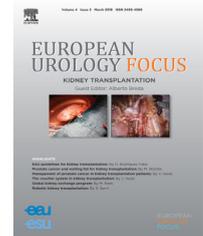


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Guidelines

CME article

## Management of Urosepsis in 2018

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### Abstract

Despite optimal treatment, urosepsis has still high morbidity and mortality rates. An updated definition and classification system for sepsis have recently been introduced. Management of urosepsis comprises four major aspects: (1) early diagnosis, (2) early empiric intravenous antimicrobial treatment, (3) identification and control of complicating factors, and (4) specific sepsis therapy. The quick sequential organ failure assessment is replacing the systemic inflammatory response syndrome scoring for rapid identification of patients with urosepsis.

**Patient summary:** Urosepsis is a serious, life-threatening complication of infections originating from the urinary tract. As urosepsis has a very high mortality rate, it is important that it is quickly spotted and that appropriate treatment is swiftly begun. Imaging of urinary tract disorders has been shown to be useful in decreasing mortality from urosepsis, and in the future microbiology techniques may also prove useful. Given the severity of urosepsis and the associated risks, large efforts need to be made to prevent high-risk infections in hospitals with appropriate prevention measures, such as the early removal of catheters used whenever possible.

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### 1. Introduction

Urosepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection originating from the urinary tract and/or male genital organs. From the perspective of both patients and urologists, the best (uro)sepsis is undoubtedly the sepsis that can be prevented. In this context it has to be highlighted that prevention measures are of

upmost importance. For example, careful choice of prophylaxis and treatment antimicrobials is crucial to avoid selection of resistant strains. Similarly, shorter hospital stays before surgery will help to decrease the risk of nosocomial infections. In addition, early removal of indwelling urethral catheters helps in decreasing the rate of nosocomial infections and thus reduces nosocomial urosepsis. Finally, attention to simple everyday techniques to assure asepsis, including routine

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use of protective disposable gloves, frequent hand disinfection, and application of infectious disease control measures can prevent cross-infections [1].

### 1.1. Sepsis-3 definitions

The previous iteration of sepsis definitions (Sepsis-2) dates back to 2001. Apart from an additional list of signs and symptoms possibly indicating sepsis, the original sepsis definition (the Bone criteria, Sepsis-1) dating from 1991 remained practically unchanged. This original concept of sepsis was based on a model consisting of four phases in a continuum. The first phase is an infection that can progress into the second phase called sepsis (combining infection with at least two of the four systemic inflammatory response syndrome [SIRS] criteria [2]) that can deteriorate towards severe sepsis (organ dysfunction) and ultimately to septic shock. The new definition states that sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. An important aim of this change was to differentiate sepsis (“bad infection”) from uncomplicated infection. Three new aspects are thus added to the previous definition. First, sepsis is life-threatening, implying a need for prompt recognition and intervention. Second, there is a dysregulated host response, which underlines the importance of both pro- and anti-inflammatory and other processes. Third, sepsis is more severe than an uncomplicated infection, meaning that organ dysfunction needs to be present. The new *sepsis* (infection with organ dysfunction) definition thus makes the old *severe sepsis* term redundant.

### 1.2. Epidemiology

Urosepsis accounts for up to 20–30% of sepsis cases and can potentially lead to septic shock, a more severe illness than sepsis alone and associated with high morbidity and mortality [2]. It is crucial to recognize urosepsis rapidly and to provide timely effective treatment, as delayed treatment results in a 7.6% increase in mortality after the onset of hypotension [3]. Sepsis and urosepsis are not uncommon. Overall, it is estimated that sepsis represents 31.5 million cases per year, with fatal outcome for 5.3 million of those cases. Furthermore, approximately 20% of sepsis survivors will have cognitive or physical disabilities. Among all sepsis cases, an estimated 9–31% are urosepsis, representing 2.8–9.8 million cases and up to 1.6 million deaths [4]. As a result, sepsis and urosepsis have become a priority for many hospitals and are recognized by the World Health Organization as a serious problem.

