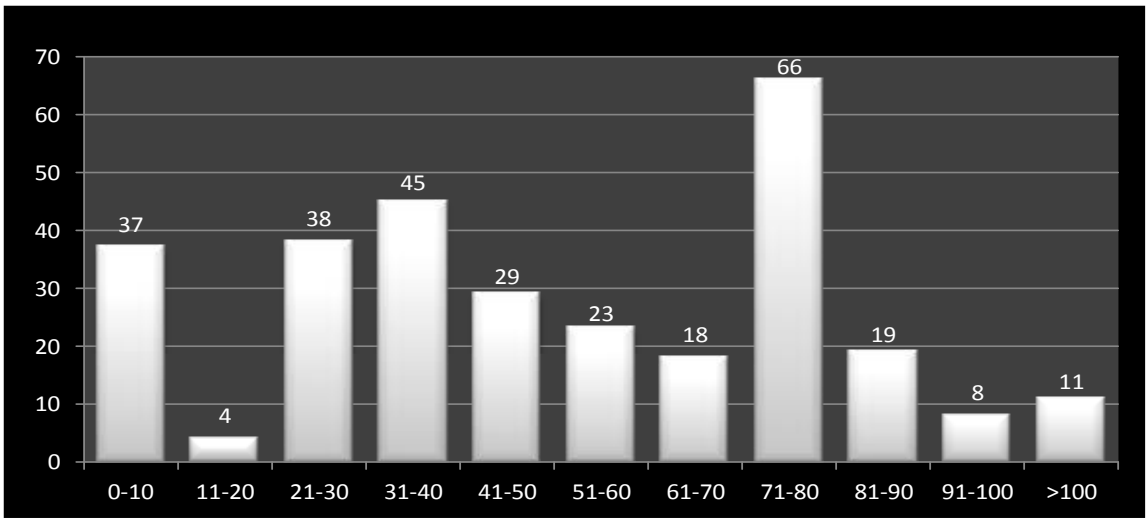
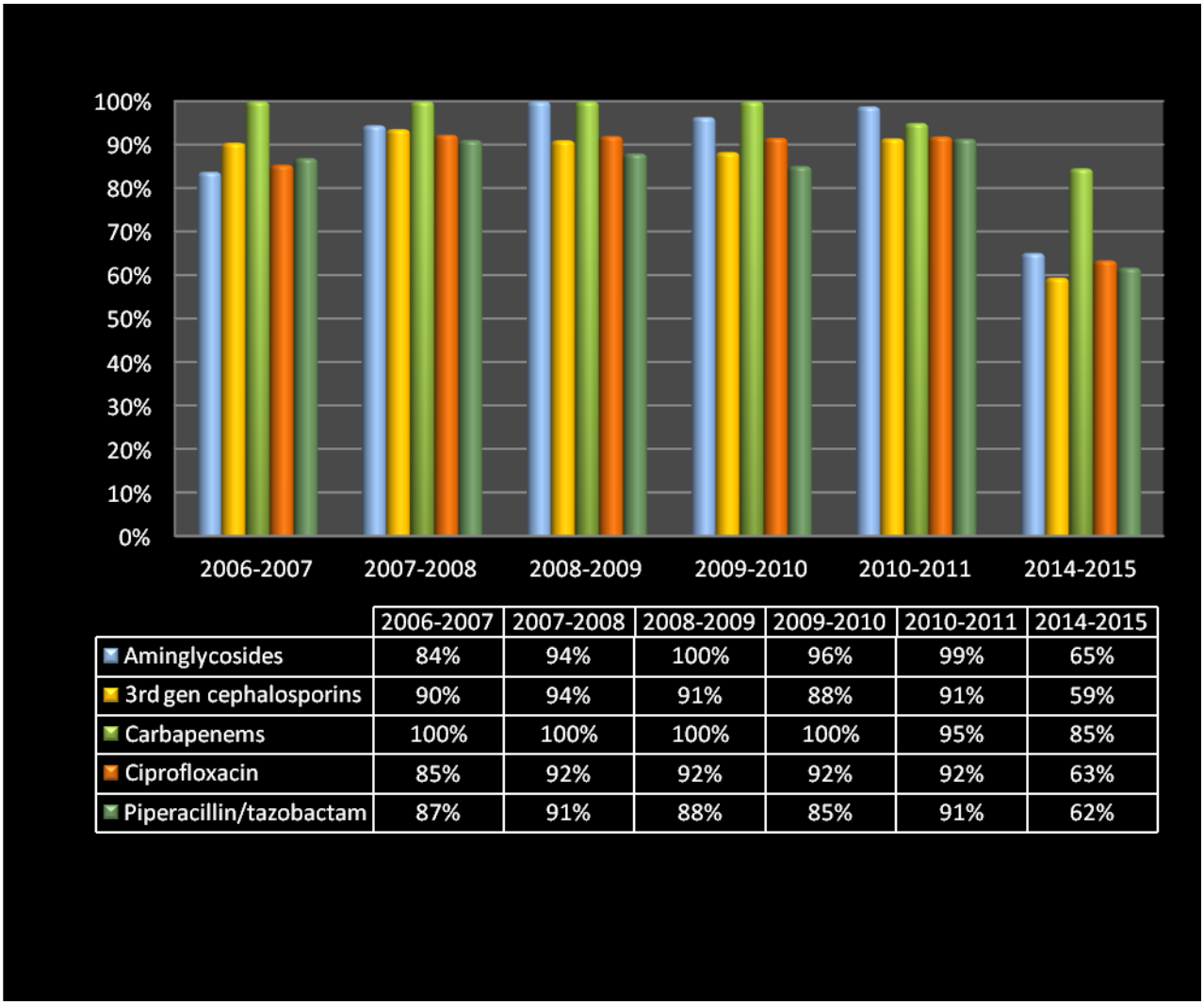


