Antimicrobial Susceptibility and Distribution of \(\beta\)-lactamases in Extended-Spectrum Cephalosporins Insensitive \textit{Klebsiella pneumoniae} in Riyadh, Saudi Arabia

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Two hundred fifty \textit{Klebsiella pneumoniae} isolates were collected during October 2013 to February 2014 from two different tertiary hospitals in Riyadh, Saudi Arabia. Eighty out of 250 isolates \textit{K. pneumoniae} were selected according to reduced susceptibility to extended-spectrum cephalosporins (ESC). Phenotypic tests for extended-spectrum \(\beta\)-lactamases (ESBLs), carbapenemases, and AmpC enzyme-producing isolates were performed to detect the resistance phenotype of the isolates. The antimicrobial susceptibility testing was done. The whole collection was found to be tigecycline, colistin and fosfomycin sensitive. The resistance rates to amoxicillin, amoxicillin/clavulanic acid, piperacillin, piperacillin/tazobactam, ceftazidime, cefotaxime, ceftriaxone, cefoxitin, imipenem, amikacin, ciprofloxacin, sulphamethoxazole/trimethoprim, tetracycline were 100%, 95%, 90%, 48.75%, 77.5%, 86.25%, 86.25%, 55%, 3.75%, 7.5%, 70%, 88.75%, and 83.60%, respectively. ESBLs, carbapenemase, and AmpC production were seen in 80%, 25% and 13.75% of ESC insensitive \textit{K. pneumoniae} isolates, respectively. The prevalence of metallo- and non-metallo carbapenemase producing \textit{K. pneumoniae} isolates were 8.75% (n= 7/80) and 17.5% (n=14/80), respectively. All carbapenemase producers were also found to be ESBLs positive and/or AmpC positive. Our study documented the high rate of antibiotic resistances and high prevalences of ESBLs, AmpC and carbapenemases in \textit{K. pneumoniae} isolates.

**Key words:** AmpC, ESBL, carbapenemases, \textit{Klebsiella pneumoniae}, Saudi Arabia.

\textit{Klebsiella pneumoniae} is Gram negative, non motile, encapsulated, facultative anaerobic, lactose fermenting, rod shaped bacterium. \textit{K. pneumoniae} is common opportunistic pathogen of nosocomial infections that are associated with pneumonia, urinary tract infection (UTI), bacteremia, septicemia as well as bacterial meningitis and biliary tract infection (Grover et al., 2013; Struve and Krogfelt, 2004). Unsystematic antibiotic use is a major factor that often results in multi drug resistant strains. \(\beta\)-lactams are the most frequently used antimicrobials for empirical therapy (Grover et al., 2013). Increasing antimicrobial resistance, especially towards third and fourth generation cephalosporins, cephamycins, and carbapenems have been reported in the last decade and poses serious therapeutic problems when treating \textit{K. pneumoniae} infections in humans (Pfeifer et al., 2010). Production of \(\beta\)-lactamases is one of the tactics adopted by bacteria to develop...
resistance to β-lactams. Broad-spectrum β-lactamases are known to hydrolyze amino- and uriedopenicillins and first generation cephalosporins. ESBLs are known to hydrolyze all penicillins, extended-spectrum cephalosporins (ESC) and monobactams, but they lack hydrolytic activity on cephapencins and carbanepens. ESBLs are inhibited by β-lactamase inhibitors (clavulanic acid, tazobactam, sulbactam). AmpC β-lactamases confer resistance to penicillins, cephalosporins, cephapencins and monobactams. The organisms develop resistance to β-lactam/β-lactamase inhibitor combinations but are usually sensitive to carbaepenems. This lack of inhibition by cephapenins and β-lactamase inhibitors differentiates AmpC producers from the ESBL producers. Mechanism of resistance in AmpC can be chromosomal or plasmid mediated (Philippon et al., 2002). Carbaepenems have become the drug of choice for serious infections by gram negative hospital associated pathogens including ESBL and AmpC producing Enterobacteriaceae (Pitout, 2008; Philippon et al., 2002). Carbaepenem resistance in Enterobacteriaceae has been largely due to acquisition of carbaepenemase genes belonging to Ambler classes A, B and D β-lactamases (Queenan and Bush, 2007). There are some limited studies which characterize ESBL and carbaepenemases and there is no study is undertaken to characterize AmpC in Riyadh, Saudi Arabia. Therefore this study was devoted to update the resistance profile of K. pneumoniae isolates in Riyadh, Saudi Arabia during October 2013 to February 2014 and to characterize the phenotypic resistance mechanisms to β-lactam antibiotics.