## 2. Pathogenesis

The complex pathogenesis of urosepsis starts when uropathogens or their products stimulate the host innate immune system.

### 2.1. Host response to pathogen invasion

Stimulation of the host immune system involves pattern recognition receptors such as toll-like receptors (eg, TLR-4

and damage-associated molecular pattern receptors and results in the secretion of large amounts of pro-inflammatory cytokines (eg, IL-1 and IL-6). The initial pro-inflammatory phase is followed by a counter-regulatory anti-inflammatory response, leading to an immunosuppressive state. In urosepsis, as in other types of sepsis, the host response determines the severity and clearly influences the outcome [5].

### 2.2. Pathogens

In urosepsis, as opposed to other type of sepsis, the most commonly isolated pathogen is *Escherichia coli*, followed by other Enterobacteriaceae. In contrast to pulmonary or abdominal sepsis, most cases of urosepsis are caused by a single microorganism. At present, extended-spectrum  $\beta$ -lactamase (ESBL) Enterobacteriaceae (including *E. coli*) pose a serious threat to patients. Such bacteria (multiple drug-resistant Enterobacteriaceae) can account for up to 45% of all Enterobacteriaceae [6]. In such cases, initial empiric therapy is often inappropriate. It is therefore crucial to rapidly isolate the microbial pathogen, as an appropriate definitive treatment significantly improves the chances of survival in cases of ESBL infection [7].

## 3. Recognizing urosepsis

### 3.1. Clinical recognition using sequential organ failure assessment

Patients with sepsis may show many different clinical symptoms and signs. The task force evaluated those that best identify organ dysfunction. The electronic health care records for 1.3 million patients in the 12 hospitals of the University of Pittsburgh Medical Center conglomerate was used as the discovery database. To characterize the possibility of sepsis, three different scores were evaluated: the systemic inflammatory response syndrome (SIRS) criteria, the logistic organ dysfunction system (LODS) score, and the sepsis-related organ failure assessment (SOFA) score (Table 1). Importantly, the SIRS and SOFA scores offer comparable discriminative value for non-intensive care unit (ICU) patients. However, for ICU patients, SOFA and LODS were superior to SIRS. A SOFA score  $\geq 2$  was associated with a 10% risk of hospital mortality among patients with suspected infection; these patients had a two- to 25-fold higher risk of dying compared with patients with a SOFA score of  $< 2$ .

### 3.2. Quick SOFA score (qSOFA)

The qSOFA consists of three variables: abnormal mentation (ie, new-onset agitation, altered mentation with Glasgow Coma Scale score  $\leq 14$ , drowsiness, confusion, or coma), respiratory rate ( $\geq 22$  breaths/min), and systolic blood pressure ( $\leq 100$  mm Hg). When two of the three variables were present in a ward or emergency department patient, this equated to a risk of dying of approximately 8%, whereas

**Table 1 – Comparison of sepsis assessment instruments.**

qSOFA	SOFA	SIRS and sepsis
Altered mental status (1 point) (Glasgow Coma Scale <15)	PaO <sub>2</sub> (1 point)	Temperature >38 °C or <36 °C
Respiratory rate ≥22 breaths/min (1 point)	FiO <sub>2</sub> (1 point)	Heart rate >90 beats/min
SBP ≤100 mm Hg (1 point)	Platelet count (1 point)	Respiratory rate >20 breaths/min (or PaCO <sub>2</sub> <32 mm Hg)
	Glasgow Coma Scale (1 point)	WBCs <sup>a</sup> >12 000/mm <sup>3</sup> or <4000/mm <sup>3</sup>
	Bilirubin (1 point)	<b>Sepsis criteria</b> SIRS + source of infection <sup>b</sup>
	Level of hypotension (1–4 points)	<b>Severe sepsis criteria</b> Lactic acidosis, SBP <90 mm Hg (or SBP drop ≥40 mm Hg)
	Creatinine (1–4 points)	<b>Septic shock criteria</b> Severe sepsis with hypotension despite adequate fluid resuscitation

SOFA = sepsis-related organ failure assessment; qSOFA = quick SOFA; SIRS = systemic inflammatory response syndrome; SBP = systolic blood pressure; PaO<sub>2</sub> = partial pressure of oxygen in blood; FiO<sub>2</sub> = fraction of inspired oxygen; WBC = white blood cell.

