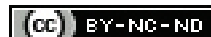


Clinical Profile and Outcome Analysis among Patients with Urosepsis at a Tertiary Care Centre: A Retrospective Cohort Study

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ABSTRACT

Introduction: Urosepsis is a systemic reaction of the body to a bacterial infection of the urogenital organs with the risk of life-threatening complications including septic shock.

Aim: To assess the profile of patients with urosepsis and to analyse outcomes in patient management at a tertiary care centre.

Materials and Methods: A retrospective cohort, single-centre study was conducted at PSG Institute of Medical Science and Research, Coimbatore, Tamil Nadu, India, between January 2015 and December 2019 including patients of either sex, aged ≥ 20 to < 80 years, with a confirmed diagnosis of urosepsis. Clinical report forms were reviewed to obtain patient characteristics (including age, sex, co-morbid conditions and clinical data). Blood, pus, urine culture data were evaluated to identify the source of infection. Details of upper and lower urinary tract symptoms and their imaging and urological intervention done were also recorded. Analysis of the data was done using descriptive statistics.

Results: A total of 582 patients with urosepsis were included in this study. The majority of patients belonged to the age group of 41-60 years (n=315). The most frequent radiological diagnosis

was infected hydronephrosis with calculus disease (n=237). The associated co-morbid conditions contributing to the perpetuation of urosepsis were Type II Diabetes Mellitus (T2DM), systemic hypertension, chronic kidney disease, decompensated liver disease, neurological disease, and coronary artery disease. *Escherichia coli* was the most commonly observed uropathogen (57.90%) in this study. Bilateral Double-J (DJ) stenting was usually preferred in patients with infected hydronephrosis and acute pyelonephritis (n=85, 76.58%). The insertion of a suprapubic catheter was more frequent among patients with obstructive lower urinary tract symptoms. Multivariate analysis showed that urosepsis with emphysematous pyelonephritis, uncontrolled diabetes, and persistent hypotension inspite of inotropic agents had a prolonged intensive care unit and higher mortality rate.

Conclusion: Renal salvage is achievable in majority of cases with early surgical intervention, either DJ stenting or percutaneous nephrostomy. Suprapubic catheterisation is indicated in urosepsis patients with predominant lower urinary tract symptoms. An early diagnosis and an appropriate treatment can reduce the costs of hospitalisation, morbidity, mortality and better outcome.

Keywords: Bilateral double-J stenting, Diabetes mellitus, Pyonephrosis, Suprapubic catheter

INTRODUCTION

Urosepsis is a systemic inflammatory response of the body to infection of the urogenital tract with the risk of life-threatening complications including septic shock. Severe urosepsis involving the urinary tract and the male reproductive system is recognised as an important global health problem. Complicated Urinary Tract Infection (UTI) occurs in patients with structural or functional abnormalities such as structural malformations, strictures, calculi, or tumours [1]. The incidence of sepsis has been consistently increasing in Asian, European, and the United States populations over the past few decades [1]. The Global Burden of Disease Study report 2017, estimated 48.9 million cases of sepsis, 11.0 million sepsis-related death globally, and 640-1600 sepsis incidence per 1,00,000 population. About 25-30% urosepsis related death occurs in India [2].

Elderly patients, male sex, and medical co-morbidities including Diabetes Mellitus (DM), immunocompromised patients, renal failure, malignancy, acquired immunodeficiency syndromes (AIDS) are recognised as independent associated risk factor for urosepsis. Severe urosepsis has a high mortality rate of 20-40% particularly in special vulnerable groups [3].

Urosepsis is most frequently caused by a gram-negative organism like *Escherichia coli* followed by *Proteus*, *Enterobacter*, *Klebsiella*, and *Pseudomonas aeruginosa* [4]. Bacteria can invade the urinary tract by haematogenous, ascending, or lymphatic pathways. The prognosis of urosepsis depends on the cause and

severity of the inflammatory response as well as the type and virulence of bacteria, clinical responsiveness to the treatment, and patient's general clinical status. The complications may be fatal if the condition remains untreated for a longer period of time [4]. Patients with urosepsis should be recognised at an early stage and treated appropriately to prevent acute kidney injury and multiorgan dysfunction.