MATERIALS AND METHODS

Bacterial isolates

K. pneumoniae isolates (n=250) were isolated from clinical specimens submitted for bacteriological testing from in-patients admitted to hospital A and hospital B, Riyadh, Saudi Arabia. K. pneumoniae isolates were collected over a period of 5 months from October 2013 to February 2014. Eighty out of 250 isolates were selected according to reduced susceptibility (zone diameter of ≤ 22 mm and/or MIC ≤ 1μg/mL) to any ESC (ceftazidime, cefotaxime, or aztreonam). With regard to the specimen site, K. pneumoniae were obtained from stool specimens (n = 23), wound swab (n = 14), urine (n = 12), endotracheal tube specimens (n = 9), sputum (n = 7), blood (n = 4), bed sore (n = 2), tissue culture (n = 2), high vaginal swab (n = 1), urethral swab (n = 1), umbilical (n = 1), cerebrospinal fluid (n = 1), aseptic fluid (n = 1), gastroectomy swab (n = 1), and catheter tip specimen (n = 1).

Bacterial Identification

Identification of K. pneumoniae was done on the basis of Gram staining, colony morphologies on MacConkey’s agar, oxidase reaction, and the biochemical tests included in the API 20E identification kit (Biomerieux, Marcy l’Etoile, France). The identified strains were stored in glycerol broth cultures at-70°C.

Preparation of inocula

Three to five well isolated colonies from an overnight tryptone soy agar plate (Merck®, Darmstadt, Germany,) were suspended in 5 mL saline (0.9% NaCl) using Vortex mixer (Daigger®, NY, USA) to obtain an inoculum equivalent to 0.5 McFarland standard. The suspension was measured spectrophotometry using Spectrophotometer (LKB® Ultrospec) at 560 nm to give absorbance 0.1-0.14. The obtained suspension was diluted 1:100 in 0.9% saline to obtain~ 5x10^5 CFU/mL. This suspension was swabbed on a Mueller-Hinton agar plate (Scharlau®, Sentmenat, Spain) and allowed to dry completely. Those plates were ready for the susceptibility testing and β-lactamase screening.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed by the disc diffusion method according to Clinical and Laboratory Standards Institute guidelines (CLSI, 2013). The antibiotics tested were amoxicillin (AMX 20mg), amoxicillin/clavulanate (AMC 20/10mg), piperacillin (PIP 100mg), piperacillin+tazobactam (TZP 100/10mg), cefotaxime (CTX 30mg), cefuroxime (CRO 30mg), ceftazidime (CAZ 30mg), imipenem (IMP 10mg), aztreonam (ATM), cefoxitin (FOX 30mg), cefotetan (CTT 30mg), anikacin (AN 30mg), ciprofloxacan (CIP 5mg), sulphamethoxazole/trimethoprim (SXT 23.75/1.25 mg), and tetracycline (TE 30 mg) (Becton, Dickinson and company, MD, USA).

The minimum inhibitory concentration (MIC) was determined by an E-strip test (Liofilchem s.r.l, Roseto, Italy) as described by the manufacturer. A laboratory control strain,
**Escherichia coli** ATCC 25922, was used in the sensitivity test and in the MIC determination. MIC to imipenem (IMP), doripenem (DOR), ertapenem (ERT), cefotetan (CTT), cefoxitin (FOX), ceftazidime (CAZ), cefepime (FEP), colistin (COL), fosfomycin (FOS), and tigecycline (TGC) was determined.

