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FIVE-YEAR ANTIMICROBIAL SUSCEPTIBILITY TRENDS AMONG PATHOGENS CAUSING URINARY TRACT INFECTION FROM A TERTIARY CARE HOSPITAL IN HIMACHAL PRADESH, INDIA

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Keywords:

Urinary tract infection, Antimicrobial resistance, Gram positive, Gram negative, Uropathogens, Escherichia coli, Antibiotics

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ABSTRACT: Introduction: Urinary tract infection is the most frequent infection reported worldwide till now. To better understanding regarding epidemiology and emerging antimicrobial resistance among bacterial uropathogens, we studied the demographic distribution and antibiotic susceptibility pattern of microorganisms causing UTI in our local hospital-based study. **Materials and Methods:** We analysed the retrospective data of laboratory confirmed UTIs, from January 2017 to December 2021. Causative agents of UTI, along with their demographic profile, distribution and their antibiogram was determined by using conventional methods. On the basis of that, 5-year multiple antibiotic resistance index was calculated to determine the resistance pattern of isolated bacterial uropathogens. **Results**: During study period, total 9426 samples were received. Out of which, 1133 (12.01%) showed significant bacteriuria with monomicrobial growth. With 64.17% isolation from female patients with predominance age group 16-60 years. From 1133 positive isolates, gram negative and gram positive isolates were reported in 298 (26.30%) and 835 (73.69%) isolates respectively, with predominance of *E. coli* (52.25%) followed by *Enterococcus* spp. (18.36%) *Klebsiella* spp. (8.21%). Multiple antibiotic resistance index over the 5 years study period found to be inconsistent and persistently high. **Conclusion:** The antimicrobial susceptibility data collected in our study suggest that antibiotic resistance is an emerging and common problem among bacterial uropathogens. This calls for routine and timely proper diagnosis of UTI along with its culture sensitivity results, that will help in definitive treatment rather than prescribing an empirical therapy.

INTRODUCTION: Prescribing antibiotics empirically for Urinary tract infection (UTI) is a complex and imposes a great challenge for physician as well as for the patient under treatment [1].

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Despite the guidelines present for the UTI treatment, even then there is a great debate regarding the choice of antibiotics to be prescribed differ among physicians [2].

Antibiotics prescribed according to guidelines even pose major challenge as the resistance / sensitivity pattern of pathogens vary widely according to region, age, gender, general conditions, associated various comorbidities, source of infection of the patient to be treated [3, 4]. Hence, it is must to find out the sensitivity of pathogens, of that particular geographic area from time to time and also must update antibiotic policies for regional treatment. It is always found that Escherichia coli (*E. coli*) [5, 6, 7] is the most common uropathogen causing UTI, but we cannot neglect the fact that pathogen predominance varies region to region and also their resistance vary widely [8]. So, it is easily understandable, physicians need updated information about resistance pattern and also about pathogen predominance of that specific area to reduce treatment failure and also to reduce the spread of antibiotic resistance [9]. UTI the main stray of treatment is antibiotics, hence it become much more important to find out the sensitivity pattern of the pathogens causing it. It is a well-known fact that *E. coli*, the most common organism for UTI, is also reported Multi drug Resistance (MDR) very commonly due to presence of R- plasmid [10].

UTI associated with MDR organisms may cause complications like pyelonephritis, increase in morbidity, hence need prompt treatment to avoid its complications [11]. It is also found that prompt treatment, follow-up and empirical use of antibiotics decrease complications and also the recurrence of it [12].

In developing countries, UTI pose addition challenge related to self-medication, poor choice of empirical therapy, lack of local guidelines, misuse, and overuse or under use of antibiotics and lack of supportive treatment. It further increases the morbidity and mortality related to UTI [13, 14, 15].

Hence, there is a crucial need to prepare data related to resistance pattern prevalent in specific community, to help physicians as a guide for proper empirical and definitive treatment. This updated document also support physicians to identify the pathogen and to decrease Antimicrobial resistance (AMR) and treatment cost also.