<sup>a</sup> There is bedside WBC assay that has been shown to be accurate. Therefore, the SIRS score (at least for the first steps) can be determined at the bedside.

<sup>b</sup> Confirmed or suspected.

having all three equated to a mortality risk in excess of 20%. Still recent studies point that if the qSOFA alone is a good indicator of mortality, the previously used SIRS score remains a better indicator of sepsis [8].

### 3.3. Blood sampling and cultures

For pathogen isolation, urine and blood cultures are required. Additional culture of drainage fluid (if any) should be performed. However, treatment should be initiated as early as possible and no later than 1 h after a clinical assumption of urosepsis. Early empiric antimicrobial treatment should be directed against all likely causative uropathogens and should take into account the local drug susceptibility patterns.

### 3.4. Imaging

A recent study investigating the role of imaging in urosepsis revealed that a large proportion of patients with bacteremia with a urinary tract focus had major abnormalities detected on imaging of the urinary tract. The proportion of cases with a major or minor abnormality reached up 32% [9]. Therefore, imaging investigations such as sonography and computed tomography scans should be performed early.

## 4. Management

### 4.1. Early empiric antimicrobial treatment

Initial empiric antimicrobial therapy should provide broad antimicrobial coverage against all likely causative pathogens and should be adapted on the basis of culture results, once available (Table 2). The dosage of the antimicrobial agent is of paramount importance in patients with sepsis syndrome and should generally be high, with appropriate adjustment for renal function. Antimicrobials must be administered no later than 1 h after a clinical assumption of sepsis. With respect to local drug susceptibility patterns, a 2016 study emphasized that “It is not appropriate to use the pathogen spectrum and

resistance of other clinical diagnosis of HAUTIs [hospital-acquired urinary tract infections] as representative of urosepsis. In addition, the geographical variability of resistance rates makes it essential to have local surveillance reports on urosepsis separate from other HAUTIs in determining the appropriate empirical treatment”. Finally, urologists should keep in mind that patient characteristics such as previous urological interventions, previous urinary tract infection, hospitalization associated with previous antimicrobial administration, and the presence of a urinary catheter are often associated with a higher risk of encountering a resistant uropathogen [6]. A point that is rarely discussed in the management of urosepsis is the release of endotoxins during antimicrobial therapy. In vitro the use of some antimicrobials promotes a much stronger release of endotoxins than others. In addition, animal and human studies have shown that antimicrobials binding to PBP-2 such as imipenem, for example, promote little endotoxin release. On the contrary, antibiotics that bind to PBP-3 (eg, ceftazidime) are associated with greater endotoxin release. However, clinical studies to date in patients with Gram-negative urosepsis have shown no difference between ceftazidime and imipenem with regard to plasma endotoxin levels. Nevertheless, it should be kept in

**Table 2 – Possible antimicrobials to consider for the treatment of urosepsis.**

Antimicrobial	Dose	Duration
Cefotaxime	2 g three times daily	7–10 d <sup>a</sup>
Ceftazidime	1–2 g three times daily	7–10 d <sup>a</sup>
Ceftriaxone	1–2 g every day	7–10 d <sup>a</sup>
Cefepime	2 g twice daily	7–10 d <sup>a</sup>
Piperacillin/tazobactam	4.5 g three times daily	7–10 d <sup>a</sup>
Ceftolozane/tazobactam	1.5 g three times daily	7–10 d <sup>a</sup>
Ceftazidime/avibactam	2.5 g three times daily	7–10 d <sup>a</sup>
Gentamicin <sup>b</sup>	5 g every day	7–10 d <sup>a</sup>
Amikacin <sup>b</sup>	15 g every day	7–10 d <sup>a</sup>
Ertapenem	1 g every day	7–10 d <sup>a</sup>
Imipenem/cilastatin	0.5 g three times daily	7–10 d <sup>a</sup>
Meropenem	1 g three times daily	7–10 d <sup>a</sup>

<sup>a</sup> Treatment can be extended in the case of slow improvement.

