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TO DETERMINE THE ANTIBIOTIC SENSITIVITY OF ESCHERICHIA COLI IN URINARY TRACT INFECTIONS TO AMPICILLIN, CEFTAZIDIME, NITROFURANTOIN AND GENTAMYCIN

[1]*Dr. Arfeen Azam Khan, [2]Dr. Sumera Nawaz, [3]Dr. Dara Jamali, [4]Dr. Maria Abid, [5]Dr. Fatiha Iftikhar, [6]Dr. Shuja Rehman and [7]Mhammad Muzammil

[1,2,3]Senior Registrar, Department of Medicine. Dr. Ziauddin University and Hospital.
[4,5]Assistant Professor Altamash General Hospital
[6]Rmo, Dr. Ziauddin Hospital.
[7]MBBS at Khyper Medical Univeristy.

***Corresponding Author: Dr. Arfeen Azam Khan**
Senior Registrar, Department of Medicine. Dr. Ziauddin University and Hospital.

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ABSTRACT

Background: Urinary tract infections, in our environment most commonly caused by E.coli. Common regimens include trimethoprim silfamethoxazole, cephalosporins, floroquinolones, nitrofurantoin and aminoglycosides. Over the period of time the sensitivity pattern is expected to change and hence continuous research should be undertaken to establish the changed sensitivity of E.coli to different antibiotics. **Objective:** To determine the antibiotic sensitivity of Escherichia coli in urinary tract infections to Ampicillin, Ceftazidime, Nitrofurantoin and Gentamycin. **Study Design:** It was an observational study,analyzing urine cs reports ast a particular time. The study was cross sectional. **Setting:** The department of Medicine, Ziauddin Medical University & Hospital, Karachi. **Duration:** From 2nd June to 1st December 2016. **Material and Methods**: Total 206 samples were taken. Once sample showed E.coli growth, the patients were approached to acquire relevant data and sensitivity report given by the laboratory was studied, after which descriptive statistics were calculated and stratification was done. Chi square test(X^2) was used after considering value of P less than 0.05 as significant. **Results:** There were 224 patients in total out of which 82 were men and 124 were women. Mean duration of illness was 9.54±5.94 days. The sensitivity pattern of E.coli with ampicillin was 7.3%, ceftazidime was 19.9% sensitive, nitrofurantoin was 92.7% sensitive, and gentamycin was 30.6% sensitive. Ampicillin was significantly associated with genderwhereasnitrofurantoin with duration of illness. **Conclusion:** *E.coli*was the predominant uropathogen and its antibiotic sensitivity should be considered for starting antibiotics empirically for urinary tract infections Highest sensitivity 92.7% was observed with Nitrofurantoin.

KEYWORDS: antibiotic sensitivity, Escherichia coli, urinary trct infections, Ampicillin, Ceftazidime, Nitrofurantoin, Gentamycin.

INTRODUCTION

Urinary tract infection is considered to be one of the health diseases faced by general public all over the world with around 150 million cases documented every year.[1] "Urinary tract infections (UTI) affect any part of the urinary tract and include mainly cystitis (bladder infection), pyelonephritis (kidney infection) and urethritis (urethra infection) showing tissue damage, burning, painful urination, urgency and increased urinary frequency, suprapubic pain, pain in renal angle, fever and other systemic manifestations.".[2,3] However some cases may present without any symptoms.

Any physical or functional barrier like hypertrophied prostate tumor, renal stone, external catheter, or neurogenic disorder can contribute to the development of Urinary tract Infection. The symptoms will be organ dependent and the nature of UTI afflicting it. Commonlyinvolved microbes causing Urinary Tract Infection are E. Coli, followed by Klebsiella pneumoniae, Proteus Mirabilis, Pseudomonas, Streptococci, Serratia, Enterobacter and Gram -ve enteric bacteria and yeasts.

