International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

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A Panel of International Experts was convened by the Infectious Diseases Society of America (IDSA) in collaboration with the European Society for Microbiology and Infectious Diseases (ESCMID) to update the 1999 Uncomplicated Urinary Tract Infection Guidelines by the IDSA. Co-sponsoring organizations include the American Congress of Obstetricians and Gynecologists, American Urological Association, Association of Medical Microbiology and Infectious Diseases–Canada, and the Society for Academic Emergency Medicine. The focus of this work is treatment of women with acute uncomplicated cystitis and pyelonephritis, diagnoses limited in these guidelines to premenopausal, non-pregnant women with no known urological abnormalities or co-morbidities. The issues of in vitro resistance prevalence and the ecological adverse effects of antimicrobial therapy (collateral damage) were considered as important factors in making optimal treatment choices and thus are reflected in the rankings of recommendations.

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The process for evaluating the evidence was based on the IDSA Handbook on Clinical Practice Guideline Development and involved a systematic weighting of the quality of the evidence and the grade of recommendation (Table 1) [31]

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

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EXECUTIVE SUMMARY

BACKGROUND

Acute uncomplicated cystitis remains one of the most common indications for prescribing of antimicrobials to otherwise healthy community-dwelling women. Despite published guidelines for the optimal selection of an antimicrobial agent and duration of therapy, studies demonstrate a wide variation in prescribing practices [1–6]. The Infectious Diseases Society of America (IDSA) published a clinical practice guideline on the treatment of women with acute uncomplicated cystitis and pyelonephritis in 1999 [1]. Since then, antimicrobial resistance among uropathogens causing uncomplicated cystitis has increased, appreciation of the importance of

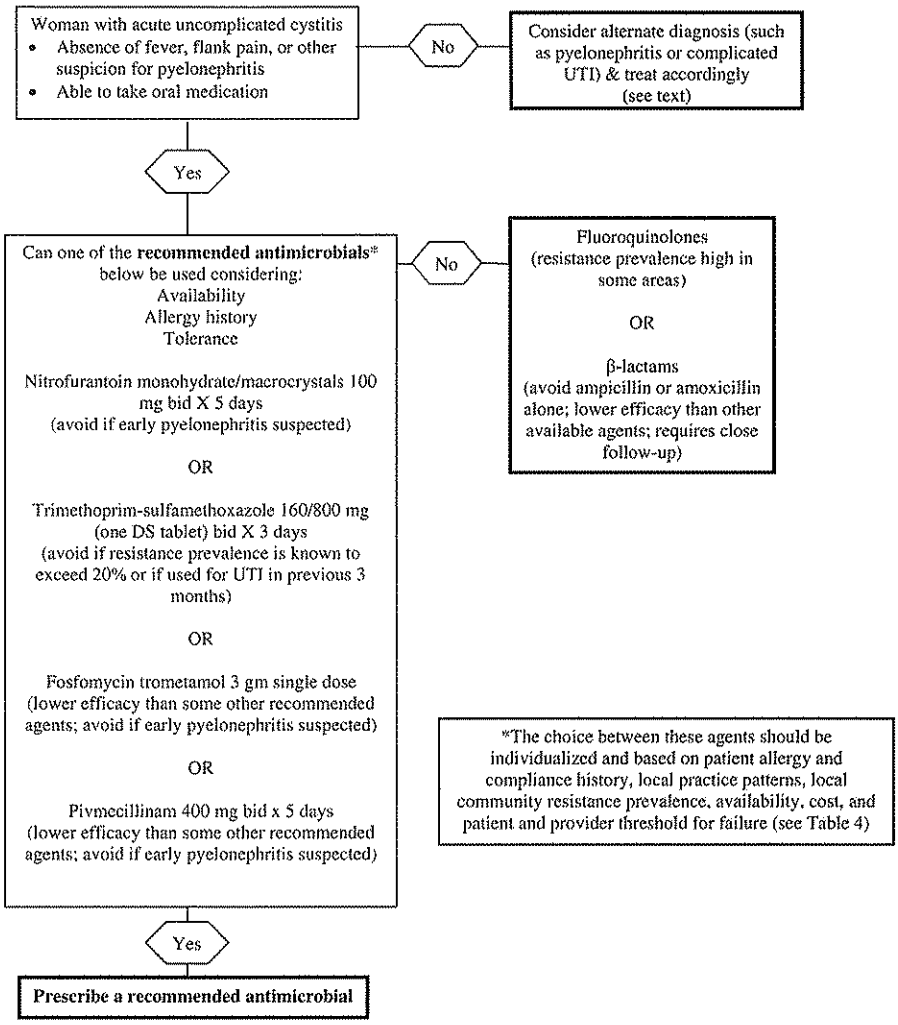

Figure 1. Approach to choosing an optimal antimicrobial agent for empirical treatment of acute uncomplicated cystitis. DS, double-strength; UTI, urinary tract infection.

the ecological adverse effects of antimicrobial therapy (collateral damage) has increased, newer agents and different durations of therapy have been studied, and clinical outcomes have increasingly been reported. In addition, women with uropathogens resistant to the treatment drug have been included in some studies, allowing for estimations of expected response rates in a "real-life" clinical setting in which empirical therapy is prescribed either without a urine culture and susceptibility testing or before such results are known. In light of these developments, an update of the guidelines was warranted.

