CLINICAL PRACTICE

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# Principles of antimicrobial therapy in urosepsis: an approach from the perspective of the infectious diseases physician

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**Abstract:** *Background: This topic is aimed to review the treatment approach in adult patients diagnosed with urosepsis, in order to decrease mortality and to maximize the outcome of the antibiotic stewardship efforts.*

*Methods: We present an approach of antibiotic therapy in urosepsis from an infectious diseases physician perspective, based on the recently published data integrating the epidemiology of the urinary tract infections in a multidisciplinary hospital from Romania.*

*Results: The principles of therapy in urosepsis should have five goals, but not limited to rapid diagnosis, specific intensive care unit treatment, obtaining urine and blood cultures, anti-infective treatment and identifying and correction of underlying risk factors. Due to the higher prognostic value, the antimicrobial therapy in urosepsis should consist in "two steps" regimen: initial antimicrobial therapy, based on "empirical" approach for the first 48 - 72 hours and directed or "definitive" antimicrobial therapy adapted to the susceptibility profile of the isolated pathogens, the penetration into the urinary tract and the patient clinical response. Clinicians should be aware of the different antibiotic susceptibility profile of the bacteria from the hospital compared to the community. Thus, the initial choice of antimicrobial agents depends on several criteria like the severity of illness and the risk factors for multidrug resistant pathogens: the immune status of the patient (age, debilitating chronic illnesses, immunosuppressive treatment or uncontrolled malignancies), broad-spectrum antimicrobial use and health care environment exposures in the previous 3 to 6 months, susceptibility of prior urinary isolates, and local community resistance prevalence of bacteria.*

*Conclusions: Our important messages highlighted the need of a holistic approach of urosepsis, in a multidisciplinary team, with integration of risk factors for AMR, focusing on the first phase of antibiotic treatment as the main driven of the survival rate.*

**Keywords:** *urosepsis, antimicrobial therapy, infectious diseases, antibiotic resistance*

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## INTRODUCTION

In about 30% of the sepsis cases, the underlying condition is related to the urinary tract infections (UTIs). The main risk factors are obstructive uropathies and most frequently, urosepsis develops in the context of health care–associated (HCA) UTIs [1]. The prognosis of urosepsis is more favorable compared to that of sepsis in general, with a mortality rate about 20–40% for severe cases. Unlike etiology in all-cause sepsis, dominated by gram-positive bacteria (GPB), the most common pathogens isolated

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in urinary sepsis are gram-negative bacteria (GNB) [2]. In March 2018, the Centers for Disease Control and Prevention released the "Hospital Toolkit for Adult Sepsis Surveillance", a guidance useful for hospitals to identify sepsis outcomes and evaluate the effectiveness of sepsis prevention efforts [3].

In our perspective, one of the main causes of failure to antibiotic treatment in sepsis is related to the antimicrobial resistance (AMR) and inadequate spectrum of the prescribed antibiotics at the beginning. Therefore, this topic aims to review the treatment approach in adult septic patients with acute complicated UTIs, in order to decrease mortality and to follow the antibiotic stewardship recommendations.

## ETIOLOGY AND SUSCEPTIBILITY OF ISOLATED STRAINS

Worldwide, the etiology of urosepsis is dominated by enterobacteriaceae, with Escherichia coli (E. coli) accounting for about 52% of the cases, followed by Klebsiella species (spp), Pseudomonas aeruginosa, Enterobacter spp and GPB, such as enterococci (5%) [4]. In 2017, among the strains isolated from the urology department of our Romanian tertiary hospital, E. coli was encountered in 59.2% of all cases of UTIs, followed by other GNB like Klebsiella pneumoniae (K. pneumoniae) [unpublished data].

It has been reported that the resistance rates of pathogens in urosepsis are higher than 10% for almost all antibiotics. The European Antimicrobial Resistance Surveillance Network for 2016 showed that more than half (58.6%) of the E. coli isolates were resistant to at least one of the antimicrobial groups under regular surveillance (aminopenicillins, fluoroquinolones, third-generation cephalosporins, aminoglycosides and carbapenems) [5].

According to the European Centre for Disease Prevention and Control, the level of E. coli resistance to carbapenems remained rare in 2016 (< 0.1% ), with a national percentage ranging from 0% to 1%, meanwhile for K. pneumoniae, data showed large differences, ranging from 0% to 66.9% [6]. Carbapenem-resistant enterobacteriaceae (CRE) represents a significant threat to patients and healthcare systems in all European countries, being associated with high mortality, especially due to the delay in administration of effective treatment and limited treatment options [6]. Despite the fact that in 2016 the E. coli carbapenem resistance level in Romania has dropped from 1.9% to 1%, the reported rates of AMR are very high and rising in comparison to other European countries [7].

