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PREVALENCE OF URINARY TRACT PATHOGENS AND ANTIMICROBIAL RESISTANCE PATTERNS IN CHILDREN AGED 1 TO 12 YEARS

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ABSTRACT

Background: *Urinary tract infections (UTIs) are counted among the most common infections in children. Most commonly, members of Enterobacteriacea, particularly urinary pathogenic strains of Esch. coli and Enterobacter aerogenes are the primary causative organisms of UTIs in different parts of the world. In spite of the availability and use of the antimicrobial drugs, UTIs caused by bacteria have been showing increasing trends. Antibiotics are a mainstay in the treatment of bacterial infections, though their use is a primary risk factor for the development of antibiotic resistance. Antibiotic resistance is a growing problem in pediatric urology as demonstrated by increased urinary pathogen resistance. The extensive and inappropriate use of antimicrobial agents has invariably resulted in the development of antibiotic resistance which, in recent years, has become a major problem worldwide. Increasing antibiotic resistance among urinary pathogens to commonly prescribed drugs has become a global reality today. Complex pediatric patients with histories of hospitalizations, prior antibiotic exposure, and recurrent UTIs are also at high risk for acquiring UTIs due to extended spectrum beta-lactamase [ESBL] producing organisms. Data regarding the impact of in vitro antibiotic susceptibility testing interpretation on UTI treatment outcomes is lacking. The resistance of bacteria causing urinary tract infection (UTI) to commonly prescribed antibiotics is increasing both in developing as well as in developed countries. Resistance has emerged even to more potent antimicrobial agents.* ***Objective:*** *To determine the prevalence and to find out the causative agents of UTI and their antibiotic resistance pattern among suspected UTI patients in children.* ***Methodology and Results:*** *A total of 512 urine samples were collected from out patients of age between 1 to 12 years of both sex of children at Serum Analysis Center Pvt. Ltd. [Referral Laboratory]; Howrah; West Bengal; India between December 2016 to November 2017. The urine samples were cultured on HiCrome UTI Agra media and Eosin Methylene Blue Agar media [EMB] and the bacterial isolates were identified by gram staining and conventional biochemical methods. Antimicrobial susceptibility testing was performed by Kirby Bauer disk diffusion method according to the current National Committee for Clinical Laboratory Standards (NCCLS) guidelines. Among the 512 urine samples examined [1 to 12 years of children], included 276 (54.0%) in Male child & 236 (46.0%) in Female child and 220 (42.9%) of urinary pathogens are isolated. The bacteria were isolates 104 (37.7%) of male child and 116 (49.2%) of female child. In patient of male child, 50% of Esch. coli, 34.6% of Klebsiella pneumoniae, 15.4% of others gram negative bacilli and 52.0% Extended- spectrum Beta lactamase [ESBL] stains were isolates. In patient of female child, 72.4% of Esch. coli, 20.7% of Klebsiella pneumoniae, 6.9% of others gram negative bacilli and 58.7% Extended- Spectrum Beta lactamase [ESBL] stains were isolates. Resistance rates of Esch. coli [1 to 12 years of children] isolates were 83.8% to Amoxicillin/clavulanic acid, 70.5% to Cefixime, 23.5% to Fosfomycin, 26.5% to Nitrofurantoin, 63.2% to Ofloxacin, 66.1% to Ceftriaxone, 67.6% to Cefotaxime, 22.0% to Gentamicin, 89.7% to Cefpodoxime, 63.2% to*

Ciprofloxacin, 19.2% to Tobramycin, 80.8% to Cefprozil, 63.2% to Co-trimoxazole, 92.6% to Cefaclor, 70.5% to Doxycycline, 4.5% to Amikacin, 57.4% to Levofloxacin, 58.9% to Tetracycline and 89.8% to Cefalexin. Resistance rates of Klebsiella pneumoniae [1 to 12 years of children] isolates were 66.7% to Amoxicillin/clavulanic acid, 43.3% to Cefixime, 23.3% to Fosfomycin, 63.3% to Nitrofurantoin, 20.0% to Ofloxacin, 43.3% to Ceftriaxone, 43.3% to Cefotaxime, 13.3% to Gentamicin, 90.0% to Cefpodoxime, 23.3% to Ciprofloxacin, 13.3% to Tobramycin, 76.6% to Cefprozil, 50.0% to Co-trimoxazole, 73.3% to Cefaclor, 33.3% to Doxycycline, 6.6% to Amikacin, 20.0% to Levofloxacin, 36.7% to Tetracycline and 80.0% to Cefalexin. Resistance rates of Others Gram negative Bacilli [1 to 12 years of children] isolates were 75.0% to Amoxicillin/clavulanic acid, 33.4% to Cefixime, 33.4% to Fosfomycin, 41.7% to Nitrofurantoin, 16.7% to Ofloxacin, 66.7% to Ceftriaxone, 16.7% to Cefotaxime, 8.3% to Gentamicin, 91.6% to Cefpodoxime, 25.0% to Ciprofloxacin, 8.3% to Tobramycin, 91.6% to Cefprozil, 41.7% to Co-trimoxazole, 91.6% to Cefaclor, 41.7% to Doxycycline, 8.3% to Amikacin, 8.3% to Levofloxacin, 41.7% to Tetracycline and 91.6% to Cefalexin. ***Conclusion:*** *High prevalence of drug-resistant urinary tract pathogens, particularly to commonly use of oral antibiotics in UTI like Amoxicillin/clavulanate, Cefixime, Cefpodoxime, Cefprozil, Cephalexin and Co-trimoxazole (Trimethoprim/sulfamethoxazole) among children suggests cautious use of antibiotic therapy for the treatment. Finally, we suggest that empirical antibiotic selection should be based on knowledge of the local prevalence of bacterial organisms and antibiotic sensitivities rather than on universal guidelines.*

KEY WORDS

Urinary tract infections; Antibiotic resistance; Pediatrics; Antibiogram.

INTRODUCTION

Urinary tract infections (UTIs) are a common problem in pediatric patients. Resistance to common antibiotic agents appears to be increasing over time, although resistance rates may vary based on geographic region or country. Prior antibiotic exposure is a pertinent risk factor for acquiring resistant organisms during a first UTI and recurrent UTI. Judicious prescribing of antibiotics for common pediatric conditions is needed to prevent additional resistance from occurring. Complex pediatric patients with histories of hospitalizations, prior antibiotic exposure, and recurrent UTIs are also at high risk for acquiring UTIs due to extended spectrum beta-lactamase-producing organisms. Data regarding the impact of in vitro antibiotic susceptibility testing interpretation on UTI treatment outcomes is lacking.

A urinary tract infection (UTI) is one of the most important causes of morbidity and mortality in the developing countries like India. Acute urinary tract infections are relatively common in children, with 8 percent of girls and 2 percent of boys having at least one episode by seven years of age, and between 30% and 40% will have another episode within two years. [1-2] Several studies has demonstrated that the geographical variability of pathogen occurrence in case of UTI among inpatients and outpatients populations is limited by the predominance of gram-negative species usually Enterobactericeae and particularly *Esch. coli* and *Enterobacter aerogenes* in various regions of the world. [3-4]

The most common pathogen is *Escherichia coli*, accounting for approximately 85 percent of urinary tract infections in children. Renal parenchyma defects are present in 3 to 15 percent of children within one to two years of their first diagnosed urinary tract infection. Clinical signs and symptoms of a urinary tract infection depend on the age of the child, but all febrile children two to 24 months of age with no obvious cause of infection should be evaluated for urinary tract infection (with the exception of circumcised boys older than 12 months). Evaluation of older children may depend on the clinical presentation and symptoms that point toward a urinary source (e.g., leukocyte esterase or nitrite present on dipstick testing; pyuria of at least 10 white blood cells per high-power field and bacteriuria on microscopy).

The worldwide increase of urinary pathogens resistant to former first line antibiotics, such as cotrimoxazole, fluoroquinolones and cephalosporins, has had detrimental consequences not only for treatment but also for prophylaxis of infectious complications after urological interventions. A paradigm shift concerning asymptomatic bacteriuria has had a great impact on the definition and management of UTIs today [5–8].