MATERIALS AND METHODS: This retrospective study was conducted at Maharishi Markandeshwar Medical College and Hospital, (720 bedded hospital) Solan, Himachal Pradesh from January 2017 to December 2021. During study period, midstream clean catched urine samples (clinically suspected cases of UTI) were received from various clinical departments of hospital. Inclusion criteria: Specimens showing significant bacteriuria (10^5CFU/ml).

Exclusion Criteria:

1. Specimens showing non-significant bacteriuria.
2. Specimens showing mixed or polymicrobial flora.

Ethical approval letter was obtained from Institutional Ethical Committee (vid no: MMMCH/IEC/22/533 dated: July 28, 2022) after reviewing the study plan.

Data Collection:

Identification and Antimicrobial Susceptibility Testing: Processing of received samples was done in department of Microbiology. Various variables like age, sex, departments were also collected for these samples. After receiving the samples in laboratory, culture was done on cystine lactose-electrolyte deficient (CLED) agar and blood agar. Colonies showing significant no. of bacteriuria (10^5CFU/ml) were subjected to gram staining. Depending upon staining results; further identification of pathogen was done by putting various biochemical tests as per standard protocols: For gram positive cocci: catalase test and coagulase test was done. For confirmation of isolated gram negative bacilli: catalase test, oxidase test followed by various biochemical reactions like triple sugar iron agar, indole test; Methyl red test, Voges–Proskauer test; citrate utilization test; urease production test; nitrate reduction test; and sugar fermentation tests [16]. Antibiotic susceptibility testing (AST) of all isolates was done by Modified Kirby bauer disc diffusion method on Muller Hinton agar as per Clinical and Laboratory Standards Institute (CLSI) guidelines. For AST, broth culture (log phase) inoculums with a turbidity equivalent to McFarland 0.5 standard (1.5 × 108 CFU/ml) was prepared from the isolates and lawn culture was done on the MuellerHinton agar. After drying of the plate, different-different antibiotic discs were applied to the agar surface to determine its susceptibility by incubating for 18 hours at 37ºC [17].

Extended Spectrum β-lactmases (ESBL) Test: *E.coli* and *Klebisella* spp. were also screened for extended spectrum βlactamases (ESBLs) by using disc diffusion method. In the presumptive test of detection for ESBL producers, all isolates of these 2 species were screened for susceptibility to ceftazidime (30 µg) and cefotaxime (30 µg) antibiotic discs (HiMedia, Mumbai). If zones of inhibition were found to be ≤22 mm and ≤27 mm for ceftazidime and cefotaxime respectively, indicating ESBL production. Then these isolates were subjected to phenotypic confirmatory test of combined disc assay as per CLSI guidelines. A ≥5mm increase in zone diameter of either of two above mentioned antimicrobial tested in combination with clavulanate vs the zone diameter of agent tested alone, indicates ESBL production. *E. coli* ATCC 25922 strain was used as quality control strain [18]. Further analysis of data was done by using WHONET 5.6 software (WHO, Boston, MA, USA).

Multiple Antibiotic Resistance Index (MAR Index) Calculation: Index [19] of the sample would be a/ (b * c), where a is the aggregate antibiotic resistance score of all isolates from the sample, b is the number of antibiotics, and c is the number of isolates from the sample

RESULTS: During period of study i.e. from January 2017 to December 2021, total 9426 samples were received and processing was done. Out of 9426 samples, 1133 (12.01%) were showed significant bacteriuria with monomicrobial growth. Out of these 1133 positive isolates, 298 (26.30%) were gram positive isolates and 835 (73.69%) were gram negative isolates.

