Etiologies and Microbiological Profile of Complicated Urinary Tract Infections, among Patients Admitted in a Tertiary Care Hospital

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Abstract

Background
Urinary tract infections (UTIs) are one of the most prevalent infections worldwide, with an estimated incidence of 18/1000 person per year. A complicated urinary tract infection(cUTI) is defined as an infection of the upper or lower urinary tract, with either a structural or functional abnormality. Such infections present a challenge for clinicians because of greater frequency of resistant microorganisms, prolonged treatment and recurrences.

Objective
To describe the etiologies, demographic characteristics and microbiological profile of patients admitted with Complicated Urinary tract infections in a tertiary care hospital.

Methods
This is a retrospective analysis through medical chart review of all patients admitted to the hospital, who met the criteria of complicated UTI, from January 2008 to March 2016. Data was extracted concerning demographics, etiologies, severe clinical manifestations, micro organisms implicated and frequency of multidrug resistant organisms. Data was entered into SPSS version 21, analyzed and expressed as median, range, numbers or percentage.

Results
206 patients were included in the study, 101 (49%) were males. Median (IQR) age was 45 (16-62) years. Commonest etiologies identified were obstruction in 81 (39%), prior use of antibiotics 81 (39%), diabetes mellitus 71 (34%), chronic renal insufficiency 71 (34%) and indwelling catheter in 68 (33%). The most common organism seen in both blood and urine cultures were *Escherichia Coli*, with Multi drug resistant organisms in 87% in blood, and 69% in urine. Sepsis was present in 82% and renal failure in 58% patients.

Conclusion
Given the varied etiologies, high prevalence of resistant microorganisms and severe manifestations, identification of underlying conditions and appropriate use of antimicrobials is imperative in decreasing the severity of cUTI.

Key words
cUTI, Multidrug resistance

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Introduction

Urinary tract infections (UTIs) are one of the most prevalent infections worldwide, with an estimated incidence of 18/1000 person per year.[1] Categorized into uncomplicated versus complicated, the former is seen in healthy, sexually active young women, while the latter occurs in all age groups with structural or functional abnormalities of the genitourinary system, or compromised host defense.[2]

Structural urinary tract abnormalities that lead to infection due to stasis include stones, strictures, prostatic hypertrophy, tumors and congenital malformations. Indwelling urinary catheters lead to recurrent episodes due to presence of biofilms, that harbor resistant organism. Instrumentation of the genitourinary tract often leads to bacteremia and sepsis, if appropriate antibiotic prophylaxis is not administered. Neurogenic bladder and spinal cord abnormalities also cause complicated UTIs (cUTI).[2-5]

Metabolic abnormalities like diabetes, renal failure, pregnancy, immuno suppression due to steroids, chemotherapy, transplant recipients and malignancies, are all known risk factors of cUTI. UTI in males without any structural or functional risk factor is itself categorized as complicated, warrants further investigation to look for an abnormality.[2-4] Prolonged antibiotic use and nosocomial acquisition can result in serious infections with resistant organisms.[1,2]

The microorganisms implicated in cUTIs are more resistant, requiring prolonged therapies, often in collaboration with an urologist. Protracted hospital courses with frequent recurrences are common, with complications like abscesses, sepsis, renal failure or treatment failure. Extended spectrum beta lactamase (ESBL) - producing gram-negative bacilli, especially *Escherichia coli* that respond only to broad spectrum intravenous antibiotics are increasingly being isolated from such patients.[1,2]

The rationale of this study was based on the fact that, the

prolonged duration of therapy, broader antibiotic coverage, increased length of hospital stay and therefore increased costs, associated with complicated UTI, they have become an important entity to address. To our knowledge, very limited literature exists, especially from Pakistan, which addresses the commonly associated conditions, common pathogens and their susceptibilities. The proposed study aims to gather information on these variables in patients admitted to The Indus Hospital (TIH) with a diagnosis of complicated UTI.