Fig 1: Prevalence of *K. pneumoniae* by age range

Table 1: Demographic, clinical and microbiological data

Parameter	Nosocomial (N = 238)	Community -acquired (N = 60)	RR	95% CI	*p*-Value
Age	55.3 ± 29.1	31.1 ± 13.7	–	-29 to -19	<0.001
Female, n (%)	141 (75%)	47 (25%)	0.76	0.64 to 0.90	= 0.005
Site of isolation					
Blood, n (%)	12(4%)	0			
Genitourinary, n (%)	93 (39%)	43 (72%)	0.55	0.44 to 0.68	= 0.000006
Respiratory, n (%)	74(31%)	0	–	–	–
Skin and skin structure infection, n (%)	43(18%)	10 (17%)	1.08	0.58 to 2.03	= 0.82
Other*, n (%)	16(7%)	7 (12%)	0.58	0.25 to 1.34	= 0.22
Intensity of culturing (susceptibility patterns)					
Antibiotic Class	Susceptible N, (%)	Resistant N, (%)	RR	95% CI	*p*-Value
Cephalosporin, n (%)	516 (58)	378 (42)	1.27	1.14 to1.41	0.001
1st generation	168 (56.38)	130 (43.62)	1.34	1.09 to 1.66	0.008
2nd generation	171 (57.38)	127 (42.62)	1.28	1.04 to 1.60	0.023
3rd generation	177 (59.40)	121 (40.60) (ESBLs)	1.18	0.96 to 1.47	0.131
Aminoglycoside, n (%)	194 (65.10)	104 (34.90)	0.93	0.74 to 1.16	0.507
Quinilone, n (%)	189 (63.42)	109 (36.58)	0.10	0.80 to 1.24	0.984
Carbapenem, n (%)	252 (84.56)	46 (15.44) (CRE)	0.32	0.23 to 0.43	<0.001
Piperacillin/tazobactam, n (%)	184 (61.74)	114 (38.26)	1.07	0.87 to 1.33	0.536
Sulfamethoxazole/trimethoprim, n (%)	178 (59.73)	120 (40.27)	1.17	0.94 to 1.45	0.167

RR = relative risk or risk ratio. CI =confidence interval; n = number of patients.



	2006-2007	2007-2008	2008-2009	2009-2010	2010-2011	2014-2015
Aminglycosides	84%	94%	100%	96%	99%	65%
3rd gen cephalosporins	90%	94%	91%	88%	91%	59%
Carbapenems	100%	100%	100%	100%	95%	85%
Ciprofloxacin	85%	92%	92%	92%	92%	63%
Piperacillin/tazobactam	87%	91%	88%	85%	91%	62%

Fig 2: Susceptibility of *K. pneumoniae* to Antibiotic classes

The increase in ESBL-producing *Klebsiella pneumoniae* can be attributable to the extensive use of third-generation cephalosporin in this study. Reports from elsewhere state that extended spectrum *β*-lactamase enzymes were first described in *K. pneumonia* and *Serratia marcescens* isolates in 1983 in Europe [16] and in *K. pneumoniae* and *Escherichia coli* isolates in 1989 in the United States [17]. Since then, there has been a marked increase in the incidence of bacteria that produce ESBL enzymes. There is strong agreement between the ESBL-producing *K. pneumoniae* data in our report compared to other reports elsewhere in that ESBLs were recorded at 41% in our report compared to 91% in the 2006-2011 surveillance report, a 50% increase (Figure 2). Our results correlate with findings from the United States where the proportion of *K. pneumoniae* strains resistant to ceftazidime increased from 1.5% in 1987 to 3.6% in 1991, and by 1993 as many as 20% of the strains were resistant to ceftazidime in some teaching hospitals [18,19]. Of 824 *K. pneumoniae* strains isolated from 15 hospitals in New York City during 1999, 34% expressed ESBL enzymes [20].

