Urosepsis: Overview of the Diagnostic and Treatment Challenges

FLORIAN M. E. WAGENLEHNER,1 ADRIAN PILATZ,1 WOLFGANG WEIDNER,1 and KURT G. NABER2
1Clinic for Urology, Pediatric Urology and Andrology, Justus-Liebig-University Gießen, D-35390 Gießen, Germany; 2Technical University, 80333 Munich, Germany

ABSTRACT Urosepsis is defined as sepsis caused by an infection in the urogenital tract. In approximately 30% of all septic patients the infectious focus is localized in the urogenital tract, mainly due to obstructions at various levels, such as ureteral stones. Urosepsis may also occur after operations in the urogenital tract. In urosepsis, complete bacteria and components of the bacterial cell wall from the urogenital tract trigger the host inflammatory event and act as exogenous pyrogens on eukaryotic target cells of patients. A burst of second messenger molecules leads to several different stages of the septic process, from hyperactivity to immunosuppression. As pyelonephritis is the most frequent cause for urosepsis, the kidney function is therefore most important in terms of cause and as a target organ for dysfunction in the course of the sepsis.

Since effective antimicrobial therapy must be initiated early during sepsis, the empiric intravenous therapy should be initiated immediately after microbiological sampling. For the selection of appropriate antimicrobials, it is important to know risk factors for resistant organisms and whether the sepsis is primary or secondary and community or nosocomially acquired. In addition, the preceding antimicrobial therapies should be recorded as precisely as possible. Resistance surveillance should, in any case, be performed locally to adjust for the best suitable empiric treatment. Treatment challenges arise from the rapid increase of antibiotic resistance in Gram-negative bacteria, especially extended-spectrum β-lactamase (ESBL)-producing bacteria. Treatment of urosepsis comprises four basic strategies I) supportive therapy (stabilizing and maintaining blood pressure), II) antimicrobial therapy, III) control or elimination of the complicating factor, and IV) specific sepsis therapy.

DEFINITIONS OF UROSEPSIS

Urosepsis is defined as sepsis caused by an infection in the urogenital tract (Table 1). 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; cancer patients receiving chemotherapy or corticosteroids; and patients with acquired immunodeficiency syndromes. However, all patients can be affected by bacterial species capable of inducing inflammation within the urinary tract.

Sepsis is a systemic response to infection. The signs and symptoms of systemic inflammatory response syndrome (SIRS), which were initially considered to be ‘mandatory’ for the diagnosis of sepsis (1, 2), are now considered to be alerting symptoms (3). Many other clinical or biological symptoms must be considered.

Received: 4 July 2012. Accepted: 24 March 2015. Published: 4 September 2015
Editors: Matthew A. Mulvey, University of Utah, Salt Lake City, UT; Ann E. Stapleton, University of Washington, Seattle, WA; and David J. Klumpp, Northwestern University, Chicago, IL
Correspondence: Florian M.E. Wagenlehner, Wagenlehner@aol.com
© 2015 American Society for Microbiology. All rights reserved.
The classifications of sepsis differentiate severity levels:

(a) severe sepsis is defined as sepsis associated with organ dysfunction;
(b) septic shock is persistence of hypoperfusion or hypotension despite fluid resuscitation, and
(c) refractory septic shock is defined by an absence of response to therapy.

For therapeutic purposes, the diagnostic criteria of sepsis should identify patients at an early stage of the syndrome, prompting urologists and intensive-care specialists to search for and treat infection, apply

### Table 1: Definitions

**Infection:** Presence of organisms in a normally sterile site that is usually, but not necessarily, accompanied by an inflammatory host response

**Bacteremia:** Bacteria present in blood as confirmed by culture. May be transient

**Systemic inflammatory response syndrome (SIRS):** Response to a wide variety of clinical insults, which can be infectious, as in sepsis, but may be non-infectious in etiology (e.g., burns, pancreatitis). This systemic response is manifested by two or more of the following conditions:

- Temperature >38°C or <36°C
- Heart rate >90 beats/min
- Respiratory rate >20 breaths/min or PaCO2 <32 mm Hg (<4.3k Pa)
- WBC >12,000 cells/mm³ or <4,000 cells/mm³ or ≥10% immature (band) forms

**Sepsis:** Activation of the inflammatory process due to infection

**Hypotension:** A systolic blood pressure of <90 mmHg or a reduction of >40 mmHg from baseline in the absence of other causes of hypotension

**Severe sepsis:** Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration of mental status

**Septic shock:** Sepsis with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are on inotropes or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured

**Refractory septic shock:** Septic shock that lasts for more than 1 hour and does not respond to fluid administration or pharmacological intervention

### Table 2: Clinical diagnostic criteria of sepsis and septic shock

<table>
<thead>
<tr>
<th>Criterion I</th>
<th>Presence of bacteremia (positive blood culture) or clinical suspicion of sepsis. Bacteremia can be of low inoculum (&lt;10 bacteria/ml) or of short duration. Multiple blood cultures are recommended.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criterion II</td>
<td>Systemic inflammatory response syndrome [SIRS]</td>
</tr>
<tr>
<td>Body temperature</td>
<td>≥38°C or &lt;36°C</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>≥90 beats/min</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>≥20 breaths/min</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>PaCO2 ≤32 mm Hg</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>&gt;12,000/µl or ≤4,000/µl</td>
</tr>
<tr>
<td>Segmented neutrophils</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Criterion III</td>
<td>Multiple organ dysfunction syndrome [MODS]</td>
</tr>
<tr>
<td>Circulation:</td>
<td>Arterial systolic blood pressure ≤90 mm Hg or mean arterial blood pressure ≤70 mm Hg during ≥1 hour despite adequate fluid resuscitation and adequate intravascular volume or use of vasopressors, in order to maintain systolic blood pressure ≥90 mm Hg.</td>
</tr>
<tr>
<td>Kidney:</td>
<td>Urine production &lt;0.5 ml/kg body weight/hour during 1 hour despite adequate fluid resuscitation.</td>
</tr>
<tr>
<td>Lung:</td>
<td>PaO2 ≤75 mm Hg (at ambient air) or PaO2/FiO2 ≤300 (acute lung injury), or PaO2/FiO2 ≤200 (acute respiratory distress syndrome) at assisted ventilation [PaO2, arterial O2-partial pressure; FiO2, inspiratory O2 concentration].</td>
</tr>
<tr>
<td>Thrombocytopenia:</td>
<td>Platelets ≤80,000/µl or decrease of platelets ≥50% within 3 days.</td>
</tr>
<tr>
<td>Metabolic acidosis:</td>
<td>Blood pH ≤7.30 or base excess ≥5 mmol/l; plasma lactate ≥1.5 fold of normal.</td>
</tr>
<tr>
<td>Encephalopathy:</td>
<td>Somnolence, agitation, coma, confusion.</td>
</tr>
</tbody>
</table>

**Following these criteria sepsis can be classified in three grades:**

**Simple sepsis**

<table>
<thead>
<tr>
<th>Criterion I + ≥2 Criterion II</th>
<th>Lethality</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2 Criterion II</td>
<td>7%</td>
</tr>
<tr>
<td>-3 Criterion II</td>
<td>10%</td>
</tr>
<tr>
<td>-4 Criterion II</td>
<td>17%</td>
</tr>
</tbody>
</table>

**Severe sepsis**

| Criterion I + ≥2 Criterion II + ≥1 Criterion III per affected organ (kidney, lung, liver) lethality increases + 15% to + 20% |

**Septic shock**

| Criterion I + ≥2 Criterion II + therapy-refractory arterial hypotension ≤90 mmHg |
|----------------------------------------------------------------|-----------------|
| Lethality                       | 50% to 80%     |
appropriate therapy, and monitor for organ failure and other complications (4).

