Antibiotic susceptibility patterns of bacterial isolates of patients with upper respiratory tract infections

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To evaluate the antibiotic susceptibility patterns in URTIs reporting to tertiary hospitals of Lahore. A cross-sectional study employing 259 culture sensitivity reports obtained from tertiary care hospitals of Lahore. Using SPSS, descriptive statistics were used to estimate frequencies and percentages. In URTIs, S. aureus (5%) was the frequent gram-positive isolate followed by MRSA (1.5%) and MSSA (1.5%), while P. aeruginosa (15.8%) was the prevalent gram-negative isolate followed by Klebsiella (13.1%) and E. coli (6.9%). Against P. aeruginosa, ceftazidime (7.7%), cefuroxime/ceftriaxone (4.6%), amoxicillin (4.3%) and ciprofloxacin (4.2%), were tested resistant, while imipenem (11.2%), ciprofloxacin (9.2%), amikacin (9.2%), meropenem/ levofloxacin/gentamicin (8.1%) and piptaz (6.9%) were found sensitive. Against Klebsiella, carbepenems (7.3%), amikacin (6.5%), ciprofloxacin (5.4%) and gentamicin (5%) were tested sensitive, whereas, ceftazidime (8.5%), ceftriaxone (5.8%), cefaclor (5.5%), ampicillin (4.6%), co-amoxiclave (4.2%) and ciftazidime/ciprofloxacin (3.8%) were found resistant. Overall, imipenem (35%), meropenem (30.8%) and amikacin (31.9%) were the three most sensitive antibiotics, while ceftazidime (25.4%), ceftriaxone (19.2%) and ampicillin (18.5%) were the three most resistant antibiotics. Data suggested that P.aeruginosa and Klebsiella, were the most frequent bacterial isolates in URTIs of Lahore. These isolates were resistant to ampicillin, cefuroxime and ceftazidime, but were sensitive to carbapenem and aminoglycosides.

Keywords: Ceftazidime. P. aeruginosa. Amikacin. URTIs. Pakistan. Antibiotic Resistance.

INTRODUCTION

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Upper respiratory tract infection (URTI) represents a persistent health issue among all the age groups, and is considered as the most common reason of consultation and hospitalization, thus imposes enormous burden on the society (Ahmed *et al.*, 2018). The most common bacterial causes of RTIs include, *Streptococcus*, *Klebsiella*, *Pseudomonas, Staphylococcus* and *Haemophilus influenza* (Siddalingappa *et al.*, 2013), nevertheless, the causative pathogens are not identified in almost 50% of the cases (Akter *et al.*, 2014). Recently, it is estimated that the global antibiotic consumption, expressed in defined daily doses (DDDs), increased from 21.1 to 34.8 billion DDDs - an increase of 65% from 2000 to 2015 (Klein *et al.*, 2018). This increase in global antibiotic consumption was primarily driven by increased consumption in low middle-income countries (LMICs), including Pakistan. In this context, between 2000 and 2015, the highest surge in antibiotic consumption was observed among LMICs, i-e., 103% in India, 79% in China and 65% in Pakistan (Klein *et al.*, 2018).

Antibiotics are prescribed more frequently in URTIs, but irrational and abundant use of antibiotics

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increase the chances of resistance among different species and effect the cost of total treatment (Lawrence, Jevakumar, 2013). A recent study from USA suggested that 51% of patients with acute URTIs were prescribed with antibiotics although 20% of them didn't require antibiotics (Khudhair et al., 2017; Pallasch, 2003). Antibiotic resistance not only results in severe infections leading to increase mortality but can also contribute towards undue financial burden (Avorn et al., 1987; Lönnroth et al., 2015). In UK, 25,000 patient die every year due to hospital acquired infections caused by multi drug resistant microorganisms (Prestinaci et al., 2015). According to one estimate, Streptococcus pneumonia and Moraxella catarrhalis are found in 54% and 72% of children, respectively, in first year of their lives (Faden et al., 1997), while 44% children between 2 – 4 years of age exhibited colonies of *Hemophilus* influenza (Faden et al., 1997).

In developing countries URTIs are more frequently reported at primary care centers and are of great concern due to almost non-existing standard prescribing/treatment guidelines, or even if available, poor compliance by the prescribers have significant impact on patient's finances along with increase chances of antimicrobial resistance (Sulis et al., 2020). In Pakistan, The Medical Microbiology and Infectious Diseases Society of Pakistan (MMIDSP) in collaboration with Pakistan Antimicrobial Resistance Network (PARN) developed antimicrobial use guidelines and strongly advocate to use these guidelines as an antimicrobial empiric therapy tool, but not as a substitute for conclusive culture and sensitivity reported treatment (MMIDSP, 2019), with greater emphasis on the use of amoxiclays, benzyl penicillin and clarithromycin as preferred antibiotics in otitis, group A strep pharyngitis and community acquired pneumonia, respectively. Yet most of the physicians start antibiotic therapy assuming that culture would be positive rather than performing culture sensitivity test and treat patient empirically, but not according to standard criteria (Leekha et al., 2011). A recent study from Punjab, Pakistan suggested that the antimicrobials were prescribed in primacy health care centers sans any standard treatment guidelines (STGs) by the health care professionals (Sarwar et al., 2018). Likewise, we have reported previously that majority of surgeons in a tertiary care hospital of Lahore used empiric antibiotic therapy in post-surgical prophylaxis rather than following any STGs (Butt et al., 2019). A study from Pakistan demonstrated that 97% of the isolated strains of Streptococcus pneumoniae from children's blood with acute lower respiratory tract infection were resistant to at least one antimicrobial drug, while, 62% exhibited decreased susceptibility to co-trimoxazole, 39% were resistant to chloramphenicol and 31% were fully resistant (Mastro et al., 1991). However, most of the isolates were susceptible to erythromycin, cefaclor, cephalothin, ceftriaxone, cefuroxime, rifampicin, vancomycin, and clindamycin (Mastro et al., 1991). Unfortunately, in Pakistan, it is very difficult to implement nationwide standard antibiotic prescribing guidelines because of multiple factors, such as doctor's default believes about the use of antibiotics, availability of selected medicines as per the doctor's wish, unethical practices by the doctor, drug retailer and manufacturer, poor regulatory practices and non-availability of hygienic conditions (Alshami, Mohamed Ibrahim, Abdoraboo, 2011; Saleem et al., 2016; Butt et al., 2019).

