CONTINUING MEDICAL EDUCATION

Urosepsis—Etiology, Diagnosis, and Treatment

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SUMMARY

Background: Sepsis is among the most common causes of death in Germany. Urosepsis accounts for 9–31% of all cases and has a mortality of 20–40%, which is low compared with that of sepsis in general. As the population ages, the incidence of urosepsis is likely to rise.

Methods: Review of pertinent articles and guidelines retrieved by a selective search in PubMed.

Results: Enterobacteria and Gram-positive organisms are the pathogens that most commonly cause urosepsis. The diagnosis can and must be made early on the basis of the typical clinical features, altered vital signs, and laboratory abnormalities, so that timely treatment can be initiated. 80% of cases are due to obstructive uropathy. The diagnostic evaluation includes physical examination, blood cultures, urinalysis, procalcitonin measurement, and ultrasonography. In one study, each additional hour of delay in the treatment of urosepsis with antibiotics was found to lower the survival rate by 7.6%. Antibiotics should be chosen in consideration of local resistance patterns and the expected pathogen spectrum.

Conclusion: Urologists, intensive care specialists, and microbiologists should all be involved in the interdisciplinary treatment of urosepsis. Patients' outcomes have improved recently, probably because of the frequent use of minimally invasive treatments to neutralize foci of infection. New biomarkers and new treatments still need to be validated in multicenter trials.

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The sepsis syndrome, a complex inflammatory host response to infection, carries a high mortality and is the main cause of death of patients in non-cardiac intensive care. Nonetheless, early sepsis is often not recognized in everyday clinical practice (1, 2).

Depending on geographical location, 9–31% of all cases of sepsis arise from an infection of the urogenital tract and are therefore designated as urosepsis (3). As the population ages, urological comorbidities (e.g. such as those associated with indwelling bladder catheter use) can be expected to become more common, and the incidence of urosepsis is thus likely to rise.

Learning objectives

This article is intended to inform readers about:

- The definition of urosepsis and the distinctions between sepsis, severe sepsis, and septic shock.
- Risk factors for sepsis and the most common causes of urosepsis.
- The crucial importance of time in the diagnosis and treatment of urosepsis.
- The pathophysiology of the sepsis syndrome.
- The diagnostic evaluation and the cause-directed, supportive, and adjunctive treatment of urosepsis.

Methods

This review is based on pertinent articles published up to August 2015 that were retrieved by a selective search in PubMed, as well as on the following guidelines:

- The guideline of the Surviving Sepsis Campaign (SSC) [January 2013] (4)
- The guideline of the European Association of Urology [March 2015] (5)

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The sepsis syndrome

Sepsis is the main cause of death of patients in non-cardiac intensive care.

BOX

Diagnostic criteria for sepsis, severe sepsis, and septic shock, according to the German Sepsis Society (*Deutsche Sepsis-Gesellschaft*) (2)

I. Demonstration of infection

Diagnosis of an infection by microbiological demonstration or clinical criteria

II. Systemic inflammatory response syndrome (SIRS) (at least 2 criteria) (6)

Body temperature: $\geq 38^{\circ}\text{C}$ or $\leq 36^{\circ}\text{C}$

Tachycardia: $\geq 90/\text{min}$

Tachypnea: $\geq 20/\text{min}$

Respiratory alkalosis: $p_a\text{CO}_2 \leq 32 \text{ mm Hg}$ ($< 4.3 \text{ kPa}$)

Leukocyte count: leukocytosis $\geq 12/\text{nL}$ or leukopenia $\leq 4/\text{nL}$ or band

forms $\geq 10\%$ (= left shift, i.e., increased percentage of immature neutrophilic granulocytes and granulocyte precursors)

III. Acute organ dysfunction (at least 1 criterion)

Acute encephalopathy: decreased wakefulness, disorientation, agitation, delirium

Relative or absolute thrombocytopenia: decline by $>30\%$ in 24 h or $\leq 100/\text{nL}$

Arterial hypoxemia: $p_a\text{O}_2 \leq 75 \text{ mm Hg}$ ($\leq 10 \text{ kPa}$) on room air or $p_a\text{O}_2/\text{F}_i\text{O}_2 \leq 250 \text{ mm Hg}$ ($\leq 33 \text{ kPa}$)

Renal dysfunction: urine output $\leq 0.5 \text{ mL/kg/h}$ for at least 2 hours despite fluid administration, and/or rise of the serum creatinine level $> 2 \times$ upper limit of normal

Metabolic acidosis: base excess $\leq 5 \text{ mmol/L}$ or lactate $> 1.5 \times$ upper limit of normal*

Sepsis: criteria I and II

Severe sepsis: criteria I, II, and III

Septic shock: criteria I and II and SBP $\leq 90 \text{ mm Hg}$ for at least 1 h or

MAP $\leq 65 \text{ mm Hg}$ or need for vasopressors to keep SBP $>90 \text{ mm Hg}$ or

MAP $>65 \text{ mm Hg}$. Hypotension is present despite fluid administration and is not explicable by other causes.