However, for complicated, nosocomial and severe UTI including pyelonephritis, antibiotic therapy will still be a corner stone in combination with treatment of the underlying complicating conditions. Unfortunately, there are few new antimicrobial drugs in the pipelines of pharmaceutical companies with prospects to overcome the problem of multi and extended drug resistant urinary pathogens [9].

Urinary tract infections (UTIs) are the most common serious bacterial infections in infants and young children. Infection of the urinary tract may be limited to the bladder, one or both kidneys, or both sites. In general, infections of the bladder (cystitis), although they cause substantial morbidity, are not regarded as serious bacterial infections. By contrast, infections that involve the kidney (pyelonephritis) may cause both acute morbidity and lead to scarring with the consequences of hypertension, preeclampsia, and chronic renal disease. Accordingly, differentiation of the site of infection has received considerable attention.

Antibiotics are medicines used to prevent and treat bacterial infections. Antibiotic resistance occurs when bacteria change in response to the use of these medicines. Bacteria, not humans or animals, become antibiotic-resistant. These bacteria may infect humans and animals, and the infections they cause are harder to treat than those caused by non-resistant bacteria. Antibiotic resistance leads to higher medical costs, prolonged hospital stays, and increased mortality.

Antimicrobial resistance among urinary tract isolates has recently been reported with an increased frequency all over the world. [10-13] The world urgently needs to change the way it prescribes and uses antibiotics. Even if new medicines are developed, without behavior change, antibiotic resistance will remain a major threat. Behavior changes must also include actions to reduce the spread of infections through vaccination, hand washing, practicing safer sex, and good food hygiene.

For more than half a century, antibiotic drugs have ensured that potentially life-threatening bacterial infections are treatable. Today, however, more and more bacterial infections fail to respond to antibiotic treatment. A federal task force recently warned that antibiotic resistance is “a growing menace to all people” and concluded that if nothing is done, treatments for common infections will become “increasingly limited and expensive- and, in some cases, nonexistent.”

Table 1. Antibiotics Commonly Used to Treat Urinary Tract Infections in Children

Antibiotic	*Dosing*	*Common adverse effects*
Amoxicillin/clavulanate (Augmentin)	25 to 45 mg per kg per day, divided every 12 hours	Diarrhea, nausea/vomiting, rash
Cefixime (Suprax)	8 mg per kg every 24 hours or divided every 12 hours	Abdominal pain, diarrhea, flatulence, rash
Cefpodoxime	10 mg per kg per day, divided every 12 hours	Abdominal pain, diarrhea, nausea, rash
Cefprozil (Cefzil)	30 mg per kg per day, divided every 12 hours	Abdominal pain, diarrhea, elevated results on liver function tests, nausea
Cephalexin (Keflex)	25 to 50 mg per kg per day, divided every 6 to 12 hours	Diarrhea, headache, nausea/vomiting, rash
Trimethoprim/ sulfamethoxazole (Bactrim, Septra)	8 to 10 mg per kg per day, divided every 12 hours	Diarrhea, nausea/vomiting, photosensitivity, rash

Knowledge regarding common urinary pathogens and their changing of susceptibility patterns to drug will help in improving prescribing decisions in general practice, since one of the most important factors to consider when selecting appropriate antimicrobial therapy is the prevalence of resistance in the community.

MATERIALS AND METHODS

[I] Study Population, Design, and Setting:

The current study was conducted in the Department of Microbiology, Serum Analysis Center Pvt. Ltd. [Referral Laboratory]; Howrah; West Bengal; India; from December 2016 to November 2017.

[II] Patient Evaluation:

A prospective analysis was done on 512 of outpatients. All patients were within ages 1 to 12 of children, comprising of both male and female. All samples received consisted 276 of male child and 236 of female child.

[III] Categories Age Group:

[i] Preschool aged Children: 1to 5 Years.

[ii] School aged Children: >5 to 12 Years.

[IV] Collection of Urine Sample:

Early morning mid-stream urine samples were collected using sterile, wide mouthed container with screw cap tops. [14] On the urine sample bottles were indicated name, age, sex, and time of collection along with requisition forms.

[V] Sample Processing:

A calibrated sterile micron wire loop for the semi-quantitative method was used for the plating and it has a 4.0 mm diameter designed to deliver 0.01 ml. A loopful of the well mixed urine sample was inoculated on HiCrome UTI Agar media and EMB [Eosin Methylene Blue] Agar media. The plate was incubated aerobically at 37^0centrigade for overnight. The plates were then examined macroscopically and microscopically for bacterial growth. The bacterial colonies were counted and multiplied by 100 to give an estimate of the number of bacteria present per mililiter of urine. Culture results were interpreted according to the standard criteria and a growth of > 10^5 colony forming unit [CFU] /ml was considered as significant bacteriuria [15]. The urine samples were analyzed bacteriological using the methods [14, 16, 17].

[VI] Identification of Isolates:

The isolates were identified using colony morphology, Gram staining, Motility test, Indole test, Citrate test [Simmons Citrate Agar media], Urease test [Urease Agar media + 40% Urea], Triple Sugar Iron Agar media, ONPG [Ortho-nitrophenyl beta-D-galactopyranoside] and Oxidase test [14, 17].

[VIII] Antimicrobial susceptibility testing:

All isolates were tested for antimicrobial susceptibility on Muller Hinton Agar by the standard Bauer et al. disc diffusion method [18] recommended by the Clinical and Laboratory Standards institute (CLSI) [19]. Antibiotic agents (disks) were obtained from Hi Media Laboratories, Pvt. Ltd; Mumbai. Appropriate quality control strains were used to validate the results of the antimicrobial disk. *Esch. coli,* ATCC 25922, and *Pseudomonas aeruginosa*, ATCC 27853 was used as quality control strains [17].

[VIII] Extended-spectrum Beta-lactamase (ESBL) detection by the CLSI phenotype method:

The CLSI ESBL confirmatory test with cefotaxime [30mcg] and Cefotaxime/Clavulanic acid [30+10 mcg] were performed for all isolates using the disc diffusion method on Mueller-Hinton Agar plates. Susceptibility test results were interpreted according to criteria established by the CLSI [20].

RESULTS

For the twelve months of this study, 512 urine samples were received and cultured. There were 276 (54.0%) male child and 236 (46.0%) female child giving a total of 512 children who enrolled in this study. Their age ranged from 1 to 12 years. Among the cultures screened, bacteriuria of 10^5 cfu/ml of urine was found in 220 (42.9%) of the samples. A total of 292 (57.0%) of the urine samples were culture negative. 104 (37.7%) were isolated from male child and 116 (49.2%) from female child.

Table: 2. Different age groups of total sample.

Age Group	Total Population	Male child	Female child
1 to 12 years	512	276 (54.0%)	236 (46.0%)
1 to 5 years	312	170 (54.5%)	142 (45.5%)
>5 to 12 years	200	106 (53.0%)	94 (47.0%)

Table: 3. Prevalence of UTI in different age groups.

Age Group	Total Population	Positive culture	Negative culture
1 to 12 years	512	220 (42.9 %)	292 (57.0%)
1 to 5 years	312	148 (47.4%)	164 (52.6%)
>5 to 12 years	200	72 (36.0%)	128 (64.0%)

Table: 4. Prevalence of UTI in different age groups with Male & Female child.

Age Group	Total Population in Male child	Positive culture in Male child	Total Population in Female child	Positive culture in Female child
1 to 12 years	276	104 (37.7%)	236	116 (49.2%)
1 to 5 years	170	74 (43.6%)	142	74 (52.2%)
>5 to 12 years	106	30 (28.3%)	94	42 (44.7%)

Table: 5. Prevalence of pathogens isolated on urine culture with age group of 1 to 12 years.

Pathogens	Male child [No: 104]	Female child [No.:116]
Esch. coli	52 (50.0%)	84 (72.4%)
Klebsiella pneumoniae	36 (34.6%)	24 (20.7%)
Others Gram Negative Bacilli	16 (15.4%)	8 (6.9%)
ESBL Stain	54 (52.0%)	68 (58.7%)

Table: 6. Prevalence of pathogens isolated on urine culture with age group of 1 to 5 years.