In this regard, the misuse of antibiotic can only be avoided by evaluating culture sensitivity pattern of pathogen towards specific drugs, since resistance against anti-microbial drugs is directly linked with clinical practice (Saleem *et al.*, 2019). However, a very few literature evidences from Pakistan are available that evaluated the susceptibility patterns of various routinely used antibiotics in upper respiratory tract infections among patients reporting to specialized tertiary care hospitals of Lahore, Pakistan.

MATERIAL AND METHODS

Ethical Approval

The study was approved by the Ethical Committee on Human Research, University of Balochistan, Pakistan, ref #.2002/UB-2016/R-376 and Institutional Review Board (IRB), ref# 5330 of the hospital. Hospital laboratory staff obtained informed consent from patients to use their culture sensetivity reports for research purpose.

Study Design

A descriptive crossectional study was designed to esitmate the antibiotic suceptibility patterns in URTIs using laboratory culture data from tertiary care hospitals of Lahroe, Pakistan. Laboratory record data of 259 patients with RTIs of both male (n=169) and female (n=90) were obtained from specialized tertiary care hospitals of Lahore, Pakistan. Data collection period was of 6-month; June 2018 to December 2018, that included information retrival, segregating the data based on study inclusion and exclusion criteria and appropriate documentation. Laboratory data was collected by assessing all eligible patient's records listed in hospital's health information system (HIS) with confirmed upper respiratory tract infections (URTIs). Convenient sampling method was used to include the culture sensitivity reports at the time of access to the laboratory records. Out ot total, in private hospital category, 74 reports were from National hospital & medical centre (NHMC), 38 from Doctors hospital & medical centre (DHMC) and 25 from Hameed Latif hospital (HLH). In public hospital category, 34 reports were obtained from Mayo hospital (MH), 43 from Jinnah hospital & 45 from Lahore General hospital (LGH). Data obtained was sectioned into five main divisions, i-e., general demographics (age, gender), suceptibility patterns depending upon the antibiotic classes, i-e., penicillin, aminoglycosides, quinolones, carbapenems and cephalosporins. Bacteria were categorized into gram positive and negative strains based on gram staning by Chughtai Lab, Lahore - one of the largest pathology lab in Punjab, Pakistan. The degree of antibiotic susceptiblity was defined as per ISO 20776-1 standard (Rodloff et al., 2008) - a threshold based assessment to determine the degree of antibiotic effectiveness as described below;

Sensitive/Suceptible (S): suceptible bacterial strain to a given antibiotic, if the *in vitro* inhibition with the concentration of this drug resulted in higher likelihood of therapeutic success

Intermediate (I): a bacterial strain is considered intermediate to a drug, if the *in vitro* inhibition with the

concentration of this drug is associated with uncertain therapeutic effect.

Resistant (R): a bacterial strain is considered resistant to a given antibiotic if the *in vitro* inhibition with the concentration of this drug is associated with higher likelihood of therapeutic failure.

Study Settings

The data was collected from the laboratory records of specialized tertiary care, public and private, hospitals of Lahore.

Public sector: Mayo hospital 1600 beded tertiary care hospital loacted in the East of Lahore, Jinnah hospital; 1200 beded tertiary care hospital located in the middle of Lahore & Lahore general hospital; 1200 beded tertiary care hospital located in the West of Lahore.

Private sector: National hospital & medical centre; 250 beded hospital with all specialities located at defence housing authority (DHA), North of Lahore, Doctors hospital & medical centre; 250 beded hospital with all specialities located in Johar town, South of Lahore & Hameed Latif hospital; 180 beded hospital with multi specialities located in the middle of Lahore.

Study Population

The laboratory culture snesitivity reports of 259 patients (males=169, female=90) having confirmed upper respiratory tract infections (URTIs) were obtained from Chugtai lab collection center located within or outside the hospitals. Both in-patient and out-patient samples were included having confirmed diagnosis of URTIs (Jain *et al.*, 2001; Fendrick *et al.*, 2001). Patient's samples were included as per the study inclusion and exclusion criteria given below.

Inclusion criteria: The laboratory culture sensitivity report of patients above 18 and below 74 years of age with confirmed diagnosis of URTIs (Runny nose, tonsillitis, pharyngitis, sinusitis, otitis media, cough, sore throat or common cold), irrespective of gender, ethnicity, financial, employment status and disease duration and willing to participate were included in the study.

Exclusion criteria: All laboratory culture sensitivity report of patients below 18 and above 74 years of age having unconfirmed diagnosis, multiple infections and not willing to participate were excluded from the study.

Data Collection

Data was collected by employing comprehensive instrument of measure designed after extensive literature review (Mahdi et al., 2014; Carroll, Larry, 1996; Reimer, Carroll, 1998; Heikkinen et al., 2002). The questionnaire was sent to subject expert/academician for content validation, thereafter their expert opinion was incorporated to make the questionnaire more simple and objective driven. The reliability of the questionnaire was evaluated with Cronbach's alpha (0.78) using SPSS version 22. Face validation of the questionnaire was done by conducting a pilot study by collecting data of 20 samples and additional information gathered during data collection was incorporated in the final data collection form. The data obtained during the pilot study was not included in the final analysis. The field administrator docuemnted all the necessary parameters by evaluationg laboratory culture sensitivity reports of the enrolled subjects. The questionnaire was outlined into the following sections; basic demographic, specimen type, organisim type & name and drug culture sensitivity pattern.

Data Analysis

Data were analyzed using SPSS (IBM, version 22), unless otherwise stated. Descriptive analysis was

performed to estimate the percentages and frequencies via cross-tabulation. Data was segregated based on the pathogens according to susceptiblity patterns against each class of antibiotics coded as resistant, sensitive and intermediate.