The focus of this guideline is treatment of women with acute uncomplicated cystitis and pyelonephritis, diagnoses limited in these guidelines to premenopausal, nonpregnant women with no known urological abnormalities or comorbidities. It should be noted that women who are postmenopausal or have well-controlled diabetes without urological sequelae may be considered by some experts to have uncomplicated urinary tract infection (UTI), but a discussion of specific management of these groups is outside the scope of this guideline. In addition, management of recurrent cystitis and of UTI in pregnant women, prevention of UTI, and diagnosis of UTI are all important issues that are not addressed in this guideline. The issues of in vitro resistance prevalence and the potential for collateral damage were considered as important factors in making optimal treatment choices and thus are reflected in the rankings of recommendations.

Summarized below are the recommendations made in the 2010 guideline update. The Panel followed a process used in the development of other IDSA guidelines which included a systematic weighting of the quality of the evidence and the grade of recommendation [32] (Table 1). A detailed description of the methods, background, and evidence summaries that support

each of the recommendations can be found in the full text of the guideline.

I.What Is the Optimal Treatment for Acute Uncomplicated Cystitis?

***Recommendations* (Figure 1).**

1. Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for 5 days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage (defined above) and efficacy comparable to 3 days of trimethoprim-sulfamethoxazole (A-I).

2. Trimethoprim-sulfamethoxazole (160/800 mg [1 double-strength tablet] twice-daily for 3 days) is an appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20% or if the infecting strain is known to be susceptible (A-I).

i. The threshold of 20% as the resistance prevalence at which the agent is no longer recommended for empirical treatment of acute cystitis is based on expert opinion derived from clinical, in vitro, and mathematical modeling studies (B-III).

ii. In some countries and regions, trimethoprim (100 mg twice daily for 3 days) is the preferred agent and is considered equivalent to trimethoprim-sulfamethoxazole on the basis of data presented in the original guideline (A-III) [1].

iii. Data are insufficient to make a recommendation for other cystitis antimicrobials as to what resistance prevalence should be used to preclude their use for empirical treatment of acute cystitis.

3. Fosfomycin trometamol (3 g in a single dose) is an appropriate choice for therapy where it is available due to minimal resistance and propensity for collateral damage, but it appears to have inferior efficacy compared with standard short-course regimens according to data submitted to the US Food and Drug Administration (FDA) and summarized in the Medical Letter (A-I) [7].

4. Pivmecillinam (400 mg bid for 3–7 days) is an appropriate choice for therapy in regions where it is available (availability limited to some European countries; not licensed and/or available for use in North America), because of minimal resistance and propensity for collateral damage, but it may have inferior efficacy compared with other available therapies (A-I).

5. The fluoroquinolones, ofloxacin, ciprofloxacin, and levofloxacin, are highly efficacious in 3-day regimens (A-I) but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis (A-III).

6. β-Lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in 3–7-day regimens are appropriate choices for therapy when other recommended agents cannot be used (B-I). Other β-lactams, such as cephalexin, are less well studied but may also be appropriate in certain settings (B-III). The β-lactams generally have inferior efficacy and more adverse effects, compared with other UTI antimicrobials (B-I). For these reasons, β-lactams other than pivmecillinam should be used with caution for uncomplicated cystitis.

7. Amoxicillin or ampicillin should not be used for empirical treatment given the relatively poor efficacy, as discussed in the 1999 guidelines [1] and the very high prevalence of antimicrobial resistance to these agents worldwide [8–11] (A-III).

II.What Is the Treatment for Acute Pyelonephritis?

Recommendations

8. In patients suspected of having pyelonephritis, a urine culture and susceptibility test should always be performed, and initial empirical therapy should be tailored appropriately on the basis of the infecting uropathogen (A-III).

9. Oral ciprofloxacin (500 mg twice daily) for 7 days, with or without an initial 400-mg dose of intravenous ciprofloxacin, is an appropriate choice for therapy in patients not requiring hospitalization where the prevalence of resistance of community uropathogens to fluoroquinolones is not known to exceed 10% (A-I). If an initial one-time intravenous agent is used, a long-acting antimicrobial, such as 1 g of ceftriaxone or a consolidated 24-h dose of an aminoglycoside, could be used in lieu of an intravenous fluoroquinolone (B-III). If the prevalence of fluoroquinolone resistance is thought to exceed 10%, an initial 1-time intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone (B-III) or a consolidated 24-h dose of an aminoglycoside, is recommended (B-III).

i. Data are insufficient to make a recommendation about what fluoroquinolone resistance level requires an alternative agent in conjunction with or to replace a fluoroquinolone for treatment of pyelonephritis.

10. A once-daily oral fluoroquinolone, including ciprofloxacin (1000 mg extended release for 7 days)or levofloxacin (750 mg for 5 days), is an appropriate choice for therapy in patients not requiring hospitalization where the prevalence of resistance of community uropathogens is not known to exceed 10% (B-II). If the prevalence of fluoroquinolone resistance is thought to exceed 10%, an initial intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone (B-III) or a consolidated 24-h dose of an aminoglycoside, is recommended (B-III).