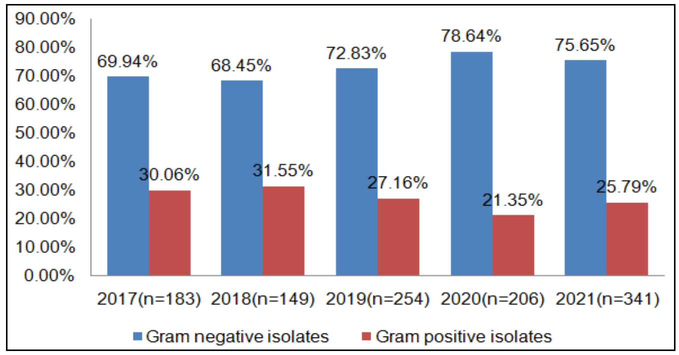

FIG. 1: SHOWING YEAR WISE DISTRIBUTION OF ISOLATED BACTERIAL UROPATHOGENS

TABLE 1: DISTRIBUTION OF ISOLATED GRAM POSITIVE ORGANISMS

Name	2017	2018	2019	2020	2021	Total
Enterococcus spp.	44 (80%)	40(85.10%)	50(72.47%)	30(68.18%)	44(53.01%)	208(69.79%)
Staphylococcus aureus	08(14.54%)	6(12.77%)	16(23.18%)	11(25%)	33(39.76%)	74(24.84%)
Staphylococcus saprophyticus	03(5.46%)	1(2.13%)	2(2.90%)	3(6.82%)	6(7.23%)	15(5.04%)
Streptococcus viridans			1(1.45%)			1(.33%)
Total	55 (30.06%)	47 (31.54%)	69 (27.16%)	44 (21.35%)	83 (25.79%)	298 (26.30%)

Out of 298 gram positive isolates, *Enterococcus* spp. was the most common isolated spp. i.e. (208; 69.79%), followed by *Staphylococcus aureus* (74; 24.84%), *Staphylococcus saprophyticus* (15; 5.04%) **Table 1.** Most common isolates among gram negative organisms were *E. coli* (592; 70.89%), followed by *Klebsiella* spp. (93; 11.13%), *Pseudomonas aeruginosa* (61; 7.30%), *Citrobacter* spp. (35; 4.19%) and *Acinetobacter baumannii* (19; 2.27%). Others very less frequently isolated gram negative bacteria were: *Enterobacter* spp. (15; 1.80%). *Proteus* spp. (15; 1.79%). Only 2 (.24%) isolates of each *Aeromonasveronii biovarsobria* and *Salmonella Typhi* and 1 (.12%) isolate of each *Morganellamorganii ss. Morganii*, *Providencia* sp. were isolated **Table 2.**

TABLE 2: DISTRIBUTION OF ISOLATED GRAM NEGATIVE ORGANISMS

Name	2017	2018	2019	2020	2021	Total
Acinetobacter baumannii	4(3.12%)	5(1.5%)	6(3.24%)	4(2.46%)	-	19(2.27%)
Citrobacter spp.	6(4.6%)	-	2(1.08%)	11(6.79%)	16(6.20%)	35(4.19%)
Enterobacter spp.	1(.78%)	-	2(1.08%)	4(2.4%)	8(3.10%)	15(1.80%)
Escherichia coli	88(68.75%)	73(71.56%)	127(68.65%)	105(64.81%)	198(76.74%)	591(70.89%)
Klebsiella spp.	15(11.71%)	8(7.84%)	16(8.64%0	26(16.04%)	28(10.86%)	93(11.13%)
Proteus spp.	1(.78%)	5(4.62%)	6(3.24%)	3(1.85%)	-	15(1.79%)
Pseudomonas aeruginosa	11(8.5%)	9(8.82%)	24(12.97%)	9(5.56%)	8(3.10%)	61(7.30%)
Aeromonasveronii biovarsobria	-	1(.98%)	1(.54%)	-	-	2(.24%)
Morganellamorganii ss. Morganii	-	-	1(.54%)	-	-	1(.12%)
Providencia sp.	-	1(.98%)	-	-	-	1(.12%)

Salmonella typhi	2(1.5%)	-	-	-	-	2(.24%)
Total	128 (69.94%)	102 (68.45%)	185 (72.83%)	162 (78.64%)	258 (75.65%)	835 (73.69%)

TABLE 3: DISTRIBUTION OF BACTERIAL UROPATHOGENS ON THE BASIS OF SEX DISTRIBUTION OVER THE PERIOD OF 5 YEARS (2017-2021) N=1133

Sex	Total isolates n= 1133	Gram positive n=298	Gram negative n=835
Male	406 (35.83%)	86(28.86%)	320(38.32%)
Female	727 (64.17%)	212(71.14%)	515(61.67%)