Methods

The study was conducted at TIH, a 150 bedded tertiary care hospital in Karachi. After approval from Institutional Review Board (IRB # IRD_IRB_2015_08_002), data was collected retrospectively of patients admitted with Complicated UTI from January 2008 to February 2016 Patients were identified using TIH's medical records using the keywords: complicated UTI, recurrent UTI, Urosepsis.

Inclusion criteria

All patients fulfilling the criteria of Complicated UTI i.e. having etiologies consisting of peruretheral, suprapubic and nephrostomy catheters, upper and lower urinary tract obstruction, age less than 15 years, male gender, diabetes mellitus, immuno suppression, renal insufficiency, renal stones (single or multiple), surgery of the urinary tract within last 2 weeks and prior to last 2 weeks, congenital or acquired structural abnormalities of the urinary tract, voiding dysfunction, pregnancy, nosocomial acquisition and eight weeks prior use of antibiotics were included. Patients were enrolled irrespective of age and gender, based on positive urine cultures (defined as 10^2CFU/ml of a uropathogen isolated in single urine specimen)[6] and symptoms and signs suggestive of urinary tract infection (dysuria, frequency, hesitancy, lower abdominal and flank pain with tenderness) with or without fever. The study population included patients admitted under the specialties of Urology including pediatric urology, Nephrology, General Medicine and Infectious Diseases.

Exclusion criteria

Patients admitted only for urological procedures and having asymptomatic bacteriuria were excluded.

The following variables were entered on the data extraction sheet: identifiable and demographic data including age, gender, dates of admission and discharge. Clinical data including severe manifestations were noted. Laboratory data i.e., the results of urine culture and blood cultures and their drug sensitivity patterns, as obtained by standard laboratory techniques of hospital's microbiology lab were also noted.

Operational Definitions

Uncomplicated UTI

Infection in a structurally and neurologically normal Urinary tract.[6]

Complicated UTI

A complicated urinary tract infection is that which occurs in a patient with an anatomically abnormal urinary tract or significant medical or surgical comorbidities.[2]

Extended spectrum beta lactamases (ESBL)

Extended-spectrum beta-lactamases (ESBL) are enzymes produced by Gram negative bacteria (mainly *E. coli* and *Klebsiella pneumoniae* but also *K. oxytoca*, *Proteus spp*, *Acinetobacter spp*, and others) responsible for resistance against penicillins, cephalosporins and aztreonam.[7]

Multidrug resistant organisms (MDROs)

Defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories.[8]

Nosocomial UTI

Refers to urinary tract infection acquired in a hospital. Risk factors include catheter associated (CAUTI) and Antibiotic use >7 days.[5]

Catheter associated UTI (CAUTI)

Defined as presence of symptoms or signs compatible with UTI with no other identified source of infection along with $>10^3$ cfu/mL of 1 or more bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 h.[9]

Acquired Structural Abnormality

Refers to anatomical/structural abnormalities of urinary tract acquired after birth as a consequence of either a chronic infection or surgical manipulation.

Data Analysis

Data was entered into SPSS software version 21 (SPSS Inc, Chicago, Ill, USA). Age was presented as median (IQR). All the qualitative variables like gender, etiologies and microbiological profile were presented as frequency and percentage.

Results

A total of 206 patients were enrolled in the study. 101 patients (49%) were males. There was one pregnant female. Median (IQR) age was 45 (16-62) years. Median (IQR) age of males was 44 (11-69) and females 48.42 (23-59) (table not shown). 153 (74.3%) were =15 years, 50 (24%) patients were less than 15 years old, and 3 had missing information (2%).