11. Oral trimethoprim-sulfamethoxazole (160/800 mg [1 double-strength tablet] twice-daily for 14 days) is an appropriate choice for therapy if the uropathogen is known to be susceptible (A-I). If trimethoprim-sulfamethoxazole is used when the susceptibility is not known, an initial intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone (B-II) or a consolidated 24-h dose of an aminoglycoside, is recommended (B-III).

12. Oral β-lactam agents are less effective than other available agents for treatment of pyelonephritis (B-III). If an oral β-lactam agent is used, an initial intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone (B-II) or a consolidated 24-h dose of an aminoglycoside, is recommended (B-III).
i. Data are insufficient to modify the previous guideline recommendation for a duration of therapy of 10–14 days for treatment of pyelonephritis with a β-lactam agent.

13. Women with pyelonephritis requiring hospitalization should be initially treated with an intravenous antimicrobial regimen, such as a fluoroquinolone; an aminoglycoside, with or without ampicillin; an extended-spectrum cephalosporin or extended-spectrum penicillin, with or without an aminoglycoside; or a carbapenem. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results (B-III).

INTRODUCTION

The focus of this guideline is management of women with acute uncomplicated cystitis and pyelonephritis who are not pregnant and have no known urological abnormalities or co-morbidities. An optimal approach to therapy includes consideration of antimicrobial resistance and collateral damage.

Consideration of Antimicrobial Resistance

The microbial spectrum of uncomplicated cystitis and pyelonephritis consists mainly of *Escherichia coli* (75%–95%), with occasional other species of Enterobacteriaceae, such as *Proteus mirabilis* and *Klebsiella pneumoniae*, and *Staphylococcus saprophyticus*. Other gram-negative and gram-positive species are rarely isolated in uncomplicated UTIs. Therefore, local antimicrobial susceptibility patterns of *E. coli* in particular should be considered in empirical antimicrobial selection for uncomplicated UTIs. Since the resistance patterns of *E. coli* strains causing uncomplicated UTI varies considerably between regions and countries, a specific treatment recommendation may not be universally suitable for all regions or countries.

Active surveillance studies of in vitro susceptibility of uropathogens in women with uncomplicated cystitis are helpful in making decisions about empirical therapy. Four large studies reporting in vitro susceptibility of *E. coli* causing uncomplicated UTI in North America and Europe were reviewed [8–11]. All of these demonstrate considerable geographic variability in susceptibility. For example, resistance rates for all antimicrobials were higher in US medical centers than in Canadian medical centers and were usually higher in Portugal and Spain than other European countries. In general, resistance rates >20% were reported in all regions for ampicillin, and in many countries and regions for trimethoprim with or without sulfamethoxazole. Fluoroquinolone resistance rates were still <10% in most parts of North America and Europe, but there was a clear trend for increasing resistance compared with previous years. Moreover, the resistance data for nalidixic acid in these studies suggest that >10% (in some countries, >20%) of the *E. coli* strains have acquired resistance genes for quinolones [10, 11]. First- and second-generation oral cephalosporins and amoxicillin-clavulanic acid also show regional variability, but the resistance rates were generally <10%. Despite wide variability in antimicrobial susceptibility among the different countries studied, nitrofurantoin, fosfomycin, and mecillinam (the latter 2 not tested in the Canadian study) had good in vitro activity in all the countries investigated. Thus, these 3 antimicrobials could be considered appropriate antimicrobials for empirical therapy in most regions [8–11]. Given a trend toward increasing resistance, compared with previous years, for most antimicrobials, continued monitoring of this data to evaluate rates over time is necessary for sustained optimization of empirical therapy [12].

Because local in vitro resistance rates are not always known, and change over time is anticipated, identification of individual predictors of resistance can also be useful to informing empirical antimicrobial choice. In 2 studies evaluating epidemiological predictors of resistance, the use of trimethoprim-sulfamethoxazole in the preceding 3–6 months was an independent risk factor for trimethoprim-sulfamethoxazole resistance in women with acute uncomplicated cystitis [13, 14]. In addition, 2 US-based studies demonstrated that travel outside the United States in the preceding 3–6 months was independently associated with trimethoprim-sulfamethoxazole resistance [15, 16]. Predictors of resistance to other cystitis antimicrobials are not as well studied but in general support the findings that exposure to the drug or to an area with endemic resistance are important factors to consider [17, 18]. Local resistance rates reported in hospital antibiograms are often skewed by cultures of samples obtained from inpatients or those with complicated infection and may not predict susceptibilities in women with uncomplicated community-acquired infection, in whom resistance rates tend to be lower [18, 19]. Prospective and unbiased resistance surveillance of uncomplicated uropathogens at the local practice and/or health care system levels is critical for informing empirical antimicrobial decisions. In the absence of such

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5. SEPSIS SYNDROME IN UROLOGY (UROSEPSIS)

5.1 Summary and recommendations

Patients with urosepsis should be diagnosed at an early stage, especially in the case of a complicated UTI. The systemic inflammatory response syndrome, known as SIRS (fever or hypothermia, hyperleukocytosis or leukopenia, tachycardia, tachypnoea), is recognised as the first event in a cascade to multi-organ failure. Mortality is considerably increased when severe sepsis or septic shock are present, although the prognosis of urosepsis is globally better than that of sepsis from other infectious sites.

