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ORIGINAL RESEARCH

TO DETERMINE ANTIBIOTIC SUSCEPTIBILITY PATTERN IN KLEBSIELLA SPECIES AMONG VARIOUS CLINICAL SAMPLES AT TERTIARY CARE HOSPITAL IN NORTH INDIA

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ABSTRACT

Background: Klebsiella species has been considered as a major pathogen responsible for hospital acquired infections. Out of the six ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella Pneumoniae, Acinetobacter Baumanii, Pseudomonas Aeroginosa and Enterobacter species), Klebsiella is the most encountered organism. Resistance in Klebsiella species due to production of extended spectrum beta lactamases and carbapenemases is growing, resulting in higher mortality,increased hospital stay and higher therapeutic cost .The present study highlights the need for continued monitoring of AST patterns and also emphasizes on formulation of sound antibiotic policy in the hospital.

Methodology: The present retrospective study was conducted in the Department of Microbiology, GMCH, Amritsar from November 2021 to May 2022. 1747Klebsiella isolates from various 7572 clinical samples (urine, pus, blood, wound and sputum) were included in the study and samples were obtained from both inpatients and outpatients, of all age groups and of both sexes. Antimicrobial susceptibility testing was done for all the isolates using antimicrobial discs (Ampicillin, Gentamicin, Cefepime, Amikacin, Piperacillin tazobactam, Imipenem, Ciprofloxacin, PolyB, Cefotaxime, Meropenem, Colistin, Nitrofurantoin, and Norfloxacin) on Mueller-Hinton agar plates by Kirby-Bauer disc diffusion method according to the CLSI guidelines 2021

Results: Overall Klebsiella isolates was reported in 23.07% of all the samples. Out of 1747 Klebsiella isolates, K.pneumoniae and K. oxytoca was revealed in 91.35% and 8.64% of the Klebsiella isolates respectively. Maximum resistance was shown by ampicillin (100%). In this study, maximum sensitivity was shown with Colistin and Polymyxin-B i.e. 99.66% and 99.26% respectively

Conclusion: As the multidrug resistant strains of Klebsiella species are constantly increasing. Knowledge about the resistance pattern of these bacterial strains will help in the judicial use of antibiotics, formulation of antibiotic policies apt for the hospitals and implementation of infection control programs.

Keywords: Blood Stream Infections; Klebsiella, Antibiotics

INTRODUCTION

In 1883 Friedlander isolated a capsulated bacillus from the lungs of patients who had died of pneumonia[1]. This was named after him as Friedlander s bacillus. Later on this organism was given the generic name of Klebsiella, which is ubiquitously present and reported worldwide .Klebsiella species has been considered as a major pathogen responsible for hospital acquired infections. Out of the six ESKAPE pathogens, Klebsiella is the most encountered organism[2]. It is a gram negative, non-motile, encapsulated, lactose fermenting, facultative anaerobe belonging to the Enterobacteriaceae family[3]. It is the second most popular member of the aerobic bacterial flora of the human intestine and is also present as commensal of oropharynx and skin.

Klebsiella species cause 3–8% of all nosocomial infections and are widely recognized as important pathogens in genitourinary infections, bronchopneumonia, wound, soft tissue and blood stream infections (BSI)[4]. The leading Klebsiella species giving rise to human infections are Klebsiella pneumoniae and Klebsiella oxytoca. Klebsiella pneumoniae accounts for 75-86% of all Klebsiella species reported while Klebsiella oxytoca accounts for 13%-25% isolates[5]. Klebsiella pneumonia is the most common cause of hospital respiratory infections in premature neonates in Intensive Care Units and the second most common cause of urinary tract infections and bacteremia. It is thought to be an opportunistic pathogen responsible for nosocomial infections in hospitalized patients and a causative organism for antibiotic-associated hemorrhagic colitis (AAHC) in humans. Klebsiella oxytoca may also be especially pathogenic due to the secretion of cytotoxin[6].

Recently, World Health Organization also warned the community that multidrug resistant bacteria are emerging worldwide which is a big challenge to healthcare. Clinical isolates of Klebsiella species are generally resistant to wide range of antibiotics and always naturally resistant to Ampicillin and amoxicillin. Beta lactam antibiotics are most common treatment options for such infections. Extended spectrum Beta lactamases are often found in Enterobacteriaceae family of gram negative bacilli especially Klebsiella species, E coli and proteus[7]. There are three mechanisms that can cause antibiotic resistance: prevention of interaction of drug with target organisms, decreased uptake due to either an increased efflux or a decreased influx of antimicrobial agent and enzymatic modification or destruction of the compound[8].

