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Complicated Urinary Tract Infection in a Tertiary Care Center in South India

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Abstract

Context: Knowledge of microbiology and antibiotic susceptibility of complicated urinary tract infection (cUTI) is essential for defining the empirical treatment

Aims: 1) To find out the common presenting symptomatology associated with cUTI 2) To determine the distribution of bacterial strains isolated from cUTI 3) To identify Extended Spectrum Beta Lactamase (ESBL) producers in the different populations of uropathogens 4)To determine the resistance pattern of these bacteria. *Settings and Design:* Prospective study was done in a tertiary care centre in Bangalore from l January, 2008 to 31st December, 2008. *Methods and Material:* The study included all the patients who were admitted or visited the outpatient departments in the hospital and had urinary tract infection confirmed by positive urine culture reports. *Results:* Dysuria (31.4%) was the most common symptom with cUTI patients. *Escherichia coli* accounted to 65.7% of the total infection. 66.78% of the total *Escherichia coli* were ESBL positive. A high degree of resistance was recorded for first generation fluoroquinolones (76.9%) among the isolates in our study. *Conclusions:* A unified antibiotic protocol is necessitated to limit this increase and reduce the squeal of cUTI.

Key-words: complicated urinary tract infection, Extended Spectrum Beta Lactamase, Antibiotic Resistance.

Introduction

Complicated urinary tract infection (cUTI) is defined in various ways by different authors. Stamm et al [1] have defined cUTI as that which occurs in a patient with anatomically abnormal urinary tract or significant medical or surgical co morbidities. Nicolle et al [2] defined complicated urinary tract infection as that occurring in individuals with functional or structural abnormalities of the genitourinary tract. The definition is basically needed for the differing line of management of cUTI as against uncomplicated urinary tract infection. The uropathogens causing cUTI and their antibiotic sensitivity pattern varies considerably not only from that in acute uncomplicated UTI but also with time. The emergence of extended spectrum beta lactamase species has further complicated the treatment of UTI. Knowledge of microbiology and antibiotic susceptibility of cUTI is essential for defining the empirical treatment. Various studies have been done recently in many countries to identify the common organisms causing cUTI and to establish a standard empirical line of treatment for the same. Yildiz et al [3] from their recent study reported that Gram negative organisms were the most common uropathogens causing cUTI in the pediatric age group. E. coli was the most common organism causing cUTI in a study done by Peterson et al [4] in the United States. However similar studies in India are very few. This study was done to find out the present uropathogen profile causing cUTI in our center and their antibiotic susceptibility patterns.

Subjects and Methods:

Study subjects: This prospective study was done in a tertiary care centre in Bangalore from 1 January, 2008 to 31st December, 2008. The study included all the patients who were admitted or visited the outpatient departments in the hospital and had urinary tract infection confirmed by positive urine culture reports. Patients who had no symptoms suggestive of urinary tract infection at the time of admission were excluded from the study. Patients were classified as having cUTI based on the criteria defined by Rubenstein and Schaeffer [5] (Table 1). Data regarding demographic characteristics, symptoms, catheterization, organisms causing urinary tract infection and their antibiotic resistance pattern were collected.

Table 1: Identification of patients with Complicated Urinary Tract Infections [5]

1. Men
2. Children
3. Nosocomial infection
4. Women
   a. Known lesion on prior diagnosis
   b. Functional or structural urinary tract anomaly
   c. Obstruction (e.g. Stone, Uretero-Pelvic Junction obstruction)
   d. Pregnancy
   e. Diabetes
   f. Spinal cord injury
   g. Neurological disorders (e.g. Multiple sclerosis) that affects bladder function
   h. Indwelling catheter
   i. Co morbidities that predispose to papillary necrosis (e.g. Sickle cell disease, severe diabetes, analgesic abuse, pseudomonas species infection)
   j. Infection with an unusual organism (e.g. tuberculosis)
5. Suspected lesion based on history
   a. Unresolved Urinary Tract Infections -failed response to antimicrobial therapy
   b. Bacterial persistence (recurrent Urinary Tract Infections with the same organism)
   c. Infection with urea splitting organism
   d. Recurrent febrile Urinary Tract Infections as a child
6. Suspected lesion based on symptoms
   a. Febrile Urinary Tract Infections (especially > 3 days)
   b. Renal colic
   c. Gross hematuria

Statistical Analysis: The analysis was done using the statistical software package-SPSS Version 11. Age, gender, organisms causing cUTI, their antibiotic sensitivity and resistance, symptomatology of these patients and risk factors for urinary tract infection were included as variables in the model.

Results

A total of 458 patients were included in the study. The patients were between newborn and 96 years of age (Table 2).