EPIDEMIOLOGY OF UROSEPSIS
Urinary tract infections (UTIs) can manifest in a wide clinical range from bacteriuria with no or limited clinical symptoms, to sepsis, severe sepsis, or septic shock. In approximately 30% of all septic patients, the infectious focus is localized in the urogenital tract and arises from infections of the parenchymatous urogenital organs, e.g., kidneys, prostate, or testicles. This may comprise obstructive diseases of the urinary tract, such as ureteral stones, stenosis of the collecting system, tumor formations, or anomalies of the urinary system. Urosepsis may also occur after operations in the urogenital tract. In patients with nosocomial UTI treated in urology, the prevalence of urosepsis was, on average, about 12% in a multinational surveillance study (5).

Severe sepsis is a critical situation with a reported mortality rate ranging from 20% to 50% (6–8). Severe sepsis and septic shock are also the major causes of admission and death in intensive-care units (ICUs) (2). In the U.S., there is a steady increase in the number of cases of severe sepsis, from 415,280 cases in 2003 to 711,736 in 2007. The total hospital costs for all patients with severe sepsis also increased by 57%, from $15.4 billion in 2003 to $24.3 billion in 2007 (9). Sepsis is more common in men than in women (6). In recent years, the incidence of sepsis has increased (6,10), but the associated mortality has decreased, suggesting improved management of patients (6,10). Most severe sepsis cases reported in the literature are related to pulmonary (50%) or abdominal infections (24%), with the urogenital tract accounting for only 5% (11) to 7% (12). Urosepsis, however, may still show high mortality rates of 25% to 60% in special patient groups (13). Hofmann (14) analyzed 59 patients (54% females) treated for uroseptic shock and hospitalized over a 10-year period: 78% of patients showed urinary obstruction as predisposing factors, mainly due to nephrolithiasis, and the remaining 22% patients also had uropathies with significant impact on urodynamics. Seventeen percent of patients developed urosepsis after urological interventions. Ninety-two percent of patients needed operative intervention and at that time 24% underwent nephrectomy. Of the 12% patients who died due to the critical illness, no intervention was performed. A consistent finding, however, is that the mortality associated with sepsis from a urinary source is substantially lower than all other sources.

PATHOPHYSIOLOGY OF UROSEPSIS
Microorganisms reach the urinary tract mostly by way of the intraluminal-ascending route, more rarely by hematogenous or lymphatic routes. Inflammation is the physiologic response of the body to infection and is mediated by the release of soluble substances by cells of the immune system. For urosepsis to be established from the urinary tract, the pathogens or pathogenic factors have to reach the bloodstream (15). The risk of bacteremia is increased in severe urogenital infections, such as pyelonephritis and acute bacterial prostatitis (ABP), and is facilitated by obstruction of the urinary tract. The systemic inflammatory response syndrome (SIRS) is then triggered: an initially overwhelming proinflammatory reaction, activated by mediators such as bacterial toxins, is accompanied by a counter-regulatory anti-inflammatory response syndrome (CARS) (16).

Complete bacteria and components of the bacterial cell wall act as exogenous pyrogens on eukaryotic target cells of patients. These include lipopolysaccharides (LPS), especially the lipid A component (endotoxin) of the outer membrane of Gram-negative bacteria; the peptidoglycan, teichoic acid lipoteichoic acids of Gram-positive bacteria; and toxins like toxic-shock syndrome toxin 1 and Staphylococcus aureus toxin A (17). Many of these factors bind to cellular receptors and co-receptors of the innate immune system (e.g., CD 14, “Toll-like receptors” TLR2 and TLR4, CD 18, and selectin) on the surface of macrophages, neutrophils, endothelial cells, and others. Intracellular messenger molecules, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-xB) or protein-kinase C, are activated, which induce transcription of mediator genes and thus the synthesis of numerous endogenous mediators, such as cytokines.

Cytokines as Markers of the Septic Response
Cytokines are produced with different kinetics and are classified into pro-inflammatory and anti-inflammatory cytokines. Tumor necrosis factor (TNF)-α and interleukin (IL)-1 are the most important pro-inflammatory cytokines and exhibit similar biologic properties. They influence the temperature-regulatory centers in the hypothalamus, which results in fever. They also have an effect on the formatio reticularis in the brain stem that renders the patient somnolent and comatose. Release of adrenocorticotropic hormone (ACTH) in the pituitary gland is increased, which stimulates the adrenal gland. These factors also stimulate hematopoietic growth factors leading to the formation of new neutrophils and the release of stored ones. The neutrophils are additionally
activated and produce bactericidal substances, such as proteases and oxygen radicals. B and T lymphocytes are stimulated for synthesis of antibodies and cellular immune reaction.

In the continuing septic process, however, apoptosis of B cells, CD4-helper cells, and follicular-dendritic cells cause an anti-inflammatory immune suppression, called transient-immune paralysis (18). In the liver, the production of acute-phase proteins (C-reactive protein, α1-antitrypsin, and complement factors) is triggered. The muscular protein is degraded and the released amino acids are used for antibody synthesis. In endothelial cells, the production of platelet-activating factor (PAF) and nitric oxide (NO) is triggered, leading to a decreased vessel tone. The endothelial cells are damaged and increased permeability results. Surface receptors of endothelial cells and neutrophils are upregulated, increasing the mutual adhesiveness. Additionally, the endothelial procoagulatory activity and the synthesis of a plasminogen activator-inhibitor substance is increased, which activates the blood-coagulation system (11, 17, 19–22). The cytokines IL-4 and IL-10, among others, act as anti-inflammatories and inhibit the formation of IL-1 and TNF (11, 21).

All of these factors may act on target organs and are responsible for the local and systemic effects within the target organs (11, 19, 21, 22). Sepsis may indicate an immune system that is severely compromised and unable to eradicate pathogens or a nonregulated and excessive activation of inflammation, or both. A genetic predisposition likely explains different outcomes in septic patients. Mechanisms of organ failure and death in patients with sepsis remain only partially understood (11).