However, in the usual scenario, UTI are caused by a single pathogen. In some complicated cases multiple organismscan be involved specially on a background of urinary stones or structuralabnormality. A concentration of more than 10•cfu/ml of bacteria collected in mid-stream urine is considered significant for UTI. However this number is lower for symptomless patients and patients taking antibiotics, drinking copious amounts of

water, urinary obstruction and pyelonephritis secondary to hematogenous spread. UTI is the most prevalent hospital acquired infection. Noteworthy differences in various organisms responsible for community and hospital acquired cases are important to identify." UTls are usually more prevalent in females as compared to men, the exception being men aged over 60 years with Prostatic hypertrophy." Women are more susceptible due to shorter urethra, proximity with anal opening and optimal duration of treatment recommended in men. Usually, 7-10 days treatment has been the center of discussion for some time. Emphasis by various studies on the consequences of short course antibiotic regimes like those comprising of 3 days or even single dose antibiotics in women have been conducted. An International group of experts concluded that a 3-day courses of Trimethoprim and Quinolones are just as effective as their longer regimes. The same was concluded for β Lactams but shorter courses are however, considered less effective hence further investigations are warranted. As forNitrofurantoin, it also requires further studies before something tangible can be established.

A study in Ethiopia showed be very resistant to E.coli to Erythromycin with percentage of (89.4%), Amoxycillin (86.0%) and Tetracycline (72.6%).[16] Another study about UTI and sensitivity pattern of antibiotics in pregnant women at Khartoum North Hospital in Sudan showed resistance to Amoxicillin, Naladyxic Acid, Nitrofurantoin and Ciprofloxacin.[17]

Various antibiotics are used to treat E.coli. common regimens include trimethoprim-silfamethoxazole, cephalosporins, floroquinolones, nitrofurantoin and aminoglycosides.[18]E.coli has different levels of sensitivity for different antibioticst. The research of 2001 indicated the levels of sensitivity as Ampicillin – 26%, Ceftazidime – 20%, Nitrofurantoin – 79.5%, Gentamycin – 65%

Over the period of time the sensitivity pattern is expected to change and hence continuous research should be undertaken to establish the changed sensitivity of E.coli to different antibiotics.[19] E. coli is gaining resistance against these antibiotics. Hence the objective of this research is to ascertain the sensitivity pattern of E.coli causing UTI to various antibiotics during the recent period as standard regimens for empirical therapy must be assessed periodically in light of changing susceptibility patterns.[20] To keep our research focused only the following antibiotics were studied: Ampicillin, Ceftazidime, Nitrofurantoin, Gentamycin. Last research according to available data was done in 2001 and after a lapse of 15 years it is needed to do a sensitivity study.

4.2 OBJECTIVE

Is to study the antibiotics sensitivity organism of urinary tract infections of E.coli from Ampicillin, Ceftazidime, Nitrofurantoin and Gentamycin.

4.3 Operation Definition

- **E.coli induced UTI:** Urine samples shown gram negative rods which were fast lactose fermenters and urease positive.
- **Sensitivity to Ampicillin:** Demonstrated a Zone of Inhibition compared to standard control by Disc Diffusion method around a disc loaded with Ampicillin.
- **Sensitivity to Ceftazidime:** Demonstrated a Zone of Inhibition compared to standard control by Disc Diffusion method around a disc loaded with Ceftazidime.
- **Sensitivity to Nitrofurantoin:** Demonstrated a Zone of Inhibition compared to standard control by Disc Diffusion method around a disc loaded with Nitrofurantoin.
- **Sensitivity to Gentamycin:** Demonstrated a Zone of Inhibition compared to standard control by Disc Diffusion method around a disc loaded with Gentamycin.
- **Resistance to Ampicillin:** Did not demonstrate anyzoneof inhibitionarounddisc when ampicillin was loaded by disc diffusion method.
- **Resistance to Ceftazidime:** Did not demonstrate any zone of inhibition around the disc when Ceftazidime was loaded by disc diffusion method.
- **Resistance to Nitrofurantoin:** Did not demonstrate any zone of inhibition around the disc when Nitrofurantoin was loaded by disc diffusion method.
- **Resistance to Gentamycin:** Did not demonstrate any zone of inhibition around the disc when Gentamycin was loaded by disc diffusion method.