Among 1133 bacterial isolates, 64.17% were isolated from female patients and only 35.83% were isolated from male patients **Fig. 4**. Female to male ratio was1.7:1. Gram positive isolates were also much more (71.14%) reported in female patients

TABLE 4: DISTRIBUTION OF BACTERIAL UROPATHOGENS ON THE BASIS OF AGE GROUP DISTRIBUTION OVER THE PERIOD OF 5 YEARS (2017-2021) N=1133

Age group (in years)	Total isolates n= 1133	Male n=406	Female n=727
<1-15	70 (6.17%)	40	30
16-60	767 (67.70%)	212	555
>60	296 (26.12%)	154	142

The maximum Urinary tract infection isolates (67.70%) were found in age group 16-60 years and least (6.17%) from age group <15 years. As we also observed that males were predominantly found in age group <15 years and >60 years, while females were predominantly in age group 16-60 years. **Table 5** showing that; the maximum isolates were from obstetrics and gynecology department (37.06%), followed by surgery (26.03%) and medicine department (23.91%).

TABLE 5: DISTRIBUTION OF BACTERIAL UROPATHOGENS ON THE BASIS OF LOCATION OF ISOLATION OVER THE PERIOD OF 5 YEARS (2017-2021) N=1133

Department/ ward	Total isolates n=1133	Gram positive n=298	Gram negative n=835
Medicine	271(23.91%)	82(27.52%)	189(22.63%)
Surgery	295(26.03%)	56(18.79%)	239(28.62%)
Paediatrics	43(3.79%)	13(4.36%)	30(3.59%)
OBG	420(37.06%)	128(42.95%)	292(34.97%)
MICU	11(.97%)	5(1.68%)	6(.72%)
SICU	1 (0.08%)	0	1(.12%)
Orthopaedics	37(3.26%)	10(3.35%)	27(3.23%)
Causality	44(3.88%)	3(1.01%)	41(4.91%)
Skin & VD	6(.53%)	1(0.33%)	5(.60%)
Psychiatry	5(.44%)	0	5(.60%)

OBG: Obstetrics and Gynecology, MICU: Medical Intensive Care Unit, SICU: Surgical Intensive Care Unit

TABLE 6: ANTIMICROBIAL RESISTANCE AMONG MOST FREQUENTLY ISOLATED GRAM POSITIVE ORGANISMS (N=297) FROM UTI OVER A PERIOD OF 5 YEARS

Antimicrobials	*Enterococcus spp*. (n=208)	*Staphylococcus aureus* (n=74)	Staphylococcus saprophyticus (n=15)
CIP	150 (72.11%)	32(43.24%)	5(33.33%)
LVX	144(69.23%)	NT	NT
NOR	132(63.46%)	40(54.05%)	7(46.67%)
GEN	NT	13(17.56%)	3(20%)
HLG	78 (37.5%)	NT	NT
LNZ	6 (2.89%)	4(5.40%)	1(6.66%)
NIT	47 (22.59%)	4(5.40%)	4(26.67%)
TCY	97 (59.14%)	15(20.27%)	2(13.33%)
VAN	25(12.02%)	NT	NT
AMP	79 (37.98%)	45(60.81%)	6(40%)
FOX	NT	35(45.94%)	6(40%)
SXT	NT	26(35.13%)	3(20%)

*NT: Not tested, CIP: Ciprofloxacin, LVX: Levofloxacin, NOR: Norfloxacin, GEN: Gentamicin, HLG: high level Gentamicin, LNZ: Linezolid, NIT: Nitrofurantoin, TCY: Tetracycline, VAN: Vancomycin, AMP: Ampicillin, FOX: Cefoxitin, SXT: Cotrimoxazole.