The Importance of the Neuro-Endocrine Axis

The immune system and central nervous system communicate and regulate each other via the autonomic nervous system and the hypothalamo-pituitary-adrenocortical axis (23). The sympathetic system innervates all lymphoid organs and thereby modulates the immune system. Under pathological circumstances noradrenaline can stimulate α2-receptors on the surface of macrophages and thus stimulate release of TNF-α (24). Stimulation of β-receptors inhibits release of pro-inflammatory cytokines.

Release of pro-inflammatory cytokines in response to infection stimulates hypothalamic centers activating the sympathetic-nerve system and the hypothalamo-pituitary-adrenocortical axis, inducing the expression of corticotropin-releasing hormone (CRH) or arginine-vasopressin in the hypothalamus and ACTH in the pituitary gland. The consecutive release of cortisol from the adrenal gland leads to an anti-inflammatory response by suppressing NF-κB and increasing anti-inflammatories IL-4 and IL-10 (25). The parasympathetic system acts via the vagal-nerve system sensing inflammation and informing specific centers in the brain. Release of acetyl-choline reduces pro-inflammatory cytokines as well as releasing high-mobility-group-box 1 (HMGB1), a critical pro-inflammatory mediator (26, 27).

Thus, the neuro-endocrine axis appears to be a critical regulator of systemic inflammation important for fine tuning of the inflammatory response, which might also become an important target for pharmacological intervention.

PATHOPHYSIOLOGICAL CONDITIONS ALTERING RENAL FUNCTION

Pyelonephritis is the most frequent cause for urosepsis. The renal function is therefore most important in the consideration of urosepsis (28). Impairment of renal function can be acute or chronic and unilateral or bilateral. Post-renal obstruction is one of the most frequent causes of urosepsis in urological cases. The obstruction causes sepsis on the one side and severely influences the pharmacokinetics of drugs, such as antibiotics, in the urinary tract on the other side. In this context the pharmacokinetics of drugs at the affected site is also significantly influenced by the total renal function and thus by the function of the contralateral kidney. Furthermore, pharmacokinetics and the concentration of an antibiotic in the kidney is influenced by its arterial and venous plasma concentration, the various renal (proximal and distal) tubular concentrations, the renal concentration in tissue, and the final urine concentration. The renal concentration of an antibiotic in tissue is complex and is a function of renal blood flow, glomerular filtration, tubular secretion and reabsorption, pyelovenous- and lymphous backflow, and the number of intact nephrons. The renal-tissue concentration of a drug is therefore difficult to assess; representative concentrations have been investigated and one of these could be the concentrations in the renal lymph that might resemble interstitial concentrations (29). Renal-lymph concentrations in unobstructed, normal, and unobstructed, but infected kidneys, have been determined for a variety of β-lactam antibiotics, aminoglycosides, and nitrofurantoin. Concentrations in the renal lymph were generally lower than the corresponding
arterial-plasma concentrations, which suggests that there is no concentration effect in the renal-interstitial space.

In acute, complete, unilateral ureteral obstruction there is still some residual glomerular filtration and tubular secretion present. An experimental study in dogs (29) showed that within the first hours of obstruction, glomerular-filtration rate, as well as the effective renal-plasma flow, decreased significantly to an average of 14% in the obstructed kidney, compared to the unobstructed kidney. The persisting turnover of urine is primarily due to pyelovenous backflow and also, but less importantly, due to drainage into the renal lymphatics. Then the concentration of a substance, such as certain antibiotics, in the renal lymph are higher than the corresponding arterial-plasma concentrations in the acute phase of an unilateral obstruction (first hours to first week) and become equal to the arterial-plasma concentrations in chronic-obstructive disease (longer than 1 week) (30).

The glomerular filtration rate is influenced by the balance of inward and outward pressures at the glomerular arterioles and Bowman’s capsule. Inward forces are significantly increased with postrenal obstruction and are the cause of reduced filtration rate (29, 31). An increasing number of nephrons will cease filtering if the ureteral pressure exceeds one-third of the mean blood pressure. The acute unilateral occlusion of a ureter results in a characteristic triphasic relationship between renal blood flow and ureteral pressure. The first phase, lasting approximately 1.5 hours, shows a rise in both ureteral pressure and renal blood flow, followed by a second phase with decline in renal blood flow and a continued increase in ureteral pressure, lasting from approximately 1.5 to 5 hours, followed by a third phase resulting in a further decline of renal blood flow accompanied by a progressive decrease in ureteral pressure. Phase I is characterized by an initial afferent-arteriolar vasodilatation followed by an efferent-arteriolar vasoconstriction in phase II and afferent-arteriolar vasoconstriction in phase III. This third phase is not seen in bilateral ureteral obstruction, which leads to a progressive rise in ureteral pressure despite a decrease in renal blood flow. Single-nephron glomerular-filtration rate declines in unilateral and bilateral ureteral occlusion, which is secondary to an increase in afferent-arteriolar resistance in unilateral occlusion, and secondary to a rise in intratubular pressure in bilateral occlusion (32). These differences between unilateral and bilateral obstruction are most probably due to substances that accumulate in bilateral obstruction or unilateral obstruction of a solitary kidney, but do not accumulate in unilateral obstruction with a functioning contralateral kidney. One important factor of these changes is the atrial-natriuretic peptide (32).

Using different antibiotic pharmacological models, mainly with β-lactam agents, the following findings in the different settings of renal functions and renal obstructions can be summarized (33):

1. In the case of a severe unilateral renal insufficiency (glomerular filtration rate 1 ml/min) but normal contralateral renal function (glomerular filtration rate 60 ml/min) the urine antibiotic concentrations of both kidneys are high, whereby the impaired kidney achieves half the urine concentration of the intact kidney.
2. In the case of a bilateral renal insufficiency, the urinary antibiotic concentrations significantly decrease down to plasma levels in the case of severe impairment (glomerular filtration rate 2 ml/min). This difference in unilateral and bilateral renal insufficiency can be explained by the intact-nephron theory: the single nephrons, e.g., the concentration ability, remain intact in the case of physiologic prerenal conditions. In bilateral renal insufficiency there is an increased offer of solutes per nephron that results in diuresis with impaired ability for concentration (34).
3. In acute obstruction, urinary concentrations of filtered and secreted substances will at first reach a high plateau. If the ureteral pressure rises and exceeds one-third of the mean blood pressure, an increasing number of nephrons will cease filtering, resulting in decrease of glomerular filtration and also in decrease of urinary concentrations. This process is very much enhanced by infection of an obstructed kidney with the result that, in urosepsis due to obstruction, high doses of antimicrobials mainly excreted by the kidneys are necessary.
4. In acute unilateral obstruction the urinary antibiotic concentrations of the obstructed kidney are almost as high as those of the normal unobstructed kidney, which is also due to the maximal urinary concentration in acute obstruction.
5. Even in chronic unilateral obstruction rather high urinary antibiotic concentrations are achieved, depending on the function of the contralateral kidney.

