Current efficacy of antibiotics against Klebsiella isolates from urine samples – A multi-centric experience in Karachi

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Abstract: Due to emergence of bacterial resistant strains, the effectiveness of current antibiotic treatment without culture/sensitivity testing is questionable. Our study aims to assess the present sensitivity profiles of Klebsiella isolates from urine samples and provide options for empiric prescription in critically ill patients. Klebsiella pneumoniae isolates collected over a period of 28 months till January 2011 from 1,617 urine samples of subjects presenting with Urinary Tract Infections were identified at a local diagnostic lab using standard protocol and subjected to Kirby-Bauer disk diffusion sensitivity testing. MICs were also estimated by E-nephelometry. Among 20 drugs used, low sensitivity was found to amoxicillin (0.1%), doxycycline (11.5%), nitrofurantoin (15.5%), amoxiclav (18.2%), gentamicin (35.4%), pipemicid acid, cephradine (40.3%) and cotrimoxazole (43.1%). The isolates were more sensitive to cefuroxime (55.9%), cefixime (57.7%), ciprofloxacin (62.5%), ofloxacin (63%), ceftriaxone (66.2%), ceftazidime (66.4%), cefotaxime (66.6%), fosfomycin (77.5%) and amikacin (89.4%). The most effective were cefoperazone.sulbactam (95.8%), piperacillin.tazobactam (95.7%) and imipenem (97.7%). Self-medication, lack of awareness, and the misuse of antibiotics by doctors has exacerbated the menace of microbial resistance. The study warrants the prudent choice of drugs in adherence with prevailing sensitivity profiles.

Keywords: Klebsiella pneumoniae, antibiotics, antimicrobial resistance, clinical isolates, urinary tract infection.

INTRODUCTION

Klebsiella pneumoniae carbapenemase (KPC) - producing isolates have been reported in various countries including USA, France, Sweden, Norway, Brazil, Poland, China, Israel and Greece (Hirsch and Tam, 2010). Klebsiella is said to be responsible for 10% of nosocomial bacterial infections (Amin et al., 2009). Despite large burden of infections in developing countries, there is serious lack of epidemiological data addressing risk factors, incidence and management (Ganatra and Zaidi, 2010). Increase in its resistance is attributed to overuse of antibiotics and the rapid evolution of complex resistance mechanisms in bacteria (Gootz, 2010). Patients with prior antibiotic exposure exhibit more resistance and are associated with increased mortality (Johnson et al., 2011).

Multidrug resistance in gram negative bacteria is apparently increasing in association with plasmid- and chromosomal-encoded- beta-lactamases (Bush, 2010). Data reported to the CDC showed that carbapenem-resistant K. pneumoniae (CPKP) of all Klebsiella isolates increased from <1% in 2000 to 8% in 2007 and their treatment had not been established (Hirsch and Tam, 2010). Klebsiella has reportedly been the second most commonly encountered septic organism in patients (Javed and Memon, 2009; Yoon et al., 2011; Johnson et al., 2011), the most prevalent organism in outdoor patients and in patients with Urinary Tract Infections (UTI) (Muntaz et al., 2007; Farooqi et al., 2000), and the second most common uropathogen involved in nosocomial infection (Khan et al., 2010).

With emergence of highly resistant KPC- producing bacteria, the available choice of treatment is becoming narrower. Carbapenems like imipenem and meropenem are often the last resort for patients with Klebsiella infections like pneumonia or UTI. Alarmingly, there have been cases of CRKP infections with no other antibiotics currently in market to treat such resistant cases, thereby leading to enhanced focus on prevention of such infections in hospital and community settings. Though antibiotic resistance is a global issue, resistant organisms may be more prevalent in developing countries, including Pakistan, than in the Western world (Lagamayo, 2008). A possible reason for this could be that in a country like Pakistan, microbiological diagnosis is not available to 80% of the population, leaving doctors with no choice but to prescribe multiple antibiotics (Mushtaq et al., 2012). A study in Pakistan accordingly witnessed an increase in antibiotic resistance, for example, among K. pneumoniae causing UTI (Ullah et al., 2009).

Previous studies done in Pakistan on susceptibility patterns of pathogens causing UTI, tested only a few antibiotics, ignoring other pertinent antibiotic classes (Khan and Ahmed, 2001) and hence left clinicians with hardly any options for adequate prescription. Also, these
studies were single-centered and consequently not representative of city population as a whole (Farooqui et al., 2000; Khan and Ahmed, 2001). However, since resistance patterns continue to evolve, it is imperative to ascertain resistance patterns periodically to gauge the extent of the occurrence and provide clinicians with the provision to improve outcomes of experiential treatment. We therefore aim to determine the current resistance profile of K. pneumoniae isolated from patient urine samples collected in a diagnostic lab and its branches in Karachi as a means to offer wider drug choice for empirical therapy.