RESULTS

Prevalence of bacterial isolates

Gender wise prevalence of bacterial isolates are shown in Figure S1 & Table I. Out of total culture samples (n=259) 169 were males (65.4%) and 90 were females (34.6%). Only 42.7% males samples exhibited growth compared to 49% female samples (Figure S1). Besides, out of 259 selected culture samples, only 61.5% test reports had bacterial growth while 38.5% reports had no growth (Table I).

Data regarding gender wise prevalence of bacterial isolates are summarized in Table I. Among the grampositive category, (Staphylococcus aureus) S. aureus (5%) was the most frequent isolate followed by (Methicillin resistant staphylococcus aureus) MRSA (1.5%) and (Methicillin sensitive staphylococcus aureus) MSSA (1.5%). In gram-negative category, (Pseudomonas aeruginosa) P. aeruginosa (15.8%) was the most prevalent isolate followed by Klebsiella (13.1%) and (Escherichia coli) E. coli (6.9%). In both males and females, S. aureus (M:1.9%, F:3.1%) was the most prevalent gram-positive isolate, while, P. aeruginosa (M:11.9%, F:3.8%), Klebsiella (M:9.6%, F:3.5%) and E.coli (M:5.8%, F:1.2%) were the most prevalent gram-negative isolates (Table I). However, the frequency of unknown isolates was much higher in gram-positive (6.2%) category in comparison to gramnegative category (1.2%) (Table I).

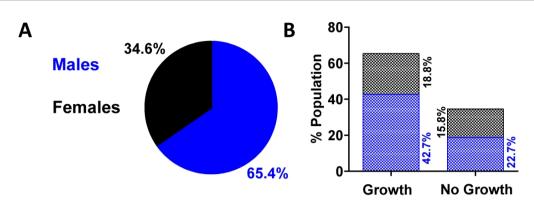


FIGURE S1 - Frequency of culture growth and susceptibility patterns of various antibiotics against Gram-positive and Gram-negative Bacteria.

Pathogen type	Pathogen	Specimen	No. of Isolates, n=259 (%)	Males, <i>n</i> =169 (%)	Females, <i>n</i> =90 (%)
	Staphylococcus. Aureus	Throat Swab	13 (5)	5 (1.9)	8 (3.1)
	Streptococcus	Throat Swab	3 (1.2)	1 (0.4)	2 (0.8)
Gram+ <i>ve</i> Bacteria	Methicillin resistant staphylococcus aureus	Throat Swab	4 (1.5)	2 (0.8)	2 (0.8)
	Methicillin Sensitive staphylococcus aureus	Throat Swab	4 (1.5)	3 (1.2)	1 (0.4)
	Others	Throat Swab	16 (6.2)	5 (1.9)	1 (0.4)
	Hemophilus. Influenza	Throat Swab	2 (0.8)	2 (0.8)	0 (0)
	Enterobactor	Ear Swab	2 (0.8)	1 (0.4)	1 (0.4)
	Proteus Mirabilis	Throat Swab	2 (0.8)	2 (0.8)	0 (0)
	Escherichia coli	Throat Swab	18 (6.9)	15(5.8)	3 (1.2)
Gram -ve Bacteria	Klebsiella	Sputum	34 (13.1)	25(9.6)	9 (3.5)
Ductoriu	Pseudomonas aeruginosa	Throat Swab	41 (15.8)	31(11.9)	10 (3.8)
	Citrobacter	Throat Swab	2 (0.8)	1 (0.4)	1 (0.4)
	Acinetobacter	Throat Swab	10 (3.8)	9 (3.5)	1 (0.4)
	Others	Throat Swab	3 (1.2)	3 (1.2)	0 (0)
	Candida	Throat Swab	11 (4.2)	5 (1.9)	6 (2.3)
No Bacterial Growth	Normal Flora	Ear Swab	4 (1.5)	1 (0.4)	3 (1.2)
Growth	None	Nasal Swab	101(38.9)	59 (22.7)	42 (16.2)

TABLE I - Gender wise prevalence of bacterial isolates

Antibiotic susceptibility patterns

Penicillin sensitivity patterns: As shown in Table II, *MSSA* in gram-positive category was sensitive with co-amoxiclave (1.5%). In gram-negative category, Piptaz had shown maximum sensitivity with *P. aeruginosa* (6.9%), *Klebsiella* (5.4%) and *E. coli* (3.1%).

Penicillin resistant patterns: MSSA was resistant to ampicillin (1.2%) and amoxicillin (1.2%). Ampicillin

(4.6%) and co-amoxiclave (4.2%) were also tested resistant to *Klebsiella*,. Ampicillin was tested resistant to *P. aeruginosa* (4.3%) and *E. coli* (3.1%), while *E. coli* was tested resistant to co-amoxiclave in 3.5% reports.

Overall, both ampicillin (18.5%) and co-amoxiclave (11.2%) were resistant to upper respiratory tract pathogens, while piptaz was found sensitive in 19.2% reports (Table II).

TABLE II - Penicillin Susceptibility Patterns against Respiratory Tract Pathogens