The diagnostic assessment includes a physical examination, blood and urine cultures, urinalysis, inflammatory biomarkers, and imaging modalities. Urine culture and sensitivity must be performed in all patients before starting empirical antimicrobial regimen. Ultrasonography, a commonly used imaging modality enables the rapid detection of infected hydronephrosis, pyonephrosis, infected urinary calculi, renal abscesses, and prostatic abscesses. Non contrast Computed Tomography-Kidney Ureter Bladder (NCCT-KUB) provides the most accurate diagnosis but increase exposes to ionising radiation. Using 3-D Computed Tomography (CT) scan image of urinary stone and surrounding anatomy can be reconstructed through multiple viewing planes [5].

Antibiotics have traditionally been the most commonly advocated treatment plan for UTI; however, increased rate of antimicrobial resistance has changed the treatment protocol. Surgical intervention with DJ stents, percutaneous drainage, percutaneous nephrostomy, suprapubic cystostomy are commonly performed in the setting of obstructive uropathy.

An early diagnosis and identification of the causative bacteria of urosepsis is important so as to facilitate proper selection and use of antimicrobial agents in any setting. Therefore, the present study aims to determine the bacteriological profile; upper and lower urinary tract symptoms of patients with symptomatic UTI. The present study also analysed the urological interventions done and its outcome. This study is important for clinicians in day to day practice to facilitate the effective surgical treatment of patients with symptoms of UTI.

MATERIALS AND METHODS

This was a retrospective cohort, single-centre study conducted at PSG Institute of Medical Science and Research, Coimbatore, Tamil Nadu, India, between January 2015 and December 2019 and the data were collated and analysed from July to December 2020. The data was collected from the medical records of the hospital. The study was approved by the Institutional Ethics Committee (PSG/IHEC/2020/Appr/Exp/158; approval date: 03 July 2020).

Inclusion criteria: Patients of either sex, aged 20-80 years, with a confirmed diagnosis of urosepsis were included in the study. Urosepsis definition was based on the presence of urogenital tract infection and systemic inflammatory response to infection.

Exclusion criteria: Patients who were admitted before January 2015 and those aged less than 20 years were excluded. Additionally, patients without confirmed diagnosis of urosepsis were excluded.

Data Collection

Clinical report forms of all the study patients were analysed to capture the following details of the patients: demographic details included age, sex and associated co-morbid conditions like DM, Coronary Artery Disease (CAD), Chronic Kidney Disease (CKD), decompensated liver disease, systemic hypertension, neurological disease. Blood, pus, urine culture data were also evaluated to identify the source of infection. Details of upper and lower urinary tract imaging (USG KUB and non contrast CT KUB) were noted and associated details of any intervention done was also documented.

The primary outcome of the study was the characteristics of patients with urosepsis, upper and lower urinary tract symptoms, and analysis of outcomes in the patient's management at the tertiary care centre.

STATISTICAL ANALYSIS

Qualitative data were presented as number (percentage) or as a number, while quantitative data were presented as mean±Standard Deviation (SD) wherever termed appropriate.

RESULTS

A total of 582 patients with urosepsis were included in this study. The average age of the patients was 53.6 years. The majority of patients belonged to the age group of 41-<60 years (n=315). The present study showed female predominance over men (54.6% vs. 45.4%). The associated co-morbid conditions are represented in [Table/Fig-1].

The most common presentation at the time of hospital admission was fever with chills, flank pain, decreased urine output, disorientation and loss of consciousness. The most frequent radiological diagnosis was infected pyonephrosis (n=237) followed by acute pyelonephritis (n=111), emphysematous pyelonephritis (n=88), perinephric abscess (n=18) and renal abscess (n=8). Urgent surgical intervention was carried out to remove the obstruction, restore renal function and improve overall general condition.

Based on the microorganism isolates from cultures, *Escherichia coli* 337 (57.90%) was the most commonly observed pathogen, followed by *Klebsiella pneumoniae* 104 (17.87%), *Proteus mirabilis*

Parameters	Number of patients (N=582)
Age (years), mean±SD	53.6±8.2
Age group (years)	
20-40	81 (13.9)
41-60	315 (54.1)
>60	186 (32.0)
Gender	
Women	318 (54.6)
Men	264 (45.4)
Co-morbidity	
CAD	46 (7.9)
CKD	112 (19.2)
DCLD	88 (15.1)
DM	445 (76.5)
Neurological disease	61 (10.5)
Systemic hypertension	316 (54.3)

[Table/Fig-1]: Demographic characteristics of patients.