Although antibiotic concentration is an important pharmacological parameter, it does not necessarily reflect antibacterial activity of an antimicrobial substance at the site of infection. (see below)
ANTIMICROBIAL THERAPY

Antimicrobials are among the most important drugs in the management of patients with severe infections (35). Inappropriate use of antimicrobials may cause therapeutic failure in the individual patient and, additionally, may contribute towards promoting the emergence of resistant pathogens that might also readily spread in the hospital setting (36). An adequate initial (i.e., in the first hour) antibiotic therapy has been shown to correlate with improved outcome in septic shock (37–39) and is therefore critical also in severe UTI. Inappropriate antimicrobial therapy in severe UTI is linked to a higher mortality rate (40), as it has been shown with other infections as well (41, 42). Empirical antibiotic therapy therefore needs to follow certain rules (43), which might be based upon the expected bacterial spectrum, the institutional-specific resistance rates and the individual patient’s requirements. Empirical initial treatment should provide broad antimicrobial coverage and should later be adapted on the basis of culture results.

Parameters for Antimicrobial Treatment in Urosepsis

If the infection involves renal or other urogenital parenchymal tissues or the patient has urosepsis, adequate serum concentrations are necessary to produce sufficiently high tissue concentrations. Therefore, administration of high-dose intravenous antimicrobials is necessary. Even in uncomplicated pyelonephritis and uncomplicated cystitis there is interstitial and intracellular invasion by the uropathogens (44–47). The antibiotic concentrations in tissue are dependent on the plasma concentrations, the specific tissue architecture, the pharmacokinetic parameters of the antibiotic drug (charge and size of molecule, protein binding, pH in the infectious focus), and the distribution of the infection in the tissue (stroma, epithelium).

Alteration of Pathophysiological Conditions During Urosepsis

Sepsis, and the treatment thereof, increases renal preload and leads to third-spacing. Both alterations result in higher clearances of antibacterial drugs (48). The increased volume of distribution as a result of edema 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 (49). On the other hand, sepsis may cause multiple-organ dysfunction, such as hepatic or renal dysfunction, resulting in decreased clearance of antibacterial drugs. Individualized dosing is therefore necessary. As β-lactams are time-dependent antibacterials, an increase in the volume of distribution or clearance will require increased dosing or administration by continuous infusion. Fluoroquinolones, on the other hand, display largely concentration-dependent activity. The volume of distribution in sepsis is not much altered by fluid shifts in the case of fluoroquinolones and therefore no alterations of standard doses are necessary, unless renal dysfunction occurs (48). In order to optimize the antibacterial activities in septic patients, the pathophysiological effects of the sepsis syndrome and the pharmacokinetic/pharmacodynamic (PK/PD) properties of the antibacterial substances need careful consideration. Therapeutic drug monitoring would be a beneficial method to optimize the individual dosing regimen.

The co-administration of various drugs may also frequently alter the pharmacokinetic behavior of some antibacterial agents. Although some interaction with co-administered drugs involve absorption or distribution, the most clinically relevant interactions during anti-infective treatment involve the metabolic and the renal elimination phase. Hydrophilic anti-infective agents are often eliminated unchanged by renal glomerular filtration and tubular secretion, and are therefore involved in competition for excretion with co-administered drugs. Therapeutic failure with these compounds may be due to hemodynamically active co-administered drugs, such as dopamine, dobutamine, and furosemide, which increase their renal clearance by means of enhanced cardiac output and/or renal blood flow (50).

PK/PD Parameters for Treatment of Severe UTI

In patients with early-onset of ventilator-associated pneumonia, Pea et al. (51) found a reduced area under the concentration-time curve (AUC) over the 12-hour dosage interval after administration of parenteral levofloxacin 500 mg twice daily. The authors explained the reduced exposure by a greater clearance of levofloxacin leading to a shorter elimination half-life. Cumulative urinary excretion confirmed the greater excretion of unchanged drug compared with healthy volunteers. Therefore, from a pharmacokinetic point of view, critically ill and septic patients should be considered a particular subpopulation (50), in whom usually recommended dosages have to be reconsidered.

Beta-lactams

While pharmacodynamic studies in UTI are relatively scarce, at least one study has documented that therapeutic success following beta-lactam therapy depends on
the time the antimicrobial concentration remains above the minimum inhibitory concentration (MIC; T>MIC). There was a significant correlation between the cumulative T>MIC in serum and bacteriological cure, wherein a cumulative T>MIC of 30 hours provided a maximal cure rate of 80% to 90% (52).

**Fluoroquinolones and Aminoglycosides**

For drugs with concentration-dependent time-kill activity, such as the aminoglycosides and the fluoroquinolones, a positive outcome appears to be more dependent on the $C_{\text{max}}$/MIC or AUC/MIC ratio. While it remains unclear which ratio is a better predictor of outcome, in either case a high ratio is desirable. In pharmacodynamic UTI studies of ciprofloxacin in mice infected with *Escherichia coli* (52), there was an obvious correlation between reduced bacterial counts and the AUC/MIC ratio. In severely ill patients (mainly patients with pneumonia) treated with ciprofloxacin, a significant breakpoint for probabilities of both clinical and microbiologic cures was an AUC/MIC ratio of 125 and higher, leading to a significantly higher cure rate (53). In any infection of the urogenital tract, however, a significant level of the bacteria (sometimes more than $10^6$/ml) is also freely floating in the urine. Therefore, high urinary concentrations of the antibiotic are needed as well (52, 54, 55). Antimicrobials primarily eliminated via renal excretion achieve high urinary concentrations, sometimes 100 to 1,000 times of the concomitant serum concentrations. Theoretically, these antimicrobials represent optimal choices for the treatment of UTIs. Besides favorable pharmacokinetics, however, an agent suitable for the treatment of severe UTI and urosepsis should also provide optimal pharmacodynamic properties at the site of infection, i.e., in the urine. Therefore, even agents modestly eliminated by renal mechanisms but with high intrinsic potency (low MIC) against the causative uropathogens, are also important considerations in antimicrobial selection (56). Correlation of those considerations to human data in complicated lower UTI showed that pharmacodynamic targets representing 90%-probability thresholds for bacterial eradication were far below the 125 AUC/MIC breakpoint, suggesting that, in addition to its plasma concentration, the high concentration of fluoroquinolones in the urine might have played a significant role in eradicating bacteria (57).

