Perspective from the Urologist

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4.1 Introduction

Traditionally, urinary tract infections (UTIs) are classified based on symptoms, laboratory data and microbiological findings. Practically, they can be divided into uncomplicated and complicated UTIs and sepsis.

Most episodes of cystitis and pyelonephritis in otherwise healthy individuals are generally considered uncomplicated. If associated with an underlying condition that increases the risk of infection or of failing therapy, they become complicated. Such conditions include poorly controlled diabetes mellitus; pregnancy; hospital-acquired infection; acute kidney injury or chronic kidney disease; suspected or known urinary tract obstruction; presence of indwelling urethral catheter, stent, nephrostomy tube or urinary diversion; functional or anatomic abnormality of urinary tract; renal transplantation; other immunocompromising condition (e.g. chronic high-dose corticosteroid use, use of immunosuppressive agents, neutropenia, advanced HIV infection, B or T leukocyte deficiency); and infection with a uropathogen with broad-spectrum antimicrobial resistance.

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The European Association of Urology (EAU) proposed a classification based on anatomical level of infection and grade of severity of infection. The authors agree with this last classification.

4.2 Cystitis

Acute cystitis refers to infection of the bladder. It is a very common UTI among women. Almost half of sexually active young women experienced at least one episode of UTI during their lifetime [1]. Risk factors include sexual intercourse, use of spermicides, vaginal postmenopausal hormonal status, history of urinary tract infection (during childhood or mother), urinary incontinence and cystocoele [2]. Only few men suffer from acute uncomplicated cystitis [3].

4.2.1 Clinical Manifestations

The diagnosis can be easily made on focused history. Typically, symptoms described are dysuria, frequency, urgency and pain during micturition. In case of complicated cystitis patients can present suprapubic pain and hematuria.

4.2.2 Diagnostic Evaluation

Laboratory diagnostic tools consist of urinalysis. Urine dipstick testing is a reasonable alternative

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to culture. A colony count of $\geq 10^3$ CFU/mL of uropathogen is diagnostic [4]. *Escherichia coli* is the main microorganism involved in the pathogenesis.

Radiographic imaging is not necessary to diagnose cystitis. Ultrasound (US) can point out mucosal oedema associated with a diffuse thickening of the bladder wall. In clinical practice, it is required in case of recurrent episodes. Generally it is more useful to rule out some complications, such as bladder stones or other bladder diseases (tumours). Other radiological examinations don't add any important information.

4.2.3 Disease Management

Antibiotic therapy is recommended in symptomatic patients. The first choice in many European countries are fosfomycin 3 g single dose, pivmecillinam 400 mg tid for 3 days and nitrofurantoin 100 mg bid for 5 days [5–7].

Alternative antibiotics include trimethoprim combined with sulphonamide and fluoroquinolone class (ciprofloxacin, levofloxacin) in 3-day regimens.

In case of complicated cystitis or suspected concomitant pyelonephritis, oral therapy with fluoroquinolones becomes the first choice.

4.3 Pyelonephritis

Acute pyelonephritis is less common than acute cystitis; the annual incidence is about 0.12 per person-year [8]. Upper UTIs occur more frequently in patients with diabetes mellitus [9].

E. coli is the causative pathogen in 70–95% of cases. Occasionally, other *Enterobacteriaceae*, such as *Proteus mirabilis* and *Klebsiella pneumoniae*, are isolated [10].

4.3.1 Pathogenesis

Pyelonephritis develops when pathogens ascend to the kidneys via the ureters but can also be caused by seeding of the kidneys from bacteremia or from bacteria in the lymphatics. Host and microbial factors that underlie progression from bladder to kidney infection require further investigation.

4.3.2 Clinical Manifestations

Acute pyelonephritis is suggested by flank pain, nausea and vomiting, fever (>38 °C), chills and costovertebral angle tenderness. Symptoms of cystitis may or may not be present [11]. Patients with acute complicated pyelonephritis may present with sepsis. In some cases they may be associated with a period of insidious, non-specific, signs and symptoms such as malaise, fatigue or abdominal pain. In diabetic patients acute pyelonephritis may also develop progression of renal parenchymal infection sometimes caused by gas-forming organisms (emphysematous pyelonephritis), with a high mortality [12].

The risk of chronic renal disease and renal insufficiency caused by pyelonephritis is low.

It is important to differentiate very early between an acute uncomplicated and complicated obstructive form of pyelonephritis, because the latter can very quickly lead to urosepsis.

