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Urosepsis: Flow is Life

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Abstract

Urosepsis is one of the important etiological factors for community as well as hospital-acquired infections. Accordingly, urosepsis is divided into community-acquired and hospital-acquired urosepsis. Obstruction to the flow of urine is a common risk factor for community-acquired urosepsis, whereas the indwelling urinary catheter is the risk for the hospital-acquired urosepsis. *E. coli* remained the most common bacteria-causing urosepsis. If not treated early and appropriately, urosepsis can complicate into septic shock and multiple organ dysfunction. The cornerstone for the improved outcome of these patients is initial resuscitation and proper antibiotic therapy and restoring the flow of urine or removing the infected urinary catheter. Community-acquired urosepsis can be prevented by removing the obstruction to flow of urine permanently. The hospital-acquired urosepsis can be prevented by strictly following catheter-associated urinary tract infection prevention bundle and removing the catheter as early as possible.

Keywords: *E. coli*, microbiology, sepsis, septic shock, community-acquired and hospital-acquired urosepsis, urine obstruction, urinary catheter

1. Introduction

The mortality from sepsis is reaching higher than prostatic and breast carcinoma; up to 31% of sepsis originated from the urogenital tract organs, and hence it is termed as urosepsis [1]. Urosepsis is a severe infection and 5% lead to severe sepsis, and it is an important aetiology for hospital-acquired infection and accounts for around 40% of the nosocomial infections [2]. About 5% of urosepsis patients complicate in severe sepsis and organ dysfunction; Patients with comorbidities are at a higher risk for urosepsis, severe sepsis and septic shock with a higher morbidity and mortality [3]. Hence, the early diagnosis and management is the key for better outcome. The presence of bacteria in the urogenital tract produces an overwhelming pro-inflammatory reaction involving macrophages and neutrophils by stimulating the cellular immunity, complement system and endothelial cells. the production of nitric oxide is triggered, which leads to a decreased vessel tone resulting in hypotension. This initial phase is followed by a counter regulatory anti-inflammatory response syndrome, leading to an immunosuppressive state, which accounts for the mortality in the longer course of sepsis. The activation of

compliment system causes coagulopathy and fibrinolysis leading to microthrombi formation and organ dysfunction [4].

The common aetiology of community-acquired urosepsis is the obstruction to the urine flow, and patient quickly tends to go into septic shock and multi-organ dysfunction due to urinary stagnation and bacterial growth. The obstruction also affects the pharmacokinetics of antibiotics. Relieving the obstruction is the cornerstone for survival of these patients, hence giving the title of the chapter.

We will discuss urosepsis in the following subheadings.

2. Epidemiology

The community acquired urosepsis is rare and commonly occurs due to structural or functional abnormality leading to urinary flow obstruction. It contributes to 5% of total sepsis case, whereas the hospital-acquired urosepsis contributes to 40% of sepsis cases [5]. Occurrence of urosepsis is more frequent in females than in males. For the community-acquired urosepsis, the frequent risk groups are the patients with obstructive uropathy. Hofmann reported that majority of obstruction to the flow of urine was due to urinary calculi (65%), tumours in 21%, gestation in 5%, urinary tract anomalies in 5% and surgical interventions in 4% of their patients [6]. Other risk factors for urosepsis are old age, female gender, immunosuppression, steroid therapy, chronic renal failure and prolonged surgical time [7]. In elderly bedbound patients, the urinary catheter is the foremost cause for urosepsis. Healthcare-associated infection frequency vary according to geographical location of the countries; prevalence of healthcare-associated infections is 4% in the United States of America, 6% in the European countries and 15.5% higher in developing countries [8, 9].

3. Classification

Urosepsis is classified into two categories.