The antimicrobial activity of many antibiotics is, however, reduced in urine as compared to standard growth medium, depending on pH and urinary contents (58). Therefore, the urinary concentrations cannot be correlated directly with standard MIC. By determining the urinary-bactericidal titer (UBT), i.e., the highest urinary dilution still bactericidal, pharmacokinetic and pharmacodynamic parameters of an antibiotic in urine are linked together. The reciprocal value of an UBT corresponds to the ratio of urinary concentration/minimal bactericidal concentration$_{\text{urine}}$.

In a study of complicated UTI and pyelonephritis, the UBTs were measured for levofloxacin and doripenem. The results showed that microbiological failures in patients treated with levofloxacin correlated well with low urinary-bactericidal activity, whereas there was no such correlation for doripenem (59). Such data evaluating antibiotic activity in patients with urosepsis are missing.

**Biofilm Infection**

Biofilm infection plays a considerable role in urosepsis, not only in association with urinary catheters, but also in scar tissue, stones, prostatitis, and in any obstructed urinary tract (60–63). For most uropathogens, the ability to form biofilms has been shown (64–70). In a study investigating virulence factors in *E. coli* strains causing bacteremia, 53% of the strains were able to produce biofilm (71). In an *in vitro* biofilm-catheter infection model, kill-curves for *Pseudomonas aeruginosa* treated with different antibiotic substances were investigated (72, 73). Beta-lactam antibiotics (piperacillin, ceftazidime) were not able to eradicate the biofilm-cells, even when concentrations up to 128-fold the minimal-bactericidal concentrations were administered. With fluoroquinolones (ciprofloxacin, levofloxacin), eradication was possible within 24 hours; however, only in concentrations that reached 32-fold the minimal-bactericidal concentrations (72, 73). Therefore, generally high dosages of antimicrobials need to be applied in conjunction with the attempt to eliminate the biofilm. If there is a chance to remove the biofilm, this should be done, e.g., by removing infected stones or catheters.

**Bacterial Spectrum in Urosepsis**

There are not many publications on the specific bacterial spectrum in urosepsis. Mainly the bacterial spectrum of complicated and nosocomially acquired UTI are taken as representative for urosepsis as well, which in general might be correct (74). The German septicemia study published in 2002 (75) discriminated the bacterial spectrum of blood-culture isolates according to their origin and showed that if the urinary tract was the source for the septicemia, the bacterial spectrum consisted of about 61% *E. coli*, 16% other enterobacteria, 8% *S. aureus,*
and 6% enterococci, underlining the predominant role of *E. coli* (Fig. 1) (75). If host defense is impaired, less-virulent organisms such as enterococci, coagulase-negative staphylococci, or *P. aeruginosa* may also cause urosepsis.

**Selection of Antimicrobials for Empiric Therapy**

Since effective antimicrobial therapy is best initiated during the first hour when sepsis is diagnosed, the empiric intravenous therapy should be initiated immediately after microbiological sampling. For the selection of appropriate antimicrobials it is important to know the site-of-origin underlying diseases, and whether the sepsis is primary or secondary and community or nosocomially acquired. In addition, the preceding antimicrobial therapies must be recorded as precisely as possible.

Resistance surveillance should always be performed locally to determine the best suitable empiric treatment. Surveillance studies have been performed using blood cultures as the data source. For example, the resistance to ciprofloxacin from the German blood-culture studies of 1983–1985, 1991–1992, 2000–2001, and 2006–2007 and the Paul Ehrlich resistance-surveillance study of 2007 are shown in Fig. 2, and to cefotaxime in Fig. 3 (75–79). *E. coli* resistance to ciprofloxacin is currently about 30% and to cefotaxime approximately 10%.

The European Antibiotic Resistance Surveillance Study comprises a network of over 900 microbiological laboratories serving some 1,500 hospitals in 33 European countries that collects routinely generated antimicrobial-susceptibility testing data on invasive infections caused by seven important bacterial pathogens. The 2011 results showed for *E. coli* 24% ciprofloxacin resistance, 9% 3rd-generation cephalosporin resistance, 12% aminoglycoside resistance, 0% carbapenem resistance, and 13% multidrug resistance. *Klebsiella pneumoniae* showed 13% ciprofloxacin resistance, 8% 3rd-generation cephalosporin resistance, 8% aminoglycoside resistance, 2% carbapenem resistance, and 8% multidrug resistance. *P. aeruginosa* had 13% ciprofloxacin resistance, 8% ceftazidime resistance, 3% piperacillin/tazobactam resistance, 7% gentamicin resistance, 8% carbapenem resistance, and 4% multidrug resistance. *S. aureus* showed 24% methicillin resistance (MRSA) and 0% vancomycin resistance (VRSA). *Enterococcus faecalis* had 1% ampicillin resistance, 5% vancomycin resistance, and 29% high-level gentamicin resistance, while *Enterococcus faecium* showed 96% ampicillin resistance, 37% vancomycin resistance, and 37% high-level gentamicin resistance (80). Thus, comparing the 2011 data to earlier reports, the numbers of MRSA have decreased by 52% since 2004, the numbers of vancomycin-resistant *E. faecalis* have increased, the number of vancomycin-resistant *E. faecium* have remained constant at a high level, and the proportion of *E. coli* isolates that are resistant to 3rd-generation cephalosporins, ciprofloxacin, and aminoglycosides and multidrug-resistant isolates are the highest annual proportions reported to date (80). Taking into account that *E. coli* is the most frequent pathogen causing severe UTI, it is
concerning that there is a continuous increase of antibiotic resistance by *E. coli*.

There is currently no consensus towards a certain resistance threshold for an antibiotic to be recommended for empiric treatment. Given the paramount importance of administering a susceptible antibiotic initially in sepsis, the resistance threshold should therefore be below 10%. Depending on the local susceptibility patterns, a third- or fourth-generation cephalosporin, piperacillin in combination with a β-lactamase inhibitor (BLI), or a


carbapenem may be appropriate. In 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 and BLI in combination with an aminoglycoside or a carbapenem may be necessary to cover a broader bacterial spectrum, including multiresistant pathogens (Tables 3 and 4). If the pretreatment 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 to the altered systemic and, especially, renal pathophysiology in patients with urosepsis and length of therapy, are equally important.

Evidence from in vitro experiments and animal and human studies indicate that antibiotic therapy may induce the release of endotoxin. Antibiotics that bind to penicillin-binding protein (PBP)-2, e.g., imipenem, are associated with little release of endotoxin, whereas antibiotics that bind to PBP-3, e.g., ceftazidime, are associated with far greater release. Whether these differences are clinically relevant could, however, not be demonstrated in a clinical study in patients with Gram-negative urosepsis (81).

**SURVIVING SEPSIS CAMPAIGN GUIDELINES**

In 2004, the Surviving Sepsis Campaign (SSC) first introduced guidelines for the management of severe sepsis and septic shock, as well as strategies for bedside implementation (20, 82, 83); these were updated in 2008 (84) and 2012 (85, 86). The treatment recommendations were organized in so-called sepsis bundles, such as a resuscitation bundle (tasks to begin immediately and to be accomplished within 6 hours) and a management bundle (tasks to be completed within 24 hours).

