

Original Research Article

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## ***In vitro* Susceptibility of Multidrug-Resistant *Klebsiella pneumoniae* Isolates from an Egyptian Tertiary Care Hospital to Tigecycline and Colistin**

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### ABSTRACT

#### Keywords

*Klebsiella pneumoniae*,  
Multidrug-resistant  
(MDR), Tigecycline,  
colistin, Minimum  
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The evolution of multidrug-resistant (MDR) *Klebsiella pneumoniae* constitutes a foremost public health issue, owing to the relatively limited antibiotic arsenal. Thereby, this research was undertaken to explore the *in vitro* susceptibility of MDR *K. pneumoniae* isolates from Mansoura University Hospital (MUH), Egypt to tigecycline and colistin. Over a 12-month study period, a total of 120 *K. pneumoniae* isolates were recovered. The MDR *K. pneumoniae* isolates accounted for 49.2% (59 out of 120). Amongst these isolates, 91.5% (54/59) were susceptible to tigecycline by Etest (MICs range; 0.25-1 µg/ml, MIC<sub>50</sub>; 0.5 µg/ml, and MIC<sub>90</sub>; 1 µg/ml), whereas 89.8% (53/59) were colistin-susceptible (MICs range; 0.5-2 µg/ml, MIC<sub>50</sub>; 1 µg/ml, and MIC<sub>90</sub>; 2 µg/ml). Extended-spectrum β-lactamase (ESBL) production was verified in 71.2% of the MDR strains, of which 95.2% and 92.9% were susceptible to tigecycline and colistin, respectively. In addition, 87.5% and 81.25% of the carbapenemase-positive-MDR *K. pneumoniae* strains displayed sensitivity to tigecycline and colistin, respectively. In conclusion, tigecycline and colistin exhibited striking *in vitro* activity against MDR *K. pneumoniae* isolates, including ESBL- and carbapenemase-producers. However, judicious use of these antibiotics is mandatory to avert the forthcoming threat of resistance to promising antibiotic classes.

### Introduction

*Klebsiella pneumoniae* is an opportunistic pathogen associated with both community-acquired and hospital-acquired infections (HAIs) worldwide (Lu *et al.*, 2017). Although this organism can be carried asymptotically in healthy individuals, it can also cause many kinds of infections in hospitalized patients, including pneumonia, wound, bloodstream, or urinary tract infections (Podschun and Ullmann, 1998).

Multidrug-resistant (MDR) *K. pneumoniae* was first described in the United States, then

in Europe, South America, and Asia (Winokur *et al.*, 2001). Established mechanisms of resistance include the production of extended-spectrum β-lactamases (ESBLs), cephalosporinases, and carbapenemases (Moradigaravand *et al.*, 2017). The most commonly accepted definition of MDR isolates includes absence of susceptibility to one or more agents in three or more antimicrobial categories active against the isolated bacteria (Magiorakos *et al.*, 2012). Developed in 1993, tigecycline is a broad-spectrum antibiotic representing the

first glycylycylcline of the tetracycline class of antibiotics (Chopra, 2001). *In vitro*, this antibiotic displays good antibacterial activity against most of aerobic and anaerobic bacteria including MDR Gram-negative bacteria (Rose and Rybak, 2006). Tigecycline was approved in 2005 by the U.S. Food and Drug Administration (FDA) for the treatment of complicated skin and skin structure infections (cSSSIs), and complicated intra-abdominal infections (cIAIs) (Peterson, 2008).

Colistin, a polymyxin E antibiotic, was used in the late 1950s to manage infections caused by Gram-negative bacteria. However, incidence of nephrotoxicity and neurotoxicity discouraged clinicians from using this antibiotic. It acts by altering the integrity of the outer membrane of Gram-negative bacteria causing cell lysis (Lim *et al.*, 2010). Currently, scarce data are available from Egypt concerning the susceptibility rates of MDR *K. pneumoniae* to tigecycline and colistin. Accordingly, this study was organized to determine the *in vitro* activity of tigecycline and colistin against MDR *K. pneumoniae* isolates retrieved from one Egyptian tertiary care hospital.

## Materials and Methods

### Study design

This prospective cohort study was performed over a period of 12 months (January to December 2016). Clinical samples were collected under strict aseptic precautions from patients admitted to Mansoura University Hospital (MUH), Mansoura, Egypt.