3.1 Community-acquired urosepsis

Community-acquired urosepsis when presents with urosepsis from the community. It accounts for 7% of all sepsis cases. It is more frequent in females and has a shorter ICU stay. Mainly caused by Gram-negative bacteria and 63% had *E. coli* with 41% having bacteraemia. Yang et al. have shown that ESBL-producing *E. coli* and *K. pneumoniae* (ESBL-EK) accounted for 20.7% of the pathogens causing

Community-acquired urosepsis	Hospital-acquired urosepsis
Obstructive uropathy or genitourinary tract abnormalities are common aetiology	Prolonged urinary catheterization is a common aetiology
Gram-negative bacteria in 85% and Gram-positive in 15% [12]	Gram-negative bacteria in 66% and Gram-negative in 21%
Source control by endoscopic stent or image-guided nephrostomy	Removal of urinary catheter is the source control
Board-spectrum antibiotics depend on local antibiogram	Initial antibiotics should cover pseudomonas

Table 1.
Differences between community-acquired urosepsis and hospital-acquired urosepsis.

bacteraemic community-acquired urinary tract infections [10]. The 28-day mortality was higher in the non-HCRI group (29%) [11].

3.2 Hospital-acquired urosepsis

Hospital-acquired urosepsis is one of the healthcare provider-related sepsis and acquired during the hospital stay. It was found in 31% of these patients; *E. coli* represents 58% of all isolations with a different resistance profile with resistance to ciprofloxacin, aminoglycosides and co-trimoxazole. The 28-day mortality in hospital-acquired urosepsis was 15% [10]. In contrast the hospital-acquired urosepsis with extended B-lactam enzyme had a significant higher mortality of 41% [10] (**Table 1**).

4. Risk factors

There are risk factors for both community- and hospital-acquired urosepsis. Community-acquired urosepsis occurs mainly in patients with obstructive uropathy, genitourinary tract structural abnormalities and carcinoma of the urinary bladder, whereas the hospital-acquired urosepsis occurs in catheterized elderly patients, on immunosuppression therapy [13, 14].

4.1 Age and gender

The combination of age more than 65 and female gender is a significant risk factor for the development of urosepsis. Bacteriuria is frequent in elderly population; more than 50% of geriatric females will have bacteriuria. A multicentre study showed that patients older than 65 years of age admitted with febrile UTIs were nearly 2.5 times more likely to develop bacteraemia than patients under the age of 65 [15].

4.2 Comorbidities

The diabetes, nephrocalcinosis and azotaemia (chronic kidney disease) are related to the increased incidence of urosepsis. van Nieuwkoop et al. reported an association between comorbid disease and urosepsis, where diabetes was significantly associated with an 80% increased risk for urosepsis. In diabetic patients, poor glycaemic control, autonomic neuropathy, higher urinary glucose, immune dysfunction and diabetic microangiopathy facilitate bacterial adherence to uroepithelium [15].

4.3 Obstructive uropathy

The number of factors causing obstruction to the urinary flow increases the risk of urosepsis significantly. The congenital factors causing obstruction to the urinary flow are ureteric or urethral strictures, phimosis, ureterocele and polycystic kidney disease, whereas the acquired aetiological factor leading to urinary flow obstruction are calculi, prostatic hypertrophy, tumours of the urinary tract, trauma, pregnancy and the radiation therapy causing fibrosis [12].

4.4 Environmental and host factors

These are the external factors that contribute to bacterial virulence, transmission of bacteria to host and compromise of host defences. This includes inappropriate and unnecessary antibiotic consumption, limited healthcare facilities and the lack of local surveillance programmes.

4.5 Voiding disabilities

Traumatic spinal injuries, cerebrovascular accidents, neurogenic bladder, cystocele and vesicoureteral reflux due to various aetiologies, either trauma or congenital, lead to increased usage of urinary catheterization and ultimately increased incidence of urosepsis. Urosepsis risks are multiplied due to indwelling long-term catheters and the spread of multidrug-resistant bacterial strains. Richards et al. showed that 23% of all cases of hospital-acquired sepsis were due to UTI and mostly seen in catheterized patients [16].

4.6 Urosurgical interventions

Trauma of urological intervention either diagnostic or therapeutic in the presence of bacteria can lead to the development of urosepsis. Common urological interventions are prostate biopsies, stone interventions and transurethral prostate resections. Urosepsis rate after these surgical interventions are transurethral resection of prostate up to 4% [17] trans rectal prostate biopsies up to 0.8% [18] lithotripsy: 1% [19] ureterostomy for stone treatment up to 9% patients will have severe sepsis [20] percutaneous kidney stone surgery up to 7% will develop sepsis [21] and up to 8% endoscopic urethrotomy patients develops sepsis [22] (Table 2).