Key recommendations were listed by category and comprise the following recommendations:

**TABLE 3** Antibiotics recommended for the treatment of urinary tract infections

<table>
<thead>
<tr>
<th>Antibiotic group</th>
<th>Substance</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aminopenicillin + BLI</strong></td>
<td>Ampicillin/sublactam</td>
<td>0.750g twice daily 0.75–3 g 3 times daily</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin/clavulanic acid</td>
<td>1g twice daily or 0.625 g 3 times daily 1.2–2.2 g 3 times daily</td>
</tr>
<tr>
<td><strong>Acylureidopenicillin + BLI</strong></td>
<td>Piperacillin/tazobactam</td>
<td>— 2.5–4.5 g 3 times daily</td>
</tr>
<tr>
<td></td>
<td>Piperacillin/Combactam</td>
<td>— 5 g 3 times daily</td>
</tr>
<tr>
<td><strong>Cephalosporin Gr. 1</strong></td>
<td>Cephalexin</td>
<td>Prophylaxis only —</td>
</tr>
<tr>
<td><strong>Cephalosporin Gr. 2</strong></td>
<td>Cefuroxime axetil</td>
<td>500 mg twice daily —</td>
</tr>
<tr>
<td></td>
<td>Cefuroxime</td>
<td>— 0.75–1.5 g 3 times daily</td>
</tr>
<tr>
<td></td>
<td>Cefotiam</td>
<td>— 1–2 g 2–3 times daily</td>
</tr>
<tr>
<td><strong>Cephalosporin Gr. 3</strong></td>
<td>Cefpodoxime proxetil</td>
<td>200 mg twice daily —</td>
</tr>
<tr>
<td></td>
<td>Cefditoren</td>
<td>200–400 mg daily —</td>
</tr>
<tr>
<td><strong>Cephalosporin Gr. 3a</strong></td>
<td>Cefotaxime</td>
<td>— 1–2 g 2–3 times daily</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone</td>
<td>— 1–2 g daily</td>
</tr>
<tr>
<td><strong>Cephalosporin Gr. 3b</strong></td>
<td>Ceftazidime</td>
<td>— 1–2 g 2–3 times daily</td>
</tr>
<tr>
<td><strong>Cephalosporin Gr. 4</strong></td>
<td>Cefepime</td>
<td>— 2 g twice daily</td>
</tr>
<tr>
<td><strong>Carbapenem Gr. 1</strong></td>
<td>Imipenem</td>
<td>— 0.5–1 g q 6–8h</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>— 0.5–1 g 3 times daily</td>
</tr>
<tr>
<td><strong>Carbapenem Gr. 2</strong></td>
<td>Doripenem</td>
<td>— 0.5 g 3 times daily</td>
</tr>
<tr>
<td><strong>Fluoroquinolone Gr. 2</strong></td>
<td>Ciprofloxacin</td>
<td>500–750 mg twice daily 400 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin XR</td>
<td>1000 mg daily —</td>
</tr>
<tr>
<td><strong>Fluoroquinolone Gr. 3</strong></td>
<td>Levofloxacin</td>
<td>500–750 mg daily 500 mg daily</td>
</tr>
</tbody>
</table>

| **Antimycotic group** | Fluconazole | 400–800 mg daily 400–800 mg daily |
|                       | Voriconazole | 4–6 mg/kg BW* daily 4–6 mg/kg BW daily |
| **Pyrimidine analog** | Flucytosine | 100–150 mg/kg BW 4 times daily |
| **Echinocandin** | Caspofungin | 50–70 mg daily |

*aIV, intravenous

*bBLI, β-lactamase inhibitor

*cBW, body weight
TABLE 4 Antibiotics recommended for the treatment of urosepsis

<table>
<thead>
<tr>
<th>Most frequent pathogens/species</th>
<th>Initial, empirical antimicrobial therapy</th>
<th>Therapy duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>Cephalosporin (group 3a/b)</td>
<td>3–5 days after defervescence or control/elimination of complicating factor</td>
</tr>
<tr>
<td>Other enterobacteria</td>
<td>Fluoroquinolone*</td>
<td></td>
</tr>
</tbody>
</table>

After urological interventions – multi-resistant pathogens

| *Pseudomonas* spp. | Anti-pseudomonas active acylaminopenicillin/BLI |
| *Proteus* spp.     | Carbapenem                                      |
| *Serratia* spp.    | ± Aminoglycoside                                |
| *Enterobacter* spp.|                                                 |

*Only in regions where fluoroquinolone resistance is below 10%*

Early goal-directed resuscitation of the septic patient during the first 6 hours after recognition. Early goal-directed therapy (8) is simply a protocol derived from components that have long been recommended as standard care for the septic patient to optimize hemodynamics and oxygen supply (Table 5). Recently, the early goal-directed therapy approach has been challenged by two multicenter studies performed in the U.S. and Australia/New Zealand showing that protocol-based resuscitation of patients in whom septic shock was diagnosed in the emergency department did not improve outcomes (87, 88).

Blood cultures before antibiotic therapy.

Imaging studies performed promptly to confirm potential source of infection.

Administration of broad-spectrum antibiotic therapy within 1 hour of diagnosis of septic shock and severe sepsis without septic shock.

Reassessment of antibiotic therapy with microbiology and clinical data to narrow coverage, when appropriate.

TABLE 5 Target parameters of early goal-directed therapy (8)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central venous pressure (CVP)</td>
<td>8–12 mm Hg</td>
</tr>
<tr>
<td>Mean arterial pressure (MAP)</td>
<td>65–90 mm Hg</td>
</tr>
<tr>
<td>Central venous oxygen (CVO₂)</td>
<td>≥70%</td>
</tr>
<tr>
<td>Hematocrit (HCT)</td>
<td>&gt;30%</td>
</tr>
<tr>
<td>Urine output</td>
<td>&gt;40 ml/h</td>
</tr>
</tbody>
</table>

A usual 7 to 10 days duration of antibiotic therapy guided by clinical response.

Source control with attention to the balance of risks and benefits of the chosen method.

Administration of crystalloid-fluid resuscitation and consideration of adding albumin in certain patient groups.

Fluid challenge to restore mean circulating-filling pressure.

Vasopressor preference for norepinephrine to maintain an initial target of mean arterial pressure ≥65 mm Hg and epinephrine when an additional vasopressor is needed.

Avoiding use of steroid therapy.

In the absence of tissue hypoperfusion, coronary artery disease, or acute hemorrhage, the hemoglobin target is 7 to 9 g/dL.

A low tidal volume and limitation of inspiratory plateau pressure strategy for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS).

Application of at least a minimal amount of positive end-expiratory pressure in acute lung injury.

