Chapter 3

Urinary tract infection and autoimmune diseases

Ana Matas[1,2], Marc Xipell[1], Marta Bodro[3], Ricard Cervera[4], and Luis F. Quintana[1,*]

[1]*Department of Nephrology and Renal Transplantation, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain;* [2]*Department of Internal Medicine, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain;* [3]*Department of Infectious diseases, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain;* [4]*Department of Autoimmune diseases, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain*

**Corresponding Author.*

1. Introduction

Infections are one of the main causes of morbidity and mortality in patients with autoimmune diseases, mostly attributed to autoimmune disease activity, the alteration of cellular and humoral immunity, immunosuppressive treatment received, and functional asplenia. Moreover, urinary tract infection (UTI) is the first cause of infection in many published cohorts of patients with autoimmune diseases, over the world. Furthermore, we must be aware of potential interactions of immunosuppressant treatment with antibiotics, which may compromise the control of symptoms of the autoimmune disease. To date, little attention has been paid to the incidence of UTI in autoimmune diseases and evidence available is scarce, and it is based mainly on studies in patients with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA).

2. Definitions and diagnosis

The definitions of UTI in patients with autoimmune diseases are usually adopted from the accepted definitions in the general population. Asymptomatic bacteriuria (AB) is defined as a urine culture yielding significant growth of urinary tract pathogens ($\geq 10^5$ colony forming units (CFU)/mL) in the absence of symptoms attributable to infection. Cystitis is defined by the presence of bacteriuria and clinical manifestations such as dysuria, frequency, or urinary urgency in the absence of pyelonephritis criteria. Prostatitis is characterized by

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discomfort referred to the lower urogenital and perineal and/or ejaculatory discomfort. Acute prostatitis is presented as fever and chills accompanied by urinary symptoms such as dysuria, frequency, and perineal pain. Typically, patients with acute pyelonephritis (AP) present with fever and chills. The diagnosis is definite when there is pain over the area of the kidney. Patients with fever (with or without lumbar pain) and urine culture positive for urinary tract pathogens ($\geq 10^5$ CFU/mL) are diagnosed as having AP.

Relapse is defined as the isolation of the same microorganisms that caused the preceding infection, with the same antibiotic sensitivity pattern, in a urine culture obtained $\geq$2 weeks after finishing the previous treatment. Recurrent infection is commonly defined as three or more episodes of symptomatic UTI over a 12-month period or two episodes in the previous 6 months.

The diagnostic approach in patients with recurrent UTI must be meticulous in order to rule out the existence of anatomical or functional changes.

3. Epidemiology and risk factors

Patients with autoimmune disease have a higher incidence of UTI compared with general population, especially in patients with SLE. The incidence of UTI in patients with SLE ranges between 50 and 150 episodes per 100 patients-year, compared with the 0.9 episodes per 100 patients-year for general population. In RA, population represents an annual incidence of 2 episodes per 100 patients-year. UTI occurs predominately in females (90%). Importantly, some authors have reported that UTIs are one of the two main causes of infection in these patients and a main cause of admission to hospital and death in SLE/RA patients. Relapse and recurrence of UTI was common, especially in females.

Risk factors associated with UTI in patients with autoimmune diseases are described in Table 3.1. Age, female gender, immunosuppressive therapies, previous cases of UTI, disease activity, long disease duration, thrombocytopenia, and hospital admission were associated with UTI. Also, chronic kidney disease, anatomical and functional abnormalities in urinary tract (e.g., vesicoureteral reflux or incontinence) constitute independent risk factors for infection.

The role of the immunosuppressive agents as risk factors associated with UTI has been analyzed in some studies. Long-term oral steroids as sole therapy have been identified as the most readily modifiable risk factor for UTI. Also, cytotoxic agents, such as cyclophosphamide, azathioprine, or mycophenolate, increase the risk of UTI, especially when they are administered in combination. Biologic therapy also plays a role in favoring UTI. Patients with RA treated with these agents have an increased risk of serious and nonserious infections at 12 months (especially in the first 6 months), compared with traditional disease-modifying antirheumatic drugs. Similar outcomes have been found in some cohorts of SLE patients.