5. Diagnosis

Typical presentation in community-acquired urosepsis patients is triad of loin pain, fever and leukocytosis. Hospital-acquired urosepsis patients frequently manifest leukocytosis and hypotension. Urosepsis quickly complicates into septic shock with multiple organ dysfunction. One third of these patients will have septic shock with tachycardia and tachypnea and other organ dysfunctions [12].

5.1 Laboratory work-up

Apart from complete blood count (CBC) and electrolyte monitoring, the serum C-reactive protein and procalcitonin (PCT) levels should be obtained. They will tell us the patient deterioration and presence of sepsis and septic shock. Serum lactate will give diagnostic as well as prognostic value [11].

Risk factors	
Age and gender	More than 65 years and female
Comorbidities	Diabetes mellitus, nephrocalcinosis and chronic kidney disease
Obstructive uropathy	Ureteric, urethral strictures, phimosis, ureterocele, polycystic kidney disease, calculi, prostatic hypertrophy, tumours of the urinary tract, trauma, pregnancy and the radiation therapy
Environmental and host factors	Bacterial virulence, transmission of bacteria to host and compromise of host defences
Voiding disabilities	Traumatic spinal injuries, cerebrovascular accidents, neurogenic bladder, cystocele and vesicoureteral reflux
Urosurgical interventions	Prostate biopsies, stone interventions and transurethral prostate resections

Table 2.
Risk factors for urosepsis.

5.2 Urine culture

Urinary culture and sensitivity are important not only in the diagnosis but also equally important in the management of urosepsis. The culture should be done within hours or persevered properly. A positive culture is highly diagnostic, and negative culture will rule out the urinary infections.

5.3 Blood culture

As significant number of urosepsis patients had Gram-negative bacteraemia, which correspond to the severe sepsis and septic shock.

5.4 Imaging studies

Imaging studies will help in diagnosing renal calculi as well as urosepsis aetiology and complications.

5.4.1 Abdominal radiography

Abdominal radiography has a limited value; it shows the presence and extent of calcification and calculi within the renal system. It is of help in monitoring change in position and increase in size or number of renal stones. Intravenous urography gives the anatomical details of the urinary system. It also helps in the diagnosis of reflux nephropathy and papillary necrosis.

5.4.2 Ultrasound scan

Ultrasound is routinely performed in emergency department. It helps in the diagnosis of renal stone, prostate and bladder pathologies. It is one of the common imaging studies for the patients presenting to emergency with loin pain.

5.4.3 CT scan and MRI abdomen

These modalities of imaging studies will accurately diagnose microabscesses in the kidney and other genital organs. It will accurately diagnose the bacterial nephritis, renal microabscesses, perinephric abscesses, hydronephrosis and emphysematous pyelonephritis [12] (**Figure 1**).

Figure 1.
Renal USG showing calculi.

6. Microbiology and microbial resistance in urosepsis

Urinary culture is not specific for diagnosis, but it rules out the origin of urosepsis if it is negative. It should be obtained at midstream and procedure immediately. Blood cultures must also be taken before administrating the antimicrobial agent, can be ones results are available. Blood cultures can be positive in up to 41% of the cultures [23]. About 93% of the patients admitted with community-acquired urosepsis had *E. coli* growth, whereas 66% of the hospital-acquired urosepsis patients grow *E. coli*. Interesting factor is that the urinary catheter-associated urosepsis is associated with Gram-positive infections. *Candida* infections are common in patients with stents in the urinary tract. In female patients, the *E.coli* urosepsis is common as compared to the male patients (92 and 60%, respectively) [23] (Table 3).

Risk factors	Common organism
Community-acquired urosepsis	Gram-positive bacteria 15% Gram-negative bacteria 85%
Hospital-acquired urosepsis	Gram-positive bacteria 21% Gram-negative bacteria (66%) with increased frequency of ESBL, multidrug resistance fluoroquinolone resistance and aminoglycoside resistance
Patients with prolonged and infected ureteric stents	<i>Candida</i> species
Patients with diabetes mellitus	<i>E. coli</i> , <i>Klebsiella pneumoniae</i> , <i>Proteus</i> and <i>Pseudomonas</i> causing emphysematous pyelonephritis, rarely <i>Candida</i> and <i>Cryptococcus</i>

Table 3.
Bacteriology of urosepsis.