		Penicillin Susceptibility Patterns											
Pathogen Type	Pathogen	Amoxicillin, n (%)			Aı	mpicillin, <i>i</i>	ı (%)	Co-a	amoxiclave	e, n (%)	Р	iptaz, n (%	(0)
J F -		S	R	Ι	S	R	Ι	S	R	Ι	S	R	I
	S. aureus	1 (0.4)	2 (0.8)	10 (3.8)	0 (0)	1 (0.4)	12 (4.6)	2 (0.8)	1 (0.4)	10 (3.8)	0 (0)	0 (0)	13 (5)
Gram+ve	Streptococcus	1 (0.4)	0 (0)	2 (0.8)	2 (0.8)	1 (0.4)	0 (0)	2 (0.8)	0 (0)	1 (0.4)	1 (0.4)	0 (0)	2 (0.8)
Bacteria	MRSA	0 (0)	2 (0.8)	2 (0.8)	0 (0)	2 (0.8)	2 (0.8)	0 (0)	2 (0.8)	2 (0.8)	0 (0)	0 (0)	4 (1.5)
	MSSA	0 (0)	3 (1.2)	1 (0.4)	0 (0)	3 (1.2)	1 (0.4)	4 (1.5)	0 (0)	0 (0)	0 (0)	0 (0)	4 (1.5)
	Others	0 (0)	4 (1.9)	1 (0.4)	0 (0)	4 (1.9)	1 (0.4)	2 (0.8)	1 (0.4)	3 (1.2)	0 (0)	0 (0)	6 (2.3)
	H. Influenzae	0 (0)	0 (0)	2 (0.8)	1 (0.4)	1 (0.4)	0 (0)	0 (0)	0 (0)	2 (0.8)	1 (0.4)	0 (0)	1 (0.4)
	Enterobactor	0 (0)	0 (0)	2 (0.8)	0 (0)	1 (0.4)	1 (0.4)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	2 (0.8)
	P. Mirabilis	1 (0.4)	0 (0)	1 (0.4)	1 (0.4)	1 (0.4)	0 (0)	1 (0.4)	0 (0)	1 (0.4)	0 (0)	0 (0)	2 (0.8)
	E. coli	0 (0)	0 (0)	18 (6.9)	2 (0.8)	8 (3.1)	8 (3.1)	1 (0.4)	9 (3.5)	8 (3.1)	8 (3.1)	3 (1.2)	7 (2.7)
Gram-ve Bacteria	Klebsiella	0 (0)	3 (1.2)	31 (11.9)	1 (0.4)	12 (4.6)	21 (8.1)	3 (1.2)	11 (4.2)	20 (7.7)	14 (5.4)	4 (1.5)	16 (6.2
	P. aeruginosa	0 (0)	0 (0)	41 (15.8)	1 (0.4)	11 (4.3)	29 (11.2)	4 (1.5)	2 (0.8)	35 (13.5)	18 (6.9)	6 (2.3)	17 (6.5)
	Citrobacter	0 (0)	0 (0)	2 (0.8)	1 (0.4)	1 (0.4)	0 (0)	1 (0.4)	1 (0.4)	0 (0)	0 (0)	0 (0)	2 (0.8)
	Acinetobacter	0 (0)	0 (0)	10 (3.8)	1 (0.4)	1 (0.4)	8 (3.1)	1 (0.4)	0 (0)	9 (3.5)	5 (1.9)	2 (0.8)	3 (1.2)
	Others	0 (0)	1 (0.4)	2 (0.8)	0(0)	1 (0.4)	2 (0.8)	1 (0.4)	0 (0)	2 (0.8)	0 (0)	0 (0)	3 (1.2)
No	Candida	0 (0)	0 (0)	11 (4.2)	0(0)	1 (0.4)	10 (3.8)	0 (0)	1 (0.4)	10 (3.8)	1 (0.4)	0 (0)	10 (3.8
Bacterial	Normal Flora	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)
Growth	None	0 (0)	0 (0)	101 (38.8)	0 (0)	0 (0)	100 (38.5)	0 (0)	0 (0)	100 (38.5)	0 (0)	0 (0)	99 (38.
Fotal		3 (1.2)	15 (6.2)	241 (92.7)	10 (3.8)	49 (18.5)	199 (76.9)	22 (8.5)	28 (11.2)	209 (80.4)	48 (19.2)	15 (5.8)	195 (75

Abbreviations: S; sensitive, R; resistant, I: intermediate, S. aureus: Staphylococcus aureus, MRSA: Methicillin resistant staphylococcus aureus, MSSA: Methicillin sensitive staphylococcus aureus, H. Influenza: Hemophilus influenza, P. merabilis: Proteus merabilis, E. coli: Escherichia coli, P. aeruginosa: Pseudomonas aeruginosa.

Cephalosporin sensitivity patterns: in gram-positive category, *MSSA* was found sensitive with ceftazidime (1.5%), cefaclor (1.5%) and ceftriaxone (1.5%). Out of total, 2.7% *Klebsiella* isolates were sensitive with

ceftazidime and ceftriaxone, while, 6.9% and 3.1% *P. aeruginosa* isolates were sensitive with ceftazidime and ceftriaxone, respectively (Table III).

TABLE III - Cephalosporin Susceptibility Patterns against Respiratory Tract Pathogens

		Cephalosporin Susceptibility Patterns												
Pathogen Type	Pathogen	Ceftazidime, n (%)			Ce	faclore, <i>n</i>	(%)	Ce	furoxime,	n (%)	Cef	triaxone, <i>i</i>	ı (%)	
Type		S	R	I	S	R	Ι	S	R	I	S	R	Ι	
	S. aureus	1 (0.4)	2 (0.8)	10 (3.8)	1 (0.4)	0 (0)	12 (4.6)	1 (0.4)	2 (0.8)	10 (3.8)	2 (0.8)	2 (0.8)	9 (3.5)	
	Streptococcus	3 (1.2)	0 (0)	0 (0)	2 (0.8)	0 (0)	1 (0.4)	1 (0.4)	0 (0)	2 (0.8)	3 (1.2)	0 (0)	0 (0)	
Gram +ve Bacteria	MRSA	0 (0)	2 (0.8)	2 (0.8)	0 (0)	1 (0.4)	3 (1.2)	0 (0)	2 (0.8)	2 (0.8)	0 (0)	2 (0.8)	2 (0.8)	
Ductoria	MSSA	4 (1.5)	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	3 (1.2)	0 (0)	1 (0.4)	4 (1.5)	0 (0)	0 (0)	
	Others	3 (1.2)	1 (0.4)	2 (0.8)	3 (1.2)	1 (0.4)	2 (0.8)	4 (1.5)	1 (0.4)	1 (0.4)	4 (1.5)	1 (0.4)	1 (0.4)	
	H. Influenzae	1 (0.4)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.4)	2 (0.8)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.4)	
	Enterobactor	1 (0.4)	1 (0.4)	0 (0)	0 (0)	1 (0.4)	1 (0.4)	0 (0)	1 (0.4)	1 (0.4)	0 (0)	1 (0.4)	1 (0.4)	
	P. Mirabilis	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	2 (0.8)	2 (0.8)	0 (0)	0 (0)	1 (0.4)	1 (0.4)	0 (0)	
	E. coli	7 (2.7)	10 (3.8)	1 (0.4)	2 (0.8)	9 (3.5)	7 (2.7)	2 (0.8)	9 (3.5)	7 (2.7)	5 (1.9)	7 (2.7)	6 (2.3)	
Gram-ve	Klebsiella	7 (2.7)	22 (8.5)	5 (1.9)	3 (1.2)	13 (5.5)	17 (6.5)	4 (1.5)	8 (3.1)	22 (8.5)	7 (2.7)	15 (5.8)	11 (4.2)	
Bacteria	P. aeruginosa	18 (6.9)	20 (7.7)	3 (1.2)	3 (1.2)	10 (3.8)	28 (10.8)	1 (0.4)	12 (4.6)	28 (10.8)	8 (3.1)	12 (4.6)	21 (8.8)	
	Citrobacter	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	2 (0.8)	1 (0.4)	1 (0.4)	0 (0)	2 (0.8)	0 (0)	0 (0)	
	Acinetobacter	2 (0.8)	5 (1.9)	2 (0.8)	1 (0.4)	2 (0.8)	7 (2.7)	0 (0)	2 (0.8)	8 (3.1)	1 (0.4)	7 (2.7)	2 (0.8)	
	Others	2 (0.8)	0 (0)	1 (0.4)	0 (0)	1 (0.4)	2 (0.8)	1 (0.4)	1 (0.4)	1 (0.4)	2 (0.8)	0 (0)	1 (0.4)	
	Candida	0 (0)	1 (0.4)	10 (3.8)	0 (0)	1 (0.4)	10 (3.8)	0 (0)	1 (0.4)	10 (3.8)	0 (0)	1 (0.4)	10 (3.8)	
No Bacterial	Normal Flora	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)	
Growth	None	0 (0)	2 (0.8)	99 (38.1)	0 (0)	0 (0)	101 (38.8)	0 (0)	0 (0)	100 (38.7)	0 (0)	1 (0.4)	100 (38.5)	
Total		49 (18.8)	66 (25.4)	143 (55)	20 (7.7)	39 (15)	200 (76.9)	22 (8.5)	40 (15.4)	197 (76.2)	40 (15.4)	50 (19.2)	169 (65)	

