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Evaluation and Treatment Urosepsis

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Abstract Urosepsis is a severe, and sometimes fatal, infection starting in the urinary tract leading to systemic infection and complicated by patient immune and inflammatory responses. The practicing urologist should recognize the multiple risk factors that may increase the risk of urosepsis and follow early goal-directed therapy. In many cases, the urologist is involved to alleviate the source of infection and in a team-based approach, can alter patient outcome. Urosepsis after common urological procedures is often preventable with the use of antimicrobial prophylaxis.

Keywords Urosepsis · Septic shock · Severe sepsis · Complicated urinary tract infection · Urinary tract infection

Introduction

Urosepsis is defined as sepsis caused by infection of the urogenital tract and is characterized by a systemic and deleterious host response to the infection. This can lead to severe sepsis and septic shock which are major healthcare problems. The urinary tract contributes to up to 9–31 % of cases of sepsis [1].

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About one third of sepsis cases can result in death. Urologists working together with the internist need to outline a timely plan to resuscitate the patients presenting with urosepsis and diagnose the source of their sepsis. The initial goals of therapy influence the final outcome. The prognosis of sepsis is better in women than in men and may be related to increased levels of anti-inflammatory mediators [2]. Severe sepsis occurs more frequently and leads to more deaths in black than in white individuals explained by a higher likelihood of being hospitalized with infection and a higher risk of developing acute organ dysfunction [3].

Risk Factors

Urinary tract infections (UTI) vary in their severity and symptoms. Bacteriuria is the presence of bacteria in the urine, which is normally sterile but may not always be suggestive of an infection. Asymptomatic bacteriuria is most commonly seen in patients with chronic indwelling catheters. An uncomplicated UTI is defined as an infection in a patient with no functional or structural abnormalities, and its most common population is in young females. A complicated UTI is seen in a patient with any structural or functional abnormalities, any male, any immunocompromised patient, and any infection with multidrug-resistant bacteria [4]. Structural and/or functional abnormalities include but are not limited to outflow obstruction (congenital anomalies, stone, benign prostatic hyperplasia, urethral stricture), and impaired voiding (neurogenic bladder, vesicoureteral reflux) [5]. Furthermore, any foreign body within the genitourinary tract that promotes bacterial/fungal colonization including indwelling foley catheter, ureteral stent, or nephrostomy tube is a risk factor for UTI. Special patient populations at risk for complicated UTIs include poorly controlled diabetics, HIV or transplant patients,

malnourished patients, debilitated and institutionalized elderly, and chronic steroid users [4]. Of special note, any patient with hospital-acquired UTI or with recent history of healthcare exposure is at an increased risk of septic shock from multidrug-resistant organisms [6, 7].

Definitions

Urosepsis can result from a complicated urogenital tract infection. Urologists should be familiar with the following terminology as critical care management depends on continuously reassessing the level and severity of sepsis. Recognition of the early clinical manifestations of sepsis is imperative for early detection and treatment. Systemic inflammatory response syndrome (SIRS) is a systemic response to insult which may be infectious or noninfectious including trauma, fulminant pancreatitis, or burn/thermal injury. Classically, SIRS is defined when at least two of these four of the following criteria are met: temperature less than 36° or greater than 38°, tachycardia greater than 90 beats per minute, tachypnea with respiratory rate greater than 20, and leukocytosis greater than 12,000 or Leukopenia less than 4000 [8]. Sepsis is defined as SIRS in combination with documented or suspected infection. Severe sepsis is a worsening progression leading to tissue hypoperfusion or organ dysfunction related to infection. Clinical findings include hyperlactatemia, oliguria, hyperbilirubinemia, acute lung injury, and coagulopathy [8]. Ultimately, septic shock is sepsis-induced hypotension defined by systolic blood pressure less than 90 mmHg despite adequate fluid resuscitation [8]. Septic shock may lead to multi organ dysfunction syndrome and carries a high mortality rate.