MATERIALS AND METHODS

Design and setting
Our review was a multi-centric retrospective study done from November 2008 to January 2011. Samples were collected from routine patient s coming to all 19 branches of Dr. Essa’s Laboratory and Diagnostic Centre in key areas of Karachi, Pakistan.

Clinical isolates
A total of 1,617 mid-stream clean catch urine samples yielding K. pneumoniae were included in the study. Isolates were identified by standard protocol and API-20 E system (Biomerieux) and subjected to Kirby-Bauer disk diffusion sensitivity. MICs were also estimated by E-nephelometry. Clinical isolates were tested for their sensitivity; resistance or intermediate response to these 20 locally available drugs using Oxoid discs: amikacin, gentamicin, amoxicillin, amoxiclav (Augmentin), imipenem, piperacillin.tazobactam, ceftriaxone, cefuroxime, cefixime, cefotaxime, ceftazidime, ceftriaxone, fosfomycin, pipemidic acid, oflaxacin, ciprofloxacin, doxycycline, cotrimoxazole, nitrofurantoin and cefoperazone-sulbactam. Zone diameters for each antibiotic were interpreted as Resistant, Intermediate or Sensitive. The antibiotics were from Oxoid. The zone diameters were estimated using calipers and according to the method recommended by the National Committee for Clinical Laboratory Standards (NCCLS, 1987) and the WHO.

Patient data
Subjects were either self-referrals or referred by physicians. Data of age, sex, date of investigation and any history of antibiotic usage were recorded from patients presenting with suggestive UTI. Data was analyzed using SPSS version 16.0. In case of missing values in records, the reported percentage in results is the valid percentage, ignoring missing values.

RESULTS
Out of a total of 1,617 isolates of K. pneumoniae reviewed, 19.3% (n=312) were from males and 80.7% (n=1302) from females. Table 1 shows sensitivity profile of all 20 antibiotics used: A total of 22 isolates were carbapenem-resistant. The resistance profile of imipenem is shown in fig. 1. Popularly prescribed drugs that performed poorly included amoxiclav (Augmentin) (18.2%), nitrofurantoin (15.5%), doxycycline (11.5%),

<table>
<thead>
<tr>
<th>Name of Antibiotics</th>
<th>Sensitivity Percentages</th>
<th>Resistance Percentages</th>
<th>Intermediate Percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>97.7</td>
<td>1.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Piperacillin.Tazobactam</td>
<td>95.7</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>Cefoperazone.Sulbactam</td>
<td>95.8</td>
<td>1.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Amikacin</td>
<td>89.4</td>
<td>4.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>77.5</td>
<td>10.7</td>
<td>11.9</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>66.6</td>
<td>26.3</td>
<td>7.1</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>66.4</td>
<td>26.7</td>
<td>6.9</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>66.2</td>
<td>26.6</td>
<td>7.2</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>63</td>
<td>33.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>62.5</td>
<td>34.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Cefixime</td>
<td>57.7</td>
<td>36.1</td>
<td>6.2</td>
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<tr>
<td>Cefuroxime</td>
<td>55.9</td>
<td>37.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>43.1</td>
<td>53.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Cephradine</td>
<td>40.3</td>
<td>48.9</td>
<td>10.8</td>
</tr>
<tr>
<td>Pipemidic acid</td>
<td>36.6</td>
<td>54.6</td>
<td>8.8</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>35.4</td>
<td>46.7</td>
<td>17.8</td>
</tr>
<tr>
<td>Augmentin (amoxiclav)</td>
<td>18.2</td>
<td>76.7</td>
<td>5.1</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>15.5</td>
<td>30.5</td>
<td>54.1</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>11.5</td>
<td>81.2</td>
<td>7.3</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0.1</td>
<td>99.6</td>
<td>0.3</td>
</tr>
</tbody>
</table>
and particularly amoxicillin (0.1%).

A majority of the subjects (31.7%; n=497) were aged 15-30 years. The mean age of our patients was 38.91 ± 21.53 with a range of 0-94. Fig. 2 shows age-wise distribution of the cases.

**DISCUSSION**

Clinically, UTI is said to exist when $10^5$ bacteria or more per ml of urine are found in a mid-stream specimen (Khan et al., 2010), a common baseline which was adhered to in our retrospective data. *K. pneumoniae*, an important uropathogen, is also said to be the most common cause of illness in humans after respiratory tract infections (Ram et al., 2000), thereby demanding tailored treatment.

In our study, imipenem with an efficacy of 97.7% was found to be the most effective drug against *K. pneumoniae* isolates as has been reported by Shah et al. (2010) and Mehran et al. (2010). Our results are also consistent with those observed recently on the efficacy of the drug (Akhtar, 2010; Hawser et al., 2011) and was more than the 92.5% sensitivity to carbapenems reported in Islamabad (Amin et al., 2009) and 85.1% in Egypt (Ashour and El-Sharif et al., 2009). One study in India showed only 46.66% antibiotic efficacy for imipenem (Shah et al., 2010), while another study also in India...
considered imipenem efficacy to be as high as 99.2% (Abhilash et al., 2010) although Klebsiella isolates have been showing increased resistances the world over (Ullah et al., 2009).