Abbreviations: S; sensitive, R; resistant, I: intermediate, S. aureus: Staphylococcus aureus, MRSA: Methicillin resistant staphylococcus aureus, MSSA: Methicillin sensitive staphylococcus aureus, H. Influenza: Hemophilus influenza, P. merabilis: Proteus merabilis, E. coli: Escherichia coli, P. aeruginosa: Pseudomonas aeruginosa.

Cephalosporin resistant patterns: In gram-negative category, *Klebsiella* was tested resistant to ceftazidime (8.5%), ceftriaxone (5.8%) and cefaclor (5.5%). *P. aeruginosa* was resistant to ceftazidime (7.7%), cefuroxime (4.6%), ceftriaxone (4.6%) and cefaclor

(3.8%). Besides, *E. coli* was tested resistant to ceftazidime in 3.8% cases followed by cefaclor (3.5%) and cefuroxime (3.5%) (Table III).

Overall, upper respiratory tract pathogens (URTPs) demonstrated significant resistance towards

cephalosporin, ceftazidime (25.4%), ceftriaxone (19.2%), cefuroxime (15.4%) and cefaclor (15%), but were sensitive with ceftazidime (18.8%), ceftriaxone (15.4%), cefuroxime (8.5%) and cefaclor (7.7%) (Table III).

Carbepenems and aminoglycosides sensitivity patterns: both imepenem (1.5%) and meropenem (1.5%) were tested sensitive with *MSSA*. Against gram-negative microorganisms, imipenem was tested sensitive with *P. aeruginosa* (11.2%), *Klebsiella* (7.3%) and *E. coli* (5.4%). Meropenem was tested sensitive with *P. aeruginosa* (8.1%), *Klebsiella* (7.3%) and *E. coli* (5.8%).

In aminoglycosides class, *MSSA* was sensitive for both gentamicin and amikacin in 1.5% of the isolates. Gentamicin was tested sensitive with *P. aeruginosa* (8.1%), *Klebsiella* (5%) and *E. coli* (3.8%), while 9.2%, 6.5% and 4.2% of *P. aeruginosa*, *Klebsiella* and *E. coli* isolates were tested sensitive with amikacin, respectively. Tobramycin was tested sensitive with *P. aeruginosa* (2.3%), *Klebsiella* (2.3%) and *E. coli* (1.9%).

Overall, compared to other antibiotics, imipenem (35.1%) and meropenem (30.8%) exhibited better efficacy/ sensitivity against URTPs (Table IV).