Klebsiella species that produce Klebsiella pneumoniae carbapenemases (KPC) are of serious concern as they have high level resistance against most antibiotics. These KPC enzymes efficiently hydrolyze carbapenemases well as other beta lactam antibiotics[7]. Klebsiella strains acquire a multidrug resistant phenotype through horizontal transfer of antimicrobial genes either carried by transposons and transfer is usually mediated by mobile genetic elements integrons[9].

The enzyme NDM-1, of klebsiella pneumonia encoded by bla NDM-1, has increased the rate of Carbapenem-resistant isolates posing threat to antibiotics such as β-lactams, aminoglycosides and fluoroquinolones[10]. Combination therapy for K. pneumoniae infections is commonly used due to the organisms ability to obtain resistance to distinct classes of antibiotics[11].Due to a drastic increase in the antibiotic resistance pattern encountered among Klebsiella species, it is imperious to know the institutional prevalence and susceptibility profile. Hence the present study was conducted to evaluate antibiotic susceptibility pattern of klebsiella species obtained from various clinical samples at tertiary care hospital. This study will help in updating the knowledge of the drug resistance and antibiotic susceptibility pattern in a particular region which might be useful in clinical practice.

MATERIAL AND METHODS

The present cross sectional was conducted in the Department of Microbiology, GMCH, Amritsar from November 2021 to May 2022. The study was conducted after taking permission from the institutional ethical committee. Klebsiella isolates from various clinical samples (urine, pus, blood, wound and sputum) were included in the study after correlating with clinical history whereas bacteria other than Klebsiella isolates were excluded from this study

SAMPLE COLLECTION

Samples were obtained from both inpatients and outpatients, of all age groups and of both sexes. Samples should be preferably collected prior to institution of therapy. Ensure that specimen and requisition form are filled with patient's personal details, source of specimen, date, time of collection and admission details.

- Pus: The pus samples were either aspirated by disposable syringes or collected onto sterile cotton tipped swabs.
- Sputum: Early morning sputum samples are preferable, but samples collected at other days are also acceptable. It should be clearly differentiated from saliva and should be rejected if it is saliva.
- Urine: Clean voided midstream urine was collected into screw top containers .Mid-stream urine samples were collected during this period with universal safety precautions and were transported to the laboratory without delay.
- Wound: Wound sample was obtained using swabs. Cleanse the wound margins and superior area thoroughly with sterile saline, removing all superficial exudates & overlying debris. Now gently roll the swab over the surface of the wound to obtain the sample.
- Blood samples: These were collected under strict aseptic precautions by venipuncture in 20 ml of BHI Broth supplemented with 0.03% SPS (microexpress).

SAMPLE CHARACTERIZATION

Pus, sputum, wound, blood and urine samples were aseptically inoculated on to Blood and MacConkey agar plates and incubated overnight at 37C. Klebsiella isolates were identified by their morphology of large dome shaped colonies on blood agar and lactose fermenting mucoid colonies on Macconkey agar. It was included in family Enterobacteriaceae as it is

gram negative bacilli, motile, aerobe and facultative anaerobe ,non-fastidious, ferments glucose to produce acid/gas, reduces nitrate to nitrite ,produces catalase, oxidase negative. Further identification to species level was done by applying battery of biochemical tests as shown in table. like IMVIC, TSI, urease, amino acid decarboxylase test.

Table 2: Biochemical test used in identification of Klebsiella species

Biochemical test	Klebsiella pneumonia	K. oxytoca
Indole production test	-	+
Methyl red test	-	-
Voges-proskeaur test	+	+
Citrate utilization test	+	+
Urease production test	+	+
Triple sugar iron	A/A	A/A
GAS	+	+
Arginine decarboxylase	+	+
Lysine decarboxylase	+	+

ANTIMICROBIAL SUSCEPTIBILITY TESTING

Was done for all the isolates on Mueller-Hinton agar plates by Kirby-Bauer disc diffusion method according to the CLSI guidelines 2012 (CLSI, 2012). The antibiotics tested were Ampicillin, Gentamicin, Cefoxitin, Cotrimoxazole, Amikacin, Ceftazidime, Aztreonam, Piperacillin, Imipenem, Ciprofloxacin, Cefotaxime, Meropenem, Tazobactam, Colistin, Nitrofurantoin, Chloramphenicol and Norfloxacin. Top of 3 to 5 similar looking colonies of the organism were picked with the loop and transferred to 5 ml of peptone water in a tube and inoculated for 2 to 3 hrs at 37^0c. After comparing turbidity with 0.5 Mcfarland opacity standard, a lawn culture was obtained with the help of sterile cotton swab and then the antibiotic discs were applied. Within 15 minutes of inoculation of plates ,Plates were incubated at 37 degree c for 18 to 24 hrs. After incubation the diameter of the clear zone around the disc was measured under transmitted light and results interpreted according to the clinical and laboratory standards institute (CLSI) guidelines.