### Isolation and identification of *K. pneumoniae*

Processing of different kinds of clinical samples was achieved in the microbiology laboratory at the Microbiology Diagnostics

and Infection Control Unit (MDICU), Faculty of Medicine, Mansoura University, Egypt. *K. pneumoniae* isolates were identified based on their colony morphology, Gram staining characters, and results of the relevant biochemical reactions (Winn *et al.*, 2006).

### Antimicrobial susceptibility testing

Susceptibility of *K. pneumoniae* isolates to antibiotics was determined by the Kirby-Bauer's disc diffusion method on Muller-Hinton agar (MHA) plates (Oxoid Ltd., Basingstoke, UK) in accord with the recommendations of the Clinical and Laboratory Standards Institute (CLSI, 2016).

Antibiotic discs (Oxoid Ltd., Basingstoke, UK) used included amoxicillin (AML; 25 µg), amoxicillin/clavulanic acid (AMC; 20/10 µg), piperacillin/tazobactam (TZP; 100/10 µg), cefuroxime (CXM; 30 µg), ceftazidime (CAZ; 30 µg), ceftriaxone (CRO; 30 µg), cefotaxime (CTX; 30 µg), cefepime (FEP; 30 µg), cefoperazone/sulbactam (SCF; 75/30 µg), aztreonam (ATM; 30 µg), chloramphenicol (C; 30 µg), tetracycline (TE; 30 µg), rifampicin (RD; 30 µg), imipenem (IPM; 10 µg), meropenem (MEM; 10 µg), amikacin (AK; 30 µg), gentamicin (CN; 10 µg), ciprofloxacin (CIP; 10 µg), levofloxacin (LEV; 5 µg), trimethoprim/sulfamethoxazole (SXT; 1.25/23.75 µg), and tigecycline (TGC; 15 µg). Tigecycline susceptibility results were interpreted on the basis of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints (EUCAST, 2016). *Escherichia coli* (*E. coli*) ATCC 25922 (American Type Culture Collection, Rockville, MD) was used for quality control.

### Phenotypic detection of ESBL-producing strains

The screening test for detection of ESBL production was done as part of the routine

susceptibility testing according to the criteria set by the CLSI (CLSI, 2016). The confirmatory test for ESBL production was performed using the double-disc synergy test (DDST) with *E. coli* ATCC 25922 (ESBL-negative strain) and *K. pneumoniae* ATCC 700603 (ESBL-positive strain) were used for quality control purposes (CLSI, 2016).

### **Screening for carbapenemase production**

The modified Hodge test (MHT) was used for screening for carbapenemase production according to the CLSI recommendations using *E. coli* ATCC 25922 (CLSI, 2016).

### **Determination of the minimum inhibitory concentrations (MICs) of tigecycline and colistin**

The MICs of tigecycline (Oxoid Ltd., Basingstoke, UK) and colistin (AB Biodisk, Solna, Sweden) were assessed using the commercial MIC Etest strips as per the manufacturer's instructions.

The concentrations of tigecycline used were 0.015 to 256 µg/ml, and the concentrations of colistin were 0.016 to 256 µg/ml.

The results were interpreted according to the EUCAST breakpoints for *Enterobacteriaceae* (EUCAST, 2016).

MIC values that inhibited 50% and 90% of the isolates were accepted as MIC<sub>50</sub> and MIC<sub>90</sub>, respectively. *E. coli* ATCC 25922 was included concurrently as a quality control strain in each run of MIC measurements.

### **Statistical analyses**

All statistical analyses were performed using IBM-SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). A *P*-value < 0.05 was considered to be statistically-significant.

### **Ethical considerations**

The design of this study was approved by the local institutional review board. Informed consent was obtained from all participants included in this study.

### **Results and Discussion**

#### **Bacterial isolates**

During the study period, a total of 120 consecutive, non-duplicate (single isolate/patient) isolates of *K. pneumoniae* were identified. These isolates were most frequently recovered from blood (33.3%), followed by sputum (23.4%), urine (16.7%), wound swabs (10.8%), endotracheal aspirates (8.3%), and throat swabs (7.5%).