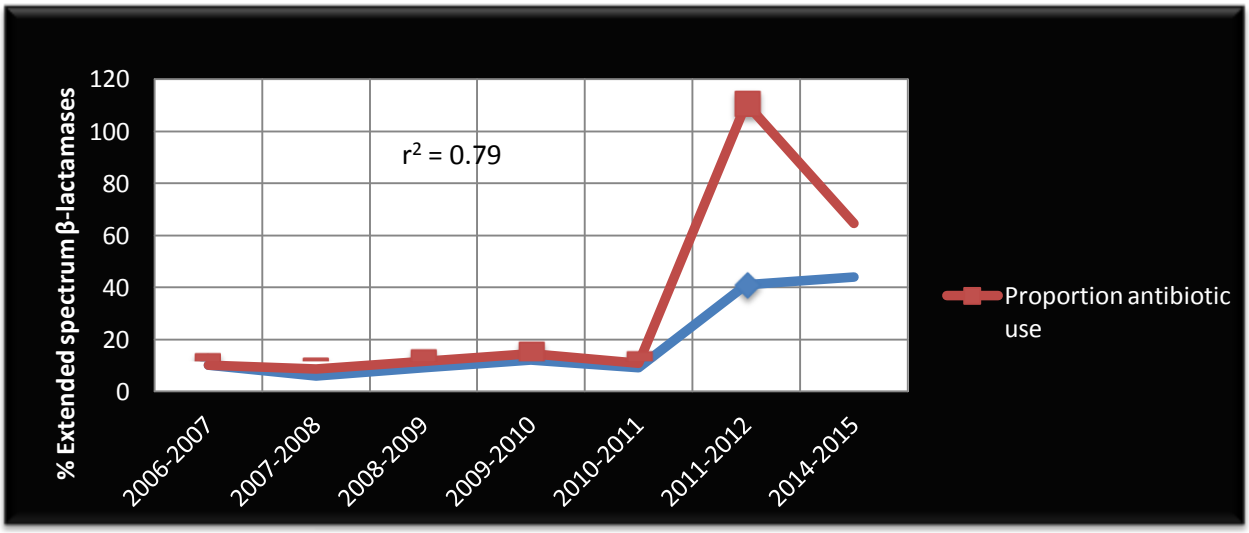


Fig 3: Proportion of 3rd generation use versus ESBL-producing

There was a strong correlation (r^2 = 0.79) between the proportion of third generation cephalosporin used and the production of ESBLs (Figure 3). Epidemiological studies suggest that the increasingly widespread use of third-generation cephalosporin is a major risk factor that has contributed to the emergence of ESBL-producing *K. pneumoniae* [21-23]. Several additional risk factors for colonization and infection with ESBL-producing organisms (not included in our report) have been reported and include: arterial and central venous catheterization, gastrointestinal tract colonization with ESBL-producing organisms, prolonged length of stay in an intensive-care unit, low birth weight in preterm infants, prior antibiotic use, and mechanical ventilation [20-22]. Furthermore, there is strong agreement between our findings and reports from elsewhere [23] in that patients in the long-term unit (medical service) were identified as mostly affected (44%) due to increased length of stay as well as patients in the ICU (41%). Carriage of this organism increases dramatically among hospitalized patients, as colonization rates increase in direct proportion to the length of stay [23] (Figure 4).

Outbreaks of ESBL-producing organisms have been described. Asymptomatic patients colonized with ESBL-producing *K. pneumoniae* can serve as reservoirs for this pathogen with subsequent patient-to-patient spread via the hands of health care workers. In addition, contaminated patient-care items and artificial fingernails worn by health care workers have been implicated in transmission [24-27]. Most studies have demonstrated a poor adherence to infection control policies as an important factor. Outbreaks of ESBL-producing *K. pneumoniae* in NICUs have been notable for high attack rates and large numbers of colonized infants [28]. The neonates at greatest risk for colonization are those with a longer length of stay, a lower estimated gestational age and/or a lower birth weight [23].

