Uncomplicated and complicated urinary tract infections in adults: the Infectious diseases specialist's perspective

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ABSTRACT

Urinary tract infection (UTI) is one of the most common bacterial ~~infection~~infections either in the outpatient and inpatient (hospitalized) setting. Women are more commonly affected than men. The distinction between uncomplicated and complicated UTI is based on gender and/or presence of risk factors and it is used to guide the choice and duration of antibiotic treatment. Acute cystitis and pyelonephritis in healthy premenopausal non-pregnant women without urinary tract abnormality is classified as uncomplicated. All others are considered complicated UTI. Clinical classification is based on a continuum with cystitis as the less severe form and urosepsis the most severe. *Escherichia coli* remains the microorganism more frequently responsible of UTI but with different prevalence according to characteristic of host and the epidemiology (community-acquired or health-care associated). Empirical treatment of uncomplicated and complicated UTI is becoming increasingly challenging due to the widespread emergence of resistance to several class of antibiotics (fluoroquinolones, trimethoprim-sulfametoxazole, beta-lactams). Of even great concern is the emergence of Enterobactariaceae-carbapenemase producing micro-~~-~~organisms that leaves few or no alternatives for treatment of nosocomial UTI.

Urinary tract infections (UTIs) are responsible in Western countries of thousands of outpatient visits as well as emergency and hospital admissions [1,2]. The clinical syndromes associated with UTIs may range from asymptomatic bacteriuria to the more severe picture of pyelonephritis and urosepsis sometimes designated (including also prostatitis in men) as "febrile urinary tract infections" [3,4]. However, the concept of uncomplicated and complicated urinary tract infection (c-UTI) still remains a matter of concern because severe infections or those with invasive tissue involvement are sometimes erroneously indicated as c-UTI. [3,5,6]. The concept and the categorization of c-UTI was introduced by a panel of experts of the Infectious Diseases Society of America (IDSA) in order to make more easy the evaluation of antimicrobial treatment in different setting.[7] It should be acknowledged that the term "uncomplicated" refers to any infection observed in patients without known structural or functional risk factors that will render the individual more prone to develop UTI. [8,9]

Although the classification of any disease is generally far from to be perfect and acceptable by everyone involved in their management, we believe that the UTI classification developed by the European Association of Urology (EAU) and the European Section of Infection in Urology (ESIU) is currently the best working approach to be considered.[10,11]

This classification is organized in five main categories (clinical criteria, possible risk factors, pathogens, mode of acquisition of UTI and therapeutic options) (Table 1). [11,12] The clinical criteria are arranged by syndromes : urethritis (UR), cystitis (CY), pyelonephritis (PY), urosepsis (US) and male accessory gland infections (*i.e.*, prostatitis, vesiculitis, epididymitis and orchitis). The latter, together with urethritis are not considered here given the great variability of clinical presentation. It should be highlighted that asymptomatic bacteriuria is not considered an infection but rather a risk factor that need to be treated only in selected circumstances such as pregnancy or surgery of the urinary tract. Considering the three clinical syndromes –CY, PY, UR- a grading of severity was suggested with six items that include at the extremes the less severe form -cystitis (grade 1)- and the more severe form- uroseptic shock (grade 6) (Table 2). As far as risk factors, the difficulty to

weight all categories in a proper way due to the lack of solid data have led to the propose to use a new system for phenotyping designated with the acronym ORENUC (Table 3).

In the era of widespread diffusion of multidrug-resistant bacteria in some cases with very limited or absent antimicrobial options it is imperative to recognize and manage UTIs in the appropriate manner.

~~Asymptomatica~~Asymptomatic bacteriuria

Asymptomatic bacteriuria is defined as the absence of urinary symptoms and a positive urine culture (midstream sample of urine with at least 10^5 CFU/mL) with the same bacterial strain in two consecutive samples (for women) and in a single sample for men.[13]

Screening and treatment for asymptomatic bacteriuria is not recommended unless in pregnant women and for individuals prior to perform transurethral resection of the prostate (TURP) or other instrumental procedures responsible of mucosal bleeding. [13] Asymptomatic bacteriuria is reported in 4-7% of pregnant women and should always be treated because of high risk of progression to UTI including pyelonephritis (20-30 fold compared with non pregnant women).[14,15] A Cochrane meta-analysis regarding more than 2300 pregnant women shows that antibiotic treatment is effective in terms of eradication and prevention of pyelonephritis. The estimated number of individuals needed to treat to prevent 1 episode of pyelonephritis is seven.[15] Moreover, asymptomatic bacteriuria in pregnant women has been associated with preterm labour and low birthweight [16,17]

Acute uncomplicated urinary tract infections

According to the EAU/ESIU classification both sporadic or recurrent community-acquired acute cystitis and pyelonephritis in healthy individuals (O, R and partially E risk factors of the ORENUC classification) are enclosed in this category of UTI. Cystitis (or lower UTI) is the most common presentation characterized by dysuria, frequency, urgency, suprapubic pain and sometimes hematuria.[8,9] It should be highlighted that dysuria can be present also in women with vaginitis and men with urethritis and those sexually acquired infections should be ruled out.[18,19] Absence of

vaginal discharge in a woman with dysuria and urgency is indicative of UTI in more than 90% of cases.[20]