*Elevated lactate levels due to inadequate perfusion can arise even if the blood pressure is within normal limits (cryptic shock); falling lactate levels seem to be at least as good an indicator for successful treatment as the central venous oxygen saturation (S_{cvO_2}) (e39).

DSG, German Sepsis Society (*Deutsche Sepsis-Gesellschaft*); MAP, mean arterial blood pressure

- The S2k-guideline of the German Sepsis Society (*Deutsche Sepsis-Gesellschaft*, DSG) and the German Interdisciplinary Association for Intensive Care and Emergency Medicine (*Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin*, DIVI) [February 2010] (2), as amended up to November 2011. This guideline is now being updated.

The evidence levels and recommendation grades reported here are in accordance with the definitions of the Oxford Centre of Evidence Based Medicine.

Definition

The DSG and the DIVI define sepsis as a complex inflammatory host response to infection (the host response itself is called the “systemic inflammatory response syndrome” [SIRS]; see *Box*). This definition is in accordance with those of analogous societies in other countries (*eBox 1*) (2, 6) (recommendation grade E, evidence level V).

If an infection has been demonstrated or is clinically suspected, and the SIRS criteria (*Box*) are met, then

Definition

Sepsis is defined as a complex inflammatory host response to infection.

Severe sepsis

If, in the setting of sepsis, at least one organ fails (multi-organ dysfunction syndrome [MODS]), then severe sepsis is present (severe sepsis = infection + SIRS + organ dysfunction).

FIGURE 1

The pathophysiology of urosepsis

Infection or trauma leads to the release of pathogens and pathogen products (pathogen-associated molecular patterns, PAMPs) and/or intrinsic signaling molecules of the body (danger-associated molecular patterns, DAMPs) that are recognized by receptors on various cells (including the complement system, endothelium, adipose tissue), so-called pattern recognition receptors (PRRs). The latter can modulate the immune response through a variety of pro- and anti-inflammatory mediators and biomarkers.

aPTT, activated partial thromboplastin time; CRP, C-reactive protein; DIC, disseminated intravascular coagulation; HMGB-1, high mobility group protein B1; LPS, lipopolysaccharide (component of Gram-negative bacterial membranes; PCT, procalcitonin.

Modified from Reinhart et al. (e43) with the kind permission of Prof. Dr. med. K. Reinhart, Department of Anesthesiology and Intensive Care Medicine, Universitätsklinik Jena, and ASM Journals

Elements of the inflammatory response

- Precipitating factors
- Recognizing sensors
- Inflammatory mediators
- The targets of these mediators

Pathophysiology

Infection or trauma leads to the release of pathogens and pathogen products that serve as PAMPs (pathogen-associated molecular patterns), and/or intrinsic signaling molecules of the body, called DAMPs (danger-associated molecular patterns).

Figure 2: Eliminating the focus of infection in obstructive pyelonephritis
a) A correctly placed double-J ureteric stent to treat obstruction due to distal ureterolithiasis. The residual contrast medium in the renal pelvis and calyx already reveals markedly reduced ectasia
b) A correctly placed nephrostomy catheter with a contrast void representing at the site of the blocking balloon (arrow) in a patient with obstruction by locally advanced prostate cancer

sepsis is present (sepsis = infection + SIRS) (2, e1).

If, in the setting of sepsis, at least one organ fails (“multi-organ dysfunction syndrome,” [MODS]), then severe sepsis is present (severe sepsis = infection + SIRS + organ dysfunction) (Box) (2, e1). In particular, acute renal failure is defined by international consensus as acute oliguria (<0.5 mL/kg/h or 45 mmol/L for ≥ 2 h) and a rise of the serum creatinine level by at least 0.5 mg/dL (e2).

Septic shock is defined as sepsis with treatment-resistant hypotension or hypoperfusion despite adequate fluid administration, resulting in the need for vasopressor drugs (Box) (2, e1).

The SIRS criteria were newly defined in an international consensus conference in 2003. The general, inflammatory, and hemodynamic variables incorporated in these criteria indicate early organ dysfunction and are interpreted as warning signs (eBox 1) (7). There is no minimum requirement for the number of criteria that must be met for SIRS to be diagnosed.

Prevalence

Despite increasing incidence, the mortality due to sepsis has markedly declined, partly because of the introduction of guidelines.

Epidemiology

In 2003, a prospective cross-sectional study entitled PRÄVALENZ carried out by the Sepsis Competence Network (SepNet) yielded the first set of specific epidemiologic data on sepsis in Germany (8). The one-day prevalence of sepsis in 310 hospitals and 454 intensive care units was assessed. 1348 of 3877 patients (34.8%) had an infection, and 30.8% of these had severe sepsis or septic shock. The related prevalence figures were, for sepsis, 85–116/100 000 persons, and, for severe sepsis or septic shock, 76–110/100 000 persons; the mean age of the affected persons was 67 years. The mortality of severe sepsis varied depending on the origin of the infection (9); it was 55.2% overall (8).

The prognosis of urosepsis is more favorable, with reported mortality rates of 20–40% for severe urosepsis (5, 10). In general, sepsis is more common in men than in women (9).