<sup>b</sup> Not studied as monotherapy in urosepsis.

mind that a great variety of endotoxins exist, and many studies only consider lipopolysaccharides. Furthermore, many studies focus on indirect evidence of endotoxin presence (ie, cytokine levels) and very few measurements are available for detecting endotoxins (LPS and other endotoxin types) in critically ill patients [10].

#### 4.2. Source control

In many cases urosepsis is linked to complicating factors (eg obstruction, abscesses, foreign bodies, stones) in the urinary tract. Drainage of obstruction and abscesses and removal of foreign bodies is the most important strategy for source control and must be performed immediately [1].

#### 4.3. Adjunctive measures

A number of additional support measures have been recommended for the optimal care of patients with urosepsis. The following list includes the most important measures recommended by the European Association of Urology guideline on urological infections [1] and general sepsis recommendations from previous studies and guidelines [2,11].

- Fluid therapy with crystalloids should be administered to increase blood pressure. However, fluid therapy with albumin can be considered if crystalloids do not result in a sufficient increase in blood pressure. During fluid therapy, vasopressors such as norepinephrine should be used primarily, or dobutamine in myocardial dysfunction; hydrocortisone should be given only if fluid and vasopressors do not achieve a mean arterial pressure of  $\geq 65$  mm Hg.
- Blood products should be given to target a hemoglobin level of 7–9 g/dl.
- Mechanical ventilation should be applied with a tidal volume of 6 ml/kg, a plateau pressure of  $\leq 30$  cm H<sub>2</sub>O, and a high positive end-expiratory pressure.
- Sedation should be minimal and neuromuscular blocking agents should be avoided.
- Glucose levels should be targeted at  $\leq 180$  mg/dl.
- Measures to prevent deep vein thrombosis should be applied. Low-molecular weight heparin administered subcutaneously is recommended.
- Stress ulcer prophylaxis should be applied in patients at risk, using proton pump inhibitors.
- Enteral nutrition should be started early (<48 h).

## 5. Conclusions

Urosepsis should still be considered as a serious threat with a high mortality rate. The first step in optimal management of urosepsis is to recognize the urosepsis, determine its severity, and monitor its evolution. For this purpose, the SOFA and qSOFA scores in particular are helpful in identifying patients with a higher risk of hospital mortality. Rapid initiation of appropriate antimicrobial therapy is a key feature in decreasing the risk of mortality. Although rapid point-of-care microbiology techniques are not yet considered a gold

standard, they might be helpful in the near future [12]. Similarly, it has been demonstrated that early detection of urinary tract disorders (obstruction or urolithiasis) via imaging or other techniques further decreases the risk of mortality. Treatment (temporary or permanent if possible) of such disorders using minimally or less invasive techniques is recommended. Finally, appropriate side measures such as fluid therapy and mechanical ventilation should be applied when needed. However, considering the severity of urosepsis and its associated risks and acknowledging the fact that all urosepsis cannot be avoided, a large effort should be made towards better prevention of such high-risk infections in hospitals. We certainly encourage all urologist to support appropriate prevention measures, such as early removal of catheters when possible.

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**Study concept and design:** Bonkat, Cai, Veeratterapillay, Bruyère, Bartoletti, Pilatz, Köves, Geerlings, Pradere, Pickard, Wagenlehner.

**Acquisition of data:** Köves, Cai, Veeratterapillay.

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**Drafting of the manuscript:** Bonkat, Cai.

**Critical revision of the manuscript for important intellectual content:** Bonkat, Cai, Veeratterapillay, Bruyère, Bartoletti, Pilatz, Köves, Geerlings, Pradere, Pickard, Wagenlehner.

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