Age group	Male(percent)	Female(percent)	Total(percent)
0-9	22(7.7)	3(1.7)	25(5.5)
10-19	8(2.8)	8(4.7)	16(3.5)
20-29	17(5.9)	10(5.8)	27(5.9)
30-39	18(6.3)	8(4.7)	26(5.7)
40-49	24(8.4)	10(5.8)	34(7.4)
50-59	57(19.9)	39(22.7)	96(21.0)
60-69	64(22.4)	39(22.7)	103(22.5)
70-79	53(18.5)	38(22.1)	91(19.9)
80-89	18(6.3)	14(8.1)	32(7.0)
90-99	5(1.7)	3(1.7)	8(1.7)
Total	286(100.0)	172(100.0)	458(100.0)

Table 2: Age and Gender wise distribution of cUTI. The mean age of cUTI patients was 55.47+/-21.51 years (95% CI- 53.50 to 57.45 years). Female to male prevalence ratio was 1:1.63.

Escherichia coli: *Escherichia coli* accounted to 65.7% (301/458) of the total infection. 66.78% (201/301) of the total *Escherichia coli* were ESBL positive. Most of the cases (206/301) were seen in the age group of 50-79 years. All the isolates were highly sensitive to Carbapenems. 99.0% of the ESBL positive isolates and 52% of the ESBL negative isolates were resistant to the first generation fluoroquinolones. The resistance rate of the isolates to Amikacin, Gentamicin and Nitrofurantoin were higher for ESBL positive strains. Resistance rates to Cotrimoxazole were higher in ESBL negative isolates.

Klebsiella: *Klebsiella* was the second most common infecting organism seen in our study. 15.9% (73/458) of the total cUTI were positive for *Klebsiella*. Of these, 60.27% (44/73) were ESBL positive. 47.94% (35/73) were seen in the age group of 50-79 years. The resistance rates to the fluoroquinolones among the ESBL positive and negative isolates were 93.2% and 27.6% respectively. The resistance rates were higher for Amikacin, Gentamicin and Nitrofurantoin and lower for Cotrimoxazole in ESBL positive isolates.

Pseudomonas:*Pseudomonas aeroginosa* was the third commonest organism seen on urine culture of cUTI patients accounting to 11.14% (51/458). 56.86% (29/51) of these patients were in the age group of 50-79 years. 29.41% of the isolates were resistant to carbapenems. The resistance rate to the first generation fluoroquinolones was 74.51%. 64.71% of the isolates were resistant to the Amikacin and Gentamicin. The resistance rates to Nitrofurantoin and Cotrimoxazole was higher compared to the other uropathogens.

Activity comparisons for the antimicrobials in our study: The antimicrobial potency and spectrum for 9 selected antimicrobial agents against the cUTI pathogens recorded in the study are summarized in Table 3. When the total bacterial spectrum is taken into consideration, Carbapenems have the least resistance (4.1%), followed by Amikacin (29.0%), and Nitrofurantoin (31.2%). A high degree of resistance was recorded for first generation fluoroquinolones (76.9%) among the isolates in our study.

Organism	IM	ME	CP	NR	OF	GE	AM	NI	CO
Citrobacter freundii	0	0	46.15	46.15	46.15	23.08	23.08	15.38	15.38
Enterobacter spp	0	0	50	50	50	40	40	30	50
Enterococcus faecalis	57.14	57.14	28.57	28.57	28.57	71.43	71.43	42.86	85.71
ESBL Positive E. coli	0	0	99.0	99.0	99.0	72.6	27.9	23.4	24.9
ESBL negative E. coli	0	0	52.0	52.0	52.0	5.0	5.0	12.0	43.0
ESBL Positive Klebsiella	0	0	93.2	93.2	93.2	81.8	59.1	79.5	6.8
ESBL negative Klebsiella	0	0	27.6	27.6	27.6	3.4	3.4	17.2	31.0
Morganelle	0	0	0	0	0	0	0	100	0
Proteus vulgaris	0	0	0	0	0	0	0	0	100
Providencia alkalifaciens	0	0	100	100	100	0	0	100	0
Pseudomonas	29.41	29.41	74.51	74.51	74.51	64.71	64.71	66.67	72.55
Total	19	19	352	352	352	233	133	143	156

Table 3: IM- Imepenem, ME-Meropenem, CP- Ciprofloxacin, NR- Norfloxacin, OF- Ofloxacin GE- Gentamicin, AM- Amikacin, NI- Nitrofurantoin, CO- Cotrimoxazole
Table 3: Resistance pattern to various antibiotics of individual uropathogens

E.coli, Klesiella, *Citrobacter freundii, Enterobacter spp, Morganelle, Proteus vulgaris* and *Providencia alkalifaciens* showed least resistance to Carbapenems. However, Carbapenems were less active against enterococci (57.14 resistant) and pseudomonas (29.41% resistant).