4.3.3 Diagnostic Evaluation

The diagnosis begins with accurate clinical history. Physical examination should include abdominal and pelvic examination, to exclude the presence of vaginitis or urethritis. Pregnancy testing is also appropriate in women of childbearing age. Urinalysis (either by microscopy or by dipstick), including the assessment of white and red blood cells and nitrites, is recommended [13].

Pyuria is present in almost all patients with complicated UTI. Colony counts $\geq 10^4$ CFU/mL of pathogen are considered indicative of relevant bacteriuria. However, pyuria and bacteriuria may be absent if the infection does not communicate with the collecting system or if it is obstructed.

Urine cultures should be obtained prior to therapy to evaluate for antimicrobial resistance.

Patients with persistent clinical symptoms after 48–72 h of appropriate antibiotic therapy should undergo radiologic evaluation of the upper urinary tract, initially with US. In addition, radiologic evaluation is warranted for patients with pyelonephritis who also present symptoms of renal colic or have history of renal stones, diabetes, history of prior urologic surgery, immunosuppression, repeated episodes of pyelonephritis or urosepsis [13].

Evaluation of the upper urinary tract with US should be performed to rule out urinary obstruction or renal stone disease. Computed tomography (CT) scan should be considered if the patient still presents fever after 72 h of treatment. CT without contrast has become the standard radiographic study for demonstrating gas-forming infections, haemorrhage, obstruction and abscesses. Contrast is needed to demonstrate localized hypodense lesions due to ischaemia. Magnetic resonance imaging (MRI) is preferred in pregnant women to avoid radiation risk to the foetus.

In clinical practice CT remains the most used exam because it is widely available, can be remotely reported and is the one that offers more information at one time, especially with regard to complications. MRI would be preferable but not always, and not in all hospitals, there is a real chance to perform such an examination in emergency conditions.

4.3.4 Disease Management

Empiric antimicrobial therapy should be initiated promptly. In mild and moderate cases of acute uncomplicated pyelonephritis, oral therapy for 10–14 days is usually sufficient. The first-line therapy is represented by fluoroquinolone (Table 4.1), contraindicated in pregnancy. A third-generation oral cephalosporin could be an alternative in case of resistance. In communities with high rates of fluoroquinolone-resistant and ESBL-producing *E. coli*, initial empirical therapy with an aminoglycoside or carbapenem has to be considered.

In patients with severe pyelonephritis, parenteral antibiotics have to be used. After

Table 4.1 Recommended initial empirical antimicrobial therapy

	Antibiotics	Daily dose	Duration of therapy	Note
Mild and moderate acute uncomplicated pyelonephritis	Ciprofloxacin	500 mg bid	7–10 days	
Oral therapy	Levofloxacin	500 mg qd	7–10 days	
	Cefotaxime	400 mg qd	10 days	Alternative, not microbiological equivalent efficacy to fluoroquinolones
	Trimethoprim-sulphamethoxazole	160/800 mg bid	14 days	Only if the pathogen is known to be susceptible
	Co-amoxiclav	0.5/0.125 g tid	14 days	
Severe acute uncomplicated pyelonephritis	Ciprofloxacin	400 mg bid		
	Levofloxacin	500 mg qd		
	Cefotaxime	2 g tid		
Parenteral therapy	Piperacillin/tazobactam	2.5–4.5 g tid		
	Amikacin	15 mg/Kg qd		
	Ertapenem	1 g qd		

improvement, the patient can be switched to an oral therapy for 1–2 weeks. Positioning urinary catheter is important in order to drain the urinary tract.

4.4 Urosepsis

Sepsis is a complex systemic inflammatory host response to bacterial infection (Table 4.2). In urosepsis the focus of infection is localized to the urogenital tract. Patients with urosepsis should be identified at an early stage and promptly treated to prevent development of organ failure and other complications. Mortality rates are high. The severity depends mostly upon the host response.

4.4.1 Pathogenesis

Complicated UTI is the commonest precursor of urosepsis. It is important to note that a patient can move from an almost harmless state to severe sepsis in a very short time. Structural and functional abnormalities such as obstruction (congenital or acquired), instrumentation, impaired voiding, metabolic abnormalities and immunodeficiencies can be associated to urosepsis.

Microorganisms reach the urinary tract byway of the ascending, haematogenous or lymphatic routes. For urosepsis to be established, the pathogens have to reach the bloodstream. Gram-negative bacilli account for majority of the cases of urosepsis. These include *E. coli* (50%), *Proteus* spp. (15%), *Enterobacter* and *Klebsiella* spp. (15%) and *Pseudomonas aeruginosa* (5%), while Gram-positive organisms are involved less frequently (15%) [14].