TABLE 3.1 Risk factors associated with urinary tract infection (UTI) in patients with autoimmune diseases.

Age Female gender
Immunosuppressive therapies - Corticosteroids - Biological therapies (infliximab, rituximab, etanercept) - Methotrexate - Cyclophosphamide
Previous UTI
Autoimmune disease activity
Thrombocytopenia
Previous hospital admission
Long disease duration
Permanent catheters
Vaginal prolapsed
Diabetes
Cancer

4. Etiology

The most common implicated microorganisms in UTI are gram-negative agents, being *Escherichia coli* the dominant pathogen accounting for over half of all infections. Other commonly found uropathogens include *Klebsiella pneumoniae*, *Enterobacter cloacae, Pseudomonas aeruginosa, Morganella morganii*, and *Proteus mirabilis. Enterococcus* spp. is probably the most frequent gram-positive agent implicated in UTI. *Proteus* and *Enterococcus* are often related to urinary catheters. *P. aeruginosa* is a cause of UTI in patients with prolonged antibiotic therapy and urinary manipulations. Regarding nonbacterial infections, *Candida* spp. and, in case of intense immunosuppressant treatment, BK virus infection must be considered.

Regarding antibiotic susceptibilities, the incidence of infections caused by multidrug-resistant bacteria has been progressively increasing worldwide during the last decade, and the emergence of these infections poses a difficult therapeutic challenge. These pathogens cause an increasing number of health care−associated infections with significant morbidity and mortality which are often associated with hospitalization and prior antibiotic use. Patients with autoimmune diseases are especially at risk to develop infections caused by multidrug-resistant organisms, due to their close relationship with the health-care system and common use of antimicrobials.

5. Clinical features

Among others, UTI can be presented mainly as cystitis or pyelonephritis. In men, the clinical spectrum of UTI also includes prostatitis, which should be considered when they present recurrent cystitis symptoms that are accompanied by pelvic or perineal pain. Among sexually active young women, if symptoms are not convincing for an UTI, a pelvic examination may be warranted, to evaluate for cervical motion or uterine tenderness, which would be suggestive of pelvic inflammatory disease. Pregnancy testing is appropriate in women of childbearing potential when the possibility of pregnancy cannot be reasonably excluded by history alone. Likewise, in young men without known structural urological pathology, as benign prostatic hyperplasia, we must also rule out sexually transmitted diseases.

Fever is an unspecific reaction to any aggression that activates the immune response, whatever the cause that triggers the inflammatory process. It is common in active lupus, systemic vasculitis (febrile connective tissue), and rheumatoid arthritis, being less frequent in scleroderma, dermatomyositis, chronic phase sarcoidosis, and Sjögren syndrome. In this sense, we must bear in mind that the presence of fever in a patient with autoimmune disease may not only be due to its underlying pathology, but it is also advisable to rule out intercurrent infectious processes.

Not all patients with acute complicated UTI present with symptoms focalizing to the urinary tract. For instance, patients with spinal cord injury and neurogenic bladder can present with autonomic dysreflexia and increased spasticity. Elderly or debilitated patients may present without clear urinary tract symptoms, with nonspecific signs or symptoms, such as falls, change in functional status, and change in mental status, or systemic signs.

Patients with acute complicated UTI may also present with sepsis, multiple organ system dysfunction, shock, and/or acute renal failure. This is more likely to occur in patients with urinary tract obstruction, recent urinary tract instrumentation, or other urinary tract abnormalities and in patients who are elderly or have associated comorbidities such as diabetes mellitus.

AP can also be complicated by progression of the upper UTI to renal corticomedullary abscess, perinephric abscess, emphysematous pyelonephritis, or papillary necrosis. Risk factors for such complications include again urinary tract obstruction and diabetes mellitus.

Xanthogranulomatous pyelonephritis is a rare variant of pyelonephritis in which there is massive destruction of the kidney by granulomatous tissue. Most cases occur in the setting of obstruction due to infected renal stones. Affected patients can present with weeks to months of insidious and nonspecific signs and symptoms, such as malaise, fatigue, nausea, or abdominal pain.