4.4 MATERIAL AND METHODS

Settings: This study was carried out in Ziauddin University & Hospital, Karachi.

Duration: Six months from 2nd June to 1st December 2016.

Sample size: The proportion of sensitivity of Ampicillin in E. coli induced UTI was 26%. Taking confidence interval 95 percentage and with error of 6% as margins hence the sample size was came out as 206 by the WHO sample size calculator.

Sample technique: Non-probability consecutive sampling was used for the study.

Study Design: Cross Sectional Study.

4.5 Sample Selection

Inclusion Criteria

- Patients aged 15 years and more of either gender male or female
- Urine culture shown growth of E. coli with more than 10000 colonies of the organism

Exclusion Criteria

- Non-consenting patients
- Patients whose urine culture and sensitivity was done from outside Ziauddin hospital
- Patients age less than 15 years
- Urine culture reports shown less than 10000 colonies of E.coli

4.6 Data Collection Procedure

The study did not require direct interaction with the patients hence, ethical issues were not raised. However once a urine samplereceived in the laboratory showed E. coli growth, the patients were approached directly or contacted on phone to acquire Informed Consent and relevant data and the sensitivity report given by the laboratory were studied as well. The Performa attached as annexure was filled.

4.7 Data Analysis Procedure

Analysis of the collected data was done via "Statistical Package for Social Sciences (SPSS)" version 17. Standard deviation and Mean were calculated for patient's age and the duration of illness. Frequency and percentage were calculated for gender and sensitivity patterns. Stratification was used to addressthe effect of modifiers like age, gender, and duration of disease on the antibiotic sensitivity pattern.After stratification Chi square ($\chi 2$) was applied with P value of 0.05 as designated as significant.

206 samples of the patients aged 15 years and more of either gender with urine culture shown growth of E. coli with more than 10000 colonies of the organism were included in the study to determine the antibiotic sensitivity of Escherichia coli to Ampicillin, Ceftazidime, Nitrofurantoin and Gentamycin. The effects of modifies on outcome was seen by calculating Descriptive statistics and stratification. After which chi square was applied with $p \leq 0.05$ considered significant.

Out of a total of 206 patients, 82 were male and 124 were female. Table-1 demonstrates the frequency distribution.

The mean age of study subjects was 64.35±18.86 years. Graph-1 illustrates the age distribution and Table-2 demonstrates the descriptive statistics of age. The age was stratified in two groups. The frequency and percentages are presented in Graph-2.

The mean duration of illness was 9.54±5.94 days. The distribution of duration of illness is presented in Graph-3. The descriptive statistics of duration of illness is presented in Table-3. The duration was stratified in two groups. The frequency and percentages are presented in Graph-4.

The sensitivity pattern of E. coli with the study antibiotics showed that ampicillin was 7.3% sensitive, ceftazidime was 19.9% sensitive, nitrofurantoin was 92.7% sensitive, and gentamycin was 30.6% sensitive. The results are presented in Table-4 to Table-7.

The stratification according to gender, age, and duration of illness was done. Post stratification association of antibiotic sensitivity was observed with these modifiers using chi square test taking p value ≤0.05 as significant.

The results disclosed that significant association of ampicillin was found with gender (p=0.030) and significant association of nitrofurantoin was found with duration of illness (P=0.000). Significant association of E. coli sensitivity with study antibiotics was not observed with gender, age, and duration of illness. The detailed results arepresented in Table-8 to Table-19.

UTI are amongst the most common and troublesome infections affecting people of all age and gender.Local Data should be guiding torch for empirical antibiotics therapy.This is the first study in 10 years in Dr. Ziauddin University Hospital, Karachi, which determines the prevalence of UTI, the effects of ages and gender on its susceptibility patterns pathogens isolated in patients ,regarding the status of antibiotics resistance patterns among organism and to improve empirical treatment recommendations in this specific region.