STATISTICAL ANALYSIS

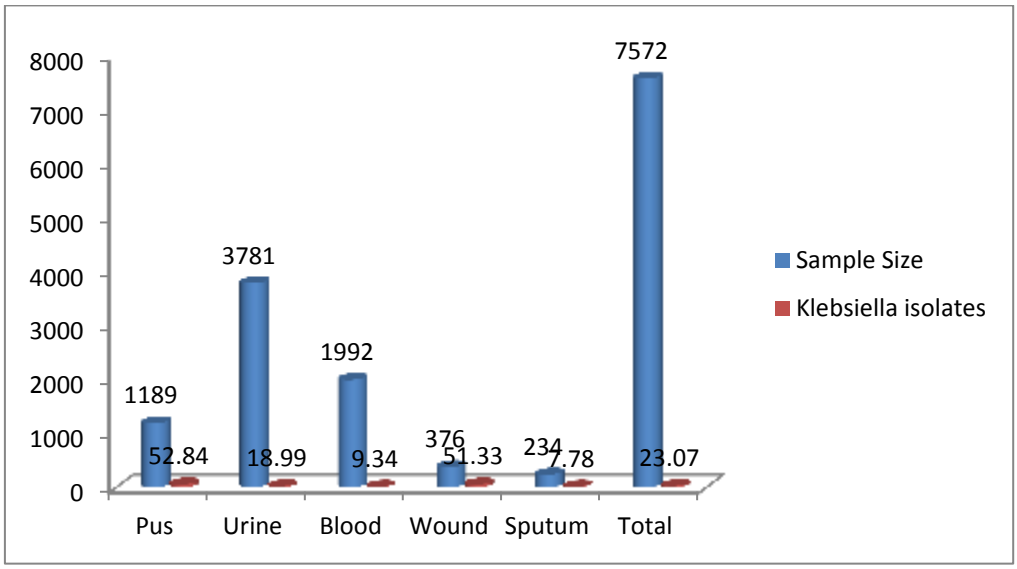
It was done using SPSS software version 24.

RESULTS

A total of 7572 samples were recruited during the study period. Out of 7572 samples, 1189, 3781, 1992, 376 and 234 were obtained from pus, urine, blood, wound and sputum respectively. Overall Klebsiella isolates was reported in 23.07% of all the samples. Individually, Klebsiella isolates was found in 52.84%, 18.99%, 9.34%, 51.33% and 7.78% of the pus, urine, blood, wound and sputum respectively (table 1, graph 1).