In a study regarding women with no new vaginal discharge or change in discharge the only variable predictive of STDs was more than one sex partner in the past year. However, it is worth noting that in women presenting to an Emergency Department with genitourinary symptoms overdiagnosis of UTI is common (up to 52%) whereas sexually transmitted infection (STI) are underdiagnosed (37%).[21] Women are most affected due to their anatomical conformation with a self reported annual incidence of 12% and an estimated lifetime risk of UTI of 60%.[22,23]

Several risk factors for development of UTI among women have been recognized: sexual intercourse, the use of spermicidal products, a new sex partner , a previous history of cystitis.[24,25]

A possible genetic predisposition is suggested although unproved by the observed increased risk of recurrent cystitis and pyelonephritis among women reporting to have ~~a first-degree relatives~~a first-degree relative with a history of UTI.[26,27]

Microbiology and treatment of acute uncomplicated UTI

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Escherichia coli is responsible for about 80% of all cases of uncomplicated community-acquired UTI followed by other Enterobacteriaceae (*i.e.*, *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp.) and to a lesser extent gram-positive microorganisms (*Staphylococcus saprophyticus*, Enterococci).[28-29]

It is a cause of concern the increasing rate of resistance to several class of antibiotics of *E. coli* isolates from individuals with uncomplicated UTI. Trimethoprim-sulfametoxazole (TMP-SMX) is now considered an appropriate empirical antibiotic choice for uncomplicated UTI only if the surveillance studies show resistance rates under 20%.[5,8,30,31] Unfortunately several surveillance studies conducted in North America (USA, Canada), in Europe and in Latin America (Brazil) reported resistance rates ranging from 16% (Canada) up to 30 % in Europe and Brazil [32-35]

Therefore the use of TMP-SMX as an empirical therapy for uncomplicated UTI requires the knowledge by the treating physician of the rates of resistance in the local community and possible

risk factors associated with *E. coli* non susceptible to TMP-SMX. In a Greek study, patients treated with amoxicillin and/or TMP-SMX in the previous 3 months had a 2-fold risk of having an infection with a TMP-SMX-resistant isolate.[35] Other studies showed that prior use of TMP-SMX and travel outside the United States in the previous 3-6 months was predictive of TMP-SMX resistance.[36] Nitrofurantoin , fosfomycin and pivmecillinam are recommended as empirical first-line therapy of acute uncomplicated cystitis by both by the United States of America and European Infectious Diseases Society guidelines (IDSA and ESCMID) and by the European Association of Urology guidelines.[12,31] Although the three previously mentioned drugs have inferior efficacy (especially fosfomycin or pivmecillinam) with respect of other antibiotics, or are inactive against *Proteus* species and some *Enterobacter* and *Klebsiella* strains (nitrofurantoin) or are not approved in the United States and some other European countries (pivmecillinam), their low resistance rates together with minimal propensity to induce "collateral damage" are the reason for which they are recommended as first line choices in the setting of acute uncomplicated cystitis (Table 4). Nitrofurantoin should not be used in patients with a creatinine clearance (CrCL) below 60 ml/min considering the potential risk of toxicity (especially pulmonary and neurologic toxicity) and it is considered a potentially inappropriate drug for patients older than 65 years of age.[37,38]
Both fosfomycin and nitrofurantoin should not be used if pyelonephritis is suspected.[5] The concept of "collateral damage" induced by some class of antibiotics (such as fluoroquinolones and cephalosporins), namely selection of drug-resistant or multidrug resistant organisms or increasing risk of *Clostridium difficile* infection, gained equal weight to drug efficacy in the treatment recommendations.[39] Fluoroquinolones are considered for the above mentioned reasons a second choice for acute uncomplicated cystitis but a recent study from USA encompassing the period 2002 to 2011 shows that they are the most frequently prescribed antibiotics (49% overall) in the outpatient setting.[40] An even higher rate (62.7%) of prescribing a fluoroquinolone (*i.e.*, ciprofloxacin) has been reported in a study regarding treatment of outpatient males with UTI.[41] Oral β-lactam antibiotics (*i.e.*, amoxicillin, amoxicillin-clavulanate, cefaclor, cefpodoxime-proxetil) are

considered an options when first-line agents cannot be used but the increasing worldwide prevalence of extended-spectrum β-lactamase (ESBL)-producing *E. coli* is a matter of concern and can be associated with high rates of treatment failure.[2,42,43]

As previously discussed an episode of pyelonephritis (or upper tract UTI) that occurs in a healthy premenopausal, non-pregnant women without other recognized risk factors (table 1 and 3) is considered uncomplicated. A clinical diagnosis of pyelonephritis is suspected in the presence of fever (temperature > 38°C), chills, flank pain, costovertebral-angle tenderness; other systemic symptoms such as nausea and vomiting or mental confusion can be present.[3,4,8,10,20] Symptoms suggestive for cystitis are frequently absent.