6. Supplementary tests

As said before, the definitive diagnosis of UTI is the presence of significant growth of urinary tract pathogens ($\geq 10^5$ colony CFU/mL) with concomitant symptoms of UTI. However, while pending the urine culture results, other simple tests can guide us to the diagnosis of UTI. This is important since antibiotic treatment generally must be initiated when it is suspected clinically as a UTI, even without the results of urinary culture, especially in case of severe sepsis.

6.1 Laboratory findings

Urinary dipstick, although it is not a diagnostic criterion, can guide us to the diagnosis of UTI. Pyuria, present in almost all patients with UTI, can be detected by leukocyte esterase test in a urine dipstick (sensitivity of 90% to detect more than 10 leukocytes/mm^3 with a specificity $> 95\%$), examination of urine sediment (indicative of pyuria the presence of more than five leukocytes per field (x 40)) or leukocyte urinary count in a counting-chamber (where pyuria is considered as the finding of more than 10 leukocytes/mm^3 of urine).

In urine dipstick, we can also detect the presence of nitrites. Nitrites come from the action of a bacterial enzyme (nitratorreductase) on the urinary nitrates. The bacteria should remain in contact with the nitrates for about 4 hours to produce a detectable amount of nitrites with a dipstick. The test is specific ($>90\%$) but not sensitive (50%), especially if the density of microorganisms is low (10^3; CFU/mL) or the time of urination in the bladder has been short (for instance, patients with bladder catheter). Some microorganisms such as gram-positive cocci, *Pseudomonas*, *Acinetobacter*, and *Candida* do not produce nitroreductase.

In case of fever, suspicion of pyelonephritis or systemic symptoms also is necessary to perform blood cultures.

6.2 Imaging techniques

The majority of patients with acute complicated UTI do not warrant imaging studies for diagnosis or management. Imaging is generally reserved for those who are severely ill due to complicated pyelonephritis, have persistent clinical symptoms despite 48–72 hours of appropriate antimicrobial therapy, or have suspected urinary tract obstruction. Imaging is also appropriate in patients who have recurrent UTI despite adequate treatment.

The purpose of imaging is to assess for a cause that may delay response to therapy or requires intervention, such as a calculus or obstruction, or to diagnose a complication of infection, such as a renal or perinephric abscess.

Imaging should be obtained urgently in patients with sepsis to identify any evidence of obstruction or abscess that requires urgent source control.

The first image study to consider is renal ultrasound, given its non-invasiveness and absence of nephrotoxic contrast and irradiation. Computed tomography (CT) scanning of the abdomen and pelvis is more sensitive than renal ultrasound for detecting renal abnormalities predisposing to or caused by infection, but it is more expensive and irradiates, and sometimes requires nephrotoxic contrast. CT without contrast may help in study for demonstrating calculi, gas-forming infections, hematoma, or obstruction. Contrast is generally needed to demonstrate alterations in renal perfusion, active hemorrhage, and abscesses. CT findings of pyelonephritis include localized hypodense lesions due to ischemia induced by marked neutrophilic infiltration and edema. The CT can be normal in patients with mild infection. We must do not forget that some autoimmune diseases occur in young women with childbearing potential, and irradiation must be correctly justified.

Magnetic resonance imaging is not advantageous over CT except when avoidance of contrast dye or ionizing radiation is warranted.

7. Management

As a general rule, in case of severe infection, it is recommended to reduce immunosuppressant treatment, if possible. In addition, possible interactions of antimicrobials with immunosuppressive drugs must always be taken into account. Drugs frequently used in patients with autoimmune diseases, such as tacrolimus, cyclosporine, methotrexate, or chloroquine, interact with drugs potentially useful for UTIs such as azoles, linezolid, quinolones, cotrimoxazole, etc.

To choose an appropriate antibiotic for the treatment of UTI, we recommend using the same treatment recommendations for the general population. The choice of empirical antimicrobial agents should be based on local epidemiological data, patient's history of previous organisms, and antibiotic therapies prescribed in the previous months. Once culture susceptibility results are available, switch to the narrowest spectrum antibiotic available to complete course of therapy is recommended.