As shown in **Table 6**, *Enterococcus* spp. had >60% resistance to fluoroquinolones. Resistance to high level aminoglycosides (HLG) is reported to 37.5% in our study. Vancomycin resistance to Enterococci (VRE) was found to be approximately 12%. Linezolid resistance was found higher in Staphylococcus spp. (5.40-6.66%) compared to *Enterococcus* spp. (2.9%)

TABLE 7: ANTIMICROBIAL RESISTANCE AMONG MOST FREQUENTLY ISOLATED LACTOSE FERMENTERS (N=735) FROM UTI OVER A PERIOD OF 5 YEARS

Antimicrobials	Escherichia coli (n=591)	Klebsiella spp. (n=93)	Citrobacter spp. (n=35)	Enterobacter spp. (n=15)
AMP	417(82.73%)	74(94.87%)	27(93.10%)	13(86.67%)
AMC	201(51.01%)	36(55.38%)	7(41.17%)	5(71.42%)
CFM	260(53.38%)	39(51.28%)	19(54.28%)	6(40%)
CTX	223(56.59%)	48(61.53%)	7(53.84%)	1(50%)
CPD	173(59.86%)	13(54.16%)	1(50%)	1(50%)
CAZ	310(52.36%)	61(65.59%)	23(69.68%)	7(46.67%)
CRO	392(55.10%)	48(69.56%)	20(60.60%)	6(46.15%)
CXM	316(62.69%)	51(65.38%)	18(62.06%)	6(40%)
CIP	324(64.28%)	45(48.38%)	15(51.72%)	6(40%)
NOR	380(64.18%)	47(50.53%)	17(48.57%)	7(46.67%)
OFX	386(65.20%)	50(53.76%)	16(45.71%)	9(60%)
GEN	159(26.85%)	29(44.61%)	8(42.10%)	2(33.33%)
AMK	74(14.68%)	23(29.48%)	4(13.79%)	3(21.42%)
IPM	53(8.92%)	17(18.27%)	7(20%)	2(13.33%)
NIT	43(8.53%)	28(35.89%)	12(41.37%)	3(20%)
TZP	84(14.18%)	34(36.56%)	8(22.85%)	4(26.67%)
SXT	212(42.06%)	36(46.15%)	11(37.93%)	5(35.71%)

AMP: Ampicillin, AMC: Amoxyclav, CFM: Cefuroxime, CTX: Cefotaxime, CPD: Cefpodoxime, CAZ: Ceftazidime, CRO: Ceftriaxone, CXM: Cefixime, CIP: Ciprofloxacin, NOR: Norfloxacin, OFX: Ofloxacin, GEN: Gentamicin, AMK: Amikacin, IPM: Imipenem, NIT: Nitrofurantoin, TZP: Piperacillin-Tazobactam, SXT: Cotrimoxazole.

TABLE 8: ANTIMICROBIAL RESISTANCE AMONG MOST FREQUENTLY ISOLATED NON FERMENTERS (N=95) FROM UTI OVER A PERIOD OF 5 YEARS

Antimicrobials	*Pseudomonas aeruginosa* (n=61)	*Acinetobacter baumannii* (n=19)	Proteus spp. (n=15)
AMK	11(22%)	4(26.67%)	5(35.71%)
GEN	11(26.19%)	3(30%)	6(42.85%)
FEP	10(38.46%)	8(72.72%)	NT
CAZ	11(22%)	10(66.67%)	4(26.67%)
CRO	3(27.27%)	3(37.5%)	NT
CTX	NT	10(66.67%)	4(28.75%)
IPM	7(11.47%)	0%	1(6.67%)
NIT	18(43.90%)	NT	NT
NOR	27(54%)	NT	8(57.14%)
CIP	25(50%)	8(53.33%)	6(42.85%)
LVX	25(40.98%)	6(42.85%)	6(40%)
OFX	31(50.81%)	NT	8(53.33%)
PIP	8(33.33%)	NT	NT
TZP	15(24.59%)	5(50%)	2(14.28%)

*NT: Not tested, CTX: Cefotaxime, CAZ: Ceftazidime, CRO: Ceftriaxone, CIP: Ciprofloxacin, NOR: Norfloxacin, OFX: Ofloxacin, GEN: Gentamicin, AMK: Amikacin, IPM: Imipenem, NIT: Nitrofurantoin, TZP: Piperacillin-Tazobactam, FEP: Cefepime, LVX: Levofloxacin, PIP: Piperacillin.