The treatment of urosepsis calls for the combination of adequate life-supporting care, appropriate and prompt antibiotic therapy, adjunctive measures (e.g. sympathomimetic amines, hydrocortisone, blood glucose control) and the optimal management of urinary tract disorders (LE: 1a, GR: A). The drainage of any obstruction in the urinary tract is essential as first-line treatment (LE: 1b, GR: A). Urologists are recommended to treat patients in collaboration with intensive care and infectious diseases specialists (LE; 2a, GR: B).

Urosepsis is seen in both community-acquired and healthcare associated infections. Most nosocomial urosepsis can be avoided by measures used to prevent nosocomial infection, e.g. reduction of hospital stay, early removal of indwelling urethral catheters, avoidance of unnecessary urethral catheterisation, correct use of closed catheter systems, and attention to simple daily asepsis techniques to avoid cross-infection (LE: 2a, GR: B).

5.2 Background

Urinary tract infections can manifest as bacteriuria with limited clinical symptoms, sepsis or severe sepsis, depending on localised or systemic extension. Sepsis is diagnosed when clinical evidence of infection is accompanied by signs of systemic inflammation (fever or hypothermia, tachycardia, tachypnoea, leukocyturia or leukopenia). Severe sepsis is defined by the presence of symptoms of organ dysfunction, and septic shock by the presence of persistent hypotension associated with tissue anoxia.

Severe sepsis has a mortality rate of 20-42% (1) with most reports in the literature related to pulmonary (50%) or abdominal (24%) infections, with UTIs accounting for only 5% (2). Sepsis is more common in men than in women (3). In recent years, the incidence of sepsis has increased by 8.7% per year (1), but the associated mortality has decreased, which suggests improved management of patients (total in-hospital mortality rate fell from 27.8% to 17.9% from 1995 to 2000 (4). Globally (this is not true for urosepsis), the rate of sepsis due to fungal organisms has increased while Gram-positive bacteria have become the predominant pathogen in sepsis, even if Gram-negative bacteria remain predominant in urosepsis.

In urosepsis, as in other types of sepsis, the severity depends mostly upon the host response. Patients who are more likely to develop urosepsis include: elderly patients; diabetics; immunosuppressed patients, such as transplant recipients; patients receiving cancer chemotherapy or corticosteroids; and patients with AIDS. Urosepsis also depends on local factors, such as urinary tract calculi, obstruction at any level in the urinary tract, congenital uropathy, neurogenic bladder disorders, or endoscopic manoeuvres. However, all patients can

be affected by bacterial species that are capable of inducing inflammation within the urinary tract. Moreover, it is now recognised that SIRS may be present without infection (e.g. pancreatitis, burns, or non-septic shock) (5).

For therapeutic purposes, the diagnostic criteria of sepsis should identify patients at an early stage of the syndrome, which should prompt urologists and intensive care specialists to search for and treat infection, apply appropriate therapy, and monitor for organ failure and other complications.

5.3 Definition and clinical manifestation of sepsis in urology

The clinical evidence of UTI is based on symptoms, physical examination, sonographic and radiological features, and laboratory data, such as bacteriuria and leukocyturia. The following definitions apply (Table 5.1):

- Sepsis is a systemic response to infection. The symptoms of SIRS which were initially considered to be 'mandatory' for the diagnosis of sepsis (5), are now considered to be alerting symptoms (6). Many other clinical or biological symptoms must be considered.
- Severe sepsis is associated with organ dysfunction.
- Septic shock is persistence of hypoperfusion or hypotension despite fluid resuscitation.
- Refractory septic shock is defined by an absence of response to therapy.

Table 5.1: Clinical diagnostic criteria of sepsis and septic shock (5,6)

Disorder	Definition
Infection	Presence of organisms in a normally sterile site that is usually, but not necessarily, accompanied by an inflammatory host response.
Bacteraemia	Bacteria present in blood as confirmed by culture. May be transient.
Systematic 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 aetiology (e.g. burns, or pancreatitis). This systemic response is manifested by two or more of the following conditions: - Temperature > 38°C or < 36°C - Heart rate > 90 bpm - Respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg (< 4.3 kPa) - WBC > 12,000 cells/mm^3 or < 4,000 cells/mm^3 or > 10% immature (band) forms
Sepsis	Activation of the inflammatory process due to infection.
Hypotension	Systolic blood pressure < 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 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 acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.
Refractory septic shock	Septic shock that lasts for > 1 h and does not respond to fluid administration or pharmacological intervention.

5.4 Physiology and biochemical markers

Microorganisms reach the urinary tract by way of the ascending, haematogenous, or lymphatic routes. For urosepsis to be established, the pathogens have to reach the bloodstream. The risk of bacteraemia is increased in severe UTIs, such as pyelonephritis and acute bacterial prostatitis, and is facilitated by obstruction of the urinary tract. *E. coli* remains the most prevalent microorganism. In several countries, some bacterial strains can be resistant to quinolones or third-generation cephalosporins. Some microorganisms are multi-resistant, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *P. aeruginosa* and *Serratia* sp. and

therefore difficult to treat. Most commonly, the condition develops in compromised patients (e.g. those with diabetes or immunosuppression), with typical signs of generalised sepsis associated with local signs of infection. A fatal outcome is described in 20-40% of all patients.