Etiological factors identified with frequencies (%) are shown in Table I. The most frequently observed etiologies were obstruction in 81 (39%) and prior use of antibiotics within 8 weeks also in 81 (39%) of patients. Medical and structural etiologies were categorized and their frequencies calculated, with mean age and gender distribution individually. A total of

Table I: Etiologies of Complicated Urinary tract Infections

Risk factors	n (%)
Diabetes Mellitus	70 (34)
HBA1c at time of admission; Mean (SD):	8.6 (2.4)
Indwelling catheters	68 (33)
Urethral	58 (85.3)
Suprapubic	4 (5.9)
Nephrostomy	8 (11.8)
Causes of obstruction:	81 (39.3)
Stone	32 (37.6)
BPH	19 (22.4)
VUR	16 (18.8)
Tumor	8 (9.4)
Stricture	7 (8.2)
PUV	2 (2.4)
Others	1 (1.2)
Cause of immunosuppression:	20 (9.7)
Malignancy	12 (60)
Cytotoxic drugs	6 (30)
Steroids	5 (25)
HIV	1 (5)
Others	3 (15)
Chronic renal insufficiency	71 (34)
Urolithiasis	37 (18)
Types	
Single	17 (8.3)
Multiple	20 (9.7)
Anatomical/Structural abnormality of urinary tract	71 (34.5)
Types:	
Congenital	8 (3.9)
Acquired	54 (26.2)
Both	9 (4.4)
Causes of voiding dysfunction	45 (21.8)
Neurogenic bladder	22 (48.1)
Others	13 (28.9)
Types of Urinary tract surgery	69 (33.5)
Urological procedure <2 wks.	14 (6.8)
Urological procedure>2wks	55 (26.7)
Causes of Nosocomial Acquisition	40 (19.4)
Catheterization (<1 week)	15 (37.5)
Antibiotic use (>7 days)	20 (50)
Both	5 (12.5)
Prior use of Antibiotics within 8 weeks	81 (39.3)

Abbreviations: HBA1c: Glycoslated Hemoglobin A1c, BPH: Benign prostatic hypertrophy, VUR: Vesicoureteral reflux, PUV: Posterior uretheral valve, HIV: Human immunodeficiency virus

179 patients had medical or functional etiologies, of which 46.3% had prior use of antibiotics within 8 weeks, 40.3% chronic renal insufficiency, 40% diabetes and 26% voiding dysfunction. Structural or anatomical anomalies were observed in 128 patients, of whom 31.8% had obstruction, 27% had undergone urinary tract surgery, 27% had indwelling urinary catheter and 15% had urolithiasis.

Of 206 patients, blood cultures were sent from 146 patients (71%), and grew isolates in 40 (27%) patients. The most commonly reported organism was *Escherichia. Coli*, in 29 (73%). Other organisms isolated are listed in Table II. MDROs were reported in 35 (87.5%) of these positive blood cultures.

Of 205 urine culture samples sent, 186 (91%) reported growth. The most common organism was *Escherichia. Coli*, in 133 (54%), followed by other gram-negative rods as shown in Table II. MDROs were reported in 142 (69%) of these urine cultures. Severe clinical manifestations, most common being sepsis, seen in 170 (83%) followed by renal failure in 119 (58%) and abscesses in 12(10.7%) of patients were observed

Discussion

The Indus Hospital is a tertiary care hospital with active urological and infectious disease services that jointly manage complicated urinary tract infection (cUTI). Patients who require chronic indwelling catheters, nephrostomies or ureteric stents, become colonized with bacteria that often precedes infection, which require prolonged, broad spectrum antibiotics with

Table II: Microbiology; most common organisms

Microorganisms reported in blood culture;	n (%)
Escherichia. Coli.	29 (72.5)
Klebsiellaspp	3 (7.5)
Pseudomonas Aureginosa	4 (10.0)
Candida spp	1(2.5)
Other	1(2.5)
Microorganisms reported in urine culture;	**n (%)**
Escherichia. Coli.	133 (71.5)
Klebsiella spp.	34 (18.3)
Pseudomonas aureginosa	29 (15.6)
Candida spp.	23 (12.4)
Enterococcus spp.	11 (5.9)
Proteus mirabilis	5 (2.7)
Enterobacter spp.	2(1.1)
MorganellaMorganii	2(1.1)
Acinetobacter spp.	2(1.1)
Coagulase negative staphylococcus	1(0.5)

prolonged hospitalization. Only patients admitted with symptomatic cUTI were included in this study.