In patients with renal impairment, antibiotic dosage should be adapted to the patient renal function.

In case of obstructive pyelonephritis, a derivation of the urinary tract is required, and in case of abscesses, surgical drainage may be necessary to control the infection.

Table 3.2 shows empirical treatment recommendations depending on clinical presentation and presence or absence of risk factors for multidrug-resistant organisms.

Patients presenting with cystitis should be treated for 5−7 days with an oral antibiotic, and for patients with AP, a 10- to 14-day course of antibiotics is

TABLE 3.2 Empirical treatment of urinary tract infections in patients with autoimmune diseases.

Clinical presentation	Absence of risk factors for multidrug-resistant organisms[a]	Presence of risk factors for multidrug-resistant organisms
Cystitis	Fosfomycin or second-/third-generation oral cephalosporin. Use amoxicillin/clavulanate, TMP/SMX, or ciprofloxacin[b] as alternative therapies.	Fosfomycin. In case of recurrence suspicion, consider ertapenem.
Acute uncomplicated pyelonephritis	Ceftriaxone. Use amoxicillin/clavulanate or aztreonam as alternative therapies.	Ertapenem or piperacillin-tazobactam. Use aztreonam + vancomycin/teicoplanin as alternative therapies.
Prostatitis	Second-/third-generation oral cephalosporins. Use amoxicillin/clavulanate, TMP/SMX, or ciprofloxacine as alternative therapies.	Ertapenem or piperacillin-tazobactam[c] Use aztreonam + vancomycin/teicoplanin as alternative therapies.
Severe sepsis/septic shock	Meropenem + vancomycin/teicoplanin (+amikacin, if risk factors for *Pseudomonas aeruginosa*). Use aztreonam + vancomycin/teicoplanin (+amikacin if risk factors for *P. aeruginosa*) as alternative therapies.	Meropenem + vancomycin/teicoplanin/linezolid (+amikacin if risk factors for *P. aeruginosa*)[c] Use aztreonam/colistin + vancomycin/teicoplanin/linezolid as alternative therapies.

[a] *Prior hospitalization in the previous 3 months, previous antibiotic therapy (within 1 month), previous colonization by MDR organisms.*
[b] *Treatment with quinolones is not recommended as a first option, since Escherichia coli has a resistance rate greater than 20% in general population without risk factors. However, once the urinary culture and antibiogram are available, treatment can be adjusted to the sensitivity of the isolated microorganism. In case of sensitivity to quinolones, they are a good option since they have a more selective antibacterial spectrum against urinary pathogens.*
[c] *Ceftolozane/tazobactam 1.5–3 g/8h iv can be used instead of meropenem in case of high risk of infection by P. aeruginosa resistant to β-lactams, and ceftazidime-avibactam 2.5 g/8h iv in case of high risk of infection for carbapenemase producing Enterobacteriaceae spp.*

recommended. For patients with complicated infections, an antibiotic course of at least 2 weeks is recommended and should be extended until abscesses are adequately drained and patient improvement has been achieved. For patients with acute prostatitis, a 2- to 4-week course of antibiotics is recommended.

Screening for and treatment of AB or candiduria is not routinely recommended.

The design of a long-term management or prevention of new episodes of UTI should always balance the risk and benefits for the patient. The use of nonantibiotic therapies, such as cranberry extract, L-methionine, vaccines, topical estrogens, or topical application of *Lactobacillus* could be considered.

7.1 Management of nonbacterial urinary tract infections

Urinary candidiasis: In *Candida albicans* UTI, treatment of choice is fluconazole for 14 days. In case of infection by *Candida krusei* or *Candida glabrata* azole-resistant, amphotericin B deoxycholate iv, 3−7 days, can be used.

Urinary BK virus infection: BK primary infection occurs in childhood and is usually asymptomatic. After primary infection, the virus remains latent in the epithelium of renal tubules and can be reactivated in the case of immunosuppressant treatment (especially in