Even though the incidence of sepsis is increasing (for example, from 82.7 to 240.4 cases per 100 000 persons per year in the USA over the period 1979–2000, corresponding to an average annual increase of 8.7%), the mortality due to sepsis has markedly declined (9), partly because of the introduction of guidelines (4, 11). According to Martin et al., the mortality of sepsis dropped from 27.6% in 1994 to 17.9% in 2000 (9).

Economic aspects

Sepsis carries high treatment costs (e3). The estimated total cost of treatment in intensive care in Germany is €1.77 billion per year, and the estimated direct treatment cost of all septic diseases is €5 billion per year (12, e4). Moerer et al. estimated the average cost of treating sepsis at €25 695 per patient (€1454 per day) (13).

The indirect cost of sepsis in Germany, resulting from work absences, rehabilitation, and early retirement, is estimated at €2.5–3.5 billion per year (e5).

Pathogenesis and pathophysiology

Urosepsis is a consequence of urinary tract infection. Enterobacteria are the most common pathogens:

- *E. coli* (52%)
- *Proteus spp.*
- *Enterobacter spp.*
- *Klebsiella spp.*
- *P. aeruginosa*
- and Gram-positive bacteria, such as enterococci (5%) (e6).

Common pathogens

E. coli, *Proteus spp.*, *Enterobacter spp.*, *Klebsiella spp.*, *P. aeruginosa*, and Gram-positive bacteria such as enterococci.

FIGURE 3

Diagnostic and therapeutic algorithm for urosepsis

ICU, intensive care unit. Modified from Grabe et al., Guidelines on urological infections. In: EAU-Guidelines 2015 (5)

Patients at risk of sepsis are more likely to develop bacteremia as a consequence of a urinary tract infection (eBox 2). Obstructive uropathy causes 78% of cases of urosepsis (e7). In one study involving 205 cases of urosepsis, 43% were due to urolithiasis, 25% to prostatic adenoma, 18% to urologic cancers, and 14% to other urologic diseases (e8).

The course and severity of sepsis depend both on the pathogenicity of the organism and on the nature and extent of the patient's immune response (Figure 1) (e9).

When an infection is present, bacteria or

components of the bacterial cell wall act as pathogen-associated molecular patterns (PAMP) that bind to pattern-recognition receptors (PRR) on the surface of macrophages, neutrophils, and endothelial or urothelial cells (Figure 1) (10, e10). The transcription factor NF- κ B mediates the production of pro-inflammatory cytokines such as IL-6, IL-12, and TNF α (e11–e14). The production of further mediators (chemokines, prostaglandins, thromboxans, and leukotrienes) adds to the “mediator storm” (e6). High-mobility group protein B1 (HMGB-1), which is released during cell death as a

The role of bacteria

In infection, bacteria or bacterial cell wall components act as pathogen-associated molecular patterns (PAMP) that bind to pattern-recognition receptors (PRR) on the surface of macrophages, neutrophils, and endothelial or urothelial cells.

Effects on the immune system

Infection activates the complement system and the native immune system, leading to a massive initial pro-inflammatory response.

Figure 4: Ultrasonographic findings in urosepsis

- a) Widening of the renal pelvis and calyx with tubular dilatation of the ureter due to distal ureterolithiasis (not shown).
- b) Inhomogeneous renal parenchyma at the upper pole (arrow) due to abscess formation

danger-associated molecular pattern (DAMP) or produced by macrophages in the late stage of sepsis, also binds to PRR (14). Wagenlehner et al. propose that the higher survival rate of urosepsis compared to sepsis from other causes may be due, in part, to the lesser degree of tissue damage associated with urologic surgical procedures to eliminate infectious foci. Helpful minimally invasive procedures include the internal stenting of ureteral stenoses (*Figure 2a*) and percutaneous nephrostomy (*Figure 2b*) (e15).

Effects on the immune system

Infection activates the complement system and the native immune system (*Figure 1*), leading to a massive initial pro-inflammatory response. Hematopoietic growth factors stimulate the generation of neutrophilic granulocytes, which release bactericidal substances such as proteases and oxygen radicals. Lymphocytes, too, are stimulated to produce antibodies and to mount a cell-mediated immune response. Endothelial cells are induced to make nitric oxide (NO), which, in turn, lowers vascular tone, causing hypotension. Damaged endothelium is abnormally permeable, and edema ensues (10, 14). This initial phase is followed by an opposing anti-inflammatory (immune-suppressive) phase that is responsible for the high mortality of sepsis in its later course. Macrophages and neutrophils may succumb to immune paralysis, and lymphocytes and dendritic cells display high rates of apoptosis (15).

Effects on hemostasis

The over-activated complement system is closely linked to the clotting system. Surface receptors on endothelial cells and neutrophils are up-regulated, causing increased mutual adhesiveness. Moreover, the clotting system is activated by endothelially synthesized plasminogen-activator inhibitor; this predisposes to thrombosis and to disseminated intravascular coagulation (DIC). A low antithrombin III level, Quick value, and platelet count may be the first signs of DIC. At the same time, anticoagulant substances such as protein C are inhibited, promoting systemic coagulation and leading to microcirculatory insufficiency and tissue hypoxia (4, 10, 14).