			Carbapenem Susceptibility Patterns							Aminoglycosides Susceptibility Patterns							
Pathogen Type	Pathogen	Imipenem, <i>n</i> (%)			Mero	openem,	n (%)	Gent	amicin,	n (%)	Am	ikacin, <i>n</i>	e (%)	Tob	ramycin, <i>i</i>	n (%)	
1,pc		s	R	Ι	s	R	I	s	R	I	S	R	Ι	S	R	I	
	S. aureus	2 (0.8)	0 (0)	11 (4.2)	1 (0.4)	0 (0)	12 (4.6)	2 (0.8)	1 (0.4)	10 (3.8)	5 (1.9)	2 (0.8)	6 (2.3)	0 (0)	1 (0.4)	12 (4.6)	
	Streptococcus	3 (1.2)	0 (0)	0 (0)	3 (1.2)	0 (0)	0 (0)	0 (0)	2 (0.8)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)	0 (0)	2 (0.8)	1 (0.4)	
Gram+ve Bacteria	MRSA	0 (0)	2 (0.8)	2 (0.8)	0 (0)	2 (0.8)	2 (0.8)	0 (0)	2 (0.8)	2 (0.8)	2 (0.8)	0 (0)	2 (0.8)	0 (0)	2 (0.8)	2 (0.8)	
Ducieriu	MSSA	4 (1.5)	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	2 (0.8)	2 (0.8)	0 (0)	
	Others	3 (1.2)	1 (0.4)	2 (0.8)	3 (1.2)	1 (0.4)	2 (0.8)	4 (1.5)	1 (0.4)	1 (0.4)	5 (1.9)	0 (0)	1 (0.4)	2 (0.8)	3 (1.2)	1 (0.4)	
	H. Influenzae	2 (0.8)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.4)	1 (0.4)	0 (0)	1 (0.4)	1 (0.4)	0 (0)	
	Enterobactor	1 (0.4)	0 (0)	1 (0.4)	1 (0.4)	0 (0)	1 (0.4)	0 (0)	2 (0.8)	0 (0)	1 (0.4)	0 (0)	1 (0.4)	0 (0)	1 (0.4)	1 (0.4)	
	P. Mirabilis	2 (0.8)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	1 (0.4)	0 (0)	1 (0.4)	
	E. coli	14 (5.4)	0 (0)	4 (1.5)	15 (5.8)	0 (0)	3 (1.2)	10 (3.8)	6 (2.3)	1 (0.4)	11 (4.2)	0 (0)	3 (1.2)	4 (1.5)	5 (1.9)	8 (3.1)	
Gram-ve Bacteria	Klebsilla	19 (7.3)	6 (2.3)	8 (3.1)	19 (7.3)	2 (0.8)	12 (4.6)	13 (5)	10 (3.8)	11 (4.2)	17 (6.5)	9 (3.5)	6 (2.3)	6 (2.3)	6 (2.3)	22 (8.5)	
Duciciu	P. aeruginosa	29 (11.2)	9 (3.5)	2 (0.8)	21 (8.1)	5 (1.9)	15 (5.8)	21 (8.1)	9 (3.5)	8 (3.1)	24 (9.2)	8 (3.1)	7 (2.7)	14 (5.4)	6 (2.3)	19 (7.3)	
	Citrobacter	2 (0.8)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.8)	
	Acinetobacter	6 (2.3)	3 (1.2)	1 (0.4)	2 (0.8)	1 (0.4)	7 (2.7)	3 (1.2)	4 (1.5)	3 (1.2)	3 (1.2)	1 (0.4)	6 (2.3)	2 (0.8)	1 (0.4)	7 (2.7)	
	Others	3 (1.2)	0 (0)	0(0)	3 (1.2)	0 (0)	0 (0)	3 (1.2)	0 (0)	0 (0)	3 (1.2)	0 (0)	0 (0)	0 (0)	1 (0.4)	2 (0.8)	
No	Candida	1 (0.4)	0 (0)	10 (3.8)	1 (0.4)	0 (0)	10 (3.8)	0 (0)	1 (0.4)	10 (3.8)	1 (0.4)	0 (0)	10 (3.8)	0 (0)	1 (0.4)	10 (3.8)	
	Normal Flora	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)	
Growth	None	0 (0)	1 (0.4)	100 (38.5)	1 (0.4)	0 (0)	100 (38.5)	0 (0)	0 (0)	101 (38.8)	1 (0.4)	0 (0)	100 (38.5)	0 (0)	0 (0)	101 (38.8)	
Total		91 (35.1)	23 (8.5)	145 (55.8)	80 (30.8)	11 (4.2)	168 (64.6)	64 (24.6)	39 (15)	152 (58.5)	83 (31.9)	22 (8.5)	147 (56.5)	32 (12.3)	32 (12.3)	193 (74.2)	

TABLE IV - Carbapenem and Aminoglycosides Susceptibility Patterns against Respiratory Tract Pathogens

Abbreviations: S; sensitive, R; resistant, I: intermediate, S. aureus: Staphylococcus aureus, MRSA: Methicillin resistant staphylococcus aureus, MSSA: Methicillin sensitive staphylococcus aureus, H. Influenza: Hemophilus influenza, P. merabilis: Proteus merabilis, E. coli: Escherichia coli, P. aeruginosa: Pseudomonas aeruginosa.

Carbepenems and aminoglycosides resistant patterns: Imipenem was resistant to *P. aeruginosa* (3.5%) and *Klebsiella* (2.3%).

Gentamicin was tested resistant in 3.5%, 3.8% and 2.3% isolates of *P. aeruginosa*, *Klebsiella* and *E. coli*, respectively, while 3.1% and 3.5% isolates of *P. aeruginosa* and *Klebsiella*, respectively, were resistant against amikacin (Table IV).

Overall, amikacin and gentamicin were found sensitive against 31.9% and 24.6% isolates, respectively, but were resistant to 15% URTPs (Table IV).

Quinolones sensitivity Patterns: all four antibiotics, ciprofloxacin, levofloxacin, ofloxacin and moxifloxacin were tested sensitive with MSSA (0.8%). Likewise, all four quinolones were tested sensitive with *Streptococcus* isolates (1.2%). In gram-negative class, *P. aeruginosa* was tested sensitive with ciprofloxacin (9.3%), levofloxacin (8.1%), ofloxacin (3.5%) and moxifloxacin (1.2%).

Klebsiella was tested sensitive with ciprofloxacin (5.4%), levofloxacin (3.5%), ofloxacin (3.1%) and moxifloxacin (2.7%). *E. coli* was tested sensitive with ciprofloxacin (3.1%), levofloxacin (2.7%), ofloxacin (2.7%) and moxifloxacin (2.7%) (Table V).

Quinolones resistant Patterns: all four quinolones were resistant to *MSSA* (0.8%), while only *S. aureus* (2.3%) was resistant to ciprofloxacin. *P. aeruginosa* was found resistant to ciprofloxacin (4.2%), levofloxacin (2.3%), moxifloxacin (1.9%) and ofloxacin (1.2%). *E. coli* was tested resistant to ciprofloxacin (1.9%) and levofloxacin (1.5%). Overall, highest efficacy was exhibited by ciprofloxacin (26.3%) followed by levofloxacin (20.3%), ofloxacin (14.2%) and maxofloxacin (12.3%), while resistance frequency was highest for ciprofloxacin (18%) followed by levofloxacin (11.2%), maxofoxacin (10%) and ofloxacin (6.5%) (Table V).

