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A Community Based Study on the Prevalence of *Klebsiella Pneumoniae* Causing UTI (*Urinary Tract Infection*)

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Abstract—*Antimicrobial resistance among bacterial strains is an emerging problem, worldwide. Urinary tract infection (UTIs) are one of the most common bacterial infection in human, both in the community and the hospital settings. Klebsiella pneumonia and Escherichia coli are the two pre-dominant pathogens commonly isolated in urine. Klebsiella pneumonia is becoming resistant to most of the antibiotic. These uropathogens have also developed resistance to commonly prescribe antimicrobial agents. The future of antibiogram would be the incorporation of patient related data to make information more reliable and for predicting outbreaks.*

It has been extensively reported that adult women (nearly 75%) have a higher prevalence of UTI than men, primarily owing to anatomic and physical factors. On the basis of reports by Antimicrobial Surveillance Program, isolate from Canada, USA and Latin American countries show the lowest susceptibility rates to most antimicrobial agents followed by Asian- Pacific isolates and European strains. The isolated uropathogens exhibited higher resistance to commonly used oral antibiotic such as ciprofloxacin, amoxicillin/clavulanic acid and Cefepime, OF 26 Tested antibiotic in this study, the most active antibiotic against Klebsiella pneumonia isolates were Tigecyclin, Fosfomycin and Colistin.

The result of this study will help in the empiric therapy of infection caused by Klebsiella species in Kolkata, West Bengal but continuous surverillance of antimicrobial resistance of the organism. This will help authorities to formulate antibiotic prescription policies.

Keywords*: Urinary tract infection, antibiotic, Klebsiella pneumoniae, antibiogram, uropathogens*

1. INTRODUCTION

Urinary tract infection (UTIs) are one the most common infectious disease (Kolawale *et al.,* 2009).They may be systematic or asymptomatic and either type of infection can result in serious sequelae if not appropriately (Pezzlo,1998). Although different causative agents can be responsible for UTI, bacteria are the major cause being responsible for more than 95% of UTI cases (Bonadio *et al.,* 2001).UTI is the second infection in human. Urinary infection cause fewer complications than nosocomial infections, but they occasionally can cause bacterium and death. Gram negative bacteria play an important role in UTI. Antimicrobial resistance developed by microbes against antibiotic open serious debates in this issue and recognized as a serious problem by global medicine and research community (Finch, 2004). Many factors play in the emergence of resistance (WHO,2012) from poor utilization of antimicrobial agents to the transmission of resistance bacteria from patient to patient and from healthcare workers to patients and vice versa. However the aetiology of UTI and the antibiotic susceptibility of uropathogens vary with time and location challenging the physician to treat such condition. Thus the diagnosis and empirical treatment of community-acquired UTI (CAUTI) in an outdoor setting is challenging and it is wise to select an appropriate antibiotic based on the knowledge of the prevalent uropathogens and their resistance in the community.The study has been performed to find out the present uropathogen (K.pneumoniae) profile responsible for CAUTI among the people attending Out-Patient Departments (OPD) Of this institution (Calcutta Medical College) and their antibiotic susceptibility pattern in an attempt to formulate guideline to treat CAUTI in this region.

2. REVIEW

In Egypt Khalifa *et al.,* (1997) found that the most common organism causing UTI were E.coli (47.5%) followed by Klebseilla species (17.1%), Pseudomonas aeruginosa (10.4%) and Proteus species(8.4%). Some rare organisms were also isolated, such as Candida albicans (0.28%) and Streptococcus species (0.27%). Astal *et al.,* (2002) conducted a study to assess the common

organism causing UTI in the Gaza Strip and to examine the incidence of ciprofloxacin resistance in the strains of bacteria isolated from patients suspected with UTI over a six- month period, the samples were collected from community patients from different parts of the Gaza Strip. Minimum Inhibitory Concentration (MIC) of ciprofloxacin was measured for all resistant UTI isolates. The author also showed that E.coli was the common organism causing UTI and the most effective antimicrobial agent against all the isolated uropathogen. Bennet,*et al.,* (1995) concluded that E.coli, Pseudomonas species, Klebsiella species and Enterococcus have been the predominant microorganism that cause UTIs. Klebseilla, Pseudomonas and Proteus species tend to be more resistance than E.coli to commonly used antibiotics.