These recently elaborated scientific facts are inadequately reflected in the sepsis criteria. Thus, the PIRO (predisposition, infection, response, and organ dysfunction) staging system has been developed. Although the PIRO system has not yet entered into wide clinical use, a study in more than 680 patients has demonstrated its superiority to both the well-established MEDS score and the APACHE-II score with respect to both stratification and prognosis (area under the curve [AUC] = 0.889 for need of treatment in an intensive care unit, 0.817 for organ failure, and 0.744 for 28-day mortality; $p < 0.05$) (e16).

Clinical features and diagnostic evaluation

Rapid diagnosis is essential for early goal-directed therapy (EGDT) (1). In the evaluation of urosepsis, attention must be paid both to the defining criteria for sepsis (*Box 1*)

Predisposition to thrombosis

Surface receptors on endothelial cells and neutrophils are up-regulated, causing increased mutual adhesiveness. Moreover, the clotting system is activated by endothelially synthesized plasminogen-activator inhibitor.

The PIRO staging system

PIRO stands for “predisposition, infection, response, and organ dysfunction.”

(recommendation grade C, evidence level V) and to the symptoms and signs pointing to the underlying cause of the infection: flank pain and tenderness (perhaps with radiation), dysuria/pollakisuria, urinary retention, and scrotal and/or prostatic pain. In men, the physical examination must include a digital rectal examination (tenderness indicates prostatitis, a fluctuating mass indicates a prostate abscess) and palpation of the testes (tenderness, warmth, and swelling indicate epididymorchitis). The presence of an indwelling catheter should be noted as a possible cause of infection. The diagnostic and therapeutic algorithm recommended by the European Association of Urology (EAU) is shown in *Figure 3*.

Blood cultures

Empirical antibiotic treatment should be begun only after blood cultures have been drawn (at least 2–3 pairs), preferably by aseptic peripheral venous puncture (recommendation grade C, evidence level IIb). Only about 30% of blood cultures in patients with suspected urosepsis are positive (e17). The culture bottles should be filled to the greatest extent possible, as the rate of positivity also depends on the volume of blood in the bottle (3% more false-negative findings for each ml of decreasing volume [e18]).

Urine testing

Urinalysis and urine culture must be performed in all patients with urosepsis before antibiotic treatment is begun (recommendation grade B, evidence level Ic). The findings of midstream urine culture are of limited utility in obstructive pyelonephritis, because the urine with the highest infectious load is often above the obstruction (sensitivity 30.2%, specificity 73%) (16).

Biomarkers

Urosepsis cannot be diagnosed from biomarkers alone. Among all available inflammatory markers, procalcitonin (PCT) is the best studied, and its use to confirm or rule out severe sepsis is therefore recommended (2). PCT is more reliable than the acute-phase protein CRP (17, 18) and enables the differentiation of bacterial infection from other types of infection (e19). PCT levels below 0.5 ng/mL practically rule out severe sepsis or septic shock; levels above 2 ng/mL make severe sepsis or septic shock highly likely (recommendation grade C, evidence level IIb) (2, 19). In a prospective, multicenter cohort study, the use of a PCT cutoff value of 0.25 ng/mL was found to identify

TABLE 1

Early-goal-directed therapy (EGDT) (1)

Variable	Target
Central venous pressure (CVP)	8–12 mm Hg *
Mean arterial pressure (MAP)	65–90 mm Hg
Central venous oxygen saturation (S_{vO_2})	≥ 70%
Mixed venous oxygen saturation (S_{vO_2})	≥ 65%
Hematocrit (Hct)	>30%
Urine output	>40 mL/h

* CVP >12 mm Hg for intubated patients

bacteremia in patients with febrile urinary-tract infections with 95% sensitivity (95% confidence interval [0.89–0.98]) and 50% specificity (95% confidence interval [0.46–0.55]) (20).

More than one study (ProHOSP, PRORATA) has revealed that the use of PCT-guided causally directed treatment to shorten the duration of antibiotic administration in patients with sepsis (recommendation grade C, evidence level IIb) does not elevate mortality (21, 22). Heyland et al. (2011), in a meta-analysis, confirmed that this strategy lessens antibiotic use but could not definitively rule out an increase in mortality by up to 7% (23). More light will be shed on this issue by the SISPCT study of the SepNet (NCT00832039), which is currently in progress. The purpose of the SISPCT study is to investigate the effect of adjunctive intravenous therapy with sodium selenite, and that of PCT-guided antibiotic treatment, on the survival of patients with severe sepsis and septic shock.

The cytokine IL-6 is also a marker of sepsis; its concentration is elevated in febrile urinary tract infections (e20). Unlike PCT and CRP, however, the measurement of IL-6 (or, indeed, of entire cytokine panels) has not yet been incorporated into clinical standards (e21).