#### **Antibiotic susceptibility testing patterns**

By disc diffusion method, 91.7% of *K. pneumoniae* isolates demonstrated susceptibility to tigecycline, while 78.3% of the isolates were sensitive to piperacillin/tazobactam. On the other hand, 20.8% and 16.7% of the isolates were sensitive to cefotaxime and cefuroxime, respectively. None of the test isolates showed sensitivity to amoxicillin (Table 1). By DDST, 60 *K. pneumoniae* isolates (50%) were found to be ESBL-producers. The MHT results for meropenem and imipenem resistant strains revealed that 43.4% of these isolates (23/53) had the carbapenemase phenotype.

#### **Results of the MICs of tigecycline and colistin by Etest**

Among the 120 investigated *K. pneumoniae* isolates, 93.3% were tigecycline-susceptible (MICs range; 0.06-1 µg/ml, MIC<sub>50</sub>; 0.12 µg/ml, and MIC<sub>90</sub>; 1 µg/ml). The MICs of tigecycline-resistant isolates (n = 8) ranged between 4 to 128 µg/ml. Categorical

agreement between disc diffusion test and Etest was 98.3%, as 2 *K. pneumoniae* isolates had a false resistant phenotype by disc diffusion, but they were susceptible by Etest.

The MIC<sub>50</sub> and MIC<sub>90</sub> of colistin-susceptible strains (90%) were 0.25 and 1 µg/ml, respectively (MICs range; 0.125-1 µg/ml). Twelve isolates (10%) demonstrated resistance to colistin with MICs ranged between 8 to > 256 µg/ml.

### Characteristics of the MDR *K. pneumoniae* isolates

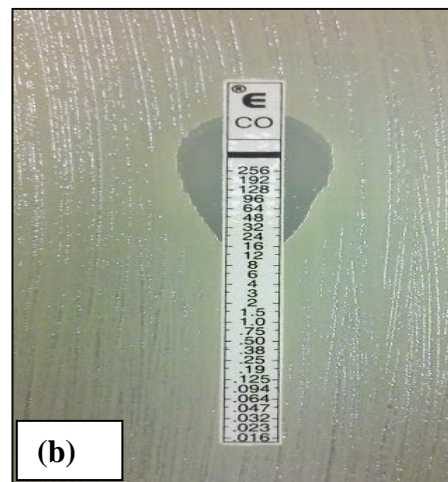
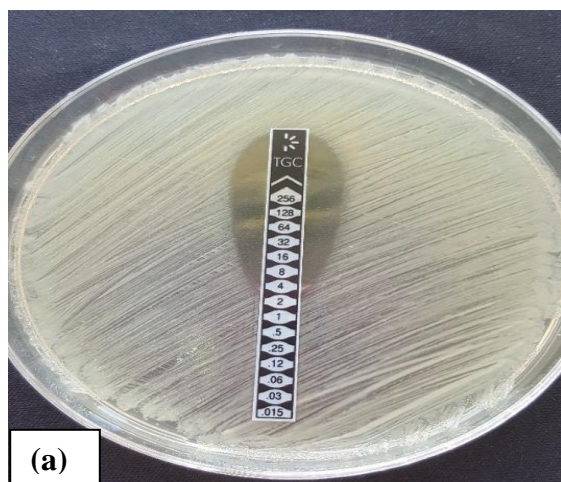
Out of 120 *K. pneumoniae*, 59 isolates were MDR (49.2%). Sample-wise distribution of these isolates is shown in Table 2. Among the MDR *K. pneumoniae* isolates, 91.5% (54/59) were susceptible to tigecycline (MICs range; 0.25-1 µg/ml, MIC<sub>50</sub>; 0.5 µg/ml, and MIC<sub>90</sub>; 1 µg/ml), and 89.8% (53/59) were colistin-susceptible (MICs range; 0.5-2 µg/ml, MIC<sub>50</sub>; 1 µg/ml, and MIC<sub>90</sub>; 2 µg/ml). No statistically-significant difference was detected between MDR *K. pneumoniae* and non-MDR isolates in respect to their susceptibility to tigecycline or colistin (*P* >

0.05). The Etest MICs of tigecycline and colistin for some representative MDR *K. pneumoniae* isolates are shown in Figure 1.

About 71.2% (n = 42) of the MDR *K. pneumoniae* isolates were confirmed to be ESBL-producers, of which 95.2% (40/42) and 92.9% (39/42) revealed tigecycline and colistin sensitivity, respectively. On the other hand, the carbapenemase phenotype was observed in 34.8% of the carbapenem-resistant-MDR *K. pneumoniae* isolates (16/46), with 87.5% (14/16) and 81.25% (13/16) of the carbapenemase-positive strains were susceptible to tigecycline and colistin, respectively.

