

Therapeutic challenges of urosepsis

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ABSTRACT

Urosepsis accounts for approximately 25% of all sepsis cases and may develop from a community or nosocomial acquired urinary tract infection (UTI). The underlying UTI is almost exclusively a complicated one with involvement of parenchymatous urogenital organs (e.g. kidneys, prostate). In urosepsis, as in other types of sepsis, the severity of sepsis depends mostly upon the host response. The treatment of urosepsis comprises four major aspects: Early goal directed therapy, early optimal pharmacodynamic exposure to antimicrobials, early control of the complicating factor in the urinary tract and specific sepsis therapy. Following these prerequisites there appear two major challenges that need to be addressed:

Firstly, time from admission to therapy is critical; the shorter the time to effective treatment, the higher the success rate. This aspect has to become incorporated into the organisational process. Secondly, adequate initial antibiotic therapy has to be insured. This goal implies however, a wide array of measures to ensure rational antibiotic policy. Both challenges are best targeted if an interdisciplinary approach at any level of the process is established, encompassing urologists, intensive care specialists, radiologists, microbiologists and clinical pharmacologists working tightly together at any time.

Keywords Sepsis treatment, SIRS, urinary tract infections, urosepsis.

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Introduction

Urinary tract infections (UTIs) can manifest in a wide clinical range from bacteriuria with limited clinical symptoms to sepsis, severe sepsis or septic shock, depending on localized or systemic extension. In 20–30% of all septic patients the infectious focus is localised in the urogenital tract [1]. However only 3–5% of urosepsis cases with resistant isolates in a veterans hospital occurred on the urology service [2]. In one study, [3] 59 patients (54% females) with uroseptic shock were analysed over a ten year period in urology departments. Seventy-eight per cent of patients showed urinary obstruction as predisposing factors and the remaining 22% showed uropathies with a significant impact on urodynamics. Seventeen per cent of patients developed urosepsis after urological interventions. Obstructive diseases of the urinary tract leading to obstructive pyelonephritis are caused in 65% by ureteral stones, in 21% by tumours, in 5% by pregnancy, in 5% by anomalies of the urinary tract and in 4% following operations [4]. In another study, from 205 analysed case histories of urosepsis, 43% resulted from urolithiasis, 25% from prostatic adenoma, 18% from urological cancer and 14% suffered other urological diseases complicated by urosepsis [5]. In patients with nosocomial UTI treated in urology departments, the prevalence of urosepsis was, on average, about 12% [6], whereas in patients with nosocomial UTI treated in other specialities the prevalence for severe sepsis was 2% and for septic shock 0.3% [7].

Severe sepsis is a critical situation with a reported mortality rate ranging from 20% to 42% [8]. Most severe sepsis cases reported in the literature are related to pulmonary (50%) or abdominal infections (24%), with UTIs accounting for approximately 5% [9] to 7% [10]. Sepsis is commoner in men than in women [8]. In recent years, the incidence of sepsis has increased [8,11], but the associated mortality has decreased suggesting improved management of patients [8,11]. Urosepsis may also show high mortality rates of 25% to 60% in special patient groups [12]. A consistent finding however is that the mortality associated with septic shock from a urinary source is substantially lower than all other sources. This may reflect the ease of dealing with the infected source through drainage, although this has not been established yet.

Definition of urosepsis

Urosepsis is defined as sepsis caused by infection of the urinary tract and/or male genital organs (e.g. prostate). The patients are affected by micro organisms capable of inducing inflammation within the urinary and male genital tract.

In urosepsis, as in other types of sepsis, the severity of sepsis depends mostly upon the host response. Patients who are more likely to develop urosepsis include elderly patients, diabetics, immunosuppressed patients such as transplant recipients, patients

receiving cancer chemotherapy or corticosteroids and patients with acquired immunodeficiency syndrome. Sepsis is a systemic inflammatory response to infection. The signs and symptoms of SIRS (systemic inflammatory response syndrome), which were initially considered to be 'mandatory' for the diagnosis of sepsis [13,14], are now considered to be alerting symptoms [15]. Many other clinical or biological symptoms must be considered. The classification of the sepsis syndrome follows different levels of criteria:

Criteria I: Proof of bacteraemia or clinical suspicion of sepsis.

Criteria II: Systemic Inflammatory Response Syndrome (SIRS)

Body temperature	≥ 38 °C or ≤ 36 °C
Tachycardia	≥ 90 beats min ⁻¹
Tachypnoea	≥ 20 breaths min ⁻¹
Respiratory alkalosis	PaCO ₂ ≤ 32 mm Hg
Leucocytes	≥ 12 000 μL ⁻¹ or ≤ 4000 μL ⁻¹ or bandforms > 10%

Criteria III: Multiple Organ Dysfunction Syndrome (MODS)

Heart, circulation Arterial systolic blood pressure
 ≤ 90 mm Hg or mean arterial blood
 pressure ≤ 70 mm Hg, ≥ 1 hour despite
 adequate fluid- or vasopressure agents
 resuscitation.