Head of bed elevation in mechanically ventilated patients unless contraindicated.

Protocols for weaning and sedation/analgesia.

Minimizing use of either intermittent-bolus sedation or continuous-infusion sedation.

Avoidance of neuromuscular blockers, if at all possible.

A protocoled approach to blood-glucose management.

Continuous veno-veno hemofiltration or intermittent hemodialysis is equivalent.

Prophylaxis for deep-vein thrombosis.

Use of stress-ulcer prophylaxis to prevent upper gastrointestinal bleeding in patients at risk.

Oral or enteral feedings.

Consideration of limitation of support where appropriate.

ALGORITHM MANAGEMENT OF UROSEPSIS

A rapid diagnosis of urosepsis is critical (8). Effective treatment eliminates the infectious focus, and improves organ perfusion. Treatment of urosepsis comprises four basic strategies:

a. supportive therapy (stabilization and maintaining blood pressure),
b. antimicrobial therapy in the first hour,
c. control or elimination of the complicating factor, and
d. specific sepsis therapy (89).

All four strategies need to be started as early as possible. A diagnosis and management algorithm is therefore helpful (Fig. 4):

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 hypovolemic, has pre-existing myocardial dysfunction, or is at late stage of the septic process, hypotension, vasoconstriction, and peripheral cyanosis may be present. The internationally accepted criteria for diagnosis of SIRS and sepsis (Table 1) should rapidly be checked in order to initiate further investigations.

If sepsis is suspected, early (i.e., first hour) supportive therapy with stabilization of the blood pressure and sufficient tissue oxygenation is mandatory. The management of fluid and electrolyte balance is a crucial aspect of patient care in sepsis syndrome, particularly when the clinical course is complicated by shock. An early (immediate) goal-directed therapy has been shown to reduce mortality in one study (8), but has been questioned in two other studies (87, 88). Volemic expansion and vasopressor therapy have considerable impact on the outcome. Early (immediate) intervention to maintain adequate tissue perfusion and oxygen delivery by prompt institution of fluid therapy, stabilization of arterial pressure, and provision of sufficient oxygen-transport capacity are highly effective (90) (Table 5).

Additional symptoms pointing to the urogenital tract should be examined: flank pain, costovertebral

FIGURE 4 Algorithm for management of urosepsis. doi:10.1128/microbiolspec.UTI-0003-2012.f4
tenderness, renal colic, pain at micturition, urinary retention, and 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 as part of the first routine laboratory tests. In the case of urosepsis, the clinical evidence of UTI is based on symptoms, physical examination, sonographic and radiological features, and laboratory data, such as bacteriuria and leukocyturia.

Immediately after microbiological sampling of urine, blood, and suspicious secretion, tissue, and abscess fluids, empirical broad-spectrum antibiotic therapy should be instigated parenterally.

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 (CT scan; urography) of the urinary tract are generally applied to specify the complicating factor.

If a complicating factor warranting treatment is identified, control and/or removal of the complicating factor should follow immediately. Drainage of any obstruction in the urinary tract and removal of foreign bodies, such as urinary catheters or stones, may themselves cause resolution of symptoms and lead to recovery. These are key components of the strategy. This condition is an absolute emergency. The way by which the complicating factor is controlled should be as least invasive as possible. The definitive elimination of the complicating factor can be performed after days or weeks, until the general condition of the patient has improved.

In parallel with the urological control of the septic focus, further intensive medical treatment encompassing specific sepsis therapy should be instigated.

is frequently found after removal of the indwelling catheter, but occurs less frequently in elderly patients. (91)

**Pyelonephritis**

The pathophysiological early alterations in pyelonephritis have recently been addressed in a uropathogenic *E. coli*-induced pyelonephritis animal model, where it was shown that epithelial signaling produced an increase in cellular oxygen consumption and affected microvascular flow by clotting, causing localized ischemia (92). The subsequent ischemic damage led to actin re-arrangement and epithelial sloughing, leading to paracellular bacterial movement. A denuded tubular basement membrane was able to hinder immediate dissemination of bacteria, giving the host time to isolate the infection by clotting. Interestingly, suppression of clotting by heparin treatment caused fatal urosepsis (92). Clinically, these findings may be relevant in antibiotic delivery in pyelonephritis patients and to the use of anticoagulants in sepsis and should therefore be followed up in clinical studies.

Clinical symptoms of pyelonephritis are unilateral or bilateral flank pain, and systemic symptoms such as fever (>38°C), chills, or malaise. Focal nephritis is limited to one or more renal lobules, comparable to lobular pneumonia. Ultrasonographic findings are of a circumscribed lesion with interrupted echoes, which break through the normal cortex-medulla organization. The CT scan shows typical wedge-shaped, poorly limited areas of diminished sonographic density. As differential diagnoses, renal abscess, tumor, and renal infarction must be taken into account. Emphysematous pyelonephritis characteristically shows gas formation in the renal parenchyma and perirenal space. Diabetes mellitus or obstructive renal disease are predisposing factors. The most frequently isolated organisms are *E. coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae*. Fermentation of glucose in Enterobacteriaceae occurs via two different metabolic pathways: mixed-acid fermentation and the butylene-glycol pathway. Organisms of the *Klebsiella-Enterobacter-Hafnia-Serratia* group, and to a lesser extent *E. coli*, use the butylene-glycol pathway and produce copious amounts of CO₂, which appears clinically as gas formation (93). Aggravated by diminished tissue perfusion, the contralateral side is often affected as well.

**Renal and Perirenal Abscess**

Clinical symptoms are rigors, fever, back or abdominal pain, flank tenderness, mass lesion and redness of the
flank, and protection of upper lumbar and paraspinous muscles. Respiratory insufficiency, hemodynamic instability, or reflexory paralytic ileus can occur. Frequent signs of renal-abscess formation are fever and increasing inflammatory parameters such as leukocytosis for more than 72 hours, despite antibiotic therapy. In this case, further imaging has to be done for diagnosis of renal abscess. Urinary culture may be negative in 14% to 20% of cases (94). Frequently isolated organisms are *E. coli*, *K. pneumoniae*, Proteus species, and *S. aureus* from hematogenous spread. The fascial limitations are open distally and the perirenal fat is in close contact with the pelvic fat tissue. A perinephritic abscess may therefore point to groin or perivesical tissue, or to the contralateral side, thus penetrating the peritoneum. Inflammation of flank, thigh, back, buttocks, and lower abdomen may occur. Blood cultures are positive in 10% to 40% of cases, and urinary cultures are positive in 50% to 80% (95). Prompt surgical treatment must be performed, such as drainage or, ultimately, nephrectomy.