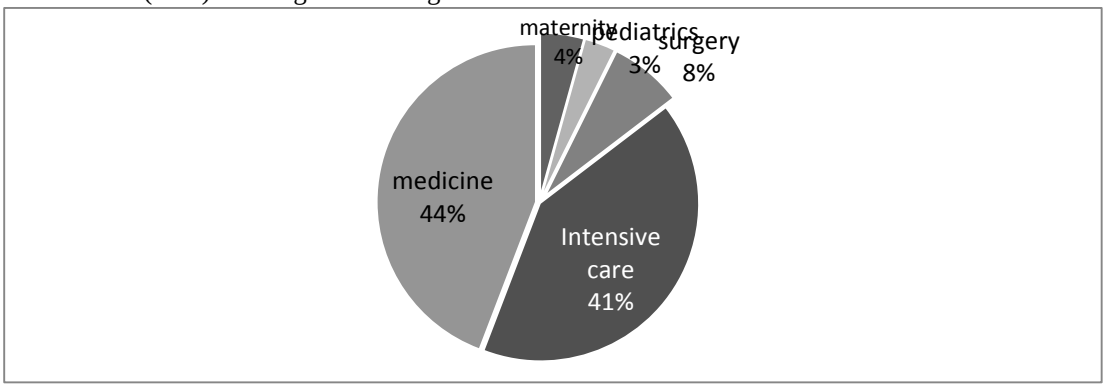


Fig 4: Isolation of nosocomial *K. pneumoniae* by service

Table 2: Relationship between carbapenem utilization and susceptibility

Year	% susceptible	Quantity used	95%CI (quantity used)	
			Lower	Upper
2007	98	9271	0.0720	0.0773
2008	99	2634	0.0932	0.0994
2009	99	3402	0.1384	0.1457
2010	100	5021	0.1199	0.1268
2011	100	4358	0.1729	0.1809
2014	95	6251	0.1214	0.1282
2015	85	4410	0.2577	0.2669

Prescribing carbapenem due to multi-drug resistance, including ESBL production (Table 2) has resulted in selection pressure that favors resistance to carbapenem through the production of *carbapenemase* [29,30] resulting in "carbapenem-resistant *K. pneumoniae*" (CRKP) [29] through production of what is known as KPC (*Klebsiella pneumoniae* carbapenemase)-type β-lactamase [29,30] which fall under what is currently known as carbapenem resistant Enterobacteriaceae (CRE) [31]. In this report, there was a weak inverse correlation (r^2 = -0.01123) between carbapenem utilization and the emergence of carbapenem resistance (Table 2). When comparing *K. pneumoniae* resistance to carbapenem between 2015 (15%) and 2007 – 2011 report (2%), it can be seen that there has been an increase in resistance no carbapenem by isolates of *K. pneumoniae* [10].

Other reports state that although CRE remain relatively uncommon in most acute-care hospitals in the United States, they have become an increasingly recognized cause of infection during the past decade, especially among *Klebsiella*, likely because of the emergence of carbapenemase-producing strains [32, 33]. In 2012, the number of facilities reporting CRE as a cause of infection was small, and spread of these organisms appears to be uneven both regionally and among facilities within regions. Fewer than 5% of short-stay acute-care hospitals reported CRE from health-care–associated infections in the first half of 2012 [32]; CRE more often were reported from LTACHs. Data from population-based surveillance suggest most CRE clinical isolates came from cultures collected outside of hospitals from patients with substantial health care exposures [31]. These findings suggest that although CRE are increasing in prevalence, their distribution is limited [31, 32].

CRE is important for several reasons. First, invasive infections (e.g., bloodstream infections) with CRE are associated with mortality rates exceeding 40% [31, 33]; this is significantly higher than mortality rates observed for carbapenem-susceptible Enterobacteriaceae. Of note, because the majority of positive cultures were from urine, overall in-hospital mortality rates associated with positive cultures were lower in the EIP CRE surveillance (4%) [33]. Second, carbapenem-resistant strains frequently possess additional resistance mechanisms that render them resistant to most available antimicrobials; pan-resistant CRE has been reported [34]. Further, novel antimicrobials for multidrug-resistant gram-negative bacilli are in early stages of development and not likely to be available soon [35]. Third, CRE can spread rapidly in health care settings [36, 3]. Fourth, Enterobacteriaceae is a common cause of community infections, and CRE have the potential to move from their current niche among health-care–exposed patients into the community [37, 38]. The *K. pneumoniae* was significantly isolated from hospitalized patients (80% vs 20%, $p < 0.001$).

CONCLUSION:

Resistance of *K. pneumoniae* to available formulary antibiotics is concerning in view of the fact that no new antibiotics are in the pipeline. What is of more concern to infectious disease specialists and healthcare systems is the rapid growth of *K. pneumoniae* species that are resistant to carbapenem, a class of drugs considered the last-line of defense. Our findings are supported by reports in another series of patients as demonstrated above. Our findings that 41% of *K pneumoniae* isolates produced ESBLs and that 15% produced KPC are disturbing. Reports have indicated that multi-drug resistant organisms are associated with increased hospital

length of stay and an increase in health care resource consumption. It's prudent that health care systems implement strategies that would arrest the spread of multi-drug resistant *K. pneumoniae*.

STUDY LIMITATIONS

The study design being retrospective poses certain challenges in missing patient data. Microbiology surveillance data were missing for certain 3 years as indicated above. Therefore, the outcomes of our findings should be interpreted with caution.

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