The study has been performed to find out the present uropathogen (K.pneumoniae) profile responsible for CAUTI among the people attending Out-Patient Departments (OPD) Of this institution (Calcutta Medical College) and their antibiotic susceptibility pattern in an attempt to formulate guideline to treat CAUTI in this region.

3. MATERIALS AND METHODS

Study area

The study was carried out in Kolkata (C .R. AVENUE), West Bengal, India within longitude 88.36E and latitude 22.53 N.

Specimen Collection and analysis

This surveillance was conducted for a period of 6 month from October , 2015 to march 2016 among urinary tract infection patients of all ages group and both sexes in Laboratory of Microbiology at Calcutta medical college and Hospital, Kolkata. A total of 2486 samples were collected during this period with safety and were transported to laboratory for chemical and microscopic examination by Schematic representation of investigation protocol.The isolated organisms were identified by standard biochemical tests and antibiotic sensitivity tests were done by using VItek2 automated analyzer and also biochemical tests were done conventionally. A random specimen is suitable for most screening purposes. A labelled container (with patient's name, Age, Sex, Date and Time of specimen collection) was taken to collect Random Urine Specimen.

Identification and Antibiotic Susceptibility Test using Vitek-2

Suspension preparation

A sterile inoculation loop was used to transfer a sufficient number of colonies of a pure culture on CLED agar. The microorganism was suspended in 3.0 ml of saline water in a 12x 75 mm clear plastic polystyrene test tube. The turbidity was adjusted in between 0.50-0.63 using a turbidity meter called Densi Chek, three standards (McFarland 0.5, 2.0, and 3.0) and one blank (McFarland 0.0) were used for the instruments verification.

Inoculation

The cards for identification and Antibiotic Susceptibility of testing were inoculated with microorganism suspensions using an integrated vacuum apparatus. A test tube containing the microorganism suspension was placed into a special rack (cassette) and the identification card was placed in the neighbouring slot while inserting the transfer tube into the corresponding suspension tube. The cassette can accommodate up to 10 tests. The filled casstte was placed manually (VITEK2 compact,Fig.1) into a vacuum chamber station.

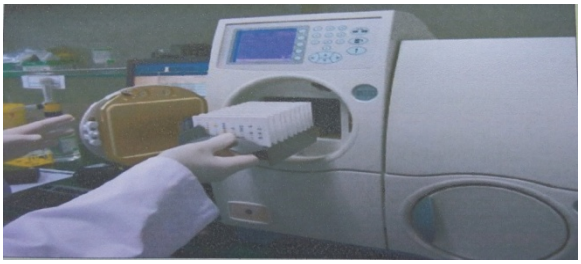

Figure 1: At the time cassette inserting into Vitek 2 compact machine.

After the vacuum is applied and air is re- introduced into the station, the organism suspension is forced through the tube micro-channels that fill all the test wells.

Card sealing and incubation

Inoculated cards are passed by a mechanism which cuts off the transfer tube seals the card prior to loading into the carousel incubator. The carousel incubator can accommodate up to 30 or up to 60 cards. All card type were incubated on line at 35.5 ± 1.0°C. Each card was removed from the carousel incubator once every 15 minutes, transported to the optical system for reaction readings, and then returned to the incubator until the next read time. Data were collected at 15 min intervals during the entire incubation period. Data was automatically recorded.