Data shown as n (%), unless otherwise specified.

CAD: Coronary artery disease; CKD: Chronic kidney disease; DCLD: Decompensated liver disease; DM: diabetes mellitus

76 (13.06%), *Enterococcus faecalis* 34 (5.84%), and fungal infection 17 (2.92%), and *Pseudomonas aeruginosa* 14 (2.41%). Overall, the presence of microbes was more frequent in urine samples. However, pus and blood cultures also grew *Escherichia coli* as the most common microbes, followed by *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and fungal infection [Table/Fig-2].

Microorganism	Pus	Urine	Blood	Total N=582
<i>Escherichia coli</i>	194 (33.33)	212 (36.43)	142 (24.40)	337 (57.90)
<i>Enterococcus faecalis</i>	18 (3.09)	24 (4.12)	10 (1.72)	34 (5.84)
Fungal infection	3 (0.52)	15 (2.58)	1 (0.17)	17 (2.92)
<i>Klebsiella pneumoniae</i>	41 (7.04)	84 (14.43)	26 (4.47)	104 (17.87)
<i>Proteus mirabilis</i>	22 (3.78)	58 (9.97)	14 (2.41)	76 (13.06)
<i>Pseudomonas aeruginosa</i>	6 (1.03)	12 (2.06)	2 (0.34)	14 (2.41)

[Table/Fig-2]: Microorganism isolates from cultures.

Data presented as n (%) multiple sample taken, patients overlapping so total not matching

Bilateral DJ stenting was performed in 85 patients with acute pyelonephritis (n=85, 76.58%) and 62 (32.63%) patients with stone in the upper urinary tract. Nephrostomy was performed in three patients with emphysematous pyelonephritis and four patients with pyonephrosis [Table/Fig-3]. Fourteen patients (77.78%) had percutaneous drainage for perinephric abscess and four patients (22.22%) had open drainage for the same complaints. Eight patients had renal abscess of whom six (75.00%) had Percutaneous drainage and two (25.00%) had open drainage in addition to DJ stenting.

Urethral stricture disease was seen in 49 patients who underwent supra pubic catheterisation. A total of 33 patients with symptoms of prostatic abscess were subjected to derroofing of the prostate with supra pubic catheterisation. Overall, the insertion of a suprapubic catheter was more frequent in patients presenting with lower urinary tract symptoms. Fourteen patients underwent orchidectomy (malignancy n=6; testicular abscess n=8), 11 patients with calculus disease underwent cystolitholapaxy [Table/Fig-4].

[Table/Fig-5] depicts the outcomes of surgical intervention in patients with urosepsis. Multivariate analysis showed that urosepsis with emphysematous pyelonephritis, uncontrolled DM, persistent hypotension inspite of ionotropic support had a prolonged intensive care unit stay and higher mortality rate. The mean duration of postoperative stay in hospital was 12.5 days for

Diagnosis	No of cases	Right DJ stenting	Left DJ stenting	Bilateral DJ stenting	PCN	PCD	Open drainage	Nephrectomy
Emphysematous pyelonephritis	88	16 (18.18)	20 (22.73)	48 (54.55)	22 (25.00)	12 (13.64)	-	3 (3.41)
Acute pyelonephritis	111	9 (8.11)	17 (15.32)	85 (76.58)	-	-	-	-
Perinephric abscess	18	3 (16.67)	4 (22.22)	11 (61.11)	-	14 (77.78)	4 (22.22)	-
Renal abscess	8	4 (50.00)	2 (25.00)	2 (25.00)	-	6 (75.00)	2 (25.00)	-
Pyonephrosis								
Stone	190	62 (32.63)	50 (26.32)	45 (23.68)	31 (16.32)	-	-	2 (1.05)
PUJO	14	4 (28.57)	6 (42.86)	-	2 (14.29)	-	-	2 (14.29)
Malignancy	33	-	-	15 (45.45)	18 (54.55)	-	-	-

[Table/Fig-3]: Upper urinary tract infections and urological intervention (N=462).