Different ~~for~~ from suspected acute uncomplicated cystitis where urinalysis and urine culture are not routinely needed, ~~for~~ in case of pyelonephritis it is recommended to always perform an urine culture before starting empirical antimicrobial treatment.[31] Especially in the emergency department patients are frequently assessed for pyuria and bacteriuria with commercially available dipstick testing for leukocyte esterase and urinary nitrites.[44] Although blood cultures are not routinely recommended in acute uncomplicated pyelonephritis given the possibility of associated bacteremia we believe that if feasible they should be done before antibiotic treatment. The recommendations about the use of radiological techniques such as ultrasound and computed tomography in the diagnosis of acute uncomplicated pyelonephritis is outside the scope of this review and the readers are referred to the appropriate chapters in this book dealing with this issue.

Empiric antimicrobial therapy for acute uncomplicated pyelonephritis should be started quickly once the diagnosis is entertained; as a general rule an antibiotic with broad-spectrum *in vitro* activity against the likely uropathogens should be used (Table 4). Additional factors to be considered in choosing an appropriate empiric drug are the local resistance data, history of exposure to the same class of antibiotics in the recent past (a factor that increase the probability of resistance), history of allergy and, if known, antimicrobial susceptibility of previous UTI strains. Oral regimens that can be used for the outpatient treatment of less severe acute uncomplicated pyelonephritis are

reported in table ~~5~~4. Given the high direct and indirect costs associated with hospital treatment of acute uncomplicated pyelonephritis there is suggestion to treat most episodes in the outpatient setting but this probably is more frequently achieved in USA than in Europe.[45-47] Clinical severe uncomplicated pyelonephritis as well as complicated pyelonephritis (risk factors and underlying) should be always managed with hospitalization of the patients. Criteria for severity of uncomplicated pyelonephritis requiring hospitalization includes high fever (> 40°C), dehydratation, hypotension, high leukocyte count.

Both IDSA/ESCMID and EAU guidelines indicate fluoroquinolones as appropriate initial empiric antibiotic for uncomplicated pyelonephritis if the prevalence of fluoroquinolone resistance of community uropathogens is known to be less than 10%.[12,31] Otherwise a long-acting intravenous antibiotics (*i.e.*, ceftriaxone) should precede oral therapy or a 24-h consolidated dose of an aminoglycoside is indicated. The use of TMP-SMX should be reserved only to episodes of uncomplicated pyelonephritis caused by susceptible microorganisms and the duration of treatment prolonged for 14 days. Oral β-lactam agents are associated with high failure rates and should be used only when susceptibility of causal microorganisms is known and for no more than 14 days.[48] However, a meta-analysis of randomized controlled trials shows that for pyelonephritis seven days of treatment is equivalent to longer treatment in terms of clinical and microbiological failure but trials that included β-lactamase were old and with small number of patients.[49] For this reason it is advisable to manage patients with short term treatment only when fluoroquinolones are used.[50]

Acute complicated urinary tract infections

As previously indicated and acknowledged by the International guidelines, the concept of complicated UTI (c-UTI) refers to both structural or functional abnormalities of the genitourinary tract or to an underlying disease that poses an increased risk of complications or therapeutic failure or poor outcome.[31,51] This definition does not account for severity or invasiveness of the infection thus giving reason for some ambiguity relative to classification, as recently suggested.[6]

Male gender “per se” is considered, when a UTI is diagnosed, responsible of c-UTI; however, in young men without systemic symptoms and no medical history and/or physical examination indicative of a causative factor it is suggested by some Authors to consider UTI as uncomplicated.[51,52] However, structural and functional abnormalities of the urinary tract associated with male’s ageing increase either the risk and the complications of UTI.[53] Among men with febrile UTI a study reported in more than 90% of cases a transient increase of serum prostate antigen and/or prostate volume.[54] It is always important to rule out unrecognized pathologies of the urinary tract that can require surgery (i.e. prostatic hypertrophy, urethral stricture, bladder and renal stones , bladder cancer) or prolonged antibiotic treatment (*i.e.*, chronic prostatitis).[54]

Special patient groups

Diabetes mellitus is a well known risk factor for recurrent UTIs, complications (persistent bacteriuria, bacteremia, bilateral renal involvement, urosepsis) and development of life-threatening peculiar picture of pyelonephritis such as emphysematous pyelonephritis.[55-63] Emphysematous pyelonephritis (EPN) is an acute necrotizing infection of the kidney characterized by the presence of gas within the renal parenchyma or perinephric tissues. Seventy-eighty percent of patients with a diagnosis of EPN had diabetes mellitus. Enteric gram-negative facultative anaerobes (i.e., *E. coli*, *Klebsiella* spp., *Proteus* spp.) able to ferment glucose and lactate to carbon dioxide are the more frequently responsible microorganisms.[62,63] Based on the extent and distribution of gas observed on CT scan a four-tier classification of EPN has been proposed with a prognostic intent.[64] However, a recent study failed to identify a mortality predictive role of such classification.[63] Percutaneous catheter drainage together with timely start of empiric antibiotic treatment (with ceftazidime or a carbapenem) seems to be able to lower mortality form 80% to 9-13%.[63,65] Emergency nephrectomy can be necessary in patients with rapid deterioration of the clinical picture.[66]