A study showed that *E. coli (79.3 was) the most common organism involved in UTI as also shown with other studied Schmiemannet al.* accounted 79.3 % followed by *K. pneumonia* 4.1 % as the culprit cases.[26-29]

Beginning with studies from developing world, a local study that was conducted about 10 years ago showed that E.Coli showed 74%, 80%, 35% and 21% to Ampicillin, Ceftazidime, Nitrofurantoin and Gentamycin respectively.[2] A study conducted in African country of Ethiopia showed that E.Coli had 86%, 3% and 13% resistance to Ampicillin, Nitrofurantoin and Gentamycin. This study also studied the sensitivity of these drugs to E.Coli and found out that the organism showed 14%, 96.4% and 81% to Ampicillin, Nitrofurantoin and Gentamycin.[4] A study in Khartoum showed that the micro-organism had resistance against Ampicillin (28.5%) and Nitrofurantoin (14.3%).[5] Another study from Portugal showed the sensitivity profile of the E.Coli against various antibiotics and found that it was 62.5%, 91.8%, 93% and 96% sensitive against Ampicillin, Ceftazidime, Nitrofurantoin and Gentamycin respectively.[8] In our setting, E.Coli showed ampicillin was 7.3% sensitive, ceftazidime was 19.9% sensitive, nitrofurantoin was 92.7% sensitive, and gentamycin was 30.6% sensitive sensitivity to Amoxiciilin, Ceftazidine, Gentamycin and Nitrofurantoin respectively.

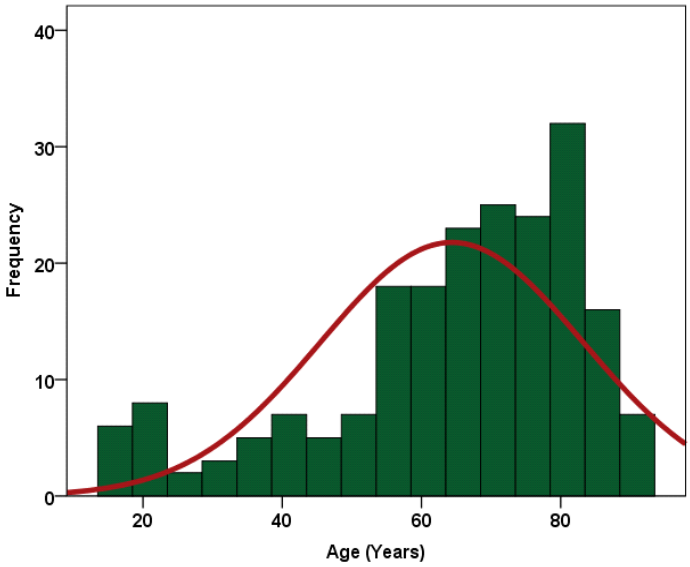
A study from India was conducted to observe the pattern of resistance pattern of E.Coli against the known antibiotics. It was found that resistance against nitrofurantoin decreased consecutively for three years years from 36.1% in the year 2012 to 18.15 %.In year

2014 it was discovered that with time, an increase in resistance to third Generation Cephalosporin from 50% to 65%. E coli had 100 percent resistance to cotrimoxazole and tetracycline. Aminoglycosides and fluroquinolones are two common drug classes of antibiotics used in the treatment of Urinary Tract Infections. E. coli demonstrated considerably high resistance of 75% and 67% respectively for these two groups which increased steadily over a course of three years. The resistance percent values of the cotrimoxazole were 76.3%. Most of the international guidelines for treating urinary tract infections acquired from community recommend co-trimoxazole, amoxicillin/ampicillin, norfloxacin as anempirical antibiotic of choice.