Kidney Production of urine < 0.5 mL kg⁻¹ body
 weight/hour despite adequate fluid
 resuscitation.

Lung PaO₂ ≤ 75 mm Hg (breathing room air)
 or PaO₂/FiO₂ ≤ 250 (assisted respiration)
 [(PaO₂, arterial O₂-partial pressure;
 FiO₂, inspiratory O₂-concentration)].

Platelets Platelets < 80 000 μL⁻¹ or decrease
 ≥ 50% in 3 days.

Metabolic Acidosis Blood-pH ≤ 7.30 or base excess
 ≥ 5 mmol L⁻¹; plasma-lactate
 ≥ 1.5 fold of normal.

Encephalopathy Somnolence, agitation, confusion, coma.

Following these criteria the sepsis syndrome is classified into 3 levels:

Sepsis: Criteria I + ≥ 2 criteria II.

Associated lethality: 2 criteria II – 7%; 3 criteria II – 10%; 4 criteria II – 17%.

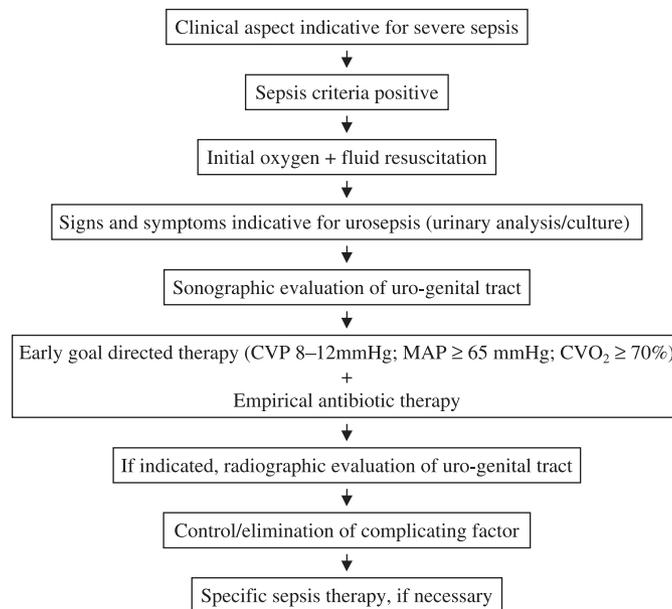
Severe sepsis: Criteria I + ≥ 2 criteria II + ≥ 1 criteria III.

Associated lethality: For each affected organ: + 15 – 20%.

Septic shock: Criteria I + ≥ 2 criteria II + refractory arterial hypotension ≤ 90 mm Hg.

Associated lethality: 50–80%.

For therapeutic purposes, the diagnostic criteria of sepsis should identify patients at an early stage of the syndrome, prompting



CVP – central venous pressure
MAP – mean arterial pressure
CVO₂ – central venous oxygenation

Figure 1 Algorithm for early goal directed management of urosepsis.

urologists and intensive care specialists to search for, and treat, infection, apply appropriate therapy and monitor for organ failure and other complications. In the case of urosepsis the clinical evidence of UTI is based upon symptoms, physical examination, sonographic and radiological features and laboratory data, such as bacteriuria and leucocyturia.

Diagnosis and management of urosepsis

A rapid diagnosis is critical to meet the requirements of early goal directed therapy [16]. A diagnosis and management algorithm is therefore helpful (Fig. 1):

Initial management

The initial patient aspect is often directive. The clinical picture of a septic patient frequently, but not always, involves warm skin, bounding pulses and hyperdynamic circulation. If the patient is hypovolaemic, has pre-existing myocardial dysfunction, or is at late stage of the septic process, hypotension, vasoconstriction and peripheral cyanosis may be present. The doctor seeing the patient at admission should rapidly check the criteria for diagnosis of sepsis, in order to initiate further investigations. If sepsis is suspected, early (immediate) goal-directed therapy has been shown to reduce mortality [16,17].

The following goals should be met:

- Fluid expansion to achieve 8–12 mmHg central venous pressure and ≥ 65 and ≤ 90 mmHg mean blood pressure.
- If the mean blood pressure ≥ 65 mmHg cannot be met, vasoactive substances should be administered.
- Oxygen delivery to achieve a central venous oxygenation of $\geq 70\%$.
- If the central venous oxygenation $\geq 70\%$ cannot be met, erythrocytes should be transfused to achieve a haematocrit $\geq 30\%$.

Following this, additional symptoms pointing to the uro-genital tract should be examined: Flank pain, costovertebral tenderness, renal colic, pain on micturition, urinary retention, prostatic or scrotal pain. A digital-rectal examination of the prostate is therefore mandatory to rule out acute prostatitis. Urinary analysis as well as urine and blood cultures must be included in the first routine laboratory tests.