TABLE 9: YEAR AND ORGANISM WISE DISTRIBUTION OF ESBL PRODUCERS

Year	*E. coli* (n=592)	*Klebsiella* spp. (n=93)	Total (n=684)
2017	33/ 88 (37.5%)	6/15 (40%)	39/103(37.86%)
2018	23/73 (31.51%)	3/8 (37.5%)	26/81(32.09%)
2019	49/127 (38.58%)	5/16 (31.25%)	54/143(37.76%)
2020	30/ 105 (28.57%)	10/ 26 (38.46%)	40/131(30.53%)
2021	70/ 198 (35.35%)	10/28 (35.71%)	80/226 (35.39%)
Total	205/592 (34.63%)	34/93 (36.56%)	239 (34.94%)

TABLE 10: CUMULATIVE MAR INDEX OF ISOLATES

Class	Name of organism	2017	2018	2019	2020	2021	Average
Gram Positive	*Enterococcus spp*. (n=208)	0.23	0.38	0.42	0.55	0.47	0.40
	Staphylococcus aureus (n=74)	0.19	0.29	0.34	0.32	0.33	0.32
	Staphylococcus saprophyticus (n=15)	0.03	0	0.16	0.48	0.37	0.27
Gram Negative fermenters	*Escherichia coli* (n=592)	0.31	0.41	0.44	0.40	0.34	0.39
	Klebsiella spp. (n=93)	0.28	0.44	0.38	0.53	0.39	0.43
	Citrobacter spp. (n=35)	0.22	0	0.02	0.43	0.41	0.36
	Enterobacter spp. (n=15)	0.29	0	0.55	0.38	0.26	0.33
Gram Negative non –fermenters	*Pseudomonas aeruginosa* (n=61)	0.11	0.29	0.29	0.32	0.21	0.25
	Acinetobacter baumannii (n=19)	0.02	0.24	0.43	0.45	0	0.30
	Proteus spp. (n=15)	0.06	0.38	0.46	0.27	0	0.37

Values of MAR higher than 0.25, pose high risk source for contamination.