5.4.1 Cytokines as markers of the septic response

Cytokines are involved in the pathogenesis of sepsis syndrome. They are peptides that regulate the amplitude and duration of the host inflammatory response. They are released from various cells including monocytes, macrophages and endothelial cells, in response to various infectious stimuli. When they become bound to specific receptors on other cells, cytokines change their behaviour in the inflammatory response. The complex balance between pro- and anti-inflammatory responses is modified in severe sepsis. An immunosuppressive phase follows the initial pro-inflammatory mechanism. Other cytokines that are associated with sepsis are interleukins (ILs) (IL-1, -6, -8) and tumour necrosis factor (TNF)-α. Sepsis may indicate an immune system that is severely compromised and unable to eradicate pathogens or a non-regulated and excessive activation of inflammation, or both. Genetic predisposition is a probable explanation of sepsis in several patients. Mechanisms of organ failure and death in patients with sepsis remain only partially understood (2).

5.4.2 Procalcitonin is a potential marker of sepsis

Procalcitonin is the propeptide of calcitonin, but is devoid of hormonal activity. Normally, levels are undetectable in healthy humans. During severe generalised infections (bacterial, parasitic and fungal) with systemic manifestations, procalcitonin levels may rise to > 100 ng/mL. In contrast, during severe viral infections or inflammatory reactions of non-infectious origin, procalcitonin levels show only a moderate or no increase. The exact site of procalcitonin production during sepsis is not known. Procalcitonin monitoring may be useful in patients likely to develop a SIRS of infectious origin. High procalcitonin levels, or an abrupt increase in levels in these patients, should prompt a search for the source of infection. Procalcitonin may be useful in differentiating between infectious and non-infectious causes of severe inflammatory status (7,8).

5.5 Prevention

Septic shock is the most frequent cause of death for patients hospitalised for community-acquired and nosocomial infection (20-40%). Sepsis initiates the cascade that progresses to severe sepsis and then septic shock in a clinical continuum. Urosepsis treatment calls for a combination of treatment of the cause (obstruction of the urinary tract), adequate life-supporting care, and appropriate antibiotic therapy (2). In such a situation, it is recommended that urologists collaborate with intensive care and infectious disease specialists for the best management of the patient.

5.5.1 Preventive measures of proven or probable efficacy (9,10)

The most effective methods to prevent nosocomial urosepsis are the same as those used to prevent other nosocomial infections:

- Isolation of all patients infected with multi-resistant organisms to avoid cross-infection.
- Prudent use of antimicrobial agents for prophylaxis and treatment of established infections, to avoid selection of resistant strains. Antibiotic agents should be chosen according to the predominant pathogens at a given site of infection in the hospital environment.
- Reduction in hospital stay. It is well known that long inpatient periods before surgery lead to a greater incidence of nosocomial infections.
- Early removal of indwelling urethral catheters, as soon as allowed by the patient's condition. Nosocomial UTIs are promoted by bladder catheterisation as well as by ureteral stenting (11). Antibiotic prophylaxis does not prevent stent colonisation, which appears in 100% of patients with a permanent ureteral stent and in 70% of those temporarily stented.
- Use of closed catheter drainage and minimisation of breaks in the integrity of the system, e.g. for urine sampling or bladder wash-out.
- Use of least-invasive methods to release urinary tract obstruction until the patient is stabilised.
- Attention to simple everyday techniques to assure asepsis, including the routine use of protective, disposable gloves, frequent hand disinfection, and using infectious disease control measures to prevent cross-infections.

5.5.2 Appropriate perioperative antimicrobial prophylaxis

For appropriate perioperative antimicrobial prophylaxis, see Chapter 15. The potential side effects of antibiotics must be considered before their administration in a prophylactic regimen.

5.5.3 Preventive measures of debatable efficacy

- Instillation of antibiotic or antiseptic drugs into catheters and drainage bags.