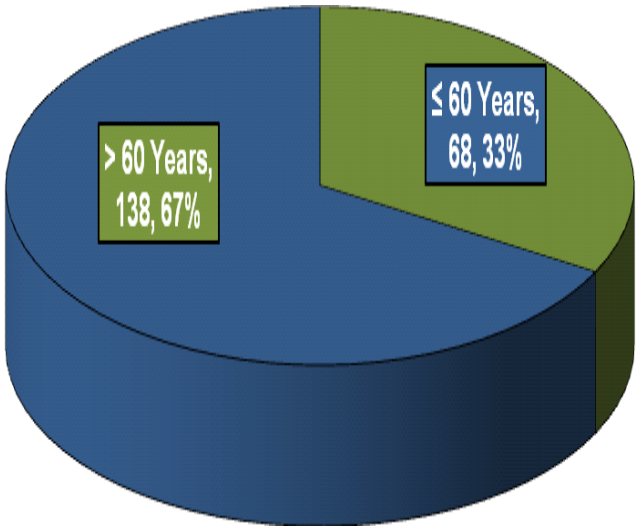
Guidelinessuggesttore assess resistance patterns of the causative bacteria to antibiotics prior to start of any antibiotic regime. Theinfectiousdiseasesociety of America has suggested that resistance of 20 percent or lower should be deemed acceptable when choosing empirical antibiotics therapies. Plethora of studies carried out across the globe have been able to demonstrate resistance of bacterial urinary pathogens to commonly prescribed antibiotics such as co-trimoxazole, amoxicillin and ampicillin. Results of our study to determine E. coli resistance to different classes of antibiotics, seem to conform with the results of previous similar studies.

Study Limitations

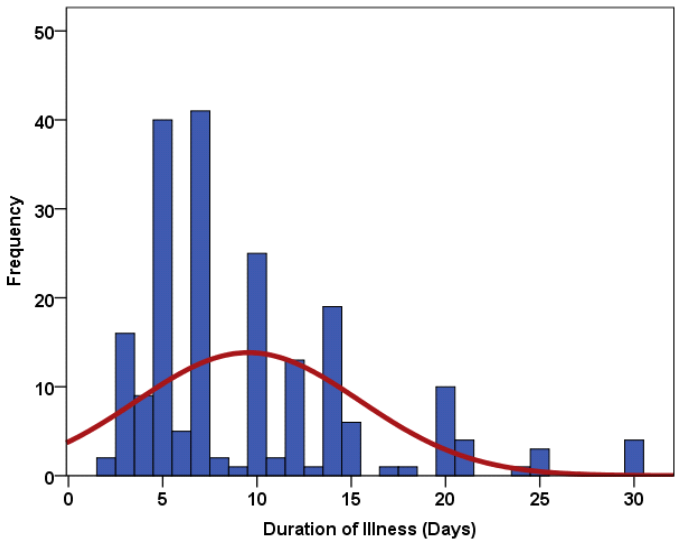
This study is a single-center experience with low male representation and nonrandomized study design which could present to be its limitations. Also it was conducted with a small sample size and in urban environment only therefore, generalizing the results to a larger population may not be possible.



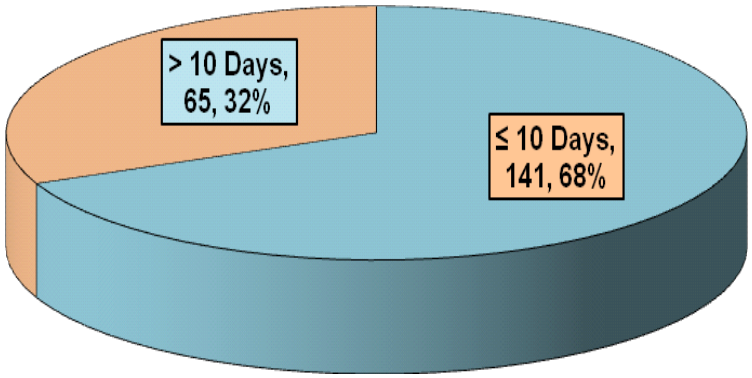
Graph–1: Histogramillustratingdistributionofage (years) (n=206).



Graph – 2: Percentage of Patients According to Age Groups (n=206).



Graph – 3: Histogram Presenting Distribution Of Duration Of Illness (Days) (N=206).



Graph – 4: Percentage Of Patients According To Duration Of Illness Groups (N=206).

Table – 1: Frequency Distribution Of Gender (N=206).