UTIs are the most common infectious complication after kidney transplantation with a reported incidence ranging from 26% to 76%.[67-69] A 38% pooled prevalence of UTI has been reported from a meta-analysis of thirteen studies with more than 3000 patients undergoing kidney

transplantation.[70] A recent study shows that kidney transplant recipient had a 72-fold higher risk for first-time hospitalization for pyelonephritis compared to matched population controls.[71] Although in the same study a declining incidence of pyelonephritis was observed during the twenty-year of observation, the researches found a 45% higher risk of graft loss and death among patients experiencing post-transplant pyelonephritis compared to those who do not have a diagnosis of pyelonephritis.[71] Female gender was a risk factor consistently associated with development of post-transplant UTIs with a pooled odds ratio of 3.11 (CI 95% 2.10-4.13).[70-73] Other recognized risk factors for post-transplant UTIs are presence and duration of indwelling catheter, acute rejection episodes, cadaveric organ recipients, older age and recurrent UTIs before transplantation.[70,73-75] UTIs are generally observed in the first 3 months after transplantation with 38% diagnosed during the first post-transplant month.[76,77]

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) and ESBL-producing *K. pneumoniae*, an emerging worldwide nosocomial problem, especially frequent in southern Europe (Greece, Italy, Romania) and with devastating consequence among frail patients, has been observed also in UTI following solid organ transplantation.[77,78] It should be noted that *Enterococcus* spp. are emerging microorganisms responsible of UTIs in the transplant setting with prevalence of 33-44%.[77,80] Appropriate treatment of these infections poses several difficulties because of the profile of resistance especially for *E. faecium*.

Pregnant women are considered at increase risk of UTIs and those with asymptomatic bacteriuria also at increased risk of developing pyelonephritis compared to women without bacteriuria.[13,81] Although most guidelines recommend screening for asymptomatic bacteriuria as a routine pregnancy practice a recent qualitative review failed to identify reliable evidence supporting screening for ASB in pregnancy probably as a consequence of the availability only of old studies and several methodological shortcomings[13,82-84] However, recent studies reported an incidence of acute antepartum pyelonephritis ranging from 0.5% to 1.3% which is less than historical reports.[85-87] Moreover, a randomized controlled trial aiming to assess the consequences of treated and untreated

ASB in pregnant women did not show any difference using a composite end-point (pyelonephritis and preterm birth).[88] Although a significant association of ASB with pyelonephritis was evident (2.4% vs 0.6%, AOR 3.9) the absolute risk of pyelonephritis in untreated ASB is low.[88] As a rule, pregnant women with acute pyelonephritis should be hospitalized and treated with parenteral antibiotics is generally recommended.[89]

Catheter-associated urinary tract infection (CA-UTI) represents the most common health-care associated infection worldwide with a 4-fold increased risk of UTI compared to those without a urinary catheter.[90,91] Placement of an indwelling urinary catheter is associated with the risk of development of bacteriuria of 3-10% per day and by day 30 bacteriuria is considered universal.[92-94] The definition of CA-UTI is an infection occurring in an individual that is currently catheterized or has been catheterized within the past 48 hours along with > 10^3 CFU/mL of > 1 bacterial species cultured from a single catheter urine specimen.[90] However, because signs and symptoms compatible with CA-UTI are non specific (*i.e.*, new onset or worsening fever, malaise, altered mental status, lethargy) other possible infectious causes should be excluded before attributing them to catheter-associated bacteriuria. The actual definition of CA-UTI was introduced in 2009 excluding catheter-associated asymptomatic bacteriuria, a condition not requiring antimicrobial treatment.[95] Bacteremia is another complication of CA-UTI with an associated mortality of 9%.[96] *E. coli* is the single organism more frequently isolated in patients with bacteriuria after short-term catheterization whereas infections among patients with long-term catheterization are generally polymicrobial and frequently with a reduced spectrum of susceptibility to most class of antibiotics.[90,97,98] The spectrum of microorganisms includes *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas aeruginosa*, coagulase-negative staphylococci, *Enterococcus* spp., *Providencia* spp., *Proteus* spp., *Morganella* spp., and *Candida* species.[99-100] The best way to avoid CA-UTI is to place a urinary catheter only when strictly indispensable as indicated by international guidelines as well as an early removal of it.[90,101] Antibiotic prophylaxis is generally not recommended on the basis of weak evidences suggesting a protective role only in some settings.[102-104] Moreover, the worldwide increase in the

rate of antibiotic resistance and the limited options of effective drugs in nosocomial-acquired infections are other reasons for not using prophylaxis for catheterized patients.