**ESBL screening**

The isolates which showed reduced susceptibility to CAZ, CTX, or ATM (zone diameter of less than or equal to 22 mm and/or MIC more than or equal 1 µg/mL) were selected to screen ESBL production (EUCAST, 2013).

**ESBL confirmatory testing**

Combination disc test and gradient test using E tests ESBL strips were performed to seek ESBL production (EUCAST, 2013).

**Combination disc test**

Two disks of CAZ (30µg) were used, each with and without clavulanate (10µg). The isolate is ESBL producer if the zone expansion diameter is ≥ 5 mm larger with clavulanate than without.

**Gradient test method**

E-test ESBL strips were in accordance with the manufacturer’s directions to seek ESBL production. The cepazidime/cefazidime-clavulanate (CAZ/CAL) ESBL Etest strip and cefepime/cefepime-clavulanate (FEP/FEL) Etest ESBL strip were used. The test is positive if ≥ 8 fold reduction is observed in the MIC of CAZ/CAL and/or FEP/FEL compared with the MIC of CAZ and/or FEP alone or if a phantom zone or deformed ellipse is present.

**AmpC screening**

Bacterial susceptibility to FOX was tested according to the standard disk diffusion method. The isolates which showing <19 mm zone size and/or MIC >8µg/mL, were selected to screen AmpC production (EUCAST, 2013).

**AmpC confirmatory testing**

E-test ESBL strip, cefotetan/cefotetan+cloxacillin (CTT/CXT), was used to seek AmpC production. The test was in accordance with the manufacturer’s directions. MIC ratio of ≥ 8 and/or the presence of a phantom zone or deformation of the ellipse were considered positive for AmpC.

**Carbapenemase screening**

Bacterial susceptibility to IMP was tested according to the standard disk diffusion method, and isolates showing <27 mm zone size and/or MIC > 0.12 µg/mL were selected to screen carbapenemase production (EUCAST, 2013).

**Modified Hodge test (MHT)**

MHT was used to detect carbapenemase production. This test was conducted according to the CLSI 2013 guidelines for search of carbapenemase production (CLSI, 2013). A 0.5 McFarland’s suspension of ATCC Escherichia coli 25922 was diluted 1:10 in sterile saline. This was inoculated on a Mueller Hinton agar plate. IMP disc was placed in the centre of the agar plate. 3-5 colonies of the test organism were picked and inoculated in a straight line, from the edge of the disc, up to a distance of at least 20 mm. The plates were incubated at 37°C overnight and they were examined next day. Isolates with cloverleaf images of inhibition zone were considered as a carbapenemase-producing K. pneumoniae.

**MBL confirmatory test**

Combination disc test and gradient test using E tests MBL strip were performed to seek MBL production (Pitout et al., 2005; EUCAST, 2013).

**Combination disc test**

Two disks of IMP (30µg) were used, each with and without ethylenediaminetetraacetic acid (EDTA) (930µg). In brief, overnight cultures at a 0.5McFarland standard were inoculated on Mueller Hinton agar. Meropenem or IMP disks were supplemented with 5 µl of 0.5M EDTA (930 µg EDTA) and the differences in zone diameters with and without EDTA were measured. The isolate is MBL producer if the zone expansion diameter is ≥ 5 mm larger with EDTA than without.

**Gradient test method**

Production of MBL was evaluated using E-test MBL strip (IMP/IMP + EDTA). A ratio of the MICs of IMP to IMP+EDTA of ≥ 8 or the presence of a phantom zone was interpreted as being positive for MBL production.

**RESULTS**

**Antimicrobial susceptibility**

The antimicrobial susceptibility testing was carried out by disc diffusion method to 80 ESC insensitive clinical isolates of K. pneumoniae. The resistant rates of antimicrobial agents are illustrated in Table 1 and Fig. 1. The whole collection of K. pneumoniae isolates was resistant
to AMX (100%). Four (5%) out of 80 isolates of *K. pneumoniae* showed intermediate resistance to IMP. The resistance rates for all isolates to AMC, PIP, PIP/TAZ, CAZ, CTX, CRO, FOX, IMP, AN, CIP, SXT and TE were 87.5%, 88.75%, 48.75%, 75%, 86.25%, 86.25%, 73.75%, 4.54%, 7.5%, 70%, 88.75%, and 78.75% respectively.