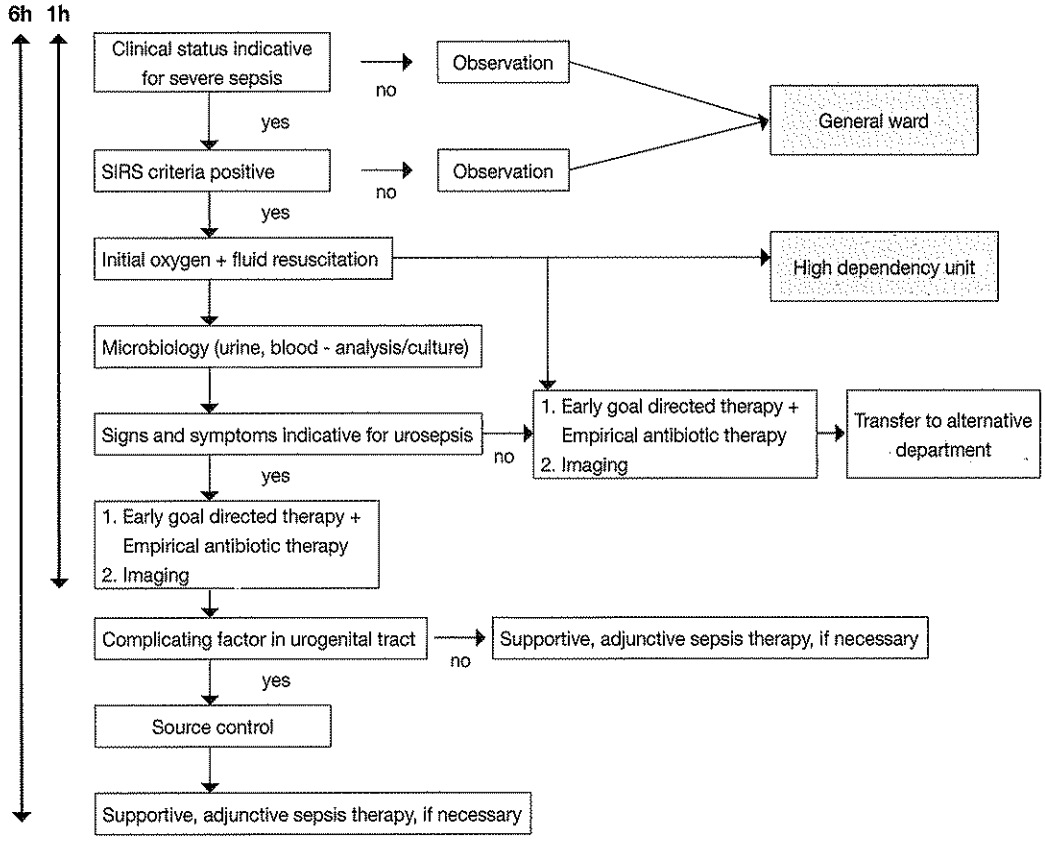
- Use of urinary catheters coated with antibiotics or silver.

5.5.4 *Ineffective or counterproductive measures*

- Continuous or intermittent bladder irrigations with antibiotics or urinary antiseptics that increase the risk of infection with resistant bacteria (9,12).
- Routine administration of antimicrobial drugs to catheterised patients, which reduces the incidence of bacteriuria only for a few days and increases the risk of infection with multi-resistant bacteria (9,12). Its use may be reserved for immunosuppressed patients.

5.6 Algorithm for the management of urosepsis

Figure 5.1: Clinical algorithm for the management of urosepsis



5.7 Treatment

5.7.1 *Clinical algorithm for management of urosepsis*

Table 5.2: Early goal directed therapy

Early goal directed therapy	
Central venous pressure (CVP)	8-12 mmHg
Mean arterial pressure (MAP)	65-90 mmHg
Central venous oxygen (CVO2)	≥ 70%
Haematocrit (HKT)	> 30 %
Urine output	> 40 mL/h

Table 5.3: Levels of therapy in sepsis

Levels of therapy in sepsis	
Causal therapy	1. Antimicrobial treatment 2. Source control
Supportive therapy	1. Haemodynamic stabilisation 2. Airways, respiration
Adjunctive therapy	1. Glucocorticosteroids 2. Intensified insulin therapy

*5.7.2 **Relief of obstruction***

Drainage of any obstruction in the urinary tract and removal of foreign bodies, such as urinary catheters or stones, should lead to resolution of symptoms and recovery. These are key components of the strategy. This condition is an absolute emergency.

*5.7.3 **Antimicrobial therapy***

Empirical initial treatment should provide broad antimicrobial coverage and should later be adapted on the basis of culture results. The dosage of the antibiotic substances is of paramount importance in patients with sepsis syndrome and should generally be high, with the exception of patients in renal failure. Antimicrobials must be administered no later than 1 h after clinical assumption of sepsis (see Figure 5.1). The antibacterial treatment options are summarised in Appendix 16.1 and 16.2.

*5.7.4 **Adjunctive measures (12,13)***

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. The use of human albumin is debatable. Early goal-directed therapy has been shown to reduce mortality (14). Volaemic expansion and vasopressor therapy have a considerable impact on the outcome. Early intervention with appropriate measures to maintain adequate tissue perfusion and oxygen delivery by prompt institution of fluid therapy, stabilisation of arterial pressure, and providing sufficient oxygen transport capacity are highly effective.

Hydrocortisone (with a debate on dosage) is useful in patients with relative insufficiency in the pituitary gland-adrenal cortex axis (adrenocorticotropin test) (15).

Tight blood glucose control by administration of insulin doses up to 50 U/h is associated with a reduction in mortality (16).

Current evidence does not support the use of human recombinant activated protein C in adults and children with severe sepsis and septic shock (17).

The best strategy has been summarised and graded according to a careful evidence-based methodology in the recently published 'Surviving Sepsis Guidelines' (18).

5.8 Conclusion

Sepsis syndrome in urology remains a severe situation with a mortality rate as high as 20-40%. A recent campaign, 'Surviving Sepsis Guidelines', aims to reduce mortality by 25% in the next few years (18). Early recognition of the symptoms may decrease the mortality by timely treatment of urinary tract disorders, e.g. obstruction, or urolithiasis. Adequate life-support measures and appropriate antibiotic treatment provide the best conditions for improving patient 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.