Pathophysiology

The above clinical manifestations of sepsis can be tracked to the pathophysiologic mechanisms that occur at the molecular level between the pathogen and the host response. First is the interaction that occurs when pathogen-associated molecular patterns (PAMP) bind to pattern-recognition receptors (PRR) on the surface of host cells that activate the complement system and innate immune system causing a pro-inflammatory response [9•]. An example of PAMP is endotoxin, a lipopolysaccharide on the outer cell wall of gram-negative bacteria that is well known to be the key initiator of gram-negative bacterial septic shock [10]. Key inflammatory cytokines include TNF-alpha, interferon gamma, and interleukin −2 [10]. During this inflammatory phase, nitric oxide is released from endothelial cells which increases vessel permeability that results in hypotension [9]. The complement system also activates the coagulative pathway which explains why severe sepsis may lead to disseminated intravascular coagulation (DIC) [11]. This initial phase is then counteracted by an anti-inflammatory and immunosuppressive state that promotes cell healing and recovery but also makes the patient susceptible to secondary infections which accounts for the mortality in the longer course of sepsis [11].

Clinical Diagnosis

Signs and symptoms indicating the urogenital system as the septic source should be assessed in all patients presenting with sepsis. Clinical evaluation should include history for symptoms of flank pain, dysuria, lower urinary tract symptoms, history of recent urological intervention, or nephrolithiasis. Physical examination should look for renal angle tenderness, epididymitis, and prostate exam for acute prostatitis. Urosepsis can frequently develop as a result of an obstructed and infected urinary focus as nephrolithiasis or strictures and can also develop in the setting after interventions in the urinary tract such as percutaneous nephrolithotomy or transrectal biopsy.

Management

Management of sepsis has improved since the well known Surviving Sepsis Campaign international guidelines were introduced in 2004. The treatment recommendations are organized into bundles, with tasks and targets to be completed in first the 6 h (resusCitation bundle) and within 24 h (management bundle) [12]. The first bundle focuses on resuscitation of patients with sepsis-induced tissue hypoperfusion with targeted goals to keep mean arterial pressure (MAP) above 65 mmHg, urine output greater than 0.5 mL/kg/h, and normalization of hyperlactatemia [12]. In addition, it recommends cultures prior to antimicrobial therapy and administration of antibiotics within 1 h of recognition of sepsis [12]. Each hour delay in the administration of effective intravenous antimicrobials is associated with a measurable increase in mortality rate [13].

The choice of empiric antibiotic treatment should be according to the local susceptibility profile. Patients who had health-care exposure should be considered as a risk factor for resistant microbial infections and should consider an antibiotic with broad coverage including antipseudomonal and multidrug-resistant *E. coli* [7]. Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis should be chosen. Pharmacokinetics of antimicrobial agents is altered in the uroseptic patient with obstructive uropathy and/or renal impairment. The activity of antibacterial drugs differ in unilateral versus bilateral renal

impairment or obstruction, are affected by changes in urinary pH, and due to biofilm infections, the minimal inhibitory concentration (MIC) of the antibacterial may be increased [14]. Thus, the choice of antimicrobial therapy should take into account these pharmacological factors. Antimicrobial regimen should be reassessed daily, and readjusting to the most appropriate single therapy should be performed as soon as the susceptibility profile is known.

Ultrasonography is the primary choice of imaging in most cases of suspected upper urinary tract infection due to its lack of harmful radiation, easy accessibility in the emergency room, and low cost [15]. Fever for more than 3 days after admission or previous histories of urolithiasis are significant factors predicting major abnormalities on ultrasound [16]. Diabetic patients and patients with known renal or urological pathology are more likely to have positive findings on imaging [15]. A renal sonogram will be sufficient to eliminate the diagnosis of obstructed pyelonephritis requiring emergency drainage of urine; however, CT scan is far better at diagnosis and may be needed in complicated cases in which further anatomical detail is important [17].