Table 1: Distribution of samples according to Klebsiella isolates

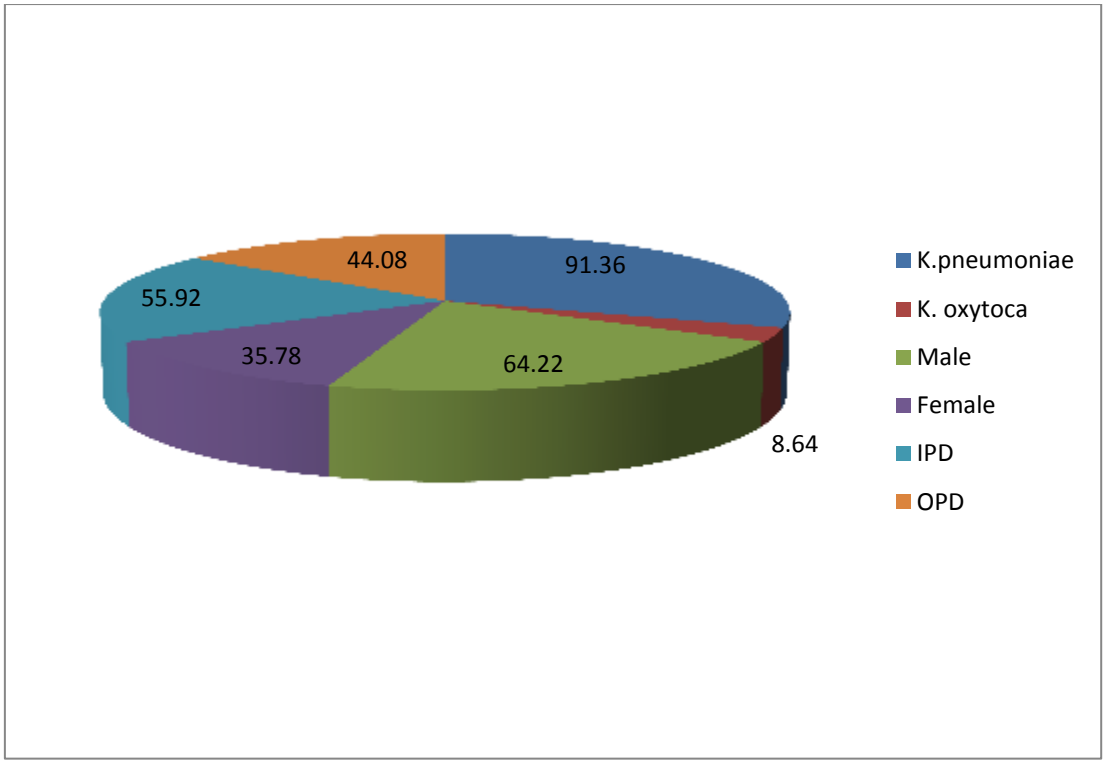
Sample Type	N	Klebsiella isolates	
		N	%
Pus	1189	624	52.84
Urine	3781	718	18.99
Blood	1992	186	9.34
Wound	376	193	51.33
Sputum	234	26	7.78
Total	7572	1747	23.07



Out of 1747 Klebsiella isolates, K.pneumoniae and K. oxytoca was revealed in 91.35% and 8.64% of the Klebsiella isolates respectively. Hence K.pneumoniae was the most common subspecies. There were comparatively more males as compared to females (table 2).

Table 2: Distribution of Klebsiella isolates based on its subspecies, gender and IPD/OPD

Variables	Klebsiella isolates	
	N=1747	%
Subspecies		
K.pneumoniae	1596	91.36
K. oxytoca	151	8.64
Gender		
Male	1122	64.22
Female	625	35.78
Department		
IPD	977	55.92
OPD	770	44.08



In this study, maximum sensitivity was shown with Colistin and Polymyxin-B i.e. 99.66% and 99.26% respectively followed by Imipenem89..71%, Meropenem 82.60%, Piperacillin/Tazobactam80.96%.Approximately 51% sensitivity was shown by amikacin and gentamycin both and minimum sensitivity shown by ampicillin i.e. 100%. Isolates from urine sample revealed that the Nitrofurantoin shows the maximum sensitivity i.e.59.33% compare to that of Norfloxacin i.e. 47.22%. Maximum resistance was shown by ampicillin (100%).Cefotaxime and Cefepime were found to be 83.34 % and 71.55% sensitive. Approximately no resistance was shown by both Polymyxin-B and Colistin (table 3).

Table 3: Antibiotic sensitivity pattern of Klebsiella species

Antibiotic	Sensitive (S)	(%)	Resistant ®	(%)
AK	902	51.63	845	48.37
AMP			1747	100
CPM	497	28.45	1250	71.55
MRP	1443	82.60	304	17.40
CIP	808	46.25	939	53.75
CTX	291	16.66	1456	83.34
GEN	904	51.75	843	48.25
PIC/TAZ	1415	80.99	332	19.01
CXM	826	47.28	921	52.72
IPM	1566	89.63	181	10.37
PB	1734	99.26	13	0.74
CL	1741	99.66	6	0.34
NIT	1037	59.36	710	40.64
NX	825	47.22	922	52.78

AK-Amikacin, AMP-Ampicillin, CPM-Cefepime, MRP-Meropenem, CIP ciprofloxacin, CTX-Cefotaxime, GEN-Gentamicin, PIC/TAZ-Piperacillintazobactam, CXM-Chloramphenicol, IPM-Imipenem, PB-polymixinB, Cl-Colistin, NIT-Nitrofurantoin, NX-Norfloxacin