Pathogens	Male child [No.: 74]	Female child [No.: 74]
Esch. coli	36 (48.6%)	54 (73.0%)
Klebsiella pneumoniae	26 (35.2%)	14 (18.9%)
Others Gram Negative Bacilli	12 (16.2%)	06 (8.1%)
ESBL Stain	40 (54.0%)	44 (59.5%)

Table: 7. Prevalence of pathogens isolated on urine culture with age group of >5 to 12 years.

Pathogens	Male child [No.: 30]	Female child [No.: 42]
Esch. coli	16 (53.3%)	30 (71.4%)
Klebsiella pneumoniae	10 (33.3%)	10 (23.8%)
Others Gram Negative Bacilli	04 (13.4%)	02 (4.8%)
ESBL Stain	14 (46.7%)	24 (57.2%)

CHILDREN: 1 TO 12 YEARS

Table: 8. Percentage of Resistant & Susceptibility of isolated *Escherichia coli* to tested antibiotic:

Antibiotics	Total Isolates: 136			
	R (No.)	R (%)	S (No.)	S (%)
Amoxicillin/Clavulanic acid	**114**	**83.8**	**22**	**16.2**
Amikacin	06	04.5	130	95.5
Gentamicin	30	22.0	106	78.0
Tobramycin	26	19.2	110	80.8
Fosfomycin	32	23.5	104	76.5
Ciprofloxacin	86	63.2	50	36.8
Ofloxacin	86	63.2	50	36.8
Levofloxacin	78	57.4	58	42.6
Nitrofurantoin	36	26.5	100	73.5
Trimethoprim/Sulfamethoxazole	**86**	**63.2**	**50**	**36.8**
Doxycycline Hydrochloride	96	70.5	40	29.5
Tetracycline	80	58.9	56	41.1
Cefixime	**96**	**70.5**	**40**	**29.5**
Ceftriaxone	90	66.1	46	33.9
Cefotaxime	92	67.6	44	32.4
Cefpodoxime	**122**	**89.7**	**14**	**10.3**
Cefprozil	**110**	**80.8**	**26**	**19.2**
Cefaclor	126	92.6	10	07.4
Cefalexin	**122**	**89.8**	**14**	**10.2**

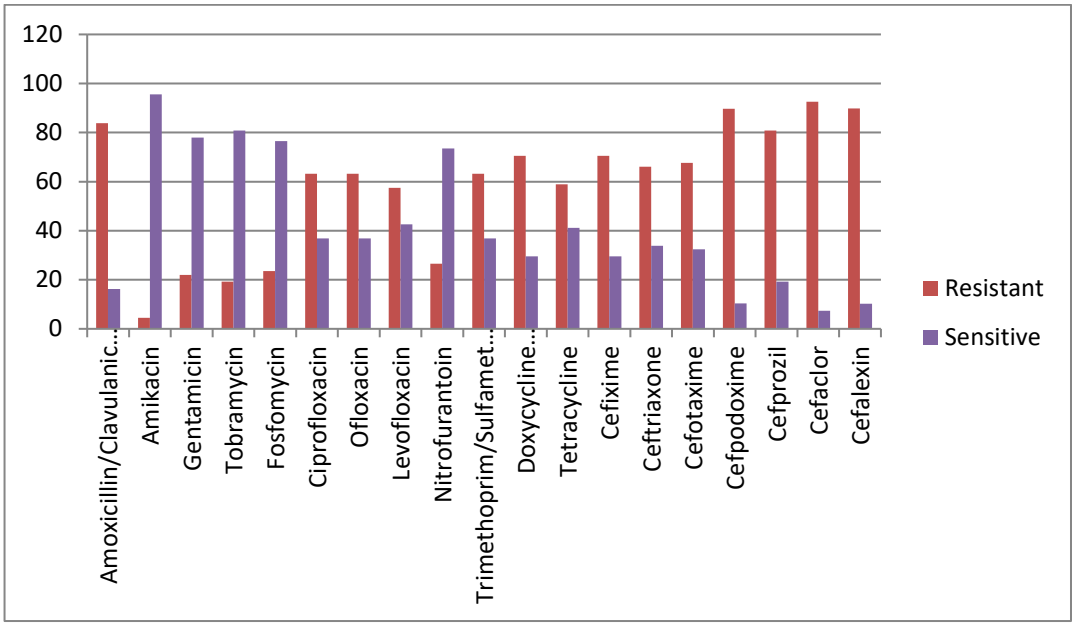

Fig: 1. Pattern of Escherichia coli Resistant & Sensitive

Table: 9. Percentage of Resistant & Susceptibility of isolated Klebsiella pneumoniae to tested antibiotic:

	Total Isolates: 60			
Antibiotics	**R (No.)**	**R (%)**	**S (No.)**	**S (%)**
Amoxicillin/Clavulanic acid	**40**	**66.7**	**20**	**33.3**
Amikacin	04	06.6	56	93.4
Gentamicin	08	13.3	52	86.7
Tobramycin	08	13.3	52	86.7
Fosfomycin	14	23.3	46	76.7
Ciprofloxacin	14	23.3	46	76.7
Ofloxacin	12	20.0	48	80.0
Levofloxacin	12	20.0	48	80.0
Nitrofurantoin	38	63.3	22	36.7
Trimethoprim/Sulfamethoxazole	**30**	**50.0**	**30**	**50.0**
Doxycycline Hydrochloride	20	33.3	40	66.7
Tetracycline	22	36.7	38	63.3
Cefixime	**26**	**43.3**	**34**	**56.7**
Ceftriaxone	26	43.3	34	56.7
Cefotaxime	26	43.3	34	56.7
Cefpodoxime	**54**	**90.0**	**06**	**10.0**
Cefprozil	**46**	**76.6**	**14**	**23.4**
Cefaclor	44	73.3	16	26.7
Cefalexin	**48**	**80.0**	**12**	**20.0**

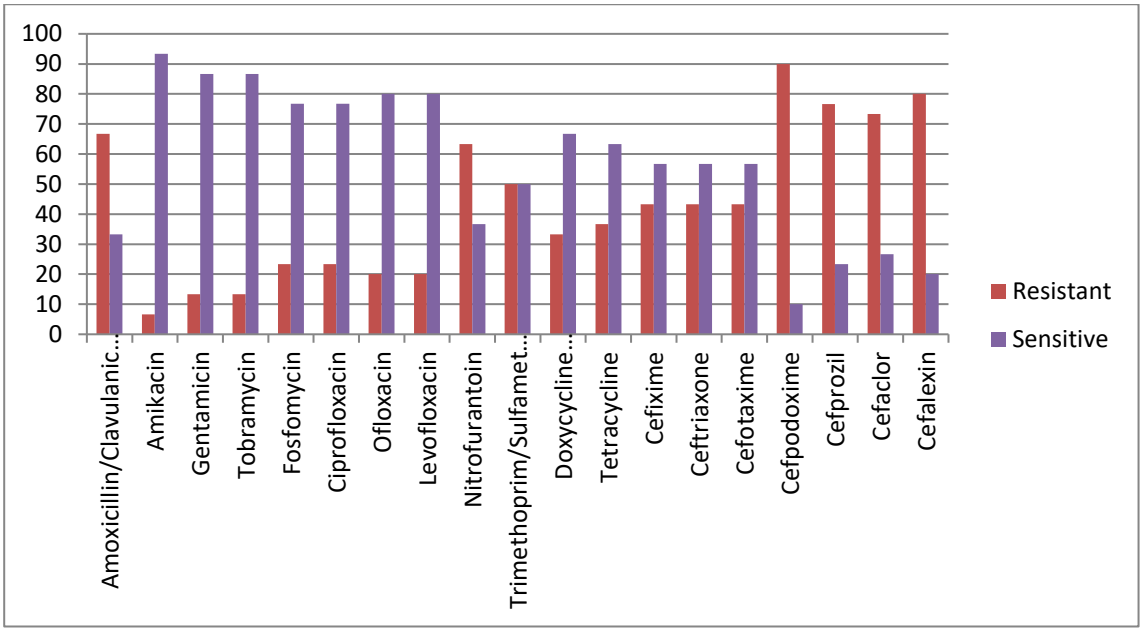

Fig: 2. Pattern of Klebsiella pneumoniae Resistant & Sensitive

Table: 10. Percentage of Resistant & Susceptibility of isolated others Gram Negative Bacilli to tested antibiotic:

	Total Isolates: 24			
Antibiotics	**R (No.)**	**R (%)**	**S (No.)**	**S (%)**
Amoxicillin/Clavulanic acid	**18**	**75.0**	**06**	**25.0**
Amikacin	02	8.3	22	91.7
Gentamicin	02	08.3	22	91.7
Tobramycin	02	08.3	22	91.7
Fosfomycin	08	33.4	16	66.6
Ciprofloxacin	06	25.0	18	75.0
Ofloxacin	04	16.7	20	83.3
Levofloxacin	02	8.3	22	91.7
Nitrofurantoin	10	41.7	14	58.3
Trimethoprim/Sulfamethoxazole	**10**	**41.7**	**14**	**58.3**
Doxycycline Hydrochloride	10	41.7	14	58.3
Tetracycline	10	41.7	14	58.3
Cefixime	**08**	**33.4**	**16**	**66.6**
Ceftriaxone	16	66.7	08	33.3
Cefotaxime	04	16.7	20	83.3
Cefpodoxime	**22**	**91.6**	**02**	**08.4**
Cefprozil	**22**	**91.6**	**02**	**08.4**
Cefaclor	22	91.6	02	08.4
Cefalexin	**22**	**91.6**	**02**	**08.4**

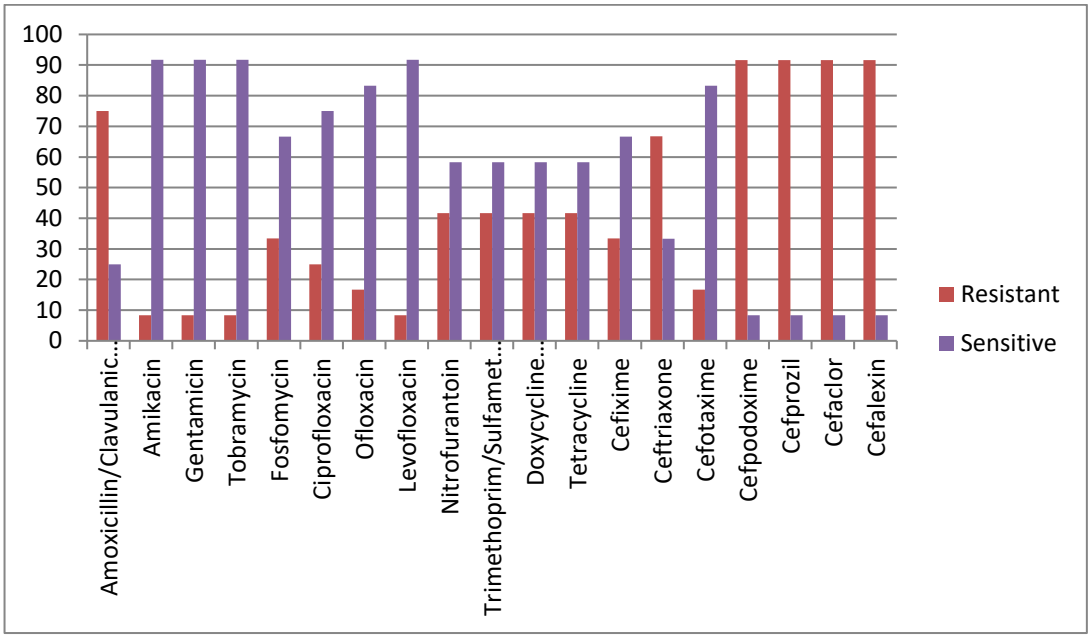

Fig: 3. Pattern of Others Gram Negative Bacilli Resistant & Sensitive

CATEGORY-I: PRE SCHOOL AGED CHILDREN [1 TO 5 YEARS]

Table: 11. Percentage of Resistant & Susceptibility of isolated *Escherichia coli* to tested antibiotic:

	Total Isolates: 90			
Antibiotics	**R (No.)**	**R (%)**	**S (No.)**	**S (%)**
Amoxicillin/Clavulanic acid	**80**	**88.9**	**10**	**11.1**
Amikacin	04	04.4	86	95.6
Gentamicin	22	24.5	68	75.5
Tobramycin	12	13.4	78	86.6
Fosfomycin	26	28.9	64	71.1
Ciprofloxacin	56	62.2	34	37.8
Ofloxacin	54	60.0	36	40.0
Levofloxacin	52	57.8	38	42.2
Nitrofurantoin	24	26.7	66	73.3
Trimethoprim/Sulfamethoxazole	**58**	**64.4**	**32**	**35.6**
Doxycycline Hydrochloride	68	75.5	22	24.5
Tetracycline	60	66.6	30	33.4
Cefixime	**62**	**68.8**	**28**	**31.2**
Ceftriaxone	58	64.5	32	35.5
Cefotaxime	58	64.5	32	35.5
Cefpodoxime	**80**	**88.8**	**10**	**11.2**
Cefprozil	**70**	**77.8**	**20**	**22.2**
Cefaclor	82	91.1	08	08.9
Cefalexin	**82**	**91.1**	**08**	**08.9**

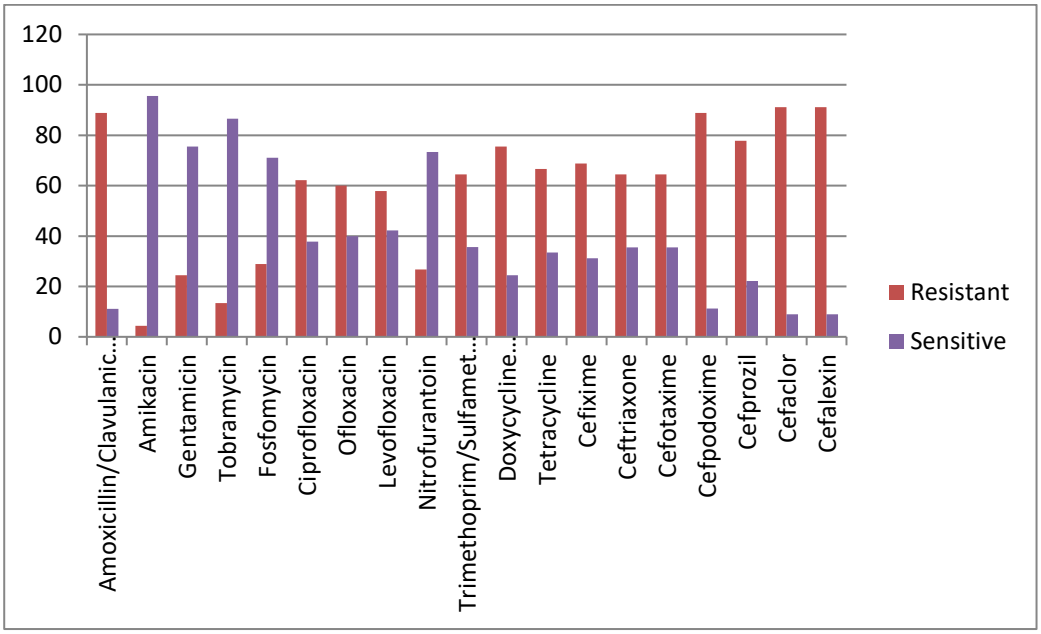

Fig: 4. Pattern of Escherichia coli Resistant & Sensitive

Table: 12. Percentage of Resistant & Susceptibility of isolated *Klebsiella pneumoniae to* tested antibiotic:

	Total Isolates: 40			
Antibiotics	**R (No.)**	**R (%)**	**S (No.)**	**S (%)**
Amoxicillin/Clavulanic acid	**30**	**75.0**	**10**	**25.0**
Amikacin	02	05.0	38	95.0
Gentamicin	06	15.0	34	85.0
Tobramycin	06	15.0	34	85.0
Fosfomycin	12	30.0	28	70.0
Ciprofloxacin	10	25.0	30	75.0
Ofloxacin	10	25.0	30	75.0
Levofloxacin	10	25.0	30	75.0
Nitrofurantoin	26	65.0	14	35.0
Trimethoprim/Sulfamethoxazole	**20**	**50.0**	**20**	**50.0**
Doxycycline Hydrochloride	18	45.0	22	55.0
Tetracycline	18	45.0	22	55.0
Cefixime	**20**	**50.0**	**20**	**50.0**
Ceftriaxone	18	45.0	22	55.0
Cefotaxime	20	50.0	20	50.0
Cefpodoxime	**36**	**90.0**	**04**	**10.0**
Cefprozil	**34**	**85.0**	**06**	**15.0**
Cefaclor	32	80.0	08	20.0
Cefalexin	**34**	**85.0**	**06**	**15.0**

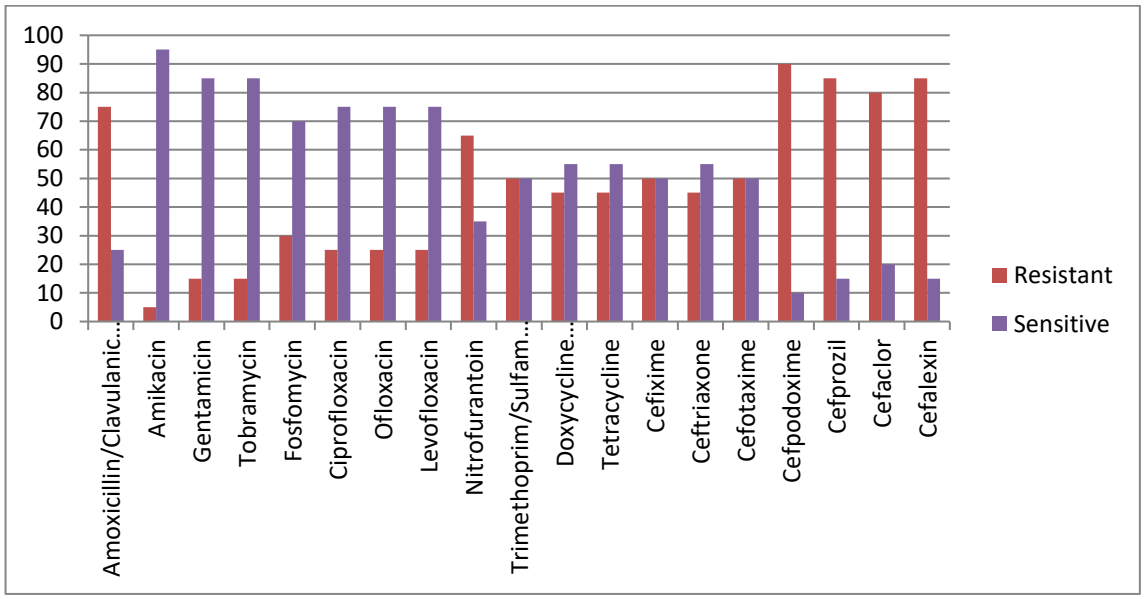

Fig: 5. Pattern of Klebsiella pneumoniae Resistant & Sensitive

Table: 13. Percentage of Resistant & Susceptibility of isolated others Gram Negative Bacilli to tested antibiotic:

	Total Isolates: 18			
Antibiotics	**R (No.)**	**R (%)**	**S (No.)**	**S (%)**
Amoxicillin/Clavulanic acid	**14**	**77.8**	**04**	**22.2**
Amikacin	01	5.5	17	94.5
Gentamicin	01	5.5	17	94.5
Tobramycin	01	5.5	17	94.5
Fosfomycin	07	38.8	11	61.2
Ciprofloxacin	04	22.2	14	77.8
Ofloxacin	03	16.6	15	83.4
Levofloxacin	01	5.5	17	94.5
Nitrofurantoin	08	44.5	10	55.5
Trimethoprim/Sulfamethoxazole	**08**	**44.5**	**10**	**55.5**
Doxycycline Hydrochloride	08	44.5	10	55.5
Tetracycline	08	44.5	10	55.5
Cefixime	**07**	**38.8**	**11**	**61.2**
Ceftriaxone	12	66.6	06	33.4
Cefotaxime	03	16.6	15	83.4
Cefpodoxime	**16**	**88.8**	**02**	**11.2**
Cefprozil	**16**	**88.8**	**02**	**11.2**
Cefaclor	16	88.8	02	11.2
Cefalexin	**16**	**88.8**	**02**	**11.2**

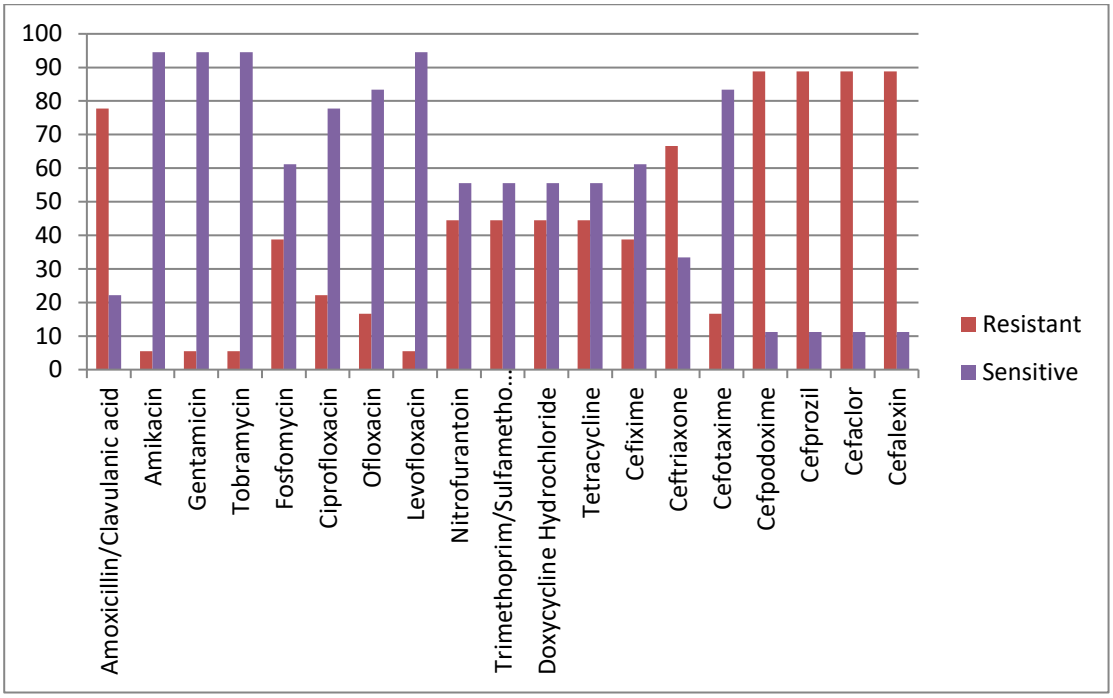

Fig: 6. Pattern of Others Gram Negative Bacilli Resistant & Sensitive

CATEGORY-II: SCHOOL AGED CHILDREN [>5 TO 12 YEARS]

Table: 14. Percentage of Resistant & Susceptibility of isolated *Escherichia coli* to tested antibiotic:

	Total Isolates: 46			
Antibiotics	**R (No.)**	**R (%)**	**S (No.)**	**S (%)**
Amoxicillin/Clavulanic acid	**34**	**74.0**	**12**	**26.0**
Amikacin	02	04.3	44	95.7
Gentamicin	08	17.4	38	82.6
Tobramycin	14	30.5	32	69.5
Fosfomycin	06	13.0	40	87.0
Ciprofloxacin	30	65.3	16	34.7
Ofloxacin	32	69.5	14	30.5
Levofloxacin	26	56.5	20	43.5
Nitrofurantoin	12	26.0	34	74.0
Trimethoprim/Sulfamethoxazole	**28**	**60.8**	**18**	**39.2**
Doxycycline Hydrochloride	28	60.8	18	39.2
Tetracycline	20	43.4	26	56.6
Cefixime	**34**	**74.0**	**12**	**26.0**
Ceftriaxone	32	69.5	14	30.5
Cefotaxime	34	74.0	12	26.0
Cefpodoxime	**42**	**91.3**	**04**	**08.7**
Cefprozil	**40**	**87.0**	**06**	**13.0**
Cefaclor	44	95.7	02	04.3
Cefalexin	**40**	**87.0**	**06**	**13.0**

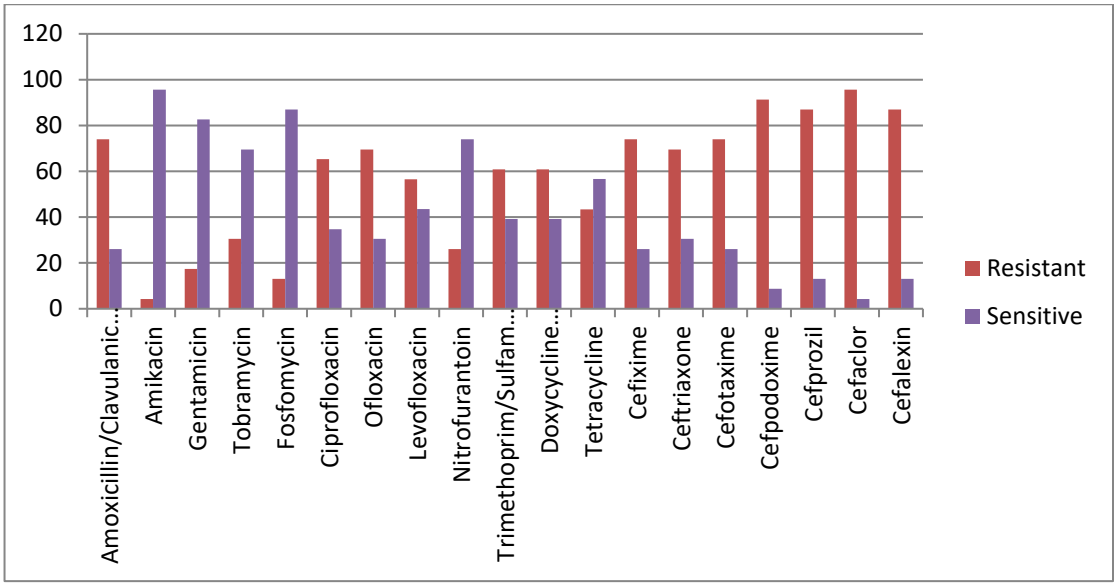

Fig: 7. Pattern of Escherichia coli Resistant & Sensitive

Table: 15. Percentage of Resistant & Susceptibility of isolated *Klebsiella pneumoniae to* tested antibiotic:

Antibiotics	Total Isolates: 20			
	R (No.)	R (%)	S (No.)	S (%)
Amoxicillin/Clavulanic acid	**10**	**50.0**	**10**	**50.0**
Amikacin	02	10.0	18	90.0
Gentamicin	02	10.0	18	90.0
Tobramycin	02	10.0	18	90.0
Fosfomycin	02	10.0	18	90.0
Ciprofloxacin	04	20.0	16	80.0
Ofloxacin	02	10.0	18	90.0
Levofloxacin	02	10.0	18	90.0
Nitrofurantoin	12	60.0	08	40.0
Trimethoprim/Sulfamethoxazole	**10**	**50.0**	**10**	**50.0**
Doxycycline Hydrochloride	02	10.0	18	90.0
Tetracycline	04	20.0	16	80.0
Cefixime	**06**	**30.0**	**13**	**70.0**
Ceftriaxone	08	40.0	12	60.0
Cefotaxime	06	30.0	14	70.0
Cefpodoxime	**18**	**90.0**	**02**	**10.0**
Cefprozil	**12**	**60.0**	**08**	**40.0**
Cefaclor	12	60.0	08	40.0
Cefalexin	**14**	**70.0**	**06**	**30.0**

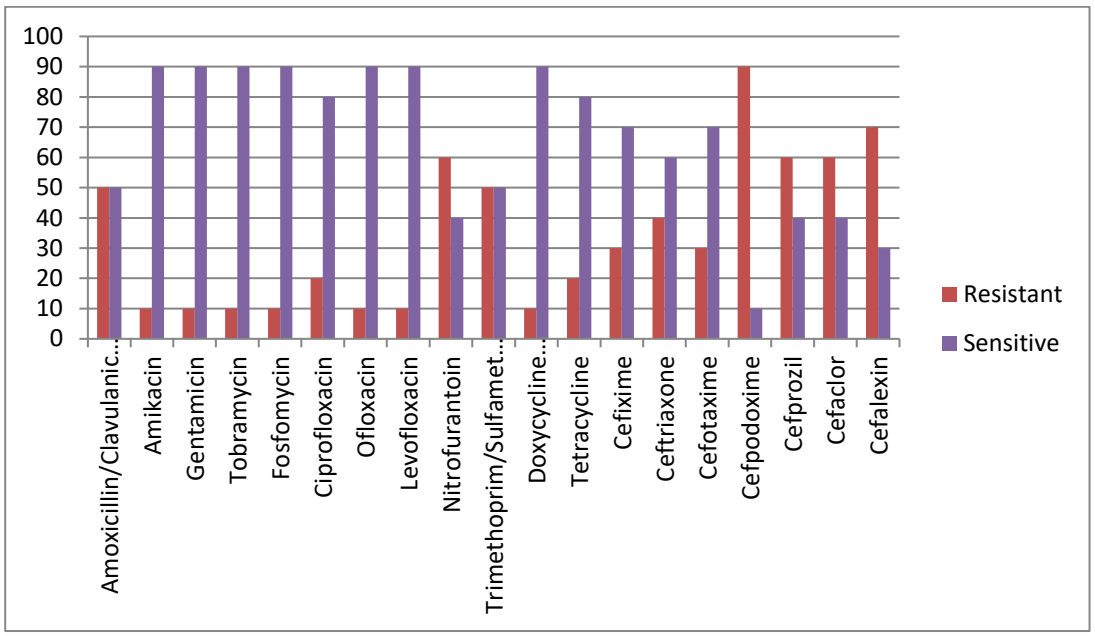

Fig: 8. Pattern of Klebsiella pneumoniae Resistant & Sensitive

Table: 16. Percentage of Resistant & Susceptibility of isolated others Gram Negative Bacilli to tested antibiotic:

Antibiotics	Total Isolates: 06			
	R (No.)	R (%)	S (No.)	S (%)
Amoxicillin/Clavulanic acid	**04**	**66.6**	**02**	**33.4**
Amikacin	01	16.6	05	83.4
Gentamicin	01	16.6	05	83.4
Tobramycin	01	16.6	05	83.4
Fosfomycin	01	16.6	05	83.4
Ciprofloxacin	02	33.3	04	66.7
Ofloxacin	01	16.6	05	83.4
Levofloxacin	01	16.6	05	83.4
Nitrofurantoin	02	33.3	04	66.7
Trimethoprim/Sulfamethoxazole	**02**	**33.3**	**04**	**66.7**
Doxycycline Hydrochloride	02	33.3	04	66.7
Tetracycline	02	33.3	04	66.7
Cefixime	**01**	**16.6**	**05**	**83.4**
Ceftriaxone	04	66.6	02	33.4
Cefotaxime	01	16.6	05	83.4
Cefpodoxime	**05**	**83.3**	**01**	**16.7**
Cefprozil	**05**	**83.3**	**01**	**16.7**
Cefaclor	05	83.3	01	16.7
Cefalexin	**05**	**83.3**	**01**	**16.7**