5.9 Acknowledgement

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5.10 References

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6. CATHETER-ASSOCIATED UTIs

Based on the EAU guidelines published in 2007 (ISBN-13:978-90-70244-59-0), the following text presents the findings of a comprehensive update produced as a collaborative effort by the ESIU (a full EAU section office), the Urological Association of Asia, the Asian Association of UTI/STD, the Western Pacific Society for Chemotherapy, the Federation of European Societies for Chemotherapy and Infection, and the International Society of Chemotherapy for Infection and Cancer. This text was recently published as "The European and Asian guidelines on management and prevention of catheter-associated urinary tract infections" (1). Since the complete document is available online, only the abstract and a summary of the recommendations are presented here.

6.1 Abstract

We surveyed the extensive literature regarding the development, therapy and prevention of catheter-associated UTIs (CAUTIs). We systematically searched for meta-analyses of randomised controlled trials available in Medline, and gave preference to the Cochrane Central Register of Controlled Trials, and also considered other relevant publications, rating them on the basis of their quality. Studies were identified through a PubMed search. The recommendations of the studies, rated according to a modification of the US Department of Health and Human Services (1992), give a close-to-evidence-based guideline for all medical disciplines, with special emphasis on urology, in which catheter care is an important issue.

The survey found that the urinary tract is the commonest source of nosocomial infection, particularly when the bladder is catheterised (LE: 2a). Most CAUTIs are derived from the patient's own colonic flora (LE: 2b) and the catheter predisposes to UTI in several ways. The most important risk factor for the development of catheter-associated bacteriuria is the duration of catheterisation (LE: 2a). Most episodes of short-term catheter-associated bacteriuria are asymptomatic and are caused by a single organism (LE: 2a). Further organisms tend to be acquired by patients who are catheterised for > 30 days.

The clinician should be aware of two priorities: the catheter system should remain closed and the duration of catheterisation should be minimal (GR: A). The use of nurse-based or electronic reminder systems to remove unnecessary catheters can decrease the duration of catheterisation and the risk of CAUTI (LE: 2a). The drainage bag should be always kept below the level of the bladder and the connecting tube (GR: B). In case of short-term catheterisation, routine prophylaxis with systemic antibiotics is not recommended (GR: B). There are sparse data about antibiotic prophylaxis in patients on long-term catheterisation, therefore, no recommendation can be made (GR: C). For patients using intermittent catheterisation, routine antibiotic prophylaxis is not recommended (GR: B). Antibiotic irrigation of the catheter and bladder is of no advantage (GR: A). Healthcare workers should be constantly aware of the risk of cross-infection between catheterised patients. They should observe protocols on hand washing and the need to use disposable gloves (GR: A).

A minority of patients can be managed with the use of the non-return (flip) valve catheters, thus avoiding the closed drainage bag. Such patients may exchange the convenience of on-demand drainage with an increased risk of infection. Patients with urethral catheters in place for ≥ 10 years should be screened annually for bladder cancer (GR: C). Clinicians should always consider alternatives to indwelling urethral catheters that are less prone to causing symptomatic infection. In appropriate patients, suprapubic catheters, condom drainage systems and intermittent catheterisation are each preferable to indwelling urethral catheterisation (GR: B). While the catheter is in place, systemic antimicrobial treatment of asymptomatic catheter-associated bacteriuria is not recommended (GR: A), except for some special cases. Routine urine culture in an asymptomatic catheterised patient is also not recommended (GR: C) because treatment is in general not necessary. Antibiotic treatment is recommended only for symptomatic infection (GR: B). After initiation of empirical treatment, usually with broad-spectrum antibiotics based on local susceptibility patterns (GR: C), the choice of antibiotics might need to be adjusted according to urine culture results (GR: B). Long-term antibiotic suppressive therapy is not effective (GR: A).