4. BIOCHEMICAL TEST

Indole test

Some bacteria can produce indole from amino acid tryptophan using the enzyme Tryptophanase. Production of indole is detected using Ehrlich's reagent or Kovac's reagent. Indole reacts with the aldehyde in the reagent to give a red color. An alcoholic layer concentrates the red color as ring at the top. Bacterium to be tested was inoculated in peptone water, which contains amino acid tryptophan and incubated overnight at 37°C. Following incubation few drops of Kovac's reagents were added (Kovac's reagent consists of para- dimethyl amiobenzaldehyde, isoamyl alcohol and con^{c}HCL Ehrlich's reagent is more sensitive in detecting indole production in anaerobes and non- fermenters)

Methyl Red (MR) test

This is to detect the ability of an organism to produce and maintain stable acid end products from glucose fermentation. Some bacteria produce large amounts of acids from glucose fermentation that they overcome the buffering action of the system. Methyl Red is a pH indicator, which remains red in color at a pH of 4.4 or less.The bacterium to be tested was inoculated into glucose phosphate broth, which contains glucose and a phosphate buffer and incubated at 37° C for 48 hours.The pHof the medium is tested by the addition of 5 drops of MR reagent. Development of red color was not observed but yellow color produced.

Voges proskauer (VP) test

While MR test is useful in detecting mixed acid producers, VP test detects butylenes glycol producers. Acetyl- methyl carbinol (acetonin) is an intermediate in the production of butylenes glycol. In this two reagents 40% KOH and alpha – naphthol are added to test broth after incubation and exposed to atmospheric oxygen. If acetone is present, it is oxidized in the presence of air and KOH to diacetyl. Diacetyl then reacts with guanidine components of peptone, in the presence of alpha-naphthol to produce red color. Role of alpha- napthol is that of a catalyst and a color intensifier. Bacterium to be tested is inoculated into glucose phosphate broth and incubated for at least 48 hours.0.6 ml of alpha- naphthol is added to the test broth and shaken 0.2ml of 40% KOH is added to the broth and shaken. The tube was allowed to stand for 15 minutes. Appearance of red color was seen.

Citrate utilization test

This test detects the ability of an organism to utilize citrates as the sole source of carbon and energy. Bacteria are inoculated on a medium containing sodium citrate and a PH indicator bromothymol blue. The medium also contains inorganic ammonium salts, which is utilized as sole source of nitrogen. Utilization of citrate involves the enzyme citritase, which breaks down citrate to oxaloacetate and acetate is further broken down to pyrovate and CO_2 .Production of Na_2CO_3 as well as NH_3 from utilization of sodium citrate and ammonium salt respectively results in alkaline pH. This results in change of medium's color from green to blue. Bacterial colonies were picked up from a straight wire and inoculated into slope of Simmon's citrate agar and incubated overnight at 37°C.The medium changes its color from green to blue.

Urease test

Some bacteria produce the enzyme unease, which catalyse the hydrolysis of urea to from ammonia and carbon dioxide. Organism that does not produce this enzyme cannot metabolize urea. Urea broth has a minimal amount yeast extract along with urea. Organism that cannot metabolize urea will have insufficient nutrients for growth. Urea hydrolysis will result in a pH increase because of the production of ammonia. The pH indicator phenol-red will turn pink with this ph increase. However, the presence of strong buffers in the medium requires a large amount of ammonia production to cause a color change. Urease broth tubes (previous prepared)from refrigerator were taken. One broth was inoculated with inoculam and other broth was kept uninoculated and incubated for 48 hours. After 24 hours of incubation color change observed.

Catalase test

Catalage is the enzyme that breaks hydrogen peroxide (H_2O_2) into H_2O and O_2.Hydrogen peroxide is often used as a topical disinfection in wounds and the bubbling that is seen is due to the evolution of O_2 gas. H_2O_2 is a potent oxidizing agent that can wreak havoc in a cell; because of this any cell that uses O_2 or can live in the presence of O_2 must have a way to get rid of the Peroxide. One of those ways is to make catalase. A small amount of growth from culture was placed onto a clean microscope slide. A few drops of H_2O_2.were added onto the smear and mixed with a toothpick. Evolution of O_2 was observed as evidenced by bubbling.