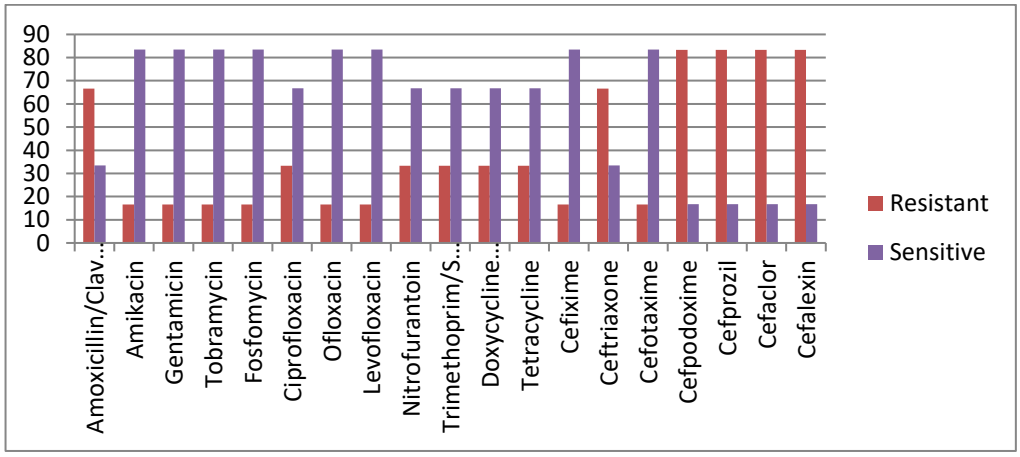

Fig: 9. Pattern of Others Gram Negative Bacilli Resistant & Sensitive

STATISTICAL ANALYSIS:

We use logistic regression approach to Statistical analyze the Results.

Model

P[Y1=1 | X1,X2,....X19]= exp(a+b1*X1+....b19*X19)/(1+exp(a+b1*X1+....b19*X19))

Y1=0 if AGE<5 and Y1=1 AGE>5

For sex

P[Y2=1 | X1,X2,....X19]= exp(a+b1*X1+....b19*X19)/(1+exp(a+b1*X1+....b19*X19))

Y2= 0 for male and Y2=1 for female

X1, X2 ...X19 are covariates. **Associated covariates are marked with Red in results.**

For Age associated covariates are marked in Red (P values<0.05), we do not find any covariate associated with Gender.

Table: 17. RESULTS FOR AGE

Variable Name	"Estimate"	"Std. Error"	"z value"	P value
"(Intercept)"	-2.302357359	0.89370155	-2.576203821	0.009989174
"Amoxicillin/clavulanic acid RS"	1.839575013	0.60615456	3.034828279	0.002406727
"Cefixime RS"	0.827381989	0.61585059	1.343478442	0.179117102
"Fosfomycin RS"	1.438148796	0.53217204	2.7024133	0.006883814
"Nitrofurantoin RS"	-0.069561375	0.40076084	-0.173573285	0.862200829
"Ofloxacin RS"	0.75233949	1.39789652	0.538193978	0.590443137
"Ceftriaxone RS"	-0.468552141	0.54684367	-0.856830137	0.391538768
"Cefotaxime RS"	-0.563343331	0.6151088	-0.915843401	0.359749036
"Gentamicin RS"	1.957797678	0.82679517	2.367935558	0.017887651
"Cefpodoxime RS"	0.846926596	0.7110837	1.19103643	0.233639284
"Ciprofloxacin RS"	-3.225313502	1.31591677	-2.45100113	0.014245951
"Tobramycin RS"	-1.807538521	0.7280213	-2.482809934	0.013035062
"Cefprozil RS"	-1.486739835	0.65477758	-2.270602851	0.023171031
"Co-trimoxazole RS"	-0.471673437	0.41926332	-1.125005243	0.260586813
"Cefaclor RS"	0.367356058	0.67855812	0.54137744	0.588247454
"Doxycycline RS"	1.054751223	0.53834724	1.959239599	0.050084734
"Amikacin RS"	-0.051323879	0.87785629	-0.058465012	0.953378231
"Levofloxacin RS"	1.555440269	0.75579721	2.058012711	0.039588913
"Tetracycline RS"	0.408484613	0.48526716	0.841772632	0.399915234
"Cefalexin RS"	0.633527187	0.63394577	0.999339715	0.317630153

Table: 18. RESULTS FOR SEX

Variable Name	"Estimate"	"Std. Error"	"z value"	P value
"(Intercept)"	-1.291779324	0.8025516	-1.609590367	0.107487313
"Amoxicillin/clavulanic acid RS"	-0.46099878	0.51687691	-0.891892772	0.372450409
"Cefixime RS"	0.256115263	0.50514036	0.507018011	0.612142181
"Fosfomycin RS"	0.341507905	0.38919393	0.877474892	0.380228751
"Nitrofurantoin RS"	-0.201563588	0.35648845	-0.565414074	0.571792154
"Ofloxacin RS"	0.366083069	0.97754933	0.374490634	0.708039324
"Ceftriaxone RS"	-0.271256618	0.44456072	-0.610167753	0.541750689
"Cefotaxime RS"	-0.833059073	0.49239399	-1.691854673	0.090673686
"Gentamicin RS"	-0.661245424	0.54233673	-1.219252508	0.222748368
"Cefpodoxime RS"	-0.681367998	0.75340185	-0.904388544	0.365789411
"Ciprofloxacin RS"	0.771431194	0.81451171	0.947108786	0.343583348
"Tobramycin RS"	0.374146476	0.5523827	0.677331989	0.498195339
"Cefprozil RS"	0.688390047	0.55993107	1.229419261	0.218914652
"Co-trimoxazole RS"	-0.641195772	0.36499132	-1.756742525	0.078961706
"Cefaclor RS"	-0.257124541	0.62933171	-0.40856759	0.682857019
"Doxycycline RS"	0.699613533	0.4586834	1.525264544	0.127193128
"Amikacin RS"	1.382992526	0.85021059	1.626647028	0.103812085
"Levofloxacin RS"	-0.708993843	0.61452353	-1.153729366	0.24861114
"Tetracycline RS"	0.787326364	0.42101408	1.870071351	0.06147391
"Cefalexin RS"	-0.138738503	0.62473402	-0.222076116	0.824254631

DISCUSSION:

Urinary tract infections which are more often seen in girls than boys are among frequently seen bacterial infections during pediatric age. [21] Community acquired urinary tract infections (UTI) cause significant illness in the first 2 years of life and is considered as common disease in school and pre-school children. [22-24] Urinary tract infection in children is a significant source of morbidity. It is generally agreed that children with UTI require further investigation and continuing urinary surveillance to minimize future complications.

Escherichia coli are the most common cause of urinary tract infection [25]. Other microorganisms include *Klebsiella pneumoniae, Enterobacter aerogenes*, *Proteus spp., Citrobacter spp*., *Pseudomonas aerugenosa, Enterococcus faecalis* [26-28].Our findings are consistent with these reports. In our study confirmed *Escherichia coli* are major urinary pathogen and urinary tract infection was more common among females than male children.