TABLE V - Quinolones Susceptibility Patterns against Respiratory Tract Pathogens

		Quinolones Susceptibility Patterns												
Pathogen Type	Pathogen	Ciprofloxacin, n (%)			Lev	ofloxacin, <i>n</i>	ı (%)	Of	loxacin, <i>n</i>	(%)	Moxifloxacin, n (%)			
rype		s	R	I	s	R	I	S	R	Ι	S	R	I	
Gram +ve Bacteria	S. aureus	4 (1.5)	6 (2.3)	3 (1.2)	1 (0.4)	1 (0.4)	10 (3.8)	1 (0.4)	1 (0.4)	11 (4.2)	1 (0.4)	0 (0)	12 (4.6)	
	streptococcus	3 (1.2)	0 (0)	0 (0)	3 (1.2)	0 (0)	0 (0)	3 (1.2)	0 (0)	0 (0)	3 (1.2)	0 (0)	0 (0)	
	MRSA	0 (0)	2 (0.8)	2 (0.8)	0 (0)	2 (0.8)	2 (0.8)	0 (0)	2 (0.8)	2 (0.8)	0 (0)	2 (0.8)	2 (0.8)	
	MSSA	2 (0.8)	2 (0.8)	0 (0)	2 (0.8)	2 (0.8)	0 (0)	2 (0.8)	2 (0.8)	0 (0)	2 (0.8)	2 (0.8)	0 (0)	
	Others	3 (1.2)	2 (0.8)	1 (0.4)	3 (1.2)	2 (0.8)	1 (0.4)	3 (1.2)	2 (0.8)	1 (0.4)	3 (1.2)	2 (0.8)	1 (0.4)	
	H. Influenzae	1 (0.4)	1 (0.4)	0 (0)	1 (0.4)	1 (0.4)	0 (0)	0 (0)	0 (0)	2 (0.8)	0 (0)	1 (0.4)	1 (0.4)	
	Enterobactor	0 (0)	1 (0.4)	1 (0.4)	0 (0)	1 (0.4)	1 (0.4)	0 (0)	0 (0)	2 (0.8)	0 (0)	1 (0.4)	1 (0.4)	
	P. Mirabilis	1 (0.4)	1 (0.4)	0 (0)	1 (0.4)	0 (0)	1 (0.4)	0 (0)	0 (0)	2 (0.8)	1 (0.4)	1 (0.4)	0 (0)	
	E. coli	8 (3.1)	5 (1.9)	4 (1.5)	7 (2.7)	4 (1.5)	6 (2.3)	7 (2.7)	2 (0.8)	9 (3.5)	7 (2.7)	2 (0.8)	9 (3.5)	
Gram -ve Bacteria	Klebsilla	14 (5.4)	10 (3.8)	9 (3.5)	9 (3.5)	8 (3.1)	16 (6.2)	8 (3.1)	4 (1.5)	22 (8.5)	7 (2.7)	7 (2.7)	20 (7.7)	
Ducieriu	P. aeruginosa	24 (9.3)	11 (4.2)	5 (1.9)	21 (8.1)	6 (2.3)	13 (5)	9 (3.5)	3 (1.2)	29 (11.2)	3 (1.2)	5 (1.9)	30 (11.5)	
	Citrobacter	2 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	2 (0.8)	1 (0.4)	1 (0.4)	0 (0)	
	Acinetobacter	2 (0.8)	5 (1.9)	3 (1.2)	3 (1.2)	1 (0.4)	6 (2.3)	1 (0.4)	0 (0)	9 (3.5)	2 (0.8)	1 (0.4)	7 (2.7)	
	Others	3 (1.2)	0 (0)	0 (0)	3 (1.2)	0 (0)	0 (0)	3 (1.2)	0 (0)	0 (0)	2 (0.8)	0 (0)	1 (0.4)	

Pathogen Type	Pathogen	Quinolones Susceptibility Patterns											
		Ciprofloxacin, n (%)			Lev	ofloxacin, <i>i</i>	ı (%)	Of	loxacin, <i>n</i>	(%)	Moxifloxacin, n (%)		
		S	R	I	S	R	Ι	S	R	I	S	R	I
No	Candida	0 (0)	1 (0.4)	10 (3.8)	0 (0)	1 (0.4)	10 (3.8)	0 (0)	1 (0.4)	10 (3.8)	0 (0)	1 (0.4)	10 (3.8)
Bacterial	Normal Flora	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)	0 (0)	0 (0)	4 (1.5)
Growth	None	1 (0.4)	0 (0)	100 (38.5)	0 (0)	0 (0)	101 (38.8)	0 (0)	0 (0)	101 (38.8)	0 (0)	0 (0)	101 (38.8)
Total		68 (26.3)	47 (18.1)	142 (54.8)	54 (20.8)	29 (11.2)	173 (66.5)	37 (14.2)	17 (6.5)	206 (79.2)	32 (12.3)	26 (10)	199 (76.5)

TABLE V - Quinolones Susc	eptibility Patterns ag	ainst Respiratory	Tract Pathogens

Abbreviations: S; sensitive, R; resistant, I: intermediate, S. aureus: Staphylococcus aureus, MRSA: Methicillin resistant staphylococcus aureus, MSSA: Methicillin sensitive staphylococcus aureus, H. Influenza: Hemophilus influenza, P. merabilis: Proteus merabilis, E. coli: Escherichia coli, P. aeruginosa: Pseudomonas aeruginosa.

DISCUSSION

Upper respiratory tract infections (URTIs) are amongst the most common and diverse group of infections in humans worldwide with prevalence rate 22% to 25% (Fleming et al., 1987). It is estimated that almost 38.5% cultures of URTIs have negative bacterial growth, indicating that such infections may be of viral origin as evident by previous report (Manikandan, Amsath, 2013). Data from the present study suggested that more than 60% cultures reports were positive for bacterial growth with S. aureus, MRSA and MSSA, as the most common gram-positive isolates, while P. aeruginosa, Klebsiella and E. coli were the most frequent gramnegative isolates in both males and females. Additionally, antibiogram showed that P. aeruginosa, Klebsiella and E. coli were most sensitive with carbapenem, while Klebsiella and P. aeruginosa exhibited highest resistance against cephalosporin. Overall, carbepenems were found highly sensitive followed by aminoglycosides, quinolones, piptaz among penicillin and cephalosporin class, while resistance was maximum against cephalosporin followed by penicillin and quinolones class of antibiotics.