Triple sugar iron agar test

Peptone yeast extract provide nitrogenous compounds, sulphur, trace elements and vitamin B complex etc. Sodium chloride maintains osmotic equilibrium. Lactose, sucrose and dextrose monohydrate are the fermentable carbohydrates. Sodium thiosulphate and Ferric OR ferrous ions make H_2S indicator system. Sodium thiosulphate is also an inactivator of halogen and can minimize its toxicity in the testing sample if any during microbial limit tests. Phenol red is the pH indicator. Organisms that ferment dextrose monohydrate produce a variety of acids varing the color of the medium from red to yellow. More amount of acids are liberated in butt region (fermentation) than in the slant (respiration).Thus the appearance of a alkaline (red) slant and an acid(yellow) butt after incubation indicates that the organism is a dextrose fermenter but is unable to ferment lactose and/ or sucrose. Bacteria that ferment lactose or sucrose (or both), in addition to dextrose, produce large amount of acid enables no reversion of PH in that region and thus bacteria exhibit an acid slant and acid butt. Gas production (CO_2) is detected by the presence of crack or bubbles in the medium,. With a sterilized straight inoculation needle picked a well- isolated colony.TSI agar slants were inoculated by first stabbing through the centre of the medium to the bottom of the tube and then streaking on the surface of the agar slant. The cap leaved slight on loose and incubate the tube at 35^0 C in ambient air for 24 hours. After incubation, acidic reaction occurred, yellowing the medium at slant and butt portion and also gas production was observed.

5. RESULTS

A Total of 2,396 urine samples were processed of them 467 (19.5%) Gram negative Bacilli (GNB) were isolated during the span of 6 months. Escherichia coli (75.4%) was the maximally isolated UTI causing bacterium, followed by Klebsiella pneumoniae (15.6%). Although K. Pneumoniae isolated were identified by using Vitek2 compact automated analyzer and also conventional biochemical tests were done. The biochemical features of K. Pneumoniae are listed in (Table 1).

Table1: Biochemical Characterization of K.pneumoniae

Biochemical Test	Result
Indole Test	Negative(-)
Methyl Red(MR) TEST	Negative(-)
Voges Proskauer(VP) Test	Positive(+)
Citrate Utilization Test	Positive(+)
Urease Test	Positive(+)
Catalase Test	Positive(+)
Triple Sugar Iron Agar test	Acid+Gas

Note: **"+"** refers to Positive test, '**-**'refers to Negative test,(A-Acid), (G-Gas).

Out of 75 K.pneumoniae isolated 57 (76%) was isolated from female and 18(24%) was isolated from male. It showed the prevalence of K, pneumoniae infection is more in female than male shown in (Fig 2a).In this study it was also found that the maximum isolates were isolated from age group of above 50 years (85.33%) followed by age group of age 21-50 years and age group 6-20 years, no K. Pneumonia was isolated from age group of 0-5 years shown in (Fig 2b).

Antibiotic Susceptibility Testing (AST) OF Klebseilla pneumoniae was carried out by the Vitek2 compact automated analyser using 2 AST CARDS (AST-N280, AST-N235,) The antibiotics used in this study were shown in (Table 2),antibiotic Sensitivity pattern of K. Pneumonia in (Table 3) and Antibiotic Sensitivity Pattern (percentage) of K.pneumoniae in (Table 4).