Antimicrobial therapy

Immediately after microbiological sampling of urine and blood, empirical broad spectrum antibiotic therapy should be started parenterally. An adequate initial (e.g. in the first hour) antibiotic therapy ensures improved outcome in septic shock [18,19]. Administration of an effective antimicrobial within the first hour of documented hypotension was associated with a survival rate of 80% in a retrospective cohort study [20]. Each hour of delay in antimicrobial administration over the ensuing 6 h was associated with an average decrease in survival of 8% [20]. Inappropriate antimicrobial therapy in severe UTI is linked to a higher mortality rate [21] as it has been shown with other infections as well [22,23]. Empirical antibiotic therapy therefore needs to follow certain rules [24], which are based upon the expected bacterial spectrum, the institutional specific resistance rates and the individual patient's requirements.

The bacterial spectrum in urosepsis may consist of 50% *E. coli*, 15% *Proteus* spp., 15% *Enterobacter* and *Klebsiella* spp., 5% *P. aeruginosa* and 15% Gram-positive organisms, according to different surveillance studies [25]. *Candida* spp. and *Pseudomonas* spp. occur as causative agents in urosepsis mainly if the host defence is impaired [26]. Viruses are not common causes of urosepsis. For patients with community acquired primary urosepsis *E. coli* and other Enterobacteriaceae can be expected to be the predominant pathogens. Depending on the local susceptibility patterns a third generation cephalosporin, piperacillin in combination with a β -lactamase inhibitor (BLI), or a fluoroquinolone, e.g. ciprofloxacin or levofloxacin, may be appropriate. Except in areas with a high (> 10%) rate of Enterobacteriaceae with extended spectrum β -lactamases (ESBL) or high (> 10%) rate of fluoroquinolone resistant *E. coli*, a combination therapy with an aminoglycoside or a carbapenem is necessary for initial empirical therapy. In the case of no, or partial,

response in secondary urosepsis, i.e. after nosocomial UTI (especially after urological interventions or in patients with long-term indwelling urinary catheters), an antipseudomonal 3rd generation cephalosporin or piperacillin/BLI in combination with an aminoglycoside, or a carbapenem may be necessary to cover a broader bacterial spectrum, including multi resistant pathogens. If the pre-treatment history is known, the same group of antimicrobials should be avoided. All alternatives have to be selected in consideration of the local susceptibility patterns.

Correct dosing in respect of the altered systemic, and especially renal, pathophysiology in patients with urosepsis and length of therapy are equally important. Sepsis and the treatment thereof result in higher clearances of antibacterial drugs [27]. The increased volume of distribution as a result of oedema in sepsis will lead to underexposure, especially of hydrophilic antimicrobials such as β -lactams and aminoglycosides, which exhibit a volume of distribution mainly restricted to the extracellular space [28]. Sepsis may cause multiple organ dysfunction such as hepatic or renal dysfunction, resulting in decreased clearance of antibacterial drugs. Increased dosing is therefore necessary. As β -lactams are time-dependent antibacterials the best administration would be by continuous infusion. Fluoroquinolones, on the other hand, display largely concentration dependent activity. The volume of distribution of fluoroquinolones in sepsis is not much influenced by fluid shifts and therefore no alterations of standard doses are necessary, unless renal dysfunction occurs [27].

Biofilm infection plays a considerable role in urosepsis, in association with urinary catheters, scar tissue, stones, prostatitis and in any obstructed urinary tract [29–32]. The minimal inhibitory concentrations (MIC) in biofilm are increased several 10 to 100-fold, therefore generally high dosages of antimicrobials need to be applied in conjunction with the attempt to eliminate the biofilm and the biofilm causing complicating factor [33].

Advanced management

If urosepsis is the putative diagnosis, sonographic examination of the urogenital organs should be followed, including sonographic examination of the prostate to rule out prostatic abscess. Further radiographic investigations (e.g. CT-scan) of the urinary tract are now generally applied to specify the complicating factor. Computed tomography compared with sonography is nowadays almost generally available and offers the possibility to quickly detect urolithiasis, and especially renal abscesses as a source of urosepsis with a high sensitivity [34]. If a complicating factor warranting treatment is identified, control and/or removal of the complicating factor should follow immediately. This procedure is frequently performed in two stages: Low level invasive treatment for control of the complicating factor (e.g. emergency drainage) and thereafter definitive elimination of the complicating factor.

Clinically there seems to be no significant difference between ureteral stent and percutaneous nephrostomy for the control of ureteral calculi [35,36]. In parallel with the urological control of the septic focus, further intensive medical treatment encompassing adjunctive sepsis therapy such as cardio-vascular support, mechanical ventilation, organ substitution, or management of endocrine insufficiency should be instigated [37,38].

Conclusion

Urosepsis remains a severe situation with a mortality rate as high as 20–40%. Early recognition of the symptoms initiating rapid management of urosepsis may decrease the mortality. A comprehensive organisational structure involving urologists, intensive care specialists, radiologists, microbiologists and clinical pharmacologists, working tightly together is essential. The prevention of urosepsis is best dependent on good practice regarding an effective and rapid management process of patients at risk.

Conflict of interest

The authors have declared that they have no conflicts of interest.

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