7. Complications

The main complications of urosepsis are bacteraemia (23%), endotoxemia (34%) and septic shock up to 2.5%. The common organ involved is the kidney [24].

7.1 Post-obstructive acute kidney injury

Up to 10% of acute kidney injury (AKI) episodes are caused by urinary tract obstruction; in the elderly, it will increase to 22% of AKI. The mechanisms in the pathogenesis of obstructive nephropathy lead to renal vasoconstriction and progressive renal fibrosis; while renal vasoconstriction is reversible after the release of obstruction, renal fibrosis may result in irreversible loss of function. Post-obstructive AKI rarely progresses to end-stage renal disease after the release of obstruction, but significant percentage (21%) of these patients have chronic renal impairment. The best time to release urinary obstruction in the setting of post-obstructive AKI is not known; in patients with sepsis, it should be performed as an emergency. The renal outcome inversely correlated with elapsed time from admission to the release of obstruction, which could suggest that the release should be performed as an emergency even in the absence of sepsis [25].

Acute pyelonephritis
Emphysematous pyelonephritis
Renal abscess
Prostatic abscess
Post-obstruction acute kidney injury
Fournier’s gangrene
Septic shock with multi-organ dysfunction

Table 4.
Complications of urosepsis.

7.2 Acute pyelonephritis

It can occur with or without urinary obstruction, common in females. If not treated appropriately, it will progress into emphysematous pyelonephritis, papillary necrosis and perinephric and renal abscess.

7.3 Emphysematous pyelonephritis

A life-threatening necrotizing infection of renal parenchyma and perinephric area, if not treated, can be fatal. Common bacteria are *E. coli*, *Klebsiella pneumoniae*, *Proteus* and *Pseudomonas*, and rarely fungi are common in patients with diabetes mellitus. It can be managed by percutaneous drainage and antibiotic and supportive care [26].

7.4 Renal abscess

It is common in patients with diabetes mellitus. The reflux and back pressure of the infected urine is the main aetiology for the renal abscesses. About 75% of renal abscesses is caused by *E. coli*. Treatments are percutaneous drainage, antibiotics and supportive care [12].

7.5 Prostatic abscess

It occurs exclusively in diabetic patients and immunosuppressed patients. Prostatic abscess can rupture into the urethra. Percutaneous drainage is key for better outcome of these patients [27].

7.6 Fournier’s gangrene

It is the necrotizing fasciitis of genitalia. Prompt diagnosis and earlier antibiotics and surgical debridement are the essential factors for better outcome [28] (Table 4).

8. Management of urosepsis

Septic shock is the most severe complication of urinary tract infection.

8.1 Initial resuscitation

Urosepsis patient will be dehydrated and febrile and may be in shock, hence initially resuscitating with fluid challenges. Fever is usually controlled by paracetamol. If after initial resuscitation, if their hemodynamic parameters is not improving, they should be started early on vasopressors. These uroseptic shock patients should be initially managed following sepsis protocols in the first hour. O₂ supplementation, IV fluid and antibacterial administration and advanced hemodynamic monitoring are useful. With the goal of central venous pressure (CVP) 8–12, intrathoracic blood volume index (ITBV) and global end-diastolic index (GEDVI) within normal range. Cardiac contractility will be monitored by cardiac index (CI), cardiac functional index (CFI) and the isovolumic contraction of the heart (D/P max). Uroseptic shock patients may have respiratory distress, earlier intubation and maintain mixed O₂ or saturation of 70% will improve the outcome [29]. Blood sugar should be maintained around 10 mmol/L. If these urosepsis patients had respiratory distress, they should be immediately intubated and ventilated. As a part of multi-organ dysfunction, these patients may be in disseminated intravenous coagulopathy and should be taken care and resuscitated with blood and blood products.

In antibiotics and bacterial resistance, proper antibiotic administration in septic shock patients improve their outcome [30].

Kumar et al. demonstrated that administration of an effective antimicrobial within the first hour of documented hypotension was associated with a survival rate of 80% [31]. Hence the initial antibiotic in these patients selected on the basis of local antibiogram and as soon as culture are available changed the antimicrobial to the narrow spectrum.