### Acute Prostatitis and Prostatic Abscess

Acute prostatitis and prostatic abscess are bacterial infections of the prostate gland. The bacterial spectrum consists of 53% to 80% *E. coli* and other enterobacteria, 19% Gram-positive bacteria, and 17% anaerobic bacteria (96). Acute bacterial prostatitis can ensue after transrectal prostate biopsy for diagnosis of prostate cancer. Recently, various studies have reported an apparent increase in the incidence of infective complications after transrectal prostate biopsies, reaching up to 5% of men suffering from symptomatic UTI and resulting in bacterial prostatitis in about 3% of patients undergoing prostate biopsies (67, 97–100). The most important risk factor seems to be the increase of fecal fluoroquinolone-resistant *E. coli* (100).

Symptoms are high fever, rigors, dysuria, urinary retention, and perineal pain. Rectal palpation reveals an enlarged, tender prostate. Prostate massage is contraindicated. In acute prostatitis the pathogens are usually detected in urine. However, the urine may be sterile in prostatic-abscess formation. Therapy consists of a combination of antibiotic therapy with broad-spectrum antibiotics, as well as the insertion of a suprapubic catheter, if there is urinary retention. If the patient had a history of fluoroquinolone treatment in the past months, fluoroquinolones should not be administered empirically. In the case of a prostatic abscess, urologic drainage is necessary (96).

### Epididymitis/Orchitis

Epididymitis is usually an ascending infection and can also involve the testis as well. Possible causes are subvesical obstruction, transurethral resection of the prostate, or an indwelling, transurethral urinary catheter, in which case the pathogens are identical with the pathogens in the urine. Of note, epididymitis is frequently involved in urogenital tuberculosis. Orchitis with the formation of a sterile hydrocele can appear in the course of polyserositis or heart insufficiency and may point to a generalized systemic disease.

### Cavernitis

Cavernitis of the penis is a rare phlegmonous infection of the cavernous bodies. Possible causes are indwelling transurethral urinary catheters, penile operations, auto-injection for erectile dysfunction, pelvic operations, or trauma. Pathogens may represent skin flora or urogenital pathogens. Treatment consists of suprapubic catheterization, broad-spectrum antibiotic therapy, and, if needed, operative debridement.

### Fournier’s gangrene

Fournier’s gangrene is a necrotizing fasciitis of dartos and Colles’ fascias. It is mainly seen in men in the fourth to seventh decade but also occurs in women or the newborn. Causes are operations or trauma in the genital or perineal region, including microlesions, or infectious processes from the rectal or urethral areas. Important predisposing factors are diabetes mellitus, liver insufficiency, chronic alcoholism, hematologic diseases, or malnutrition. Patient-related predictors of mortality are increasing age, increased comorbidity, preexisting conditions, such as congestive heart failure, renal failure, and coagulopathy, and hospital admission via transfer (101). Fatality rates were 7.5% in one large North American study (102).

The use of a Fournier’s gangrene-severity index has been shown to correlate well with the course of the disease. A Fournier’s gangrene-severity index-threshold value of nine was significantly associated with outcome (103): A score greater than nine showed a 75% probability of death, while a score of nine or less was associated with a 78% probability of survival (103).

The infectious process follows anatomically preformed spaces. The superficial perineal fascia is fixed dorsally at the transverse deep-perineal muscle and laterally at the iliac bone and merges ventrally in the superficial abdominal fascia. Hence, a ventrally open and craniodorsally and laterally closed space is formed (Colles’ space) that facilitates the spread of infection.
In contrast to gas gangrene, the fascial borders are respected in Fournier’s gangrene. A mixed bacterial flora is seen, consisting of Gram-positive cocci, enterobacteria, and anaerobic bacteria. The released toxins facilitate platelet aggregation and entrapment of complement, which, in conjunction with the release of heparinase by anaerobic bacteria, leads to small-vessel thrombosis and tissue necrosis. The destruction of tissue enhances the potential of acute renal failure. Fournier’s gangrene is a rapidly progressing infection leading to septic shock, if not treated in time.

Therapy consists of immediate, operative debridement, followed by subsequent operations, until the infectious process has been controlled. A suprapubic catheter is advisable and a colostomy needs to be performed in some cases in which continuous fecal contamination of the wound is inevitable. A combination of antibiotic therapy with broad-spectrum β-lactam antibiotics, fluoroquinolones, and clindamycin is recommended.

PREVENTION OF UROSEPSIS
Septic shock is the most frequent cause of death for patients hospitalized for both community- and nosocomial-acquired infection (20% to 40%). Sepsis initiates the cascade that progresses to severe sepsis and then septic shock in a clinical continuum. Urosepsis treatment calls for the early combination of treatment of the cause (obstruction), adequate life-supporting care, and appropriate antibiotic therapy. In such a situation, it is recommended that urologists collaborate early with intensive-care and infectious-disease specialists for the best management of the patient (104).

The most effective methods to prevent nosocomial urosepsis are the same as those used to prevent other nosocomial infections. As most urosepsis cases are due to obstruction of the urinary tract at some level, the development of the full picture of septic shock can frequently be prevented by performing an early de-obstruction procedure. A patient with a so-called “infected hydronephrosis” is an absolute emergency. Before starting the de-obstruction procedure, an empirical antibiotic treatment needs to be administered.

There are no randomized data available. However, in a historical cohort study it was shown that, despite antimicrobial therapy, appropriate urological intervention was very important. Of 49 patients with urosepsis due to pyonephrosis, 22% died despite intensive care, but no patient died if pyonephrosis was treated by nephrectomy or, in a few cases, by nephrostomy drainage before urosepsis developed (105).

CONCLUSION
Sepsis syndrome in urology remains a severe situation with a mortality rate as high as 20% to 40%. A recent campaign, ‘Surviving Sepsis Guidelines’, aimed at reducing mortality by 25% in the next few years (20, 84). Early recognition of the symptoms may decrease the mortality by timely treatment of urinary tract disorders, e.g., obstruction by urolithiasis. Adequate life-support measures and appropriate antibiotic treatment, including optimized dosing, provide the best conditions for improving patients’ survival. The prevention of sepsis syndrome is dependent on good practice to avoid nosocomial infections and using antibiotic prophylaxis and therapy in a prudent and well-accepted manner.

ACKNOWLEDGMENTS
Conflicts of interest: F. Wagenlehner is a consultant at the following companies: Achaogen, Astellas, Astra-Zeneca, Bionorica, Cubist/MD, Galenius, Leo Pharma, Medpace, MerLion, OM-Pharma/Vifor, Remepx Pharm, Rosen Pharma, Shionogi.

K. Naber is a consultant at the following companies: Basilea, Bayer, Bionorica, Boehringer Ingelheim, Cubist/MSD, Daiichi Sankyo, Galenius, Leo Pharma, Melinta, MerLion, OM-Pharma/Vifor, Paratek, Pierre Fabre, Remepx Pharm, Rosen Pharma, Shionogi, Zambon.

A. Pilatz and W. Weidner declare no conflicts of interest.

REFERENCES