6.2 Summary of recommendations

Recommendation		GR
General aspects		
1.	Written catheter care protocols are necessary.	B
2.	Health care workers should observe protocols on hand hygiene and the need to use disposable gloves between catheterised patients.	A
Catheter insertion and choice of catheter		
3.	An indwelling catheter should be introduced under antiseptic conditions.	B
4.	Urethral trauma should be minimised by the use of adequate lubricant and the smallest possible catheter calibre.	B
5.	Antibiotic-impregnated catheters may decrease the frequency of asymptomatic bacteriuria within 1 week. There is, however, no evidence that they decrease symptomatic infection. Therefore, they cannot be recommended routinely.	B
6.	Silver alloy catheters significantly reduce the incidence of asymptomatic bacteriuria, but only for < 1 week. There was some evidence of reduced risk for symptomatic UTI. Therefore, they may be useful in some settings.	B
Prevention		
7.	The catheter system should remain closed.	A
8.	The duration of catheterisation should be minimal.	A
9.	Topical antiseptics or antibiotics applied to the catheter, urethra or meatus are not recommended.	A
10.	Benefits from prophylactic antibiotics and antiseptic substances have never been established, therefore, they are not recommended.	A
11.	Removal of the indwelling catheter after non-urological operation before midnight might be beneficial.	B
12.	Long-term indwelling catheters should be changed at intervals adapted to the individual patient, but must be changed before blockage is likely to occur, however, there is no evidence for the exact intervals of changing catheters.	B
13.	Chronic antibiotic suppressive therapy is generally not recommended.	A
14.	The drainage bag should always be kept below the level of the bladder and the connecting tube.	B
Diagnostics		
15.	Routine urine culture in asymptomatic catheterised patients is not recommended.	B
16.	Urine, and in septic patients, also blood for culture must be taken before any antimicrobial therapy is started.	C
17.	Febrile episodes are only found in < 10% of catheterised patients living in a long-term facility. It is therefore extremely important to rule out other sources of fever.	A
Treatment		
18.	While the catheter is in place, systemic antimicrobial treatment of asymptomatic catheter-associated bacteriuria is not recommended, except in certain circumstances, especially before traumatic urinary tract interventions.	A
19.	In case of asymptomatic candiduria, neither systemic nor local antifungal therapy is indicated, but removal of the catheter or stent should be considered.	A/C
20.	Antimicrobial treatment is recommended only for symptomatic infection.	B
21.	In case of symptomatic CAUTI, it might be reasonable to replace or remove the catheter before starting antimicrobial therapy if the indwelling catheter has been in place for > 7 days.	B
22.	For empirical therapy, broad-spectrum antibiotics should be given based on local susceptibility patterns.	C
23.	After culture results are available, antibiotic therapy should be adjusted according to pathogen sensitivity.	B

24.	In case of candiduria associated with urinary symptoms, or if candiduria is the sign of systemic infection, systemic therapy with antifungals is indicated.	B
25.	Elderly female patients may need treatment if bacteriuria does not resolve spontaneously after catheter removal.	C
Alternative drainage systems		
26.	There is limited evidence that postoperative intermittent catheterisation reduces the risk of bacteriuria compared with indwelling catheters. No recommendation can be made.	C
27.	In appropriate patients, a suprapubic, condom drainage system or intermittent catheter is preferable to an indwelling urethral catheter.	B
28.	There is little evidence to suggest that antibiotic prophylaxis decreases bacteriuria in patients using intermittent catheterisation, therefore, it is not recommended.	B
Long-term follow up		
29.	Patients with urethral catheters in place for ≥ 10 years should be screened for bladder cancer.	C

6.3 Reference

1. Tenke P, Kovacs B, Bjerklund Johansen TE, et al. European and Asian guidelines on management and prevention of catheter-associated urinary tract infections. Int J Antimicrob Agents 2008 Feb;31 Suppl 1:S68-78.
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7. UTIs IN CHILDREN

7.1 Summary and recommendations

Urinary tract infection in children is a frequent health problem, with the incidence only a little lower than that of upper respiratory and digestive infections.

The incidence of UTI varies depending on age and sex. In the first year of life, mostly the first 3 months, UTI is more common in boys (3.7%) than in girls (2%), after which the incidence changes to 3% in girls and 1.1% in boys. Paediatric UTI is the most common cause of fever of unknown origin in boys aged < 3 years. The clinical presentation of UTI in infants and young children can vary from fever to gastrointestinal and lower or upper urinary tract symptoms.

Investigation should be undertaken after two episodes of UTI in girls and one in boys (GR: B). The objective is to rule out the unusual occurrence of obstruction, vesicoureteric reflux (VUR) and dysfunctional voiding, e.g. as caused by a neuropathic disorder.

Chronic pyelonephritic renal scarring develops very early in life due to the combination of a UTI, intrarenal reflux and VUR. It sometimes arises *in utero* due to dysplasia. Although rare, renal scarring may lead to severe long-term complications such as hypertension and chronic renal failure.

VUR is treated with long-term prophylactic antibiotics (GR: B). Surgical re-implantation or endoscopic treatment is reserved for the small number of children with breakthrough infection (GR: B).

For treatment of UTI in children, short courses are not advised and therefore treatment is continued for 5-7 days and longer (GR: A). If the child is severely ill with vomiting and dehydration, hospital admission is required and parenteral antibiotics are given initially (GR: A).

7.2 Background

The urinary tract is a common source of infection in children and infants. It represents the most common bacterial infection in children < 2 years of age (1) (LE: 2a). The outcome of a UTI is usually benign, but in early infancy, it can progress to renal scarring, especially when associated with congenital anomalies of the urinary tract. Delayed sequelae related to renal scarring include hypertension, proteinuria, renal damage and even chronic renal failure, which requires dialysis treatment in a significant number of adults (2) (LE: 2a).

The risk of UTI during the first decade of life is 1% in males and 3% in females (3). It has been suggested that 5% of schoolgirls and up to 0.5% of schoolboys undergo at least one episode of UTI during their school life. The incidence is different for children < 3 months of age, when it is more common in boys. The incidence of asymptomatic bacteriuria is 0.7-3.4% in neonates, 0.7-1.3% in infants < 3 months of age, and 0.2-0.8% in preschool boys and girls (3). The incidence of symptomatic bacteriuria is 0.14% in neonates, with a further increase to 0.7% in boys and 2.8% in girls aged < 6 months. The overall recurrence rate for the neonatal period has been reported to be 25% (3,4).