4.4.2 Clinical Manifestations

The clinical presentation may be varied. Signs and symptoms of systemic inflammatory response syndrome which were initially considered to be 'mandatory' for the diagnosis of sepsis [15] are now considered to be alerting symptoms [16]. Fever, tachycardia, tachypnea and respiratory alkalosis are the typical manifestation. Only one-third of the patients classically present with fever and chills along with hypotension.

Table 4.2 Diagnostic criteria for sepsis

• *General signs*
– Fever >38.3 °C
– Hypothermia <36 °C
– Tachycardia >90/min or >2 SD above age-specific normal value
– Tachypnea >30/min
– Impaired neurologic status
– Oedema or positive fluid balance (>20 mL/kg/d)
– Hyperglycemia (blood sugar >120 mg/dL or 7.7 mmoL/L) in the absence of previously diagnosed diabetes mellitus
• *Signs of inflammation*
– Leukocytosis >12/nL
– Leukopenia <4/nL
– Normal leukocyte count with >10% immature forms
– C-reactive protein >2 SD above normal
– Procalcitonin >2 SD above normal
• *Hemodynamic signs*
– Hypotension (SBP <90 mmHg, MAP <70 mmHg or SBP drop by >40 mmHg or to <2 SD below the age-specific normal value)
– Cardiac index (CI) >3–5 L/min/m^2
• *Organ dysfunction*
– Arterial hypoxemia ($p_aO_2/F_iO_2 < 300$)
– Acute oliguria <0.5 mL/kg/h or 45 mmoL/L for (≥ 2 h)
– Creatinine rise by (≥ 0.5 mg/dL)
– Coagulopathy (INR >1.5 or aPTT >60 s)
– Thrombocytopenia <100/nL
– Hyperbilirubinemia (total bilirubin >4 mg/dL or >70 mmoL/L)
– Ileus
• *Tissue perfusion variables*
– Lactate >2 mmol/L
– Decreased capillary refill or mottling

4.4.3 Diagnostic Evaluation

History is crucial in the evaluation of any UTI, including any previous history of infections, anti-

biotic use and a timeline of symptoms. A patient can be considered to have sepsis if he or she has evidence of bacteremia or clinical suspicion of sepsis accompanied by greater than or equal to two criteria of systemic inflammatory response syndrome as mentioned in Table 4.2.

The diagnosis of UTI, from simple cystitis to complicated pyelonephritis with sepsis, can be established with absolute certainty only by quantitative urine cultures.

Blood cultures should be done before antibiotic treatment is started. Ideally, several aerobic and anaerobic blood cultures are taken when fever is rising.

In a critically ill patient with urosepsis, CT and MRI are very useful investigations. These are the most precise methods for identifying bacterial interstitial nephritis and micro-abscesses within the kidney, perinephric abscesses, emphysematous pyelonephritis and renal papillary necrosis and can determine therapeutic choices and intervention times. Urinary unblocking, with either ureteral stenting or percutaneous nephrostomy, is mandatory.

4.4.4 Disease Management

The treatment of urosepsis needs the collaboration of a team (urologists, intensive care and intensive diseases specialists), to coordinate an adequate life-supporting care, appropriate and prompt antibiotic therapy.

Levels of therapy are divided into causal therapy (antimicrobial treatment and source control), supportive therapy (haemodynamic stabilization and airways, respiration support) and adjunctive therapy (glucocorticosteroids and intensified insulin therapy).

The drainage of any obstruction in the urinary tract is essential as first-line treatment (LE, 1a; GR, A) [17]: in case of renal abscess, percutaneous or surgical drainage, and in infected hydronephrosis, internal drainage (double J-DJ or mono J- MJ) or percutaneous nephrostomy.

If possible, specific treatment of the diagnosed infection should be started as soon as possible.

Empirical antimicrobial therapy effective against both Gram-positive and Gram-negative bacteria should be initiated. A calculated parenteral antibiotic should be reassessed once culture results become available, usually within 48–72 h.

In case of *E. coli* and other Enterobacteriaceae isolation, a third-generation cephalosporin or piperacillin in combination with a beta-lactamase inhibitor or fluoroquinolone with propensity to achieve high urinary concentration (e.g. ciprofloxacin, levofloxacin) should be used. A combination therapy with an aminoglycoside or a carbapenem may be essential in areas with high rate of fluoroquinolone resistance. Reserve antibiotics such as imipenem or meropenem if a difficult resistance situation is suspected [18].

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