The detection of specific, sepsis-associated μ RNAs and the direct demonstration of specific bacterial DNA by amplification techniques such as PCR may soon become clinically relevant, but further studies are needed (e22).

Urinalysis

Urinalysis and urine culture must be performed in all patients with urosepsis before antibiotic treatment is begun. The findings of midstream urine culture are of limited utility in obstructive pyelonephritis.

Biomarkers

Urosepsis cannot be diagnosed from biomarkers alone. Among all available inflammatory markers, procalcitonin (PCT) is the best studied.

TABLE 2

Cause-directed treatment

Empirical initial parenteral therapy as recommended by the Paul Ehrlich Society for Chemotherapy (Paul-Ehrlich-Gesellschaft für Chemotherapie e. V.)

Common pathogens	Nosocomially acquired	Community-acquired
<i>E. coli</i> * ¹ <i>Proteus mirabilis</i> <i>Pseudomonas</i> spp. <i>Enterobacteriaceae</i>	Fluoroquinolone group 2/3 + cephalosporin group 3a/3b/4 Aminopenicillin / beta- lactamase inhibitor (BLI)* ² Carbapenem group 1	Aminopenicillin/(BLI) Fluoroquinolone group 2/3 Cephalosporin group 3a Carbapenem group 2

Targeted antibiotic therapy for known pathogens as recommended by the Paul Ehrlich Society for Chemotherapy

Pathogen	Monotherapy	Combination therapy
<i>E. coli</i> <i>Klebsiella pneumoniae</i> <i>Proteus mirabilis</i>	Aminopenicillin/BLI Acylaminopenicillin/BLI Cephalosporin group 3a/3b/4 Fluoroquinolone group 2/3 Carbapenem	
ESBL-forming <i>E. coli</i> <i>Klebsiella pneumoniae</i> <i>Proteus mirabilis</i>	Carbapenem	Carbapenem + fosfomycin Carbapenem + tigecycline Colistin + fosfomycin
<i>P. aeruginosa</i>		Cephalosporin group 3b/4 + fluoroquinolone group 2/3 or fosfomycin or aminoglycoside Acylaminopenicillin/BLI + fluoroquinolone group 2/3 or fosfomycin or aminoglycoside Carbapenem group 1 + fluoroquinolone group 2/3 or fosfomycin + aminoglycoside
<i>Citrobacter freundii</i> <i>Enterobacter</i> spp. <i>Serratia marcescens</i>	Carbapenem Cephalosporin group 4 Fluoroquinolone group 2/3	
<i>Acinetobacter baumannii</i>	Carbapenem group 1	Carbapenem group 1 + fluoroquinolone group 2/3 or tigecycline Colistin + tigecycline
<i>Enterococcus faecalis</i>	Aminopenicillin (high-dosed) Acylaminopenicillin (high-dosed)	Aminopenicillin + aminoglycoside Acylaminopenicillin + aminoglycoside In penicillin allergy: glyco- peptide + aminoglycoside
<i>Enterococcus faecium</i>	Glycopeptide Daptomycin Linezolid	Glycopeptide + aminoglyco- side
Vancomycin-resistant en- terococci, usually <i>Enterococcus faecium</i> (VRE)	Linezolid Daptomycin Tigecycline	

*¹Adjust depending on local *E. coli* resistance pattern. + As a result of increasing fluoroquinolone resistance, fluoroquinolones are now inferior to a combination of cephalosporin + BLI (40). In areas with a high rate of ESBL-forming enterobacteria (>10%), carbapenem is recommended for initial treatment (e42).

*²Recommended for catheter-associated infections, which are usually mixed infections with enterococci (because of the "enterococcal gap" of cephalosporins, fluoroquinolones, and aminoglycosides)

Imaging studies

Ultrasonography is the imaging method of first choice because of its rapidity and wide availability (recommendation grade B, evidence level Ic). It enables the rapid detection of, for example, hydronephrosis (Figure 4a), renal abscesses (Figure 4b), and prostatic abscesses. Abscesses should be punctured under ultrasonographic (or other radiological) guidance, and the removed fluid should be studied microbiologically (recommendation grade D, evidence level V) (e23). If it is unclear whether obstructive pyelonephritis or merely a fixed, ectatic calyx system of the renal pelvis is present, a diagnostic puncture of the renal pelvis can be considered: low pressure and a negative urine dipstick test rule out infection, so that a nephrostomy can be avoided (e24).

If the ultrasonographic findings are equivocal, abdominal computed tomography (CT) is recommended, so that any anatomical abnormalities that have caused or exacerbated urosepsis can be identified with high sensitivity (e25, e26).

Treatment

In an oft-cited trial involving 260 patients, Rivers et al. (2001) showed that EGDT (mentioned above) lowers the mortality of severe sepsis and septic shock. In combination with the rapid correction of target variables (Table 1), EGDT lowered mortality from 46.5% to 30.5%, with a number needed to treat (NNT) of 6–8 (1). Kumar et al. confirmed the importance of timing as a prognostic factor (24, 25): the initiation of empirical antibiotic treatment within one hour of the diagnosis of hypotension was associated with an 80% survival rate. Delays in starting antibiotics were associated with an average 7.6% decline in survival rate for each hour of delay (79.9% versus 70.5% at 1–2 hours, 42.0% at 5–6 hours, and 25.4% at 9–12 hours) (25).