Data presented as n or n (%). PCD: Percutaneous drainage; PCN: Percutaneous nephrostomy; PUJO: Pelvi-ureteric junction obstruction

Diagnosis	No. of cases	SPC	Orchidectomy	Deroofing of prostate	Debridement	Cystolithotomy	Cystolitholapaxy
Calculus disease	11	6 (54.55)	-	-	-	-	11 (100.00)
Prostatitis	6	6 (100.00)	-	-	-	-	-
Prostatic abscess	33	25 (75.76)	-	33 (100.00)	-	-	-
Malignancy	06	4 (66.67)	6 (100.00)	-	-	-	-
Urethral stricture disease	49	49 (100.00)	-	-	-	-	-
Fournier's gangrene	7	5 (71.43)	-	-	7 (100.00)	-	-
Testicular abscess	8	-	8 (100.00)	-	-	-	-

[Table/Fig-4]: Lower urinary tract infections and urological intervention (N=120).

Data presented as n or n (%). SPC: Suprapubic catheter

prostatic disease and 13.7 days for Fournier's gangrene. Mortality in urosepsis was seen mostly in patients aged >65 years due to varied aetiology like bilateral emphysematous pyelonephritis (n=4), uncontrolled DM (n=12).

Diagnosis	ICU > 3 days LOS, n	Post-operative days LOS, Mean	Death, n	Readmission within 3 months, n
Emphysematous pyelonephritis	21	11.4	4	8
Acute pyelonephritis	26	07.8	2	13
Perinephric abscess	6	11.5	3	1
Renal abscess	5	09.7	1	1
Stone	39	06.6	5	18
PUJO	03	07.5	2	1
Malignancy	18	16.8	5	6
Prostatic abscess	11	12.5	1	8
Fournier's gangrene	5	13.7	1	2

[Table/Fig-5]: Outcomes of surgical intervention in patients with urosepsis.

LOS: length of stay; PUJO: Pelvic-ureteric junction obstruction

DISCUSSION

Urosepsis is most commonly caused by an obstructive pathology of the upper urinary tract of which urolithiasis and diabetic necrotised renal papillae are the commonest causes in present study. The urinary tract symptoms in urosepsis need to be assessed appropriately for precise diagnosis and management of urosepsis. The key finding of the present study were: i) Urosepsis is common in elderly patients with co-morbid conditions and is associated with a poor prognosis ii) *Escherichia coli* was the most common uropathogen responsible for urosepsis; iii) Patients with lower UTI were treated with suprapubic catheterisation technique.

In the present study, the average age of the patients was 53.6 years and the frequently associated co-morbid conditions included DM followed by hypertension, chronic kidney disease, decompensated liver disease, neurological disease, and CAD. Longer the duration of hospital stay, the worse the prognosis. The gender distribution of urosepsis varies considerably. Previous studies including the global age-standardised sepsis study (716.5 cases per 100 000 vs. 642.8 cases per 1, 00,000) demonstrated that the incidence of urosepsis was most frequent in women than men [1,2,5,6]. In parallel to

the reported studies, the present study revealed the same trend. However, these findings conflict with Australasian Resuscitation in Sepsis Evaluation (ARISE) study wherein male gender had a higher incidence of urosepsis [7].

In addition to early antibiotics, another important part of the management of urosepsis is initial fluid resuscitation with crystalloid at a minimum of 30 mL/kg [8]. Early administration of vasopressor support is essential to maintain a mean arterial pressure greater than 65 mmHg. The first choice for vasopressor support in urosepsis is nor epinephrine [9]. Blood sugar control is also recommended with insulin therapy. The approximate use of corticosteroids and blood products is also recommended. In present study, around 54% of patients in the age group 41 to ≤60 years, diagnosed with urosepsis had diabetes. An evidence-based retrospective study reported the average age of the enrolled patients as 53.8 years [1]. The burden of urosepsis in India has increased in elderly patients (>65 years) due to their co-morbid conditions, reduced immunity, and functional limitation [10,11]. The previous observational study by Qiang XH et al., reported the prevalence of urosepsis in the youngest age group (46.7 years) [12].