Management of complicated UTI

Before starting an antibiotic treatment, ~~of a~~ C-UTI patients should undergo an urine culture as well as a blood culture when it is appropriate. Recommendations regarding empirical treatment of C-UTI that can be applied to every circumstances and every patients are obviously unfeasible and therefore it is not surprising that there are no published consensus guidelines. The appropriate antibiotic choice should consider the characteristic of the patient (*i.e.*, age, drug allergies, comorbidity), the severity of the infection, the spectrum of possible uropathogens implicated and the knowledge of surveillance national and local data regarding patterns of susceptibility of the different microorganisms.[105,106] Moreover, the pharmacokinetic/pharmacodynamic characteristics of the drugs and their possible interactions should be considered in the appropriate choice. In general, fluoroquinolones are useless for urologic patients, when they were previously used for the same patient and in areas with more than 10% fluoroquinolone resistance. Carbapenem antibiotics have long been considered the drugs of choice for infections caused by ESBL-producing microorganisms.[107] However, the increasing isolation of carbapenem-resistant Enterobacteriaceae (CRE) clearly suggests the use of carbapenem-sparing regimens when appropriate. Cefepime and piperacillin-tazobactam may be reasonably alternative against ESBL-producing *E. coli* and *Klebsiella* spp. when the minimum inhibitory concentrations (MICs) are < 2 μg/mL for the former drug and < 16 μg/mL for the latter drug.[108-110] Ceftolozane-tazobactam, a recently approved combination of a cephalosporin with a β-lactamase inhibitor provides better efficacy than levofloxacin in adults with cUTI, including pyelonephritis.[111,112] This is a drug of niche for c-UTI and should be reserved only for carbapenem-sparing regimens when other alternatives are not suitable and for multi-drug-resistant (MDR)-*Pseudomonas aeruginosa*. Another carbapenem-sparing drug regimen that can be used for C-UTI caused by MDR-microrganisms is the combination of ceftazidime with avibactam a non-β-lactam β-lactamase inhibitor which is able to

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restore the in vitro activity of ceftazidime against ESBL and *K. pneumoniae* carbapenemase and Ambler Class C (*i.e.*, AmpC) and some class D β-lactamase-producing bacteria. It is not active against metallo-β-lactamase. In a randomized controlled trial ceftazidime-avibactam demonstrates superiority versus doripenem for the treatment of C-UTI including acute pyelonephritis.[113] However, to preserve its efficacy as a salvage therapy for CRE the use of ceftazidime-avibactam should be reserved for severe C-UTI caused by MDR-microorganisms.[114]

Urosepsis

Urosepsis is generally defined as a sepsis in which the source of the infection is the urinary tract and/or the prostate (in males).[115] Urosepsis represents about 25% of all cases of adult sepsis and 5% of cases evolving to severe sepsis and septic shock [116,117]

Obstructive uropathy is responsible of about 78 % of cases of urosepsis with urolithiasis being the most frequent cause.[118,119] A recent systematic review that aimed to identify risk factors for urosepsis and urosepsis-related mortality in older adults concluded for the lack of quality evidence regarding risk factors.[120] It should be recognized that a new sepsis definition published in 2016 has been adopted but several concerns have raised and its applicability in the field of urosepsis is presently unknown.[121-123] The administration of an initially adequate intravenous antibiotic is essential for optimal outcome but inadequate coverage in urosepsis may be a problem due to the lack of solid microbiological data.[124] In a German study regarding sepsis, the bacterial spectrum of urosepsis consisted of *E. coli* in 61% of cases, followed by other enterobacteria in 16%, *S. aureus* in 8% and enterococci in 6% of cases.[125] A recent point prevalence study conducted in 70 countries from 2003 to 2013 shows that the overall prevalence of *E. coli* as a cause of urosepsis was 43% followed by *Enterococcus* spp (11%) and *Klebsiella* spp. (10%) and *Pseudomonas aeruginosa* (10%).[126] Patients with a diagnosis of urosepsis had the highest resistance rates to all class of antibiotics compared with patients with other health-care-associated urinary tract infections (HAUTI).[126] Overall resistance to fluoroquinolone in Europe was reported to be 59%, 42% for ceftazidime and 34 % for piperacillin-tazobactam but as highlighted knowledge of local resistance