Amoxicillin had efficacy of 0.1%, which was consistent with findings in other studies such as that of Ullah et al. (2009). Incidentally, our data revealed that only one patient was sensitive to this antibiotic.

In addition, the first generation cephalosporin, cephradine, showed low (40.3%) sensitivity in our study, the second generation, cefuroxime, showed 55.9% efficacy, while the third generation cephalosporins; cefixime, ceftriaxone, ceftazidime and cefotaxime showed 57.7%, 66.2%, 66.4 and 66.6% efficacy respectively. In Egypt, cefotaxime, which along with ceftazidime is a potential marker for ESBL production, was reported to be significantly less effective than in our study (Ashour and El-Sharif, 2009). The same study reported ceftazidime sensitivity of 52% compared with our 66.4%, ceftriaxone sensitivity of 35.3% as opposed to our 66.2%, cefuroxime sensitivity of 32.7% compared with our 55.9%, indicating the variation of drug effects in different geographical areas. Furthermore, a study done in Iran revealed significantly higher resistance (86.6%) to ceftriaxone (Mehrgan et al., 2010) than that observed in our study in Karachi and also as reported in Egypt (Ashour and El-Sharif, 2009).

Combination antibiotics showed varying efficacies: piperacillin.tazobactam: 95.7%; cefoperazone.sultabactam: 95.8% and cotrimoxazole (Septran): 43.1 %. The results of cotrimoxazole effectiveness were noted to be currently improved as compared to the previously reported 6.52% by Ullah et al. (2009). Our study also underlined the current efficacy of piperacillin.tazobactam on our isolates for years 2009-2010 to have only 21% resistance, compared to the resistance (66.8%) for years 2005-2007 reported in Iran (Mehrgan et al., 2010). This possibly indicates evolutionary pressure encouraging the survival of resistant strains based on the extent of drug prescription by doctors during the period.

Our figures showing sensitivity of isolates to fosfomycin (77.5%) is lower than that recently reported (86.96%) in Rawalpindi (Khan et al., 2010), while the Aminoglycosides showed improved efficacy than that reported previously in India, Pakistan and Egypt (Ghanshyam et al., 2002; Ullah et al., 2009; Ashour and El-Sharif, 2009). Amikacin indeed showed an efficacy as high as 89.4% in our study while gentamicin exerted only 35.4% effectiveness; certainly, also noted in our scrutiny was one isolate that was resistant to all antibiotics except amikacin. Gentamicin was less effective than the susceptibility figure (43.4%) reported at Rawalpindi (Khan et al., 2010) and 50.4% accounted in Egypt (Ashour and El-Sharif, 2009). These significant differences may be attributed to selective pressures by drugs in different regions (Ullah et al., 2009). Our results for amikacin sensitivity were in agreement with that reported by Akhtar (2010) and Hawser et al. (2011) but in a report from neighboring Iran, the resistance to the drug was 72.8% (Mehrgan et al., 2010) as opposed to our 4.4%.

The 5-fluoroquinolone, ciprofloxacin also exerted a higher effectiveness (62.5%) than that reported by Ullah et al and Ashour et al. This may be due to a withdrawal of use of these antibiotics prior to the years of study. On the other hand, doxycycline, a tetracycline, in our data exerted poor effectiveness (11.5%), also noted in Iran (2%) in 2010 (Mehrgan et al., 2010), suggesting excessive use of the drug, inexpensive and easily available, in both areas.

As established in nature that females are more prone to UTIs because of a shorter urethra, 80.7% cases in our study were females which corroborates the results in other reports (Ram et al., 2009). However, previous reports show that Klebsiella is isolated most frequently from elderly or very young patients (Mehrgan et al., 2010), but in our survey, most of the cases i.e. 31.7% (n=497) were aged 16-30.

Nosocomial pathogens are especially multi-drug resistant due to increased selective pressure of antibiotics (Ullah et al., 2009). Sources of MDR Klebsiella include meat (Neslihan et al., 2011) and particularly catheterization and instrumentation in hospitals (Khan et al., 2010). It has been proposed that resistance in microorganisms to antibiotics emerges as rapidly as within 5 years of introduction of a new antibiotic as a therapeutic drug (Bashir et al., 2007).

This inspection of the antibiotic resistance profile of K. pneumoniae isolates emphasizes the need for implementation of the commonly-accepted but poorly- implemented concept of avoiding the misuse of antibiotics and adherence to antibiotic control policies. Solely needed is to minimize the emergence of resistant strains before prescription malpractice leads us back to the therapeutic dead-end of pre-antibiotic era. Experts have advised establishment of “antibiotic stewardship index” to gauge the proportion of a country’s gross-domestic product that is spent in publically-funded health programmes (Walsh and Toleman, 2012).

REFERENCES