First Generation Fluoroquinolones: The resistance to first generation Fluoroquinolones was very high in our study with resistance rates varying from 27.6 % (ESBL Negative Klebsiella) to 99% (ESBL Positive E.coli). While *Morganelle, Proteus vulgaris* and *Providencia alkalifaciens* showed lower resistance to the first generation fluoroquinolones, the ESBLs showed high resistance to them (93.2-99% resistance). *Citrobacter freundii* (46.15%), *Enterobacter spp* (50%) and ESBL negative organisms (27.6-52%) showed moderate resistance and Pseudomonas (74.51%) showed high resistance to first generation fluoroquinolones.

Amikacin and Gentamicin: Amikacin was active against *Morganelle, Proteus vulgaris* and *Providencia alkalifaciens* and the ESBL Negative organisms. *Citrobacter freundii* (23.08%), *Enterobacter spp* (40%) and the ESBL Positive organisms (27.9-59.1%) showed moderate resistance against Amikacin. The resistance among *Pseudomonas* (64.71%) and *Enterococcus faecalis* (71.43%) was higher compared to the other organisms. The resistance pattern to Gentamicin was similar to Amikacin except for the ESBL Positive organisms. These isolates were more resistant to Gentamicin (72.6-81.8%).

Nitrofurantoin: While *Proteus vulgaris* was completely susceptible to Nitrofurantoin, *Morganelle,* and *Providencia alkalifaciens* were resistant. Nitrofurantoin had a high rate of resistance against ESBL Positive Klebsiella (79.5%) and pseudomonas (66.67%). The antimicrobial was active against *Citrobacter freundii* (84.62%), *Enterobacter spp* (70%), *Enterococcus faecalis* (57.14%), E.coli (76.6-88%) and ESBL Negative Klebsiella (82.8%).

Cotrimoxazole: *Proteus* vulgaris was resistant to Cotrimoxazole. *Enterococcus faecalis* (85.71%) and pseudomonas (72.55%) were also highly resistant to Cotrimoxazole. This antimicrobial showed good activity against the other organisms. (Figure 1, Figure 2, Table 4)

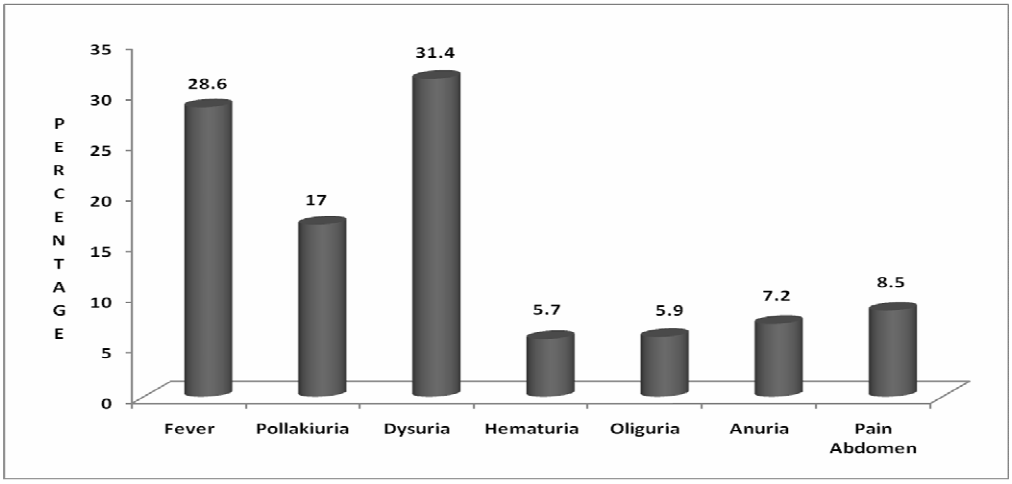

Figure 1: Common Symptoms with which the Patients Presented. Dysuria (31.4%) was the most common symptom with cUTI patients, fever (28.6%) was the next common symptom seen in these cases.

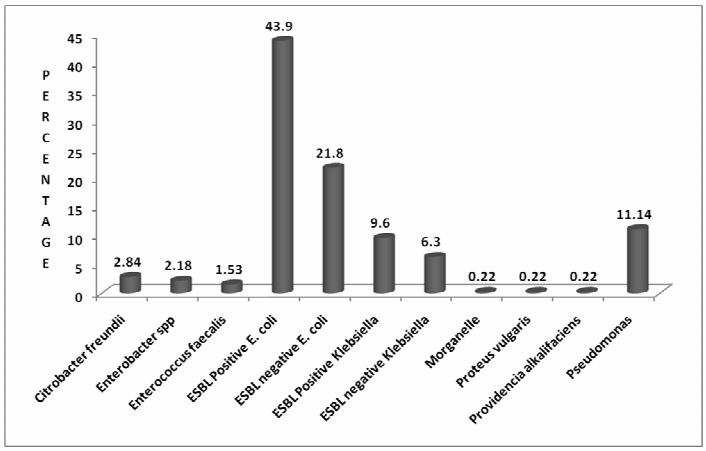

Figure 2: Frequency and distribution pattern of cUTI pathogens. E.coli (65.7%), ESBL Positive E. coli (43.9%) in particular was the most common causative organism in the study.