Table 4: Distribution of Klebsiella susceptibility based on type of admission

Antibiotic	IPD (N=977)				OPD (N=770)				p value
	S		®		S		®		
	N	%	N	%	N	%	N	%	
AK	386	39.51	591	60.49	311	40.39	459	59.61	0.59
AMP	0	0.00	977	100	0	0.00	770	100	1
CPM	265	27.12	712	72.88	232	30.13	538	69.87	0.71
MRP	768	78.61	209	21.39	675	87.66	95	12.34	0.027*
CIP	451	46.16	526	53.84	357	46.36	413	53.64	0.90
CTX	166	16.99	811	83.01	125	16.23	645	83.77	0.83
GEN	501	51.28	476	48.72	403	52.34	367	47.66	0.77
PIC/TAZ	790	80.6	187	19.14	626	81.29	144	18.71	0.05
CXM	496	50.77	481	49.23	425	55.19	345	44.81	0.44
IPM	875	89.5	102	10.44	684	88.83	86	11.16	0.23
PB	968	99.08	9	0.92	766	99.48	4	0.52	0.88
CL	976	99.90	1	0.10	765	99.35	5	0.65	0.91
NIT	396	40.53	581	59.47	314	40.78	456	59.22	0.90
NX	499	53.12	458	46.88	458	59.48	312	40.52	0.13

*: statistically significant

In total, the resistance to all antibiotics examined was in the hospitalized patients more than outpatient cases, but this difference was significant only for meropenem ($p<0.05$) as shown in table 4.

Table 5: Distribution of Klebsiella susceptibility based on type of sample

Antibiotic	Resistance										p value
	Pus		Urine		Blood		Wound		Sputum		
	N=624	%	N=718	%	N=186	%	N=193	%	N=26	%	
AK	316	50.6	340	47.4	99	53.2	83	43.0	7	26.92	0.32
AMP	624	100.0	718	100.0	186	100.0	193	100.0	26	100.00	1
CPM	496	79.5	524	73.0	102	54.8	116	60.1	12	46.15	0.052
MRP	87	13.9	78	10.9	54	29.0	79	40.9	6	23.08	0.048
CIP	329	52.7	398	55.4	97	52.2	101	52.3	14	53.85	0.84
CTX	491	78.7	652	90.8	146	78.5	148	76.7	19	73.08	0.12
GEN	312	50.0	329	45.8	95	51.1	91	47.2	16	61.54	0.23
PIC/TAZ	264	42.3	338	47.1	46	24.7	30	15.5	4	15.38	0.07
CXM	320	51.3	395	55.0	97	52.2	99	51.3	10	38.46	0.40
IPM	261	41.8	332	46.2	45	24.2	28	14.5	3	11.54	0.09

PB	3	0.5	5	0.7	2	1.1	2	1.0	1	3.85	0.28
CL	2	0.3	2	0.3	1	0.5	1	0.5	0	0.00	0.67
NIT	283	45.4	342	47.6	51	27.4	32	16.6	2	7.69	0.10
NX	321	51.4	396	55.2	96	51.6	98	50.8	11	42.31	0.25

Least resistance was found in sputum w.r.t. all the antibiotics. Maximum resistance was revealed w.r.t. urine sample (table 5).

DISCUSSION

Klebsiella has emerged as a potential virulent pathogen over the years. Previously, a common cause of community acquired pneumonia, urinary tract infections, bacteremia and neonatal septicemia, hypervirulent forms with a potential for metastatic spread has occurred. These hypervirulent forms are primarily the cause of amoebic liver abscess, meningitis and metastatic endolphthalmitis. An insight of different virulence factors and their mechanism of interference with the host immune mechanism responsible for disease causation would enable to curb their harmful effects[1].

Overall Klebsiella isolates was reported in 23.07% of all the samples. Individually, Klebsiella isolates was found in 52.84%, 18.99%, 9.34%, 51.33% and 7.78% of the pus, urine, blood, wound and sputum respectively in this study. Hence Klebsiella is most commonly found in pus and wound samples. Similar results were reported by K. Sathyavathyet al[2] in their study. According to Sunil kumar Biradaret al[13], the highest percentage of Klebsiella spp were isolated from pus (50%) followed by urine (21%), sputum (18%), blood (7%), throat swab (3%) and CSF (1%).