Early goal-directed therapy (EGDT) is now controversial, as the ProMISE, ARISE, and ProCESS trials showed no significant survival benefit from strict adherence to the EGDT protocol. It should be pointed out, however, that the septic patients' central venous oxygen saturation levels ($S_{cv}O_2$) on first contact were not below 70% in any of these three trials (26–28), whereas Rivers et al. identified $S_{cv}O_2 < 70\%$ as an indicator of the need for hemodynamic treatment (Table 1) (1). Therefore, in the absence of subgroup analyses of such high-risk patients, and in the absence of further trials, these findings cannot be considered conclusive (e27).

Imaging studies

Ultrasonography is the imaging method of first choice. It enables the rapid detection of, for example, hydronephrosis, renal abscesses, and prostatic abscesses.

In general, there are three categories of treatment for urosepsis:

- Cause-directed (antibiotic treatment and elimination of foci of infection)
- Supportive (hemodynamic and pulmonary stabilization)
- Adjunctive (glucocorticoid and insulin treatment) (Figure 3) (2, 5).

Cause-directed treatment

Antibiotic treatment should be begun as soon as possible (within an hour) after diagnosis, but only after blood and urine cultures have been obtained (recommendation grade B, evidence level Ic). The antibiotic(s) should be chosen in the light of local resistance rates and the expected pathogen spectrum. The recommendations of the Paul Ehrlich Society are reproduced in Table 2.

In view of the presence of capillary leakage leading to edema formation and lower volumes of distribution, as well as increased clearance because of the hyperdynamic circulatory situation or low clearance rates because of multiple organ dysfunction, antibiotics should generally be given initially at high doses, which are reduced later on in the course of treatment. This consideration applies above all to hydrophilic, renally eliminated antibiotics (β -lactam antibiotics and aminoglycosides) (e26, e28). In contrast, fluoroquinolones are concentration-dependent and are barely influenced by altered volumes of distribution; their doses should only be adjusted in the setting of elevated renal retention values (e26, e28). The MAXSEP trial revealed no additional benefit from dual empirical antibiotic treatment (meropenem in 298 patients vs. meropenem/moxifloxacin in 302 patients) (e29). The antibiotic regimen should be re-evaluated daily with a view toward potential de-escalation, to avoid both drug resistance and unnecessary costs (recommendation grade E, evidence level V).

The elimination of foci of infection and the early control of complicating factors are important components of causally directed treatment (recommendation grade A, evidence level Ic). In the case of an infected kidney above an obstruction, this is accomplished by internal ureteral stenting (Figure 2a) or percutaneous nephrostomy (Figure 2b). A meta-analysis did not show either of these methods to be superior to the other (29); the choice between them can be made individually.

Urosepsis due to a high residual urine volume or acute urinary retention (even without pyuria) is best treated with a transurethral bladder catheter; in the setting of acute prostatitis or epididymitis, a suprapubic catheter should be

inserted for urinary drainage at low pressure. Abscesses or infected lymphoceles requiring treatment can be drained with a pigtail catheter inserted under ultrasonographic (or other radiological) guidance (e23). Clinical decision-making in such situations should be based not only on the anatomical particulars (e.g., ureteral strictures), but also on the patient's clotting status (possibly affected by therapeutic anticoagulation).

Supportive treatment

According to the concept of early goal-directed therapy (EGDT), hemodynamic stabilization promotes the delivery of an adequate oxygen supply to the tissues. As soon as the diagnosis of urosepsis is suspected, the intravenous administration of isotonic crystalloid solution should be begun within 15 minutes, with the goal of administering at least 30 mL/kg of body weight in the first hour (proceed with caution in case of congestive heart failure) (recommendation grade A, evidence level Ic).

On the basis of the findings of the VISEP, CRYSTMAS, 6S, and CHEST trials (recommendation grade A, evidence level Ia), colloid HAES solutions are no longer recommended in the treatment of severe sepsis and septic shock (30–33). The results of the CRYSTAL trial (NCT00318942) are now pending. The findings of the SAFE trial imply that the additional administration of human albumin can be considered (recommendation grade E, evidence level V) (18).

Low mean arterial pressure (MAP < 65 mm Hg) despite volume substitution is an indication for vasopressor administration (recommendation grade B, evidence level Ic); norepinephrine is the vasopressor drug of first choice (recommendation grade E, evidence level IIb) (34). If the cardiac output is low despite volume therapy, the positive inotrope dobutamine (20 μ g/kg/min) is the catecholamine of first choice (recommendation grade E, evidence level V) (2). Once tissue perfusion is normal, and in the absence of coronary heart disease, anemia with hemoglobin values under 7 g/dL should be treated with erythrocyte concentrate transfusion (e30). Low-dose dopamine (5 μ g/kg/min) for nephroprotection is not recommended (recommendation grade A, evidence level Ia) (33).