	Frequency (n)	Percentage (%)
Male	82	39.8%
Female	124	60.2%
Total	**206**	

Table – 2: Descriptive Statistics of age (years) (n=206).

Mean ±SD	64.35±18.86
95%CI (LB – UB)	61.76 – 66.95
Median (IQR)	69.00 (24)
Range	77
Minimum	16
Maximum	93

Table 3: Descriptive Statistics Of Duration Of Illness (days) (n=206).

Mean ±SD	9.54±5.94
95%CI (LB – UB)	8.72 – 10.35
Median (IQR)	7.00 (7)
Range	28
Minimum	2
Maximum	30

Table 4: Frequency Distribution Of Sensitivity Of Ampicillin (N=206).

	Frequency (n)	Percentage (%)
Sensitive	15	7.3%
Resistant	191	92.7%
TOTAL	**206**	

Table – 5: Frequency Distribution Of Sensitivity Of Ceftazidime (N=206).

	Frequency (n)	Percentage (%)
Sensitive	41	19.9%
Resistant	165	80.1%
TOTAL	**206**	

Table – 6: Frequency Distribution Of Sensitivity Of Nitrofurantoin (N=206).

	Frequency (n)	Percentage (%)
Sensitive	191	92.7%
Resistant	15	7.3%
TOTAL	**206**	

Table – 7: Frequency Distribution Of Sensitivity Of Gentamycin (N=206).

	Frequency (n)	Percentage (%)
Sensitive	63	30.6%
Resistant	143	69.4%
TOTAL	**206**	

Table – 8: Frequency and Association Of Sensitivity Of Ampicillin With Gender (N=206).

	SENSITIVITY OF AMPICILLIN			P-Value
	Sensitive (n=15)	**Resistant** (n=191)	**TOTAL**	
MALE (n=82)	2	80	**82**	0.030*
FEMALE (n=124)	13	111	**124**	
TOTAL	**15**	**191**	**206**	

Chi Square Test ($\chi 2$) was applied.
P-value ≤ 0.05 considered as significant
Significant at 0.05 levels

Table – 9: Frequency and Association Of Sensitivity Of Ceftazidime With Gender (N=206).

	SENSITIVITY OF CEFTAZIDIME			P-Value
	Sensitive (n=41)	**Resistant** (n=165)	**TOTAL**	
MALE (n=82)	11	71	**82**	0.058**
FEMALE (n=124)	30	94	**124**	
TOTAL	**41**	**165**	**206**	

Chi Square Test ($\chi 2$) was applied.
P-value ≤ 0.05 considered as significant
Not Significant at 0.05 levels

Table – 10: Frequency and Association Of Sensitivity Of Nitrofurantoin With Gender (N=206).

	SENSITIVITY OF NITROFURANTOIN			P-Value
	Sensitive (n=191)	**Resistant** (n=15)	**TOTAL**	
MALE (n=82)	74	8	**82**	0.266**
FEMALE (n=124)	117	7	**124**	
TOTAL	**191**	**115**	**206**	

Chi Square Test ($\chi 2$) was applied
P-value ≤0.05 considered as significant
****** Not Significant at 0.05 levels

Table – 11: Frequency and Association Of Sensitivity Of Gentamycin With Gender (N=206).

	SENSITIVITY OF GENTAMYCIN			P-Value
	Sensitive (n=63)	**Resistant** (n=143)	**TOTAL**	
MALE (n=82)	23	59	**82**	0.521**
FEMALE (n=124)	40	84	**124**	
TOTAL	**63**	**143**	**206**	

Chi Square Test ($\chi 2$) was applied.
P-value ≤0.05 considered as significant
****** Not Significant at 0.05 levels

Table 12: Frequency And Association Of Sensitivity Of Ampicillin With Age (N=206).

	SENSITIVITY OF AMPICILLIN			P-Value
	Sensitive (n=15)	**Resistant** (n=191)	**TOTAL**	
≤ 60 Years (n=68)	3	65	**68**	0.394**
> 60 Years (n=138)	12	126	**138**	
TOTAL	**15**	**191**	**206**	

Chi Square Test ($\chi 2$) was applied
P-value ≤0.05 considered as significant
***** Significant at 0.05 levels

Table – 13; Frequency and Association Of Sensitivity Of Ceftazidime With Age (N=206).