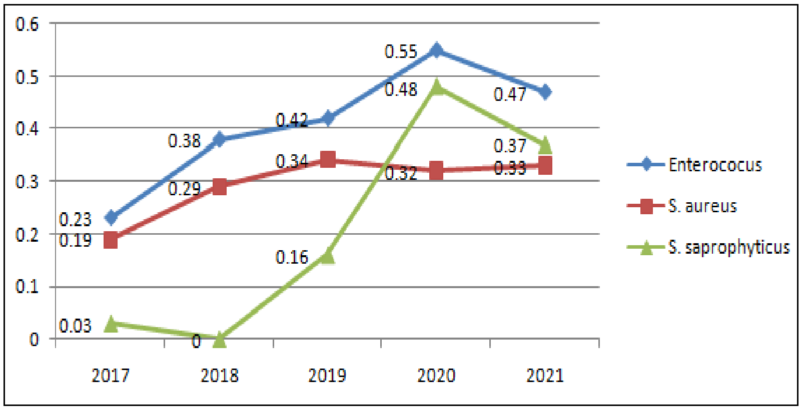

FIG. 2: CUMULATIVE MAR INDEX IN GRAM POSITIVE ISOLATES

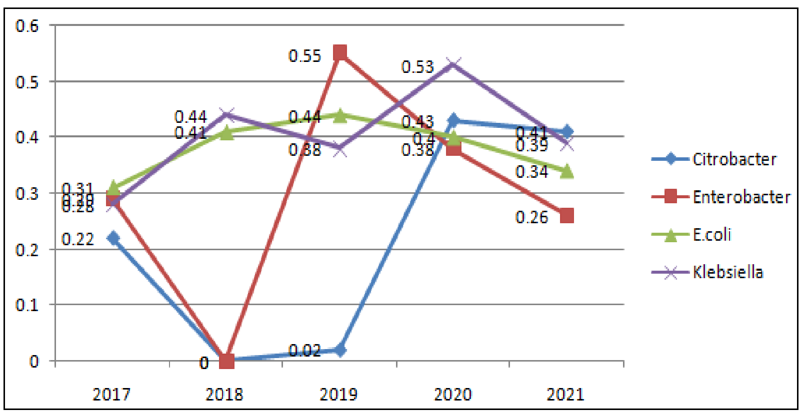

FIG. 3: CUMULATIVE MAR INDEX IN GRAM NEGATIVE (FERMENTERS) ISOLATES

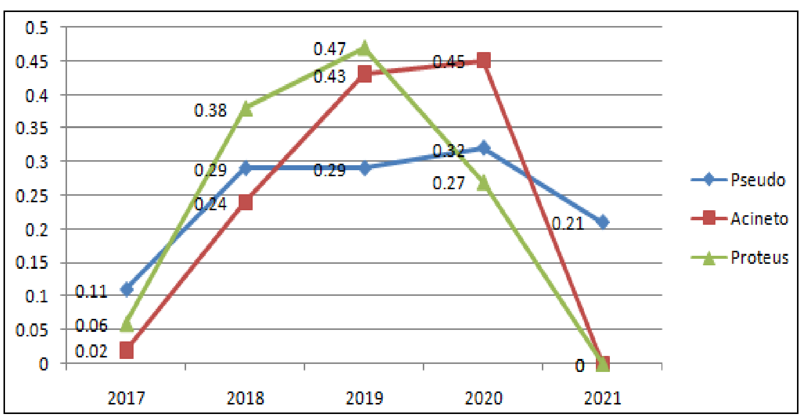

FIG. 4: CUMULATIVE MAR INDEXES IN GRAM NEGATIVE (NON FERMENTERS) ISOLATES

DISCUSSION: Due to changing trend in aetiology, pathogenesis and antimicrobial resistance, UTI will always remain a matter of concern. Due to various underlying factors like advanced age, poor hygiene, stay for long time in hospital, instrumentation, immunosuppression and various anatomical and physiological abnormalities, UTI is still a most commonly reported infection all over country [20].

In today's time, injudicious use of antibiotics increasing the rate of resistant strains. Therefore to treat the UTI effectively and adequately, knowing the causative organism of UTI along with its antibiogram is very important.

The prevalence of UTI varies across the country and also varies between different regions and areas of country. The overall prevalence of UTI in our study is 12.01%, which is very less in comparison to the results of studies conducted at Mumbai [21] (33.54%), Netherlands [22] (32.5%) and Abidjan (25.12%) [16]. But it was found to higher than the studies conducted by Beyene *et. al* (9.2%) [23] and Mwaka **et al.**[24] (10%).

In our study, isolation rate was found to be higher in females (64.71%) compared to males (35.83%), that is similar to findings of Bhargava *et al* [25]and Bitew *et al.* [26] this may be attributed to anatomical structure of genitourinary system and physiological changes infemales [26]. We also observed that maximum no. of isolates overall, were found in age group 16-60 years (67.70%). Like in another study, in age group <15 years and >60 years, male predominancy was found. This may be due to benign prostate hyperplasia and hormonal changes in old age in males [27].

In this study, gram negative organisms found predominantly (73.69%) in clinical suspected cases of UTIs. Escherichia coli (52.25%) was most commonly isolated, followed by *Klebisella* spp. (8.21%), similar to findings of many other studies [22, 28, 29]. *Enterococcus* spp. (18.36%) was also found to be an important gram-positive isolate in our study.

As we observed in our study, MAR index (table 10) is going on increasing till 2019 for most commonly isolated organism *E. coli*, this increase may be due to majority isolates developing resistant to commonly used antibiotics such as fluoroquinilones, cephalosporins *etc*. But after that slightly decline is observed, it may be due to improvement in sample collection procedure, better infection control practices and improvement in hygiene. But for *Klebisella* spp. it is noticed that MAR is variable between different years of study, it may be due to difference in isolation rate over the period. Overall MAR index for Enterobacteriacae family persistently found to be high and alarmingly. This is indicating that there is rise in MDR organisms, comparable to many other studies [30, 31, 32].

As per ESBL production concerned, found to be more for *Klebisella* spp. (36.6%) than *E. coli* (34.6%), similar to many other studies [28, 33]. While Morcoo based study reported higher rate of ESBL production in *E. coli* in their study. [31]ESBL-producers are considered to be posing more therapeutic inferences as these organisms show resistance against third generation cephalosporins, broad-spectrum ampicillin, and monobactams [33].