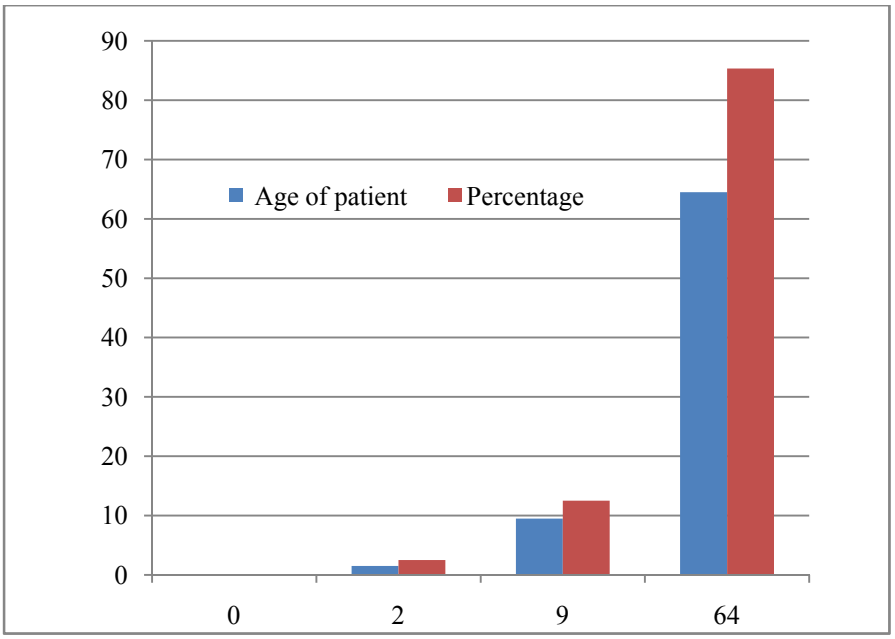

Figure 2: (a) Gender wise distribution of Culture Positively of K.pneumoniae., (b) Age Wise Distribution of Culture Positivity of Klebseilla pneumonia.

Table 2: Name and concentration of antibiotic.

Sl. No.	Antibiotic	Short form of antibiotic	Concentration used(Micro gram)	Sl. No.	Antibiotic	Antibiotic Short form	Concentration used(Micro gram)
1	Amoxicillin/Clavulanic acid	AMC	4/2,16/8,32/16	14	Imipenem	IPM	1,2,6,12
2	Ampicillin	AM	4,8,32	15	Meropenem	MEM	0.5,2,6,12
3	Ticarcillin	TIC	16,32,64	16	Amikacin	AN	8,16,64
4	Piperacillin/Tazobactam	TZP	2/4, 8/4, 24/4, 32/4, 32/8, 48/8	17	Gentamicin	GM	4,16,32
5	Cefalotin	CF	2,8,32	18	Nalidixic acid	NA	8,16,32
6	Cefoxitin	FOX	8,16,32	19	Nitrofurantoin	FT	16,32,64
7	Cefixime	CFM	0.25,1,2	20	Ciprofloxacin	CIP	0.5,2,4
8	Ceftazidime	CAZ	1,2,8,32	21	Norfloxacin	NOR	1,8,32
9	Ceftriaxone	CRO	1,2,8,32	22	Ofloxacin	OFL	0.5,1,4
10	Cefepime	FEP	2,8,16,32	23	Fosfomycin	FOS	8.16,32
11	Cefuroxime	CXM	2,8,32	24	Trimethoprim/Sulfamethoxazole	SXT	1/19,4/76,16/304
12	Cefoperazone/Sulbactam	SFP	8,16,32	25	Tigecyclin	TGC	0.75,2,4
13	Ertapenem	ETP	0.5,1,6	26	Colistin	CS	4,16,32

Table 3: Antibiotic Sensitivity pattern of K. Pneumonia.