Several lines of literature evidences suggested that the most prevalent pathogens of URTIs include *S. pneumonia, S. aureus, P. aeruginosa, E.coli, K. pneumonia* and *H. influenza*. (Vázquez *et al.,* 2018; Aljanaby, Aljanaby, 2017) Similar bacterial pathogens have been implicated in URTIs by studies reported from Pakistan (Ali, Butt, 2017; Sabir et al., 2013). We also observed that P. aeruginosa, Klebsiella, E. coli, and S. aureus were among the most common bacterial isolates in subjects having URTIs. Literature evidences suggest that gender base differences exist in the incidence and severity of respiratory tract infections (Mourtzoukou, Falagas, 2007; Falagas et al., 2007) - more common in males compared to females. We also observed that the clinical enrollments of males were greater in number compared to females. However, in Pakistan, it is highly likely that these differences might also be due to higher social interaction of males in comparison to females, thus males probably have higher propensity to contract infections. Literature evidences clearly suggest that, if indicated, the first line therapy in URTIs are penicillin antibiotics, but erythromycin can be used as alternative if allergic to penicillin, while second and third generation cephalosporin are reserved for penicillin susceptible S. pneumonia, beta lactamase producing H. influenza, beta-lacatamse negative, amoxicillin resistant H. influenza and methicillin resistant S. aureus (Zoorob et al., 2012; Hedrick, 2010). Our data suggested that carbepenems were the most frequent choices followed by aminoglycosides, quinolones, cephalosporin and penicillin. Furthermore, overall data suggested that the frequency of gram-negative bacteria in URTIs was 44% corroborating previous reports with overall frequency of 59.6% and 61% of upper respiratory tract infections from Pakistan and Karapitiya, Sri Lanka (Amarasinghe

et al., 2018). Our data further suggested that the notable gram-negative bacteria, P. aeruginosa, Klebsiella and E. coli, demonstrated maximum resistance against the antibiotics belonging to penicillin (amoxcillin) and cephalosporin (cefaclor, cefuroxime, ceftriaxone) classes, while antibiotics belonging to carbapenem (imipenem, meropenem), aminoglycosides (amikacin), quinolones (ofloxacin) and piptaz of penicillin class were among the most effective antibiotics against similar gram-negative bacteria. Similar to our findings, a study from Pakistan reported that the most frequent gram-negative isolate was P. aeruginosa (32.2%) followed by Klebsiella (16.5%) and E. coli (12.5%), while imipenem, meropenem and tazobactam were among the most effective antibiotics (Samad et al., 2017). These data suggested that in Pakistan, the irrational or misuse of antibiotics probably due to selfprescribing upon experiencing similar symptoms, nonadherence to standard treatment guidelines (Saleem et al., 2016; Butt et al., 2019), poor knowledge of clinician and the patient, and limited finances, could contribute to antimicrobial resistance towards majority of the first line and even the second line therapeutic options in various gram-negative URTPs.

Clinical implications of the study

The major burden on the health care system is transposed by URTIs, probably when inappropriate antibiotic treatment leads to therapeutic failure or increase in anti-microbial resistance (Rezal et al., 2015). Our data showed that there was complete deviation from standard treatment guidelines, besides more frequent use of broadspectrum antibiotics. Additionally, Center for Disease Control and Prevention suggest that several diagnosing criteria should be taken into account before starting with antibiotic treatment in URTIs (Harris et al., 2016), which for sure are completely ignored in majority of the hospitals of Pakistan. In Pakistan, antibiotics are prescribed without prior confirmation of infected pathogen either prophylactically due to prevailing hygienic conditions of the hospitals or for a broad spectrum coverage owing to poor knowledge about the disease - mainly because of lack of proper diagnostic facility and limited resources,

ultimately leading to the irrational use of antibiotics. Additionally, clinician's prescribing patterns are mainly governed by pharmaceutical industries using pressurizing and obliging gimmickry rather than choices made on standard treatment guidelines (STGs) - affected by nonavailability of STGs copy and poor policy implementation in the hospital. On the other side, the extent of antibiotic prescribing can be affected by several other factors, such as variations in prescribing patterns among the doctors (their education, knowledge and beliefs), characteristics of the disease and information provided by the patients - all contributed towards decision making.

Policy recommendations

It has become necessary to formulate and implement policy guidelines for prescribing antibiotics especially in cases where physician tends to prescribe antibiotics for conditions that does not warrant antibiotic treatment. The foremost attempt is to educate and train health professionals about treatment guidelines and prescribing ethics to initiate new antimicrobial stewardship program that foster appropriate treatment choices as per local antibiotic guidelines with up-to-date information on the use of antibiotics. Discourage patients on self-antibiotic prescribing with proper education and counseling by a clinical pharmacist that antibiotics are rarely required for URTIs probably because of self-limiting nature of the disease. Additionally, senior doctors must ensure rationale choices and dosing by countersigning the antibiotic prescriptions generated by junior doctors.

Limitations of the study

There are several limitations of this study. The crosssectional design of the study does not allow us to observe the susceptibility patterns over a period of time. We only have the access to culture reports, thus we are unable to crosscheck the information written on the reports with the patients and have to rely on the information given on the reports with lots of missing information that needs to be excluded from the study. A very few studies were available from Pakistan for a direct comparison of susceptibility patterns with our findings.

CONCLUSION

In conclusion, our data suggested that gram-negative bacteria, *P. aeruginosa*, *Klebsiella* and *E. coli* were among the top bacterial isolates in URTIs, in both males and females. Bacterial isolates, such as *P. aeruginosa*, *Klebsiella* and *E. coli* exhibited significant resistance against penicillin, cephalosporins and ciprofloxacin, while imipenem, meropenem, amikacin and piptaz exhibited highest sensitivity against these bacteria.

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CONTRIBUTORS

KU; collected and analyzed data, MB; analyzed data and edited the manuscript, FS; edited the manuscript and helped in study design, AAK; edited the manuscript, HS; designed the study, analyzed data and wrote the manuscript, MI; analyzed data and edited the manuscript.

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