Pulmonary stabilization to achieve an arterial oxygen saturation above 93% and a central venous oxygen saturation of at least 70% should be an early goal, with controlled, lung-sparing ventilation at low tidal volumes (6 mL/kg of body weight) and peak pressures no higher than 30 mbar, whenever adequate oxygenation (>90% by

The three categories of treatment

- Cause-directed (antibiotic treatment and elimination of foci of infection),
- Supportive (hemodynamic and pulmonary stabilization),
- Adjunctive (glucocorticoid/insulin treatment)

Supportive treatment

According to the concept of early goal-directed therapy (EGDT), hemodynamic stabilization promotes the delivery of an adequate oxygen supply to the tissues.

pulse oximetry) cannot be achieved by hemodynamic stabilization and mask oxygen administration alone (recommendation grade B, evidence level Ic).

Adjunctive treatment

Adjunctive treatment is given simultaneously with, and in addition to, supportive treatment.

Glucocorticoid treatment is controversial. Early randomized trials showed a benefit from high-dose treatment in septic shock (e31–e33), but the CORTICUS trial revealed elevated mortality (albeit without statistical significance) and a higher risk of superinfection with low-dose steroid treatment (36, e34). Only in septic shock with treatment-resistant hypotension despite vasopressor administration and volume substitution can the administration of hydrocortisone (200 mg/d) be considered as a last resort (recommendation grade E, evidence level V).

Conventional insulin treatment is superior to intensified insulin treatment for sepsis patients: in the VISEP trial, 17% of patients receiving intensified treatment developed severe hypoglycemia (blood glucose <40 mg/dL), as opposed to 4.1% of those receiving conventional treatment (30). Moreover, the NICE-SUGAR trial showed a 2.6% increase in mortality (27.5% vs. 24.9%, $p = 0.02$) attributable to intensified insulin treatment (37). Strict glycemic control is thus not indicated (recommendation grade B, evidence level Ib); rather, the glycemic target should be set between 110 mg/dL and 180 mg/dL, with regular blood sugar measurement every 1 to 2 hours (4).

On the basis of a meta-analysis of 9 small-scale studies, it is stated in the current German (DSG) guideline that the intravenous administration of selenium (a radical scavenger) can be considered in the treatment of severe sepsis and septic shock (recommendation grade C, evidence level Ia) (e35). The international SSC guideline, however, contains no such recommendation.

The administration of drotrecogin, a form of recombinant human activated protein C (rhAPC), was found to yield no relevant benefit in the PROWESS-SHOCK trial, and the drug was accordingly withdrawn from the market (e36).

Future prospects

New treatments are directed against the massive secretion of inflammatory cytokines (the “mediator storm”). In initial case reports, extracorporeal cytokine adsorption with concentration-dependent but size-specific filtering of intermediate-sized molecules (10–50 kDa) during continuous veno-venous hemodialysis dramatically lowered the

initially high concentrations of IL-6, IL-1 β , and TNF- α and lessened the need for vasopressor drugs (e37, e38). This method of treatment cannot yet be recommended, pending further evaluation in randomized, multicenter trials.

Conclusion

Urosepsis can usually be identified early in its course, and distinguished from sepsis of other causes, by a basic diagnostic evaluation consisting of physical examination, urinalysis, laboratory blood tests, and ultrasonography. Once urosepsis has been diagnosed, the treatment should be begun at once. Rapid diagnosis and the (usually) minimally invasive elimination of infectious foci have led to improved outcomes in patients with urosepsis. Nonetheless, competence networks, standardized treatment recommendations, and interdisciplinary collaboration during the acute illness and beyond will be indispensable prerequisites for further improvement.

Conflict of interest statement

The authors state that they have no conflict of interest.

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Adjunctive treatment

Adjunctive treatment is given simultaneously with, and in addition to, supportive treatment.

Overview

Urosepsis can usually be identified early in its course, and distinguished from sepsis of other causes, by a basic diagnostic evaluation consisting of physical examination, urinalysis, laboratory blood tests, and ultrasonography.

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Supplementary material
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Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

Which of these findings meets the criteria for SIRS?

- a) Respiratory frequency 18/min
- b) Leukocyte count 11/nL (= 11 000/ μ L)
- c) $p_a\text{CO}_2$ 30 mm Hg
- d) Core body temperature 36.6°C
- e) Pulse 80/min

Question 2

Low antithrombin III level, Quick value, and platelet count in a patient with urosepsis arouses suspicion of what condition?

- a) Thrombotic thrombocytopenic purpura
- b) Disseminated intravascular coagulation (DIC)
- c) Hemolytic-uremic syndrome (HUS)
- d) Von Willebrand-Jürgens syndrome
- e) Primary hyperfibrinolysis

Question 3

What marker is used to assess tissue perfusion?

- a) Lactate
- b) Erythrocyte sedimentation rate (ESR)
- c) Procalcitonin (PCT)
- d) D-dimers
- e) IL-1

Question 4

What is the supportive drug of first choice in a patient with urosepsis and low mean arterial pressure (< 65 mm Hg) despite fluid replacement?