Sl NO.	Penicillin				Cephalosporin							Carbapenem				Amino-glycoside		Quinolones					Phos-fonic acid	Sulfo-namide	Poly-ketide	Poly mixin
	AMC	AM	TIC	TZP	CF	FOX	CFM	CAZ	CRO	FEP	CXM	SFP	ETP	IPM	MEM	AN	GM	NA	FT	CIP	NOR	OFL	FOS	SXT	TGC	CS
K1	S	R	R	S	S	S	S	S	S	-	-	-	S	-	-	S	S	S	R	S	S	S	S	S	-	-
K2	R	R	R	R	R	R	R	R	R	-	-	-	R	-	-	S	S	R	R	R	R	R	S	R	-	-
K3	I	R	R	I	R	R	R	R	R	-	-	-	S	-	-	R	S	R	R	R	R	R	S	R	-	-
K4	S	R	R	S	S	S	S	S	S	-	-	-	S	-	-	S	S	S	R	S	S	S	S	S	-	-
K5	S	R	R	S	S	S	S	S	S	-	-	-	S	-	-	S	S	S	I	S	S	S	I	S	-	-
K6	S	R	R	S	R	S	R	R	R	-	-	-	S	-	-	S	S	R	R	S	S	S	S	R	-	-
K7	S	R	R	S	R	S	R	R	R	-	-	-	S	-	-	S	S	R	R	S	S	S	S	R	-	-
K8	R	S	R	S	S	S	S	S	S	-	-	-	S	-	-	S	S	S	S	S	S	S	S	S	-	-
K9	R	R	-	R	-	-	-	-	R	R	R	R	S	S	S	S	R	R	R	R	-	-	-	R	I	S
K10	R	R	R	R	R	R	R	R	R	-	-	-	R	-	-	S	S	R	R	R	R	R	S	R	-	-
K11	S	R	R	S	S	S	S	S	S	-	-	-	S	-	-	S	S	S	S	S	S	S	S	S	-	-
K12	R	R	R	R	R	R	R	R	R	-	-	-	R	-	-	S	S	R	I	R	R	R	R	R	-	-
K13	R	R	-	-	-	-	-	-	R	R	R	R	R	R	R	R	R	R	R	R	-	-	-	R	R	S
K14	S	R	R	S	R	R	R	S	R	-	-	-	S	-	-	R	R	R	R	R	R	R	S	S	-	-
K15	R	R	R	R	R	R	R	R	R	-	-	-	R	-	-	R	R	R	R	R	R	R	S	R	-	-
K16	R	R	R	R	R	R	R	R	R	-	-	-	S	-	-	S	R	R	R	R	R	R	S	S	-	-
K17	R	R	R	R	R	R	R	R	R	-	-	-	R	-	-	S	S	R	R	R	R	R	I	R	-	-
K18	S	R	R	S	S	S	S	S	S	-	-	-	S	-	-	S	S	S	I	S	S	S	S	S	-	-
K19	S	R	R	S	S	S	S	S	S	-	-	-	S	-	-	S	S	S	I	S	S	S	S	S	-	-
K20	R	R	R	R	R	R	R	R	R	-	-	-	R	-	-	S	R	R	R	R	R	R	I	R	-	-
K21	R	R	R	R	R	R	R	R	R	-	-	-	R	-	-	S	R	R	R	R	R	R	I	R	-	-
K22	S	R	R	S	S	S	S	S	S	-	-	-	S	-	-	S	S	S	S	S	S	S	S	S	-	-
K23	S	R	R	S	I	I	S	S	S	-	-	-	S	-	-	S	S	S	R	R	S	S	S	R	-	-
K24	R	R	-	R	-	-	-	-	R	R	R	R	R	R	R	R	R	R	R	R	-	-	-	S	S	S
K25	R	R	-	R	-	-	-	-	R	R	R	R	R	R	R	R	R	R	R	R	-	-	-	S	S	S
K26	I	R	R	R	R	R	R	R	R	-	-	-	S	-	-	S	R	R	R	R	R	R	R	R	-	-
K27	R	R	R	R	R	R	R	R	R	-	-	-	R	-	-	R	R	R	R	R	R	R	I	R	-	-
K28	S	R	R	S	S	S	S	S	S	-	-	-	S	-	-	S	S	S	I	S	S	S	S	S	-	-
K29	R	R	R	R	R	R	R	R	R	-	-	-	R	-	-	R	R	R	R	R	R	R	S	R	-	-
K30	R	R	-	R	-	-	-	-	R	R	R	R	R	R	R	S	S	R	R	R	-	-	-	S	S	S
K31	R	R	R	R	R	R	R	R	R	-	-	-	S	-	-	S	R	R	R	R	R	R	S	R	-	-
K32	R	R	R	R	R	R	R	R	R	-	-	-	R	-	-	R	R	R	R	R	R	R	S	R	-	-
K33	I	R	R	S	R	S	R	I	R	-	-	-	S	-	-	S	S	S	S	S	S	S	S	R	-	-
K34	R	R	-	R	-	-	-	-	R	R	R	R	R	R	R	R	R	R	R	R	-	-	-	R	R	S
K35	I	R	R	S	S	S	S	S	S	-	-	-	S	-	-	S	R	R	R	R	R	R	S	R	-	-