As the common bacteria is *E.coli* in the community-acquired urosepsis, the third generation cephalosporin and fluoroquinolones and combinations are a better choice where as in the hospital-acquired urosepsis, we should add an antipseudomonas antibiotics with combination with amino glucosides or should be initial antimicrobial therapy. Biofilm formation by microorganism is a vital factor in the progress of urosepsis, which is formed in association with urinary catheters, scar tissue and stones, and minimal inhibitory concentrations (MIC) in biofilm are increased up to 100-fold; hence, the high dosages of antibiotics needed in combination with the attempt to remove the biofilm should be considered [32].

Most of these patients' therapy for 2–3 weeks goes parallel with the relief of symptoms and sign with clinical improvement. The cultures should be repeated after 2–4 weeks of cessation of therapy [30].

8.2 Source control

Obstruction to the urinary flow is one of the foremost causes and risks for community-acquired urosepsis. This obstruction should be cleared as soon as possible, either with endoscopic insertion of stent or image-guided percutaneous drainage. The endoscopic stenting is a minimally invasive procedure hence preferred in shock patients with coagulopathy. If the patient has hydronephrosis or renal abscesses, the choice is percutaneous drainage by nephrostomy [33]. In hospital-acquired urosepsis, the indwelling urinary catheter is the frequent cause of urosepsis. In all hospitalised patients with indwelling urinary catheters, catheter-associated urinary tract infection (CAUTI) bundles should be followed strictly. It should be removed as early as possible; if still required the condom catheter can be used, and an antipseudomonal antibiotic should be started [34, 35].

9. Prevention

Community-acquired urosepsis can be prevented up to some extent by relieving the obstruction to the flow of urine or correction of the urinary tract abnormalities, whereas the hospital-acquired urosepsis can be prevented by following the CAUTI bundle, removing urinary catheter and using the condom catheters.

Preventing the urinary tract infection in females, it can be done by following few general principles such as clean genitalia, drinking plenty of water particularly after intercourse, urinating frequently and wiping from front to back.

In elderly patients, the regular use of cranberry juice or capsule may be helpful. In elderly postmenopausal patient, intravaginal oestriol therapy is useful in preventing UTI. In this group of patients, antibiotics highly effective. Other risk factor such as incontinence, cystocele should be taken care. Elderly man, incontinence of the bladder and enlargement of prostate is risk, so they should be taken care condom catheter or surgical intervention.

Endo-urological procedure such as ureteroscopy involving instrumentation of the genitourinary tract which has a risk for postoperative urosepsis. The urinary tract interventions are more risky in patients with positive preoperative urine cultures or foreign bodies within the urinary tract causing obstruction. It has been demonstrated that perioperative antibiotics reduce urosepsis after uroendoscopy [36–37].

10. Conclusion

Sepsis is a medical emergency; urosepsis is a sepsis originating from the urinary tract. Urosepsis contributes significantly to the overall epidemiology of sepsis. The common and most frequent aetiology of urosepsis is either congenital or acquired obstruction to the flow of urine. The risk factor for urosepsis varies from metabolic diseases to the renal calculi. Based upon the environment in which the patient gets infection, urosepsis is divided into community-acquired urosepsis and hospital-acquired urosepsis. In the diagnosis of urosepsis apart from monitoring blood count, acute-phase proteins and serum lactate and blood and urinary cultures, the imaging studies play an important role. If not treated early and managed properly, urosepsis can progress into pyelonephritis, renal and prostatic abscesses and septic shock.

The cornerstones for the management of urosepsis are initial organ supportive resuscitation, appropriate early antibiotics, relieving obstruction to urinary flow and the source control. Obstruction to the urine flow is the important and most frequent factor for the urosepsis as it facilitates the bacterial growth and repeated sepsis. It is of vital importance to relieve the obstruction and restore the normal flow of urine as soon as possible to reduce the morbidity and mortality.

Prevention of urosepsis starts from well hydration to the clean genitalia, periurological procedure antibiotics, maintaining free flow of urine and strictly following the CAUTI prevention bundle in the hospitalised patients.

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