If we see Imipenem resistant, found to be 10-20% for various gram negative bacilli in present study, similar to findings of Mortazavi Tabatabaei *et al* [34] On the opposite side, Hrbacek *et al* [35] and kaur *et al* [36] found almost 100% susceptibility to imipenem and meropenem in their studies. A study done at northwest Ethiopia reported 26.4% resistance to meropenem in their study from uropathogens [37]. As we know that resistance mechanism for Carbapenems is a complex process that makes it difficult for early detection. That ultimately poses a great threat for public health and socioeconomic status all over world, and there is urgent need for developing the therapeutic guidelines for treatment of such difficult organisms [38].

Contrary to other studies [16, 29] for MAR index found to be less for non-fermenters in our study, it may be due to less isolation rate for these organisms or may be due to less no. of critically ill patients involved in this study. As, it is already reported in various studies that Pseudomonas, Acinetobacter spp. and Proteus spp. are mainly responsible for health care associated infections [39]. Less rate of isolation may be due to effective infection control and prevention protocol in our hospital.

As shown in table 10, MAR index of all gram positive isolates persistently found to be higher than 0.25. But in year 2020 it is found to be highest from all the five years for all isolated gram positive isolates. This high value may be due to increase in antibiotic resistance to many of the first line antibiotics used in treatment of UTI, injudiciously and over the counter availability of antibiotics.

In our study, rate of Methicillin Resistant *Staphylococcus aureus* (MRSA) was found to be 45.94%, similar to the findings of study done at Ethiopia [40]. An Iraq-Malaysia and northwest Ethiopia based study reported lower rate of MRSA in their study i.e. 7.7% and 30% respectively, as uropathogen [41, 42]. Although there are guidelines on the management of skin colonizers of MRSA, but there is little awareness and knowledge regarding urinary colonizers with indwelling catheters as well as from community. This required an urgent response to decrease the prevalence and to prevent further spread in community.

Vancomycin resistant to *Enterococcus* was found to be 12.02% **Table 6** in present study, which is almost, equal (14.08%) to study done by Meles e *et al*. in Ethiopia [43]. On the other hands, few studies reported higher rate of Vancomycin resistant enterococci [42, 44]. Contrary to these all findings, a Study conducted in England showed only 9.8% resistant to Vancomycin by *Enterococcus* spp [45]. VRE is a great serious concern, as it increase the duration and cost of treatment and we will left only with final resort antibiotics for its treatment i.e. linezolid and daptomycin.

As per linezolid resistance concerned, it is found to be only 2.89% and 5%-6% for *Enterococcus* spp. and *Staphylococcus* spp. respectively in our study.

As we observed that resistance rate found to be inconsistent over the period of study. But one thing is clear that it is overall found to be on higher side that is a great challenge for the further. As MDR, ESBL, VRE, MRSA and imipenem resistance is found in this study. Thus, clinicians and distributors should be strict while prescribing and supply of drugs, as we are already at the verge of availability of effective treatment. Taking in the consideration of this antimicrobial resistance results, physicians can select the appropriate antibiotic as per need.

As per World Health Organization (WHO), globally human health due to antimicrobial resistance is in great threat. Even to increase the awareness regarding AMR resistance, WHO has developed a program known as Global Antimicrobial Resistance Surveillance System (GLASS) [46]. These surveillance programs are the need of hour all over the country to combat the AMR resistance. High rate of resistance is a matter of concern as it increases the sufferings of patient and poses a great burden on economics.

Limitation of Study: As it is a retrospective study, we were not able to differentiate and compare the rates of UTI between outpatients and inpatients. Secondly we had not any molecular based detection method available so this study was limited to conventional methods only.

CONCLUSION: A gradual increase in antimicrobial resistance is a great challenge for both patients and clinicians. This high resistance demands timely resolution of the problem by prescribing the antibiotics based on antibiotic susceptibility testing rather than empirical treatment. A continual review for treatment guidelines of UTI is necessary for better outcome and to prevent the emergence of resistance

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