Table 4: Bacterial spectrum and overall resistance pattern of uropathogens causing cUTI in various surveillance studies (adapted from Wagenlehner et al)

Name of the study	SENTRY[10]	ESGNI-003[11]	PEP study[12]	Straubing[13]	Present study
Year of surveillance	1998	2000	2003	2001	2008
No. of pathogens	1510	607	320	479	458
Species percentage					
Citrobacter freundii	3	2	n.r	3	2.84
Enterobacter spp	4	4	3	3	2.18
Enterococcus faecalis	13	16	9	18	1.53
E. coli	47	36	35	41	65.7
Klebsiella	11	8	10	7	15.9
Morganelle	n.r	n.r	n.r	n.r	0.22
Proteus vulgaris	5	8	7	9	0.22
Providencia alkalifaciens	n.r	n.r	n.r	n.r	0.22
Pseudomonas	8	7	13	6	11.14
Resistance rate to antibodies					
Imepenem	9	14	7	n.r	4.1
Ciprofloxacin	3-40	17	34	24	76.9
Amikacin	2	19	14	n.r	29
Gentamicin	n.r	18	34	24	50.9
Cotirmoxazole	n.r	32	45	22	34.1

n.r- not recorded

Discussion

Of the total 458 cases of cUTI, Diabetes Mellitus (42.6%) was the most common risk factor contributing to the infection followed by bladder catheterization (15.8%) and other recent urological instrumentations (18.1%). 8.7% cases had presented with recurrent UTI. Congenital anomalies were present in 4.6% cases and renal stone was found in 2% of these cases. In the present study, E.coli (65.7%) topped the list of organisms causing cUTI. The results from worldwide review are similar to the present study. Arslan et al [6] reported that E. coli was the causative agent in 78% of cUTI. 12% of these were ESBL positive. Chen et al [7] in their study done in Taiwan have reported E.coli, Proteus mirabilis and Pseudomonas aeruginosa as the most common uropathogens. Peterson et al [4] in their study done in USA have reported E.coli as the most common organism causing cUTI. A review by Lindsay Nicolle [8] on cUTI reported E.coli as the most common uropathogen with a worldwide prevalence rate of 21-54%. The prevalence of ESBL positive cases was high in our study. 66.77% of E.coli and 60.27% of *Klebsiella* Sp were ESBL positive. This alarmingly high prevalence rate has necessitated setting up of a Hospital Infection Control Committee and implementation of an antibiotic policy in the hospital to tackle the issue and to prevent further increase of the same. A varying sensitivity pattern was seen to first generation fluoroquinolones against common uropathogens. The resistance to first generation fluoroquinolones in our study varied from 27.6% to 99% for various organisms. 38% of the total E.coli isolates were resistant to first generation fluoroquinolones in the study done by Arslan et al [6]. In contrast, Gordon et al [9] reported the quinolones as the most active agents against the most prevalent UTI pathogens in North America. Peterson et al [4] have reported a resistance rate of 5-20% in their study in USA. Wagenlehner et al [10] reported 20-40% resistance rate to ciprofloxacin. Though we recorded low resistance rate to carbapenems, resistance to Amikacin and Gentamicin was high in our study as compared to the SENTRY[11], ESGNI-003 [12], PEP study [13] and Straubing [14] studies. The high rate of resistance is multifactorial including lack of antibiotic protocol for cUTI and low compliance of patients in completing the antibiotic course. The lower resistance rate to carbapenems could be due to its usage pattern in our institution. It is most commonly used in critically ill patients where the administration of appropriate doses for the full duration is ensured. The increasing rate of multi-drug resistant uropathogens and extended spectrum beta lactamase organisms pose a serious threat in treating urinary tract infection. An ongoing surveillance of urinary tract infection should be encouraged for an updated knowledge about the uropathogens causing infection and their antibiotic resistance pattern to keep the medical community informed about the emerging antibiotic resistance.

Conclusion

The fast rising prevalence of ESBL producing organisms in the causation of cUTI and their ever increasing resistance to the available antibiotics has made the management of these patient more difficult. As lesser new antibiotics are available for their management, we need to be concerned of this issue in years to come especially in tertiary care centers. A unified antibiotic protocol is necessary to limit this increase and reduce the squeal of cUTI.

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