## MANAGEMENT

In the management of septic patients, we must consider that sepsis is a life threatening condition with a directly dependent prognosis on the timeliness and accuracy of therapeutic intervention. In the latest update of the Surviving Sepsis Campaign (SSC) bundle from 2018, the most important change of the 2016 guidelines was that the 3-h and 6-h bundles have been combined into a single "hour-1 bundle" [8]. Clinicians should initiate antibiotic treatment immediately, especially in patients with hypotension, rather than waiting and extending resuscitation measures. Other measures such as obtaining blood samples, urine and blood cultures, administration of fluids and antibiotics, should all begin immediately [8].

The principles of therapy in urosepsis should follow five rules [9]. First of all, we have to establish a rapid diagnosis based on clinical and paraclinical tests: classical symptoms (dysuria, frequent urges to urinate, flank pain and/or costovertebral angle tenderness, fever, chills, pyuria), quick Sepsis Related Organ Failure Assessment score (qSOFA), biomarkers of sepsis and imaging findings [9].

In addition, a specific intensive care unit (ICU) treatment should be start with fluid replacement, supportive and adjunctive therapy as needed [9]. Obtaining urine and blood cultures prior to antibiotic administration represent another important rule [9].

On the other hand, initiation of antibiotic treatment must be adapted to the patient profile (usually broad spectrum antibiotics) after the quick assessment by the clinician and/or infectious diseases specialist [9]. The last but not least rule is addressed to identification and correction of risk factors (calculus, obstruction, renal or perinephric abscess) by the urologist [9].

## ANTIBIOTIC TREATMENT

Broad-spectrum antibiotic therapy aiming to cover all likely pathogens should be started immediately, ideally in the first hour. Data from the literature have shown an association between the rapid administration of antibiotics and improved survival in patients with sepsis. Initiation of empiric antibiotic treatment within the first hour of hypotension is associated with a survival rate of about 80% [10]. Each additional hour of delay was found to decrease the survival rate by 7.6% [10].

The initial choice of antimicrobial agents depends on several criteria like the severity of illness and the risk factors for multidrug resistant pathogens: the immune status of the patient (age, debilitating chronic illnesses, immunosuppressive treatment or uncontrolled malignancies), broad-spectrum antimicrobial use and health care environment exposures in the previous 3 to 6 months, susceptibility of prior urinary isolates, and local community resistance prevalence of bacteria. Clinicians should be aware of the different antibiotic susceptibility profile of the bacteria from the hospital compared to the community. Therefore, an accurate classification of the UTIs according to the place of acquisition of the infection is mandatory. There have been defined two major categories of infections comprising of community-acquired (CA) UTIs or health-care associated (HCA) UTIs with the following scenarios: community onset HCA UTIs or hospital onset HCA UTIs. In CA-UTIs, the possible pathogens are limited usually to susceptible enterobacteriaceae, ampicillin-susceptible Enteroccous faecalis or Staphylococcus saprophyticus. In HCA UTIs, in general we are dealing with resistant strains of bacteria such as extended spectrum beta-lactamases (ESBL)-producing enterobacteriaceae or CRE. It has been shown that inappropriate antibiotic treatment in critically ill patients was associated with decreasing in survival rate of at least 5 times in septic shock [11].

**Table 1. Choice of antibiotic therapy in urosepsis**

| **"Empirical" phase of antimicrobial therapy** *(combination therapy (ß-lactam antibiotics plus the second antimicrobial agent) is preferred especially in critically ill patients with high risk of death* | | |
|---|---|---|
| **Community-acquired UTIs#** *# in some regions the risk of ESBL enterobacteriaceae has to be considered also in community-acquired UTIs* | **Health-care associated UTIs** | |
| | *without risk of non-fermenting GNB or hemodynamically stable patient* | *risk of non-fermenting GNB or hemodynamically unstable patient* |
| Aminopenicillins +/- beta lactamase inhibitor (BLI) (Amoxicilin/ clavulanate)<br>3rd generation cephalosporins (e.g. Ceftriaxone)<br>Fluoroquinolones (e.g. Ciprofloxacin, Levofloxacin)<br>Aminoglycosides (e.g. gentamicin) | Carbapenems (e.g. Ertapenem)<br>Ureidopenicillin plus BLI (e.g. Piperacillin/tazobactam)<br>Aminoglycosides (e.g. Gentamicin, Amikacin, Netilmicin, Tobramycin)<br>Glycopeptides (e.g. Vancomycin) | Carbapenems (e.g. Imipenem, Meropenem, Doripenem)<br>Carbapenems plus BLI (e.g. Meropenem/vaborbactam)<br>Ceftolozane/Tazobactam<br>Ceftazidime/Avibactam<br>Monobactams (Aztreonam)<br>Colistin<br>Glycopeptides (e.g. Vancomycin)<br>Aminoglycosides (e.g. Gentamicin, Amikacin, Netilmicin, Tobramycin) |
| **"Directed" phase of antimicrobial therapy±,¥** | | |