rates is essential. More recent data from EARS-Net , the largest European surveillance system on antimicrobial resistance shows that for *E. coli* isolates from invasive infections the population-weighted mean percentage for fluoroquinolone resistance is 22.8% in 2015.[78] However, 8 countries (Greece, Romania, Spain, Bulgaria, Malta, Slovakia, Italy and Cyprus) had resistance prevalence higher than 30%. Among the *E. coli* isolates that are resistant to third-generation cephalosporins (mean percentage 13.1%) 88.6% were ESBL-positive. The resistance to carbapenems of *E. coli* in Europe remained rare with only two countries (Greece and Romania) with reported resistance rates above 1%. Combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides ranged from 0% (Iceland) to 17.1% (Slovakia).[78] Antibiotic resistance against *K. pneumoniae* is a cause of concern in Europe with more than one third of isolates reported in 2015 that were resistant to at least one antimicrobial under surveillance (*i.e.*, fluoroquinolones, aminoglycosides, third generation cephalosporins and carbapenems) and 4.7% of all *K. pneumoniae* isolates resistant to all groups of antibiotics. An increasing rise of carbapenem-resistant strains was observed with three countries (Greece, Italy and Romania) with reported resistance percentages higher than any other country (61.9%, 33.5% and 24.7%, respectively).[78] Moreover, the high percentages of ESBL-positive *K. pneumoniae* resistant to third-generation cephalosporins (85.3%) may lead to an increased use of carbapenems with an obvious increase of Enterobacteriaceae carbapenemase-producing. As far as *Pseudomonas aeruginosa* is concerned , MDR was observed cumulative for 5.5% of the isolates with also a confirmed increasing trend of resistance to piperacillin-tazobactam (from 16.7% in 2012 to 18.1% in 2015).[78] Carbapenems resistance of *P. aeruginosa* is also high (> 25% of isolates) in 8 countries (Bulgaria, Lithuania, Hungary, Poland, Croatia, Greece, Slovakia and Romania). High-level gentamicin resistance of *Enterococcus faecalis* was reported in 31.3% of isolates in 2015 with 7 countries (Spain, Bulgaria, Lithuania, Hungary, Poland, Italy, Slovakia) having percentages higher than 40%. A significant increase of vancomycin-resistant *E. faecium* was observed in 12 countries although the increase at European level from 2012 to 2015 (8.1% and 8.3%) was not statistically significant. Since enterococci have intrinsic resistance

to several class of antibiotics and displays the ability to acquire additional resistance the epidemiologic situation regarding these bacteria is harmful owing to their role in hospital-acquired urinary tract infection (HAUTI) ~~infections~~.

When urosepsis is suspected blood cultures are mandatory before starting empiric antimicrobial therapy whereas urine cultures have a low sensitivity and specificity in the presence of obstructive pyelonephritis. [118] Procalcitonin (PCT) is the best and more rapid biomarker of systemic inflammation and if available should be used for patients with suspected urosepsis. In a prospective observational study a single determination using a cut-off of PCT > 0.25 μg/L had the best diagnostic performance (sensitivity 95%, specificity 50%) in predicting bacteremia among patients with urosepsis.[127] Despite the fact that the investigators of the above cited trial suggested that adopting a PCT threshold of < 0.25 μg/L can be associated with a 40% of blood culture utilization, we believe that the appropriate use of PCT in this setting is not as a blood-culture sparing biomarker but as a guide to stop antibiotics.[128]

Recurrent UTI

Recurrent UTI is frequently observed among young healthy women without any urological alteration and it is defined as three or more urinary tract infections in the past 12 months or two episodes in the past 6 months (with at least one confirmed by a positive culture).[129] Although several risk factors have been identified or suspected (use of spermicides; sexual intercourse; new sexual partner; tampon use; a relative with history of UTI) counselling and behavioural modifications as preventive measures are generally of little efficacy. Non-antimicrobial prophylaxis with immunoactive products (*i.e.*, OM-89), with probiotics (*i.e.*, intravaginal products containing *Lactobacillus* spp.), drinking cranberry (*Vaccinium macrocarpon*) juice and the use of adhesion blockers (*i.e.*, d-mannose) are sometimes useful. [8,12,130] Antimicrobial prophylaxis with long-term low dose antibiotics or post-coital antibiotic prophylaxis is the alternative strategy. It is generally employed with nitrofurantoin (100 mg per day), cephalexin (250 mg daily), fosfomycin (3 g every 10 days) or trimethoprim-sulfametoxazole (40/200 mg daily) with an important reduction of the

risk of recurrences.[129,131] It should be highlighted that after stopping prophylaxis women experience pre-treatment rates of infection. Moreover, the increasing antimicrobial resistance need to be considered because many antibiotics commonly employed to treat UTI are now ineffective.[132] Finally, the so called "patient-initiated treatment strategy" should be considered for motivated women. ~~This mean~~This means that women learn to recognize signs and symptoms of cystitis and undergo a self-treatment with a 3 day course of an antimicrobial. [129,130]

Conclusions

Urinary tract infections are among the most frequent infectious complications with an high impact in term of suffering for the patients and cost for the healthcare systems. The increasing worldwide antimicrobial resistance of Enterobacteriaceae with ESBL and carbapenemase-producing microorganisms poses an high risk of treatment failure especially among hospitalized frail patients. Antimicrobial stewardship programme should be urgently implemented and physicians need to be aware of "collateral damage" induced by several antibiotics and educated to use them accordingly with the appropriate guidelines.