In our study an equal number of males and females admitted with cUTI were seen, similar to as described by studies.[2,4] Males with a structural/functional underlying abnormality become as susceptible as females to acquire infection.[2] Post menopausal females also account for major patient population with cUTIs[4], but were not commonly seen in our study because of non availability of gynecological services in the hospital.

All age groups can be afflicted with cUTI[2,4], but in our patients, increased incidence in the older age was due to co morbidities like diabetes, renal insufficiency, benign prostatic hypertrophy and neurogenic bladder.[10] Stefano *et al* showed the median age to be 73 years (range 66- 84).[11] Another study showed the median age to be 65.8 (30-95) years.[1] A substantial proportion of our patients were also below 15 yrs mostly with congenital abnormalities of urinary tract or stones.

The most frequent etiological factors also correspond to existing studies. *Consensus review* of epidemiology of cUTI in Asia pacific region, reported structural abnormalities in 49%, diabetes mellitus 25% and indwelling catheters in 24% patients.[12] Catheter associated urinary tract infections (CAUTI) were seen in 10-30% patients in short term and 100% patients with long term catheterization in a study.[10,13] Another study reported its frequency to be 10.8%.[14] Data from Taiwan in pediatrics showed 40% to have congenital abnormalities with vesicoureteric reflux being most common (64%).[12] The greater percentage of acquired anatomical abnormalities seen is likely sequel of obstructive pathology.

We saw the most number of patients with recent exposure to antibiotics. *Yildiz et al* also reported this as being the most common risk factor, in 81% of their patients.[1] This reflects the practice of injudicious use of antibiotics for conditions that do not warrant their use, promoting resistance and increasing risk of recurrent infections. Clinicians need to be cautious and rely on good clinical judgment before prescribing antimicrobials.

Escherichia. Coli, continues to be the most common organism isolated,[1,2,4,10,12,15-17] both in urinary and blood samples. *Yildiz et al* reported 18 and 49 patients out of 64 patients with positive blood and urine cultures respectively that grew *Escherichia. Coli*.[1] A study from Netherlands showed *Escherichia. Coli*, (47%) to be the most prevalent organism.[15] Data from India and Vietnam in the consensus review[1,12] showed prevalence of *Escherichia. Coli*, up to 65% and 47% respectively in urine culture. 57% of blood cultures grew *Escherichia. Coli,* from a study in Vietnam. *Stefano et al* reported 22.4% positive blood and urine cultures for *Escherichia. Coli*.[11] In Pakistan, existing data suggests *Escherichia. Coli*, as being the most prevalent organism in UTIs. *Farhat et al* found prevalence of Extended spectrum beta lactamases (ESBL) *Escherichia. Coli*, in nosocomial UTI to be 33.9%.[18] Another study showed prevalence of *E. coli* in Urine cultures of acute and recurrent UTIs to be 73% and 65.5% of these isolates were resistant to >8 antibiotics.[19]