- a) Colloid solution
- b) Norepinephrine
- c) Insulin
- d) Erythrocyte concentrate
- e) Low-dosed dopamine

Question 5

By what percentage does the survival rate of a sepsis patient decline for every hour of delay in starting antibiotic treatment?

- a) 3.1%
- b) 5.2%
- c) 7.6%
- d) 9.8%
- e) 12.3%

Question 6

What type of urinary diversion is preferred for a patient with urosepsis due to prostatitis?

- a) Nephrostomy
- b) A suprapubic catheter
- c) A transurethral catheter
- d) A ureteral stent
- e) A condom urinal

Question 7

What percentage of blood cultures are positive in patients with suspected urosepsis?

- a) 15%
- b) 30%
- c) 60%
- d) 75%
- e) 90%

Question 8

What is the imaging method of choice for patients with suspected urosepsis?

- a) Ultrasonography
- b) Computed tomography
- c) Magnetic resonance imaging
- d) Plain x-rays of the abdomen
- e) Cystoscopy

Question 9

What antibiotic is given as monotherapy to treat vancomycin-resistant enterococci?

- a) Fluoroquinolone
- b) Acylaminopenicillin
- c) Aminopenicillin
- d) Tigecycline
- e) Carbapenem

Question 10

What is the most common underlying cause of urosepsis in patients with obstructive uropathy, according to a recent study?

- a) Carcinoma
- b) Prostatic hyperplasia
- c) Prior surgery
- d) Ureterolithiasis
- e) Pregnancy

Supplementary material to:

Urosepsis—Etiology, Diagnosis, and Treatment

by Nici Markus Dreger*, Stephan Degener*, Parviz Ahmad-Nejad, Gabriele Wöbker, and Stephan Roth

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eBOX 1

Diagnostic criteria for sepsis according to the SCCM/ESICM/ACCP/ATS/SIS consensus conference (7)

- **Demonstration of an infection, or clinical suspicion of infection in the presence of “some” of the following criteria:**
 - **General signs**
 - Fever $>38.3^{\circ}\text{C}$
 - Hypothermia $<36^{\circ}\text{C}$
 - Tachycardia $>90/\text{min}$ or >2 SD above age-specific normal value
 - Tachypnea $>30/\text{min}$
 - Impaired neurologic status
 - Edema or positive fluid balance (>20 mL/kg/d)
 - Hyperglycemia (blood sugar >120 mg/dL or 7.7 mmol/L) in the absence of previously diagnosed diabetes mellitus
 - **Signs of inflammation**
 - Leukocytosis $>12/\text{nL}$
 - Leukopenia $<4/\text{nL}$
 - Normal leukocyte count with $>10\%$ immature forms
 - C-reactive protein >2 SD above normal
 - Procalcitonin >2 SD above normal
 - **Hemodynamic signs**
 - Hypotension (SBP <90 mm Hg, MAP <70 mm Hg or SBP drop by >40 mm Hg or to <2 SD below the age-specific normal value)
 - Cardiac index (CI) $>3\text{--}5$ L/min/m²
 - **Organ dysfunction**
 - Arterial hypoxemia ($p_a\text{O}_2 / F_i\text{O}_2 <300$)
 - Acute oliguria <0.5 mL/kg/h or 45 mmol/L for ≥ 2 h
 - Creatinine rise by ≥ 0.5 mg/dL
 - Coagulopathy (INR >1.5 or aPTT >60 s)
 - Thrombocytopenia $<100/\text{nL}$
 - Hyperbilirubinemia (total bilirubin >4 mg/dL or >70 mmol/L)
 - Ileus

Markers of tissue perfusion

Hyperlactatemia >1 mmol/L *

Reduced capillary filling or marbling

* Elevated lactate levels due to inadequate perfusion can arise even when the blood pressure is normal (cryptic shock); a falling lactate level seems to be at least as good an indicator of successful treatment as the central venous oxygen saturation (S_{cvO_2}) (e39).

ATS, American Thoracic Society; aPTT, activated partial thromboplastin time; CCP, American College of Chest Physicians; ESICM, European Society of Intensive Care Medicine; INR, international normalized ratio; MAP, mean arterial blood pressure; SCCM, Society of Critical Care Medicine; SD, standard deviation; SIS, Surgical Infection Society

eBOX 2

Risk factors for urosepsis

- Age ≥ 65 years (38)
- Diabetes mellitus
- Immune suppression*¹ (organ transplantation, chemotherapy, corticosteroid treatment, AIDS)
- Nosocomial urinary tract infection acquired on a urology ward*² (39)
- Prior urological interventions

*¹ *Candida* spp., *Pseudomonas* spp., and coagulase-negative staphylococci are more common pathogens than in non-immunosuppressed patients (e6, e40).

*² Among patients with nosocomial urinary tract infections (UTIs) acquired on urology wards, the prevalence of urosepsis is 12% (39). In contrast, patients with nosocomial UTIs acquired on non-urological wards have a 2% prevalence of severe sepsis and a 0.3% prevalence of septic shock (e41).