	SENSITIVITY OF CEFTAZIDIME			P-Value
	Sensitive (n=41)	**Resistant** (n=165)	**TOTAL**	
≤ 60 Years (n=68)	9	59	**68**	0.092**
> 60 Years (n=138)	32	106	**138**	
TOTAL	**41**	**165**	**206**	

Chi Square Test ($\chi 2$) was applied.
P-value ≤0.05 considered as significant
****** Not Significant at 0.05 levels

Table – 14: Frequency And Association Of Sensitivity Of Nitrofurantoin With Age (N=206)

	SENSITIVITY OF NITROFURANTOIN			P-Value
	Sensitive (n=191)	**Resistant** (n=15)	**TOTAL**	
≤ 60 Years (n=68)	64	4	**68**	0.778**
> 60 Years (n=138)	127	11	**138**	
TOTAL	**191**	**15**	**206**	

Chi Square Test ($\chi 2$) was applied
P-value ≤0.05 considered as significant
****** Not Significant at 0.05 levels

Table – 15: Frequency and Association Of Sensitivity Of Gentamycin With Age (N=206).

	SENSITIVITY OF GENTAMYCIN			P-Value
	Sensitive (n=63)	**Resistant** (n=143)	**TOTAL**	
≤ 60 Years (n=68)	15	53	**68**	0.062**
> 60 Years (n=138)	48	90	**138**	
TOTAL	**63**	**143**	**206**	

Chi Square Test ($\chi 2$) was applied
P-value ≤0.05 considered as significant

****** Not Significant at 0.05 levels

Table – 16: Frequency and Association of Sensitivity of Ampicillin With Duration Of Illness (N=206).

	SENSITIVITY OF AMPICILLIN			P-Value
	Sensitive (n=15)	**Resistant** (n=191)	**TOTAL**	
≤ 10 Days (n=141)	11	130	**141**	0.780**
> 10 Days (n=65)	4	61	**65**	
TOTAL	**15**	**191**	**206**	

Chi Square Test ($\chi 2$) was applied
P-value ≤0.05 considered as significant
***** Significant at 0.05 levels

Table – 17: Frequency and Association of Sensitivity of Ceftazidime With Duration Of Illness (N=206).

	SENSITIVITY OF CEFTAZIDIME			P-Value
	Sensitive (n=41)	**Resistant (n=165)**	**TOTAL**	
≤ 10 Days (n=141)	31	110	**141**	0.270**
> 10 Days (n=65)	10	55	**65**	
TOTAL	**41**	**165**	**206**	

Chi Square Test ($\chi 2$) was applied
P-value ≤0.05 considered as significant
****** Not Significant at 0.05 levels

Table – 18: Frequency and Association Of Sensitivity Of Nitrofurantoin With Duration Of Illness (N=206).

	SENSITIVITY OF NITROFURANTOIN			P-Value
	Sensitive (n=191)	**Resistant** (n=15)	**TOTAL**	
≤ 10 Days (n=141)	139	2	**141**	0.000*
> 10 Days (n=65)	52	13	**65**	
TOTAL	**191**	**15**	**206**	

Chi Square Test ($\chi 2$) was applied
P-value ≤0.05 considered as significant
***** Significant at 0.05 levels

Table – 19: Frequency and Association Of Sensitivity Of Gentamycin With Duration Of Illness (N=206).

	Sensitivity of gentamycin			P-Value
	Sensitive (n=63)	**Resistant** (n=143)	**TOTAL**	
≤ 10 Days (n=141)	43	98	**141**	0.969**
> 10 Days (n=65)	20	45	**65**	
TOTAL	**63**	**143**	**206**	

Chi Square Test ($\chi 2$) was applied
P-value ≤0.05 considered as significant
****** Not Significant at 0.05 levels

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