*±according to the antibiotic susceptibility profile of the detected pathogens*
*¥monotherapy is preferred (exception of critically ill patients with high risk of death and infections with CRE)*

The antimicrobial therapy in urosepsis consists in "two steps" regimen:

a) Initial antimicrobial therapy, based on "empirical" approach, should starts ideally, after obtaining blood and urine cultures, during the first hour of the patient presentation in the emergency room or after the diagnosis of urosepis in case of hospitalized patients. Due to the prognostic value of this treatment phase, as a general rule, the broad-spectrum antibiotics with good penetration into the urinary tract are preferred for the first 48-72 h [8];

b) Directed or "definitive" antimicrobial therapy

represent an adaptation of the initial regimen (e.g. de-escalation) according to the antibiotic susceptibility profile of the isolated pathogen, taking into account the clinical evolution of the patient [8]. The duration of definitive therapy should have a minimum duration with maximum efficiency, usually between 10 to 14 days [2];

Based on our clinical experience and the evidence base medicine, we present a personal approach, not validated in clinical trials, regarding the choice of antibiotic therapy in urosepsis (Table 1).

In addition to antimicrobial therapy, an underlying condition such as urinary obstruction, anatomical or functional urinary tract abnormalities (neurogenic bladder, bladder catheters, nephrostomy tubes, and ureteral stents), should be rapidly identified and managed [12]. One of the important issues is related to the appropriate collection of the urine sample in case of urinary tract obstruction. In case of kidney drainage (e.g. percutaneous nephrostomy) we must collect also the urine from the inserted tube in addition to the usual urine sample.

## ASSESSMENT OF TREATMENT RESPONSE

Usually, symptoms improve rapidly when antimicrobial treatment is effective, but the fever can persist at least 3 days despite the appropriate antibiotic treatment. The response to treatment is assessed by the following criteria: clinical (fever remission), biological (decreasing levels of inflammatory markers, sepsis biomarkers, alleviating organ dysfunction) and bacteriological (negative urine and blood cultures). In the PRORATA trial, a multicentre randomized controlled trial, it has been evaluated the use of procalcitonin (PCT) to reduce the patient's exposure to antibiotics in ICU. It has been shown that a strategy consisting in measurement of PCT concentration on a daily base allowed for a reduction of antibiotic consumption in ICU [13]. Also, other studies have been proposed a PCT-based algorithm for starting, continuing or stopping antibiotics in patients with sepsis in the ICU [14]. A Swiss randomized controlled trial showed that an algorithm based on PCT concentration and quantitative pyuria measurements, significantly reduces antibiotic exposure, with about 30%, without apparent negative effects on clinical outcomes [15]. In case of persistent or worsening symptoms after 72 hours of appropriate antimicrobial therapy, an additional evaluation is required in order to identify potential factors that might interfere with the favorable clinical outcome. Dosing reevaluation, especially for aminoglycosides and glycopeptides, surgical drainage of the new abscesses, assessment of the inserted tube position and permeability, repeating urine and blood cultures and readjusting treatment to the antibiotic susceptibility profile of other isolated pathogens, should be considered.

## CONCLUSIONS

Our important messages highlighted the need of a holistic approach in urosepsis, provided by a multidisciplinary team, with integration of risk factors for AMR, focusing on the first phase of antibiotic treatment as the main driven of the survival rate. The new sepsis "hour-1 bundle" and the principles of antimicrobial therapy should be followed in all emergency departments as a clinical tool intended to improve the general prognosis in urosepsis.

**Author Contributions**

*Concept: VG, AMR; Design: VG, IS, AMR; Supervision: VG, IS, AMR; Materials: CG, FA, AMR; Data collection and/or processing: CG, FA, AMR; Analysis and/or Interpretation: CG, FA, IS; Literature Search: CG, FA, AMR; Writing Manuscript: VG, AMR; Critical Review: VG, IS;*

**Disclaimer**

*The authors have no conflict of interest to declare.*

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