In the last decade, infections caused by MDR *K. pneumoniae* have increased intensely with corresponding increase in morbidity and mortality (Wu *et al.*, 2012). In the contemporary study, MDR *K. pneumoniae* isolates encompassed 49.2% of the total *K. pneumoniae* isolates. This high rate of resistance could be traced to the misguided use of antimicrobials secondary to the absence of rigorous policies that dictate the prescription of antibiotics in Egypt.

**Fig.1** (a): Etest showing the minimum inhibitory concentration (MIC) of tigecycline (TGC) against one representative MDR *K. pneumoniae* isolate (MIC = 4 µg/ml; resistant), (b): Etest showing the MIC of colistin (CO) against one representative MDR *K. pneumoniae* isolate (MIC = 16 µg/ml; resistant)





**Table.1** Antibiotic susceptibility profiles of *K. pneumoniae* isolates by disc diffusion test

| Antibiotic                                    | Susceptible strains |                |
|---|---------------------|----------------|
|   | Number (120)        | Percent (100%) |
| Tigecycline (15 µg)                           | 110                 | 91.7           |
| Piperacillin/tazobactam (100/10 µg)           | 94                  | 78.3           |
| Levofloxacin (5 µg)                           | 83                  | 69.2           |
| Amikacin (30 µg)                              | 80                  | 66.7           |
| Meropenem (10 µg)                             | 67                  | 55.8           |
| Imipenem (10 µg)                              | 67                  | 55.8           |
| Ciprofloxacin (10 µg)                         | 60                  | 50             |
| Cefoperazone/sulbactam (75/30 µg)             | 60                  | 50             |
| Cefepime (30 µg)                              | 51                  | 42.5           |
| Rifampicin (30 µg)                            | 49                  | 40.8           |
| Tetracycline (30 µg)                          | 49                  | 40.8           |
| Aztreonam (30 µg)                             | 48                  | 40             |
| Gentamicin (10 µg)                            | 48                  | 40             |
| Ceftriaxone (30 µg)                           | 40                  | 33.3           |
| Trimethoprim/sulfamethoxazole (1.25/23.75 µg) | 33                  | 27.5           |
| Chloramphenicol (30 µg)                       | 32                  | 26.7           |
| Ceftazidime (30 µg)                           | 31                  | 25.8           |
| Cefotaxime (30 µg)                            | 25                  | 20.8           |
| Cefuroxime (30 µg)                            | 20                  | 16.7           |
| Amoxicillin/clavulanic acid (20/10 µg)        | 11                  | 9.2            |
| Amoxicillin (25 µg)                           | 0                   | 0              |

**Table.2** Sample-wise distribution of the recovered MDR *K. pneumoniae* isolates

| Sample       | Number | Percentage (%) |
|--------------|--------|----------------|
| Blood        | 30     | 50.8           |
| Urine        | 10     | 16.9           |
| Sputum       | 9      | 15.3           |
| ETA          | 7      | 11.9           |
| Throat swabs | 3      | 5.1            |
| Total        | 59     | 100            |

Abbreviations: MDR *K. pneumoniae*; multidrug-resistant *K. pneumoniae*, ETA; Endotracheal aspirate.

Different prevalence rates of MDR *K. pneumoniae* have been declared from different parts of the globe. In support of our conclusion, 53% MDR *K. pneumoniae* isolates were retrieved from Malaysian hospitals (Lim *et al.*, 2009). In India and Bangladesh, 54% and 56% *K. pneumoniae* isolates were found to harbor MDR

phenotype, respectively (Sikarwar and Batra, 2011, and Chakraborty *et al.*, 2016). Nevertheless, rates as high as 71.73% were detected in Pakistan (Ullah *et al.*, 2009). On the opposite side, another study conducted in Northeast Thailand illustrated that only 14% of *K. pneumoniae* isolates were MDR which is substantially lower than ours (Lim *et al.*,

2016). Such discrepant results could be ascribed to the regional variances in antibiotic usage guidelines as well as infection control strategies.