A study by Bryce et al that reviewed studies investigating the prevalence of antibiotic resistance in UTI caused by *Esch. coli* in children found that the prevalence of resistance is high, particularly in countries outside the Organization for Economic Co-operation and Development (OECD). Resistance in countries outside the OECD was: 79.8% for ampicillin, 60.3% for co-amoxiclav, 26.8% for ciprofloxacin, and 17.0% for nitrofurantoin. [29]

In a study of 607 children with reflux diagnosed by VCUG after a first or second UTI, the subjects were randomized to antibiotic prophylaxis with TMP-SMX or placebo. The risk of recurrences was reduced by 50% in the treatment group (hazard ratio, 0.50; 95% CI, 0.34-0.74). The risk of renal scarring overall did not differ significantly between the groups over 2 years. Also, the occurrence of a subsequent UTI with a TMP-SMX — resistant organism was significantly increased in the treatment group. The children enrolled were aged 2-71 months, a wider age range than the AAP guidelines currently encompass. [30]

The Results of the present study indicate a high incidence of microbial resistance to commonly use of oral antibiotics of Amoxicillin/clavulanic acid, Co-trimoxazole, Cefixime, Cefpodoxime, Cefprozil, Cefalexin in urinary tract infections among children (Table 8 to 16) and suggest the physicians to be cautious about treatment with antibiotics. Knowledge of the local antibiotic resistance helps in guiding antibiotic choice. Also, we found statistically P value <0.05 are Fosfomycin, Gentamicin, Ciprofloxacin, Tobramycin, Cefprozil and Levofloxacin as per age. (Table 17)

Antibiotic resistance is one of the world's most pressing public health problems. The antibiotic resistant organisms can quickly spread and so threaten communities with new strains of infectious disease that are more difficult to cure and more expensive to treat. Treatment failures may arise due to the resistance offered by pathogen against effective broad-spectrum antibiotics. These treatment failures and hard to treat infections may results in high death rates. [31]

Extended-spectrum beta-lactamases (ESBL) are enzymes that confer resistance to most beta-lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam. Infections with ESBL-producing organisms have been associated with poor outcomes. Community and hospital-acquired ESBL-producing Enterobacteriaceae are prevalent worldwide [32]. Reliable identification of ESBL-producing organisms in clinical laboratories can be challenging, so their prevalence is likely underestimated. Carbapenems are the best antimicrobial agent for infections caused by such organisms.

Beta-lactamases are enzymes that open the beta-lactam ring, inactivating the antibiotic. The first plasmid-mediated beta-lactamase in gram-negative bacteria was discovered in Greece in the 1960s. It was named TEM after the patient from whom it was isolated (Temoniera) [33]. Subsequently, a closely related enzyme was discovered and named TEM-2. It was identical in biochemical properties to the more common TEM-1 but differed by a single amino acid with a resulting change in the isoelectric point of the enzyme.

These two enzymes are the most common plasmid-mediated beta-lactamases in gram-negative bacteria, including Enterobacteriaceae, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae*. TEM-1 and TEM-2 hydrolyze penicillins and narrow spectrum cephalosporins, such as cephalothin or cefazolin. However, they are not effective against higher generation cephalosporins with an oxyimino side chain, such as cefotaxime, ceftazidime, ceftriaxone, or cefepime. Consequently, when these antibiotics were first introduced, they were effective against a broad group of otherwise resistant bacteria. A related but less common enzyme was termed SHV, because sulfhydryl reagents had a variable effect on substrate specificity.

Antibiotic resistance is an important issue affecting public health, and rapid detection in clinical laboratories is essential for the prompt recognition of antimicrobial-resistant organisms. Infection-control practitioners and clinicians need the clinical laboratory to rapidly identify and characterize different types of resistant bacteria efficiently to minimize the spread of these bacteria and help to select more appropriate antibiotics. This is particularly true for ESBL-producing bacteria. The epidemiology of ESBL-producing bacteria is becoming more complex with increasingly blurred boundaries between hospitals and the community. *Esch. coli* that produce CTX-M βlactamases seem to be true community ESBL producers with different behaviors from *Klebsiella spp.*, which produce TEM-derived and SHV-derived ESBLs. These bacteria have become widely prevalent in the community setting in certain areas of the world and they are most likely being imported into the hospital setting. A recent trend is the emergence of community-onset bloodstream infections caused by ESBL-producing bacteria, especially CTX-M-producing *Esch. coli*. These infections are currently rare, but it is possible that, in the near future, clinicians will be regularly confronted with hospital types of bacteria causing infections in patients from the community. β–lactums contribute a measure class of safer antibiotics. They are widely used as broad-spectrum antibiotics for all the type of infections. New generation of antibiotics is predominantly preferred in clinical use. Many newer β- lactums are expected for the clinical use and many new β- lactums are expected in future. There is a better scope, prosperity for the discovery and development of new and safer β- lactums.The structure of β- lactams, their nature, classification, chemistry to be well studied. β- lactums, their mode of action, their bactericidal properties and their future growth is seen with new hopes. In this study, in the age group of 1 to 5 years, ESBL were detected in 54.0% in male child & 59.5% in female child and the age group of >5 to 12 years, ESBL were detected in 46.7% in male child and 57.2% in female child.

Nursing-home patients may be an important reservoir of ESBL-producing multidrug-resistant *Escherichia coli* and *K. pneumoniae* [34-36]. In our study, resistance to more than one antibiotic was rather common and the spread of ESBL-producing isolates was quite alarming. The resistance rate to fluoroquinolones observed in this study was quite high, particularly in *Esch. coli*, and poses some concerns about their use in empirical treatment of UTIs. Resistance to fluoroquinolones is known to be

associated with the previous use of antibiotics, particularly fluoroquinolones, and previous reports have demonstrated that underlying urinary tract diseases predispose patients to repeated UTIs and, in turn, to exposure to antibiotics such as fluoroquinolones [37-39].

This study clearly demonstrates the development of resistance for commonly use antibiotics in children UTI. Different factors are attributable for emergence of resistance mainly include; high consumption of antibiotics, irrational use, incomplete course of therapy, and self-medication by patients, leading to the emergence of resistance and even treatment failures. One major cause of self-medication is poverty. India is an under developed country, people are used to treating themselves without obtaining prescriptions from physicians. The present situation is alarming, because it is not long before common antibiotics, an effective antibiotic would be failed to treat even simple or minor infections. Curtailed follow up of regimen also creates resistance. Generally, patients stop their treatment when they feel slight improvement and the microorganisms start adapting the environment rather than get killed. Governments must initiate different educational programs, seminars, workshops in collaboration with the media to make people aware of the consequences of self-medication, especially with broad- spectrum antibiotics. In addition to this, routine antimicrobial susceptibility testing must be timely performed to determine the current status of resistance against antimicrobial agents (MIC, E test, Disk diffusion method). Otherwise therapy failures may occur which increase the cost of the therapy as well as recovery time from the underlying disease.

CONCLUSION:

In conclusion, it is important that each country should have its own epidemiological data, and physicians should know antimicrobial resistance rates in their regions so as to arrange treatment, and prophylaxis accordingly. Antimicrobial resistance rates are increasing steadily against antibiotics expected to exert clinical efficacy in the treatment of UTI as a result of their widespread, and erroneous use. We think that at certain intervals centers should identify urinary pathogens prevalent in their regions, and aware of antimicrobial susceptibilities of these pathogens which are very important for the economy of the country, and appropriate treatment.

Antimicrobial resistance is a globally ever-increasing problem. The emergence and spread of antimicrobial resistance are complex and driven by numerous interconnected factors. The principle causes of microbial resistance are inappropriate, irrational, high consumption, and profligate use of antibiotics. The use of antimicrobials must be restricted and monitored in order to decline the resistance. The present results in increasing antibiotic resistance trends in UTI patients in children indicate that it is imperative to rationalize the use of antimicrobials and to use these conservatively. Considering the relatively increase rates of UTI and drug resistance observed in this study, continued local, regional, and national surveillance is warranted. Antibiotics should only be issued when prescribed by physicians.

Antibiotic resistance is a growing problem in pediatric urology as highlighted by the significantly increased urinary pathogen resistance to commonly use of oral antibiotics. Poor empiric prescribing practices, lack of urine testing, and nonselective use of prophylaxis exacerbate this problem. However, three small changes in practice patterns may curb the growing resistance rates: use of urine testing in order to only treat when indicated and tailor broad-spectrum therapy as able; selective application of antibiotic prophylaxis to patients; and use of local antiobiograms, particularly pediatric-specific antiobiograms, with inpatient *versus* outpatient data.

This study will provide novel, clinically important information on the diagnostic features of childhood UTI and the cost effectiveness of a validated prediction rule, to help primary care clinicians improve the efficiency of their diagnostic strategy for UTI in children. Regular monitoring is required to establish reliable information about resistance pattern of urinary pathogens for optimal empirical therapy of patients with UTIs. Finally, we suggest that empirical antibiotic selection should be based on the knowledge of local prevalence of bacterial organisms and antibiotic sensitivities rather than on universal guidelines.

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