The resistance rates at Hospital A to AMC, PIP, PIP/TAZ, CAZ, CTX, CRO, FOX, IMP, AN, CIP, SXT and TE were 93.93%, 92.42%, 51.51%, 72.72%, 87.87%, 87.87%, 83.33%, 3.03%, 9.09%, 74.24%, 92.42% and 77.27%, respectively (Table 1 and Fig. 2). On the other hand, the resistance rates at Hospital B to AMC, PIP, PIP/TAZ, CAZ, CTX, CRO, FOX, IMP, AN, CIP, SXT and TE were 100%, 71.42%, 35.71%, 85.71%, 78.57%, 78.57%, 0%, 0%, 50%, 71.42% and 85.71% respectively (Table 1 and Fig. 3).

### Table 1. Antimicrobial resistance patterns of 80 *K. pneumoniae* isolated from two hospitals, Riyadh

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Total isolates (n=80)</th>
<th>Hospital A (n=66)</th>
<th>Hospital B (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td>AMX</td>
<td>80</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>AMC</td>
<td>70</td>
<td>87.5</td>
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</tr>
<tr>
<td>PIP</td>
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<td>88.75</td>
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<tr>
<td>TZP</td>
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<td>48.75</td>
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<td>CAZ</td>
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<td>CRO</td>
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<td>AN</td>
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<td>7.5</td>
<td>6</td>
</tr>
<tr>
<td>CIP</td>
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<td>70</td>
<td>49</td>
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<tr>
<td>SXT</td>
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<tr>
<td>TE</td>
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<td>78.75</td>
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</tr>
</tbody>
</table>

### Table 2. Prevalence of ESBL, AmpC, and carbapenemases in *K. pneumoniae* isolates

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Total isolates (n=80)</th>
<th>Hospital A (n=66)</th>
<th>Hospital B (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td>ESBL</td>
<td>73</td>
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<td>60</td>
</tr>
<tr>
<td>AmpC</td>
<td>11</td>
<td>13.75</td>
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<tr>
<td>Carbapenemases</td>
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</tr>
<tr>
<td>Metallo carbapenemases</td>
<td>7</td>
<td>8.75</td>
<td>7</td>
</tr>
<tr>
<td>Non-metallo carbapenemases</td>
<td>14</td>
<td>17.5</td>
<td>11</td>
</tr>
</tbody>
</table>

**Prevalence of ESBL**

Eighty isolates which showed reduced susceptibility to CAZ, CTX, or ATM (zone diameter of less than or equal 22 mm and/or MIC more than or equal 1 µg/mL) were selected to screen ESBL by combination disc test and E test ESBL strips. The results are shown in Table 2. The prevalence of ESBL in insensitive ESC *K. pneumoniae* isolates was 91.25% (n=73/80). The prevalence of ESBL in the whole *K. pneumoniae* isolates (n=250) was 29.2% (n=73/250).

The prevalence of ESBL in insensitive ESC *K. pneumoniae* isolates in Hospital and Hospital B is shown in Table 2. The prevalence of ESBL producing *K. pneumoniae* isolates in Hospital B were 92.85% (n=13/14) while the prevalence of ESBL in Hospital A *K. pneumoniae* isolates were 90.90% (n=60/66).
Prevalence of AmpC

Forty three (53.75%) out of 80 insensitive ESC *K. pneumoniae* isolates showing reduced susceptibility to FOX, (zone diameter of <19 mm and/or MIC >8µg/mL) were selected to screen AmpC by CTT/CXT E test strips. Eleven (25.6%) out of 43 isolates, which were positive in an initial screening, were AmpC positive. The prevalence of AmpC is illustrated in Table 2. The prevalence of AmpC producing *K. pneumoniae* isolates was 13.75% (n=11/80).

The prevalence of AmpC (Table 2) producing *K. pneumoniae* isolates in Hospital B were 7.14% (n=1/14). On the other hand, the prevalence of AmpC (Table 2) positive isolates in Hospital A were 15.15% (n=10/66).