Specific anatomical diagnosis of infection requiring consideration for emergent source control (i.e., necrotizing soft tissue infection or infected kidney stone) should be sought, diagnosed, or excluded within 6 h of sepsis [12]. If a specific anatomic diagnosis of infection is found, then intervention within first 12 h with the least physiologic insult should be used [12]. Fig. 1 shows the algorithm for the timing and management in the uroseptic patient. In the case of obstructive uropathy, emergent drainage of the infected obstructed renal unit is of utmost importance. Placement of a ureteral stent has been shown to be as equally effective as percutaneous nephrostomy drainage for obstructing infected hydronephrosis secondary to ureteric calculi [18]. Definitive surgical intervention should be postponed until the patient is stable. Urgent nephrectomy is rarely required when other measures are inadequate but is associated with 20 % mortality rate [19].

Prevention

Urosepsis following common urological procedures can be reasonably preventable with antimicrobial prophylaxis. Patient-related factors affecting host response to surgical infections include advanced age, anatomic anomalies of the urinary tract, poor nutritional status, smoking, chronic corticosteroid use, immunodeficiency, externalized catheter, colonized endogenous/exogenous material, distant coexistent infection, and prolonged hospitalization [20]. Antimicrobial prophylaxis (Table 1), should be a single dose, started 30 min before the procedure and discontinued within 24 h of the end of the procedure [20]. Longer duration of antimicrobials should be considered in the situation of placement of prosthetic material, the presence of an existing infection, and the manipulation of an indwelling tube or catheter [20]. Rates of urinary tract infection following urethrocystoscopy without prophylaxis vary from 9 to 12 % [21]. For lower urinary tract endoscopy with manipulation as prostate or bladder resection, rates of urosepsis were 4.4 % and for upper-tract manipulation with ureteroscope risk is around 13–30 % [21]. Urosepsis after transrectal prostate biopsy is about 2 % and mainly occurs with multidrug-resistant *E. coli* (refractory to fluoroquinolones),

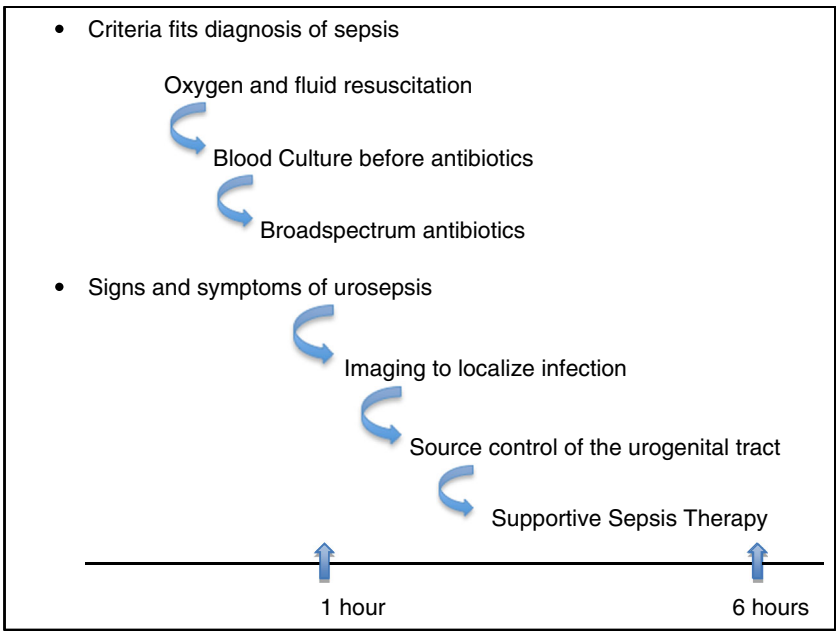

Fig. 1 Algorithm of timeline of management of urosepsis [9]

Table 1 Antimicrobial prophylaxis for urological procedures [20]