Out of 1747 Klebsiella isolates, K.pneumoniae and K. oxytoca was revealed in 91.35% and 8.64% of the Klebsiella isolates respectively. Hence K.pneumoniae was the most common subspecies. There were comparatively more males as compared to females.The higher preponderance of males as compared to females correlates well to a study conducted by Namratha KG et al where a higher incidence of Klebsiella infections were reported in males as compared to females. Klebsiella pneumoniae was the major isolate followed by Klebsiella oxytoca[14]. Similarly ArpitaNeogiet al[15] in their study showed that majority of the isolates were Klebsiella pneumoniae subsp aerogenes (89%), followed by Klebsiella Oxytoca (8%) and Klebsiella pneumoniae subsp pneumoniae (3%). In a study conducted by D. O Acheampong, L. K Boamponsem et al, Klebsiella pneumoniae was the most common isolate followed by Klebsiella oxytoca, 2 isolates of Klebsiella rhinoscleromatis and one isolate of Klebsiellaozaenae[16]. Among the 100 Klebsiella spp, 89% were Klebsiella pneumoniae and 11% were Klebsiella oxytoca. Of the 100 Klebsiella isolates, 62 were from males and 38 were from females with a male: female ratio of 1.7: 1 as mentioned by SunilkumarBiradaret al[13] in their study.

In this study, maximum sensitivity was shown with Colistin and Polymyxin-B i.e. 99.66% and 99.26% respectively followed by Imipenem 89.71%, ,Meropenem 82.60%, Piperacillin/Tazobactam80.96%.The resulting limitations for therapeutic options demands new measures for management of klebsiella hospital acquired infections. Approximately 51% sensitivity was shown by amikacin and gentamycin both and minimum sensitivity shown by ampicillin i.e. 100%. On the other hand out, isolates from urine sample revealed that the

Nitrofurantoin shows the maximum sensitivity i.e. 59.33% compare to that of Norfloxacin i.e. 47.22%. Maximum resistance was shown by ampicillin (100%).Cefotaxime and Cefepime were found to be 83.34 % and 71.55% sensitive. Approximately no resistance was shown by both Polymyxin-B and Colistin.

The decreased susceptibility to meropenem might be due to the loss of porin and the presence of plasmid mediated beta lactamases. The increasing resistance to third generation cephalosporins could be due to the production of extended spectrum beta-lactamases and Amp C beta lactamases. Similar observation was recorded by Kothari et al where the isolates showed an increasing resistance to third generation cephalosporins[11].

MrinmoySarma et al[18] too in their study showed that maximum sensitivity were shown with Polymyxin-B and Colistini.c 100% followed by Meropenem 81.33%, 56% sensitivity was shown by amikacin and gentamycin both. Resistance showed against the Klebsiella species isolates aganist Ampicillin 64%, Ciprofloxacin 57.33%, followed by Gentamycin 44% . K.Sathyavathy et al in their study showed maximum susceptibility to imipenem 93% ,Meropenem 91%,Piperacillin -Tazobactam 77.5 % and Amikacin 71%.

ArpitaNeogi et al[15] in their study reported that Klebsiella isolates were sensitive to imipenem (96.8%), gentamicin (83.6%), amikacin (78.2%), levofloxacin (81.9%), meropenem (77.42%) piperacillin/ tazobactam (70.37%) and cefepime (64.3%), followed by third generation cephalosporins cefoperazone (54.8%) and ceftazidime (38.47%). They were least susceptible to amoxicillin and clavulanic acid combination (3.2%).

In K.Sathyavathyet al[12] study, Klebsiella species showed maximum susceptibility towards Imipenem 93%, Meropenem 91%, Piperacillin-Tazobactam 78.7% and Amikacin 71%. A study by Sadafguldin et al. showed susceptibility to imipenem 90.5%, Piperacillin-Tazobactam 77.5% and amikacin 78.4%. Namratha et al showed 53% sensitivity to Nitrofurantoin in their study[14].

In in the present study, the resistance to all antibiotics examined was in the hospitalized patients more than outpatient cases, but this difference was significant only for meropenem ($p<0.05$). Least resistance was found in sputum w.r.t. all the antibiotics. Maximum resistance was revealed w.r.t. urine sample. Similar results were reported by JamshidAyatollahiet al[19] in their study.

LIMITATIONS OF THE STUDY

The study was a phenotypic study of the virulence factors and speciation was done by the conventional biochemical methods. Automated methods would give a better insight into the virulence factors, drug resistance pattern and enable management of Klebsiella infections.

CONCLUSION

Klebsiella infections are a significant cause of mortality and morbidity amongst the patients. Therefore, the study of infections caused due to Klebsiella and their virulence factors coupled with the antimicrobial susceptibility pattern would be of utmost importance in combating the growing menace. As the multidrug resistant strains of Klebsiella species are constantly increasing. Knowledge about the resistance pattern of these bacterial strains will help in the judicial use of antibiotics, formulation of antibiotic policies apt for the hospitals and implementation of infection control programs.

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