Other organisms isolated also correspond to previous literature.[2,4,12] 23 urine cultures were positive for *Enterococcus* but only 3 represented true infections, associated with nosocomial acquisition and long term catheterization and treated accordingly as patients were symptomatic. One patient had *Group B streptococcu*s isolated from a perinephric collection. Studies report *Enterococcus* as the most common gram positive organism implicated in complicated UTIs, specially associated with nosocomial acquisition, catheterization and immunosuppression such as diabetes.[2,4,13,20-23] Similarly, *Candida* and multidrug resistant *Pseudomonas aeruginosa* is commonly seen in infections associated with long term catheterization and nosocomial settings.[2,10,12,17] In our study 29 patients had *Candida* growing in their urine cultures but only 6 of them were found to have true infection, the rest were colonizers, concomitantly seen with other microorganisms in catheterized patients. The 6 patients treated for candiduria including one for candidemia (with urinary tract as the source) all had nosocomial acquisition specially with prolonged catheterization, use of broad spectrum antibiotics and some degree of immunosppression related to uncontrolled diabetes or renal failure. All developed fever with no other source identified, *Candida*isolated in more than one culture and consisted of both albican and non-albican species. These findings correlate with previous studies where *Candida spp* is found to be a common pathogen in complicated UTIs.[2,4,10,20,21,24] Data from Taiwan in 2009 showed 26.6% *Candida* isolated in nosocomial UTIs, followed by *E. coli*, *Pseudomonas* and *Enterococcus*. While *Protues spp* and *Providenciastuarrti* are mostly isolated from patients with urolithiasis.[2,4,10] In this study *Proteus spp* was seen as a cause of complicated UTI in 4 patients associated with either renal stones or obstruction, none was associated with Sepsis. The most common drug resistant organism reported in literature are the ESBL producing *E. coli* and other *Enterobacteriaceae*. Taneja reported that out of 21.8% of positive isolates 22.1 % were HDRUs (highly drug resistant uropathogens) i.e. resistant to quinolones, 3rd generation cephalosporins and aminoglycosides. *E. coli* (32.6%), *Klebsiella spp (*16.6%) and *P.aeruginosa* (28.5%) were the most resistant isolates.[25] *Hseuh et al* showed that 33% of *E. coli* in urinary isolates in Asia Pacific region were ESBL positive, 60% of which belonged to India.[12] *SMART* study showed 50% of *E. coli* isolate to be resistant to quinolones and > 30% to be resistant to 3rd generation cephalosporin.[26] *Pseudomonas aeruginosa* was found to be carbapenem resistant in 14/29 (48%) isolates, *MDR Acinetobacter* and *MDR Pseudomonas* were reported in 3/14 (21%) and 3/29(10%) of patients respectively in a study from Taiwan in 2005.[12,27] In our isolates, a very high frequency of *MDROs* (Multi drug resistant organisms) was seen in both urine and blood cultures, especially in patients with recent instrumentation, hospitalization, prolonged indwelling catheter

and repeated antibiotic use. This is alarming, as choice for empirical antimicrobials becomes narrower, with use of broad-spectrum agents like carbapenems and Colistin as initial therapy becoming common. Increasing resistance to carbapenems especially in nosocomial settings was also observed in our study.

Three patients were admitted with emphysematous pyelonephritis and treated surgically. Abscesses were seen in case of obstruction due to stones and in patients with diabetes, needing therapy up to 3-6 weeks, with drainage. High frequency of renal failure corresponds to previous studies[2,4,12] attributable to pre- existing renal dysfunction and high frequency of septicemia leading to multiorgan dysfunction. *Stefano et al* reported all 49 patients to have pyonephrosis and sepsis, 42.9% of whom were also in shock and 14.3% had multiorgan dysfunction.[11] Study in Vietnam found 30% patients with pyonephrosis, 19% urosepsis, and <5% cases with perirenal abscess with skin fistula.[12] The significant number of patients with sepsis should alert clinicians to assess patient for signs of this life threatening condition, and start broad spectrum antimicrobials promptly.

The limitation of this study was its retrospective design; further studies are needed to determine antimicrobial susceptibilities and outcomes in cUTI.

Conclusion

Complicated UTI can be a very challenging condition to treat, given the wide range of risk factors, high prevalence of resistant microorganisms and severe manifestations. Identification of underlying conditions and appropriate use of antimicrobials is imperative in decreasing the severity of this condition. We should be vigilant in assessing severity given the high prevalence of resistant microorganisms and sepsis in this group of patients.

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Conflicts of Interest: None

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