Prevalence of carbapenemase

Twenty five (31.25%) out of insensitive ESC 80 isolates showing reduced susceptibility to IMP (zone diameter of <30 mm and/or MIC > 0.12 µg/mL) were selected to screen carbapenemase by MHT. Twenty one (84%) out of 25 isolates, which were positive in an initial screening, were carbapenemase positive. The prevalence of carbapenemase (Table 2) producing *K. pneumoniae* isolates were 26.25% (n=21/80). The prevalence of metallo- and non- metallo carbapenemase (Table 2) producing *K. pneumoniae* were 33.33% (n=7/21) and 66.66% (n=14/21) respectively. The prevalence of metallo- and non- metallo carbapenemase (Table 2) producing *K. pneumoniae* isolates among whole collection were 8.75% (n=7/80) and 17.5% (n=14/80) respectively. The prevalence of carbapenemase positive isolates in Hospital B were 21.4% (n=3/14), while, the prevalence of carbapenemase positive isolates in Hospital A were 27.27% (n = 18/66) (Table 2).

DISCUSSION

*K. pneumoniae* is mainly accountable for causing diseases such as nosocomial pneumonia, septicaemia, wound infections, UTI, and neonatal septicaemia (Rossolini et al., 2007). Resistance to ESC was first found in *K. pneumoniae* in 1983 (Knothe et al., 1983). The emergence of antibacterial resistance and the production of β-lactamases are responsible for the frequently observed empirical therapy failures in many bacterial infections. The alarming rate of resistance noted among these isolates in the present study, is of concern. Resistance of ESC insensitive isolates was found to coexist with resistance to two or more antibiotics such as piperacillin, ciprofloxacin, sulfamethoxazole/trimethoprim and tetracycline. Carbapenems, tigecycline and colistin have gained recent attention for their broad-spectrum antimicrobial activity. In the current study, 3.75% of the isolates were found to be resistant to imipenem.

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Resistance to ESC is increasing and may be mediated by upregulated chromosomal (AmpC) β-lactamases, efflux or porin loss or by acquired β-lactamases, including ESBLs, AmpC plasmid mediated and carbapenemases (Pfeifer et al., 2010). Several studies mainly focus on a variety of function enzymes produced in K. pneumoniae, including ESBLs, plasmid-mediated AmpCs, and carbapenemases (Marchaim et al., 2008). In the present study, the proportion of the ESBL positive cases was highest, followed by carbapenemases-producing stains and, AmpC-producing stains.

A few studies were undertaken to determine the prevalence of ESBL and carbapenemases in Saudi Arabia and there is not any study to characterize AmpC β-lactamases. Therefore, this study was devoted to determine the prevalence of ESBLs, AmpC and carbapenemases either metallo- or non-metallo-carbapenemases in ESC insensitive K. pneumoniae isolates. ESBLs are the major cause of resistance to ESC and monobactams while being inhibited by β-lactamase inhibitors. The prevalence of ESBLs among K. pneumoniae clinical isolates has increased significantly over the past two decades (Peirano and Pitout, 2010). The prevalence of ESBLs among K. pneumoniae clinical isolates varies worldwide, and these patterns rapidly change over time. The prevalence of ESBLs among K. pneumoniae clinical isolates from Saudi Arabia is also variable. There is a rarity of local reports on the prevalence of ESBL positive K. pneumoniae. Previous studies examining K. pneumoniae isolates in Saudi Arabia have reported prevalences of ESBL-producing K. pneumoniae ranging from 10.4 to 63% (Al-Qahtani et al., 2014; Marie et al., 2013; Tawfik et al., 2011; Al Johani et al., 2010; Ahmad et al., 2009; Al-agamy et al., 2009). In the present study, the prevalence of ESBL in insensitive ESC K. pneumoniae isolates was 91.25% (n=73/80) however, the prevalence of ESBL in the whole K. pneumoniae isolates (n=250) was 29.2% (n=73/250). The differences in ESBL prevalence are difficult to clarify and may owe to dissimilarities in the types and amounts of third-generation cephalosporins used and variations in isolate collection dates, time periods, and geographic areas.

Unlike other β-lactamases, AmpC β-lactamases are not inhibited by β-lactamase inhibitors. AmpC-producing organisms are generally resistant to broad-spectrum penicillins, cephamycins, oxyimino- and 7-α-methoxy-cephalosporins, and aztreonam, but are susceptible to cepfime, cefpirome, and carbapenems (Pitout and Laupland, 2008; Philippon et al., 2002). Phenotypic characterization of 80 isolates of ESC-insensitive K. pneumoniae was done. Among 80 ESC insensitive K. pneumoniae isolates, 92.25%, 13.75%, and 26.25% were found to have ESBL, AmpC, and carbapenemases, respectively. Co-production of AmpC β-lactamase and ESBL among the isolates in this study has been detected in four out of 80 K. pneumoniae isolates however AmpC was detected solely in 7 isolates.

Production of carbapenemases is an important mechanism for K. pneumoniae resistance to carbapenems (Nordmann et al., 2011; Queenan and Bush, 2007). These enzymes can hydrolyze not only carbapenems but also most 2-lactams except monobactam. So far, there have been about 70 kinds of carbapenemases reported in the world. Among Enterobactericeae, clinically significant carbapenemase are metallo carbapenemase which include Ambler class B (VIM, IMP and NDM) and serine carbapenemase which include Ambler class A (KPC), and Ambler class D (OXA-48) (Nordmann et al., 2011). Metallo carbapenemases are inhibited by EDTA while non-metallo carbapenemase are not inhibited by EDTA. In the present study, 25 (31.25%) out of 80 ESC insensitive K. pneumoniae isolates showed reduced susceptibility to carbapenem. These isolates screened for carbapenemase phenotypically by Modified Hodge Test. The prevalence of carbapenemase was 26.25% (21/80). Four isolates did not produce carbapenemase. In the present study, carbapenemase always coexist with ESBL-positive strains or AmpC-positive strains. To differentiate phenotypically between metallo carbapenemase and serine carbapenemase, MBL E test strip (IMP/ IMP+ EDTA) was used. The prevalence of metallo carbapenemase and non-metallo carbapenemase producing K. pneumoniae were 33.33% (n=7/21) and 66.66% (n=14/21) respectively. The present study was in agreement with the previous study in Saudi Arabia (Shibl et al., 2013). They reported that, the prevalence of metallo carbapenemase and non-metallo carbapenemase was 22% and 78%, respectively.
(Shibl et al., 2013). In most of studies in Saudi Arabia the metallo carbapenemase and non-metallo carbapenemase were mainly NDM and OXA-48, respectively (Zowawi et al., 2014; Al-agamy et al., 2013; Shibl et al., 2013). However from previous studies we can expect that OXA-48 and NDM are dominant carbapenemases in Saudi K. pneumoniae.

One of the limitations of this study is no genotypic identification of the resistance determinants of ESBL, AmpC and carbapenemases. PCRs for ESBL genes (TEM, SHV, CTX-M), for carbapenemase genes (KPC, OXA-48, VIM, IMP, NDM), and for AmpC (CMY, MOX, FOX, ACT, LAT, MIR, DHA, CIT) must been done in the future work.

CONCLUSION

In conclusion, this work provides the evidence of heterogeneity of determinants conferring ESC resistance in clinical K. pneumoniae isolates from Riyadh, Saudi Arabia. Our study revealed that ESBLs positive K. pneumoniae were resistant to the majority of ESC and other non-²-lactams, and some strains also carry AmpC and carbapenemase together, which lead to multidrug resistance. Our results also revealed that high prevalence of ESBLs, carbapenemase, and AmpC in ESC insensitive K. pneumoniae isolates. Empirical use of carbapenems for the treatment of infection caused by ESC insensitive K. pneumoniae isolates should be carefully monitored in Saudi hospitals. Tigecycline and colistin are the most active drugs against ESBL, AmpC and/or carbapenemase positive K. pneumoniae isolates.

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