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Table 1- EAU/ESIU criteria for classification and patient assessment in urinary tract infection *

I-Clinical criteria	II- Possible risk factors	III- Pathogen/aetiological agent	IV- Situation-circumstances under which UTI was acquired	V-Therapeutic options
1-Clinical presentation a. Urethritis (UR) b. Cystitis (CY) c. Pyelonephritis (PY) d. Urosepsis (US) e. Male adnexitis (MA)*	1-Patients characteristics a. Gender (male, female) b. Prematurity, newborn, young child, adolescent c. premenopause d. Pregnancy e. Postmenopause f. Elderly (geriatric: physically or mentally handicapped)	1. Bacterial load 2. Pathogens (type, species) 3. Antimicrobial susceptibility/resistance 4. Virulence	1. Community 2. Outpatient service a. Hospital setting b. Private practice 3. Inpatient service (Hospital) 4. Long-term residential accommodation, nursing home 5. Health care associated	1. Pathogen(s) is (are) susceptible against commonly used antimicrobials a. Which are available b. Which are not easily available 2. Pathogen(s) has (have) limited susceptibility against commonly used antimicrobials a. But alternative antimicrobials are available b. But alternative antimicrobials are not easily available 3. Pathogen(s) is (are) multiresistant and appropriate antimicrobials are not (or not easily) available
2- Specificity of symptoms a. UTI specific i. Lower UTI (CY): dysuria, frequency, urgency, suprapubic pain ii. Upper UTI (PY): fever, flank pain CVA tenderness b. UTI non-specific symptoms i. catheter-asociated UTI (bladder spasm, unexplained fever) ii newborn and young children iii. elderly patients (fever, confusion) iv. patients with neurogenic disorders	2-Relevant disease outside the urinary tract a. Immunosuppression i. innate ii. Acquired (AIDS) b. Diabetes mellitus c. Other disorders			
3- Severity of symptoms a. Mild	3-Nephrological risk factors-status of the			

b. Moderate c. Severe d. Septic	kidneys a. Impaired kidney function b. Kidney abscess c. Polycystic renal disease			
4- Pattern of infection a. Isolated or sporadic b. Recurrent i. Relapse ii. Reinfection c. Unresolved or chronic	4- Urological risk factors a. Functional disorders (reflux, neurogenic bladder disturbances) b. Obstruction without infectious nidus (tumor, non-infected stone) c. Obstruction with infectious nidus (stent, necrotizing tumor, infective stones)			
	5- External catheter a. Urethral b. Suprapubic c. Nephrostomy d. Others			
	6- Asymptomatic bacteriuria			

*Bjerklund Johansen TE, et al. Critical review of current definitions of urinary tract infections and proposal of an EAU/ESIU classification system. Int J Antimicrob Agents 2011;385:64-70. EAU: European Association of Urology; ESIU: European Society of Infectious Urology; UTI: urinary tract infection; CY: cystitis; PY: pyelonephritis; CVA: costovertebral angle.

Table 2- Clinical diagnosis of UTI and grading severity

Clinical diagnosis	Signs and symptoms	Laboratory alterations	Acronym	Grade of severity
Cystitis	Dysuria, urgency, frequency, suprapubic pain	WBC > 10.000/µL; urine dipstick: presence of nitritis Urine culture: positive 10^3 CFU/mL	CY-1	1
Mild and moderate pyelonephritis	Fever, chills, flank pain, costovertebral-angle tenderness	WBC > 10.000/µL; urine dipstick: presence of nitritis Urine culture: positive 10^4 CFU/mL	PN-2	2
Severe pyelonephritis*	As PN-2 plus nausea and vomiting	WBC > 12.000/µL; urine dipstick: presence of nitritis Urine culture: positive 10^4 CFU/mL	Pn-3	3
Urosepsis (simple)§	SIRS= Temperature > 38°C or < 36°C Heart rate > 90 beats min Respiratory rate > 20 breaths/min PaCo2 < 32 mm Hg With or without symptoms of cystitis or pyelonephritis	WBC > 12.000/µL or < 4000/µL; Blood culture: positive for uropathogens	US-4	4
Severe urosepsis#	Hypotension (systolic pressure < 90 mmHg, hypoperfusion (*i.e.*, lactic acidosis; oliguria; alteration of mental status)	WBC > 12.000/µL or < 4000/µL; PLTs < 80.000/µ~~u~~L or decrease > 50% within 3 days; urine dipstick: presence of nitritis PaO2 < 75 mmHg (at ambient air) Blood pH < 7.3 ; plasma lactate > 1.5 fold of normal Blood culture: positive for uropathogens	US-5	5
Uroseptic shock	Hypotension unresponsive to adequate fluid resuscitation; hypoperfusion (*i.e.*, lactic acidosis; oliguria; alteration of mental status)	Blood culture: positive for uropathogens Blood pH < 7.3 ; plasma lactate > 1.5 fold of normal; ARDS (PaO2/FiO2 ≤ 200)	US-6	6

WBC, white blood cells; § with SIRS; # As US-4 plus organ dysfunction or hypotension; ARDS, acute respiratory distress syndrome

Table 3- Host risk factors categorized according to the ORENUC system*

Type	Risk factors	Risk of more severe outcome
O	NO known risk factor (*i.e.*, healthy premenopausal women)	No
Recurrent	Sexual behaviour Post-menopausal hormone deficiency Contraceptive devices Controlled diabetes mellitus	No
Extra-urogenital	Prematurity, newborn Male gender Pregnancy Uncontrolled diabetes mellitus Relevant immunosuppression	Yes
Nephropathy	Impaired renal function Polycystic kidney	Yes
Urological	Obstructive uropathy (i.e. stone, tumor) Short term catheterization Urological surgery	Yes
Catheter	Long term catheter Non resolvable urinary obstruction Neurogenic bladder badly controlled	Yes