Among the patients diagnosed with urosepsis, DM (76.5%) was the most prevalent co-morbid condition followed by systemic hypertension (54.3%), CKD (19.2%), decompensated liver disease (15.1%), neurological disease (10.5%), and CAD (7.9%). Urosepsis tends to occur in patients with the history of DM, as the metabolic derangement and down-regulated immune response, increases frequency, severity and duration of infections [13]. A recently published observational study evaluated hypertension as the most prevalent co-morbid condition for all the patients followed by congestive heart failure, DM, rheumatoid arthritis, cancer, and acquired immune deficiency syndrome [14]. However, a recent meta-analysis showed that DM does not impair the outcome of patients with sepsis [15].

The bacteria responsible for urosepsis are gram-negative organisms, and order of most frequent uropathogen include *Escherichia coli* > *Proteus* > *Enterobacter* > *Klebsiella* and *Pseudomonas aeruginosa* species [4,16]. In a cohort study by Kidwai SS, et al., *Escherichia coli* (59%) was the most common pathogen followed by *Staphylococcus aureus* (16.4%) and *Klebsiella* (11%) [17]. Compare to the western literature, the instance of gram-positive

sepsis were less in present study. These findings were in concordance with the present study and the literature suggest that urosepsis is most commonly caused by *Escherichia coli* and that should be considered for the empirical treatment of high-risk patients [12,18].

Several reports have described varied management protocols for pyelonephritis including medical management and drainage procedures. A noteworthy study by Das D and Pal DK, alluded that pyelonephritis can be managed successfully with a less morbid DJ stenting procedure [19]. In a prospective study by Cordeiro MD et al., the patients with ureteral obstruction underwent both percutaneous nephrostomy (n=150) and ureteral stenting (n=58) [20]. In the present study, source control was predominantly achieved by DJ stenting, and very few patients with upper urinary tract diseases required nephrectomy. Similar to the previously reported studies by Shao IY et al., and Wang Z et al., [14,15], the present study also emphasises the placement of a urethral catheter and suprapubic cystostomy for the treatment of urethral strictures [21]. A number of existing studies have shown suprapubic catheterisation as an effective interventional approach in patients with lower UTI symptoms such as voiding dysfunction, spinal cord injuries, and neurogenic bladder [22-25]. In parallel to these studies, the present study showed that the majority of patients with lower UTI were treated with suprapubic catheterisation.

In urosepsis with obstructive uropathy, the increased intrarenal pelvic pressure theoretically decreases the drug delivery to the kidney; hence, it is important to use DJ stenting or percutaneous nephrostomy to facilitate urinary drainage. In the case of emphysematous pyelonephritis, early DJ stenting or percutaneous drainage is required. Suprapubic catheter insertion is preferred in individuals with acute urinary retention, chronic urinary retention, enlarged prostate with urosepsis, urethral strictures, penile urethral erosion, and contracted bladder neck [22,26,27]. This is typically performed in all the patients who have failed to respond to other conservative treatment. Despite safety, several intraoperative as well as postoperative complications are associated with suprapubic catheter insertion [28]. The present study findings show that postsurgical complications in patients with urosepsis required longer intensive care unit stay and higher mortality that was in accordance with the reported studies which may be due to hypotension during surgery [1,12]. In summary, the guidelines of the European urological association suggest that urosepsis patients be treated with adequate life support measures, appropriate and prompt antibiotic therapy, adjunctive measures and treatments of urinary tract disorders by drainage of any obstructive urinary systems [29]. The present study has evaluated upper and lower urinary tract symptoms and studied the outcome following urological intervention. It was observed that renal salvage is achievable in majority of cases with early intervention, either DJ stenting or percutaneous nephrostomy.

Limitation(s)

The limitations of the present study include single-centre retrospective design, making it difficult to interpret results and avoid bias completely. Furthermore, due to the limited study design, the present study did not show any correlation with the risk of sepsis.

CONCLUSION(S)

Renal salvage is achievable in majority of cases with early surgical intervention, either DJ stenting or percutaneous nephrostomy. Suprapubic catheterisation is indicated in urosepsis patients with predominant lower urinary tract symptoms. Comprehensive

management requires team approach with timely inputs from microbiologists, radiologists, urologist and intensive care physicians. Early recognition of symptoms followed by appropriate investigations, accurate diagnosis and early goal directed therapy is essential to improve the outcomes.

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