Procedure	Organisms	Prophylaxis indicated	Antimicrobial(s) of choice	Alternative antimicrobial(s)	Duration of therapy[a]
Lower-tract instrumentation					
Removal of external urinary catheter	GU tract[b]	If risk factors[c,d]	- Fluoroquinolone[e] - TMP-SMX[e]	- Aminoglycoside (aztreonam[f]) ± ampicillin[e] - 1st/2nd gen. cephalosporin[e] - Amoxicillin/clavulanate[e]	=24 h[e]
Cystography, urodynamic study, or simple cystourethroscopy	GU tract	If risk factors[d]	- Fluoroquinolone - TMP-SMX	- Aminoglycoside (aztreonam[f]) ± ampicillin - 1st/2nd gen. cephalosporin - Amoxicillin/clavulanate	=24 h
Cystourethroscopy with manipulation[g]	GU tract	All	- Fluoroquinolone - TMP-SMX	- Aminoglycoside (aztreonam[f]) ± ampicillin - 1st/2nd gen. cephalosporin - Amoxicillin/clavulanate	=24 h
Prostate brachytherapy or cryotherapy	Skin	Uncertain	- 1st gen. cephalosporin	- Clindamycin[h]	=24 h
Transrectal prostate biopsy	Intestine[i]	All	- Fluoroquinolone - 1st/2nd/3rd gen. cephalosporin	-TMP-SMX - Aminoglycoside (aztreonam[f])	=24 h
Upper-tract instrumentation					
Shock-wave lithotripsy	GU tract	If risk factors	- Fluoroquinolone - TMP-SMX	- Aminoglycoside (aztreonam[f]) ± ampicillin - 1st/2nd gen. cephalosporin - Amoxicillin/clavulanate	=24 h
Percutaneous renal surgery	GU tract and skin[j]	All	- 1st/2nd gen. cephalosporin - Aminoglycoside (aztreonam[f]) + metronidazole or clindamycin	- Ampicillin/sulbactam - Fluoroquinolone	=24 h
Ureteroscopy	GU tract	All	- Fluoroquinolone - TMP-SMX	- Aminoglycoside (aztreonam[f]) ± ampicillin - 1st/2nd gen. cephalosporin - Amoxicillin/clavulanate	=24 h

Key

[a] Additional antimicrobial therapy may be recommended at the time of removal of an externalized urinary catheter

[b] GU tract: Common urinary tract organisms are *E. coli*, *Proteus sp.*, *Klebsiella sp.*, *Enterococcus*

[c] See Table 1 "Patient-related factors affecting host response to surgical infections."

[d] If urine culture shows no growth prior to the procedure, antimicrobial prophylaxis is not necessary

[e] Or full course of culture-directed antimicrobials for documented infection (which is treatment, not prophylaxis)

[f] Aztreonam can be substituted for aminoglycosides in patients with renal insufficiency

[g] Includes transurethral resection of bladder tumor and prostate, and any biopsy, resection, fulguration, foreign body removal, urethral dilation or urethrotomy, or ureteral instrumentation including catheterization or stent placement/removal

[h] Clindamycin, or aminoglycoside + metronidazole or clindamycin, are general alternatives to penicillins and cephalosporins in patients with penicillin allergy, even when not specifically listed

[i] Intestine: Common intestinal organisms are *E. coli*, *Klebsiella sp.*, *Enterobacter*, *Serratia sp.*, *Serratia sp.*, *Proteus sp.*, *Enterococcus*, and Anaerobes

[j] Skin; Common skin organisms are *S. aureus*, coagulase negative *Staph. sp.*, Group A *Strep. sp.*

and carbapenem antibiotic therapy may be used [22]. Rates of urinary tract infection without prophylaxis in percutaneous renal procedures can be as high as 40 % [21]. Significant predictors of SIRS after percutaneous nephrolithotomy include multiple access tracts and a stone burden greater than 10 cm^2; renal pelvic urine and stone cultures may identify the causative organism and guide antimicrobial therapy [23]. Although antibiotic prophylaxis is an important contributor to reducing surgical site infections for open surgery, it has to be noted that the technique plays an important role. Gentle tissue handling and careful dissection without opening unnecessary planes, layered closure, and leaving a drain when required can all improve the infection rates.

Conclusion

Urosepsis is a severe host response to infection originating in the urinary tract and carries a high mortality rate. Early recognition and proper management with resuscitation and antibiotics together with elimination of the source of infection in a timely manner can change that outcome.

Compliance with Ethics Guidelines

Conflict of Interest Judy Farias, Mohamed Kamel, and Ehab Eltahawy declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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