*Smelov V et al. Improved classification of urinary tract infection: future consideration. European Urology Supplements 2016;15:71-80

Table 4- Acute uncomplicated cystitis and pyelonephritis treatment recommended by IDSA/ESCMID and EAU guidelines

Clinical syndrome	IDSA/ESCMID 2012	EAU 2015
Acute cystitis	**First-line therapy** Nitrofurantoin monohydrate/macrocristal 100 mg bid for 5 days po* Or Trimethoprim/sulfamethoxazole (TMP-SMX) 160/800 mg bid for 3 days po Or Fosfomycin trometamol 3 g single dose po Or Pivmecillinam 400 mg bid for 5 days po	**First choice** Fosfomycin trometamol 3 g single dose po Or Nitrofurantoin monohydrate/macrocristal 100 mg bid for 5 days po* Or Pivmecillinam 400 mg tid for 5 days po
	Second-line therapy Fluoroquinolones Ciprofloxacin 250 mg bid for 3 days po Levofloxacin 250 or 500 mg single dose for 3 days po **Beta-lactams** Amoxicillin-clavulanate Cefpodoxime-proxetil 100 mg bid for 5 days po	**Alternatives** Fluoroquinolones§ Ciprofloxacin 250 mg bid for 3 days po Levofloxacin 250 mg single dose for 3 days po Ofloxacin 200 mg bid for 3 days **Cephalosporins** Cefadroxil 500 mg bid for 3 days po TMP-SMX 160/800 mg bid for 3 days po§
Acute pyelonephritis (mild and moderate)	**First-line therapy** Ciprofloxacin 500 mg bid for 7 days po with or without an initial dose of 400 mg intravenous ciprofloxacin** Ciprofloxacin 1000 mg (extended release)/d for 7 days po Levofloxacin 750 mg/d for 5 days po Plus 1 g Ceftriaxone iv° or a consolidated 24-h dose of an aminoglycoside	**First choice** Ciprofloxacin 500-750 mg bid for 7-10 days po Levofloxacin 500 mg/d for 7-10 days po Levofloxacin 500 mg/d for 5 days po **Alternatives^** Cefpodoxime proxetil 200 mg bid for 10 days po Ceftibuten 400 mg/d for 10 days po Trimethoprim-sulphametoxazole 160/800 mg bid for 14 days po#

	Second-line therapy TMP-SMX 160/800 mg bid for 14 days po Plus 1 g Ceftriaxone iv*** or a consolidated 24-h dose of an aminoglycoside	
Severe acute uncomplicated pyelonephritis	**Parenteral fluoroquinolone** Ciprofloxacin 400 mg bid iv Levofloxacin 500-750 mg/d iv **Aminoglycoside** Gentamicin 5-7 mg/d iv **Extended spectrum cephalosporin** Ceftazidime 1 g tid ± an aminoglycoside iv Ampicillin-sulbactam± aminoglycoside (if gram-positive cocci are causative) iv	**First choice§§** Ciprofloxacin 400 mg bid iv Levofloxacin 250-500 mg/d iv Levofloxacin 750 mg/d iv **Alternatives** Cefotaxime 2 g tid iv Ceftriaxone 1-2 g/d iv Ceftazidime 1-2 g tid iv Cefepime 1-2 g bid iv Co-amoxiclav 1,5 g tid iv^^ Piperacillin-tazobactam 2,5-4,5 g tid iv Amikacin 15 mg/kg/d^^ Gentamicin 5 mg/kg/d^^ Ertapenem 1g /d iv Imipenem/cilastatin 0.5/0.5 g tid iv Meropenem 1 g tid iv Doripenem 0.5 g tid iv

IDSA/ESCMID, Infectious Diseases Society of America/European Society of Clinical Microbiology and Infectious Diseases; EAU, European Association of Urology; * Avoid in patients with glucose-6-phosphate dehydrogenase deficiency:; § If local resistance pattern is known (*E. coli* resistance < 20%); ** Where the prevalence of resistance of community uropathogens to fluoroquinolones is not known to exceed 10%; ° If the prevalence of fluoroquinolone resistance is thought to exceed 10%; *** When the susceptibility of TMP-SMX is not known; ^ Clinical but not microbiological equivalent efficacy compared with fluoroquinolones; # Not for initial empirical therapy; §§ After improvement, the patient can be switched to an oral regimen using one of the agents listed for oral antimicrobial therapy in mild and moderate acute uncomplicated pyelonephritis (if active against the infecting organism) to complete 1-2 week course of therapy. Therefore, only daily dose and no duration of therapy is indicated. bid: twice daily; tid: thrice daily; iv: intravenous; ^^ Not studied as monotherapy in acute uncomplicated pyelonephritis