Note: (‘K ' -Klebseilla pneumoniae, ‘R’ - Resistance, ‘S’ - Sensitivity, ' I ' - inhibition.)

Table 4: Antibiotic Sensitivity Pattern (percentage) of K.pneumoniae

Sl No	Antibiotic	Total Number. resistant organism(percentage)	Sl No	Antibiotic	Total Number. resistant organism(percentage)
1	Amoxicillin/Clavulanic acid	43(57.33%)	14	Imipenem	12(57.1%)
2	Ampicillin	70(93.33%)	15	Meropenem	12(57.1%)
3	Ticarcillin	52(100%)	16	Amikacin	19(25.3%)
4	Piperacillin	37(50.7%)	17	Gentamicin	35(46.7%)
5	Cefalotin	30(56.6%)	18	Nalidixic acid	52(69.3%)
6	Cefoxitin	22(40.7%)	19	Nitrofurantoin	45(60%)
7	Cefixime	30(55.6%)	20	Ciprofloxacin	44(58.7%)
8	Ceftazidime	27(50.9%)	21	Norfloxacin	25(46.3%)

9	Ceftriaxone	48(64.9%)	22	Ofloxacin	25(46.3%)
10	Cefepime	17(81%)	23	Fosfomycin	5(9.3%)
11	Cefuroxime	21(100%)	24	Trimethoprim/Sulfamethoxazole	41(54.7%)
12	Cefoperazone/Sulbactam	15(71.4%)	25	Tigecyclin	4(19.1%)
13	Ertapenem	25(33.8%)	26	Colistin	0(0%)

6. DISCUSSION

The experiments was carried out to study the resistance pattern of the bacterial isolates Klebsiella pneumoniae collected from urine specimens of UTI patients toward different 26 antibiotics. K.pneumoniae isolates were Tigecylin, Fosfomycin and Colistin. Increasing resistance of uropathogens of CAUTI to commonly used oral antibiotics is an alarming scenario. There is a common practice to treat CAUTI empirically without the guidance of urine culture sensitivity report. But this treatment should follow the prevalent uropathogens in that community and their antibiotic susceptibility pattern.

7. CONCLUSION

This study has clearly demonstrated Klebseilla pneumonia second highest uropathogen responsible for CAUTI in this geographical area along with high resistance of isolated K. Pneumoniae to antibiotic to Ticarcillin, Cefuroxime, Ampicillin, Cefepime, and Cefoperazone/sulbactam. Nalidixic acid and good coverages of Tigecyclin, Fosfomycin and Colistin against the most of the K, pneumoniae isolated. The most of the isolates had a high level of resistance to examine antibiotics, laboratory evidence of infection and antibiotic susceptibility testing should be carried out to help in the choice of system drugs. Considering the antibiotic susceptibility testing, cost, side effects and many other factors.Tigecyclin, Fosfomycin should be preferred for K.pneumoniae infection for patients of UTI, Colistin should be kept as reserved drug.

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