Amongst our set of MDR *K. pneumoniae* isolates, 91.5% were tigecycline-sensitive. In accord with this outcome, Araj and Ibrahim (2008), Renteria *et al.*, (2014) and Rizek *et al.*, (2015) observed that 97%, 96.8%, and 96% of the encountered MDR *K. pneumoniae* isolates were tigecycline-sensitive, respectively. In spite of these consoling results, clinical resistance to tigecycline has been increasingly reported worldwide (Sun *et al.*, 2013). This finding is upsetting, since tigecycline is one of the few clinically effective antibiotics against such MDR strains.

Etest sounds a reliable method to detect colistin MICs (Rojas *et al.*, 2017). In the current work, 89.8% of the MDR *K. pneumoniae* isolates exhibited sensitivity to colistin as determined by Etest. Concomitant with this finding, Shawky *et al.*, (2015) from a comparable study conducted in Egypt validated that 86% of their investigated isolates were colistin-sensitive. Outstandingly, Wasfi *et al.*, (2016) and Chiu *et al.*, (2017) disclosed that all of their MDR *K. pneumoniae* isolates were sensitive to colistin. Nonetheless, Tawfick *et al.*, (2016) mentioned that only 55.8 % of their MDR *K. pneumoniae* isolates collected from cancer patients at the Egyptian National Cancer Institute were colistin-sensitive. The frequent exposure of cancer patients to a multitude of antibiotics might be responsible for this high rate of colistin resistance in their study.

Extended-spectrum  $\beta$ -lactamase (ESBL)-producing *K. pneumoniae* represent authentic threat for clinicians which calls for new therapeutic agents every now and then. Noteworthy, 71.2% of the identified MDR *K.*

*pneumoniae* isolates in this study were found to be ESBL-producers, which suggests a relevance between MDR and ESBL possession. Similar rates were published by other groups of researchers (Ibrahim *et al.*, 2017).

Tigecycline susceptibility was noticed amongst 95.2% (40/42) of the detected ESBL-producing *K. pneumoniae* isolates in this work. Concordant with this finding, 98.5% tigecycline susceptibility rate was recorded amongst ESBL-producing *K. pneumoniae* collected from a nationwide Tigecycline *in vitro* Surveillance in Taiwan (Lu *et al.*, 2008). Surprisingly, only 78.8% of ESBL-producing *K. pneumoniae* isolates from a University Hospital in South-Western Germany were tigecycline-sensitive (Wienke *et al.*, 2012). Such a substantial incongruity in results could be attributed to the difference in the genetic constitution of *K. pneumoniae* strains within different countries, as well as the extent of exposure of these strains to the  $\beta$ -lactam antibiotics.

In the present study, colistin susceptibility was delineated in 92.9% (37/42) of the ESBL-producing *K. pneumoniae* isolates which concurs with results of other co-workers (Walkty *et al.*, 2009). In contrast, Galani and his group demonstrated a poor activity of colistin against *K. pneumoniae* ESBL-positive isolates (Galani *et al.*, 2008).

Advent of carbapenemase-producing *K. pneumoniae* isolates has become a crucial issue worldwide (Tada *et al.*, 2017). In the extant study, the carbapenemase phenotype was identified in 34.8% of the carbapenem-resistant-MDR *K. pneumoniae* isolates. Fortunately, tigecycline and colistin displayed a considerable activity against such strains where 87.5% and 81.25% of the carbapenemase-positive strains were susceptible to tigecycline and colistin,

respectively. These findings are in a range similar to that reported by other investigators (He *et al.*, 2015, and Zheng *et al.*, 2017).

A limitation of this study is that it is an *in vitro* study, so patients from whom the isolates were recovered did not actually receive tigecycline and or colistin therapy, accordingly the *in vivo* clinical outcome of treatment could not be deduced. Moreover, the underlying mechanisms conferring resistance to tigecycline and colistin were not elucidated, so future researches need to be carried out to decipher the aforementioned matters.

Though both tigecycline and colistin unveiled favorable *in vitro* activity against MDR *K. pneumoniae*, including ESBL-producing, as well as carbapenemase-positive strains, their prescription should be stringently audited and reserved for life-threatening infections. It is important that antibiotic policies be tailored and implemented to avoid the dissemination of these catastrophic strains. Furthermore, expansion of the existent antibiotic armamentarium by newer agents should be considered to keep pace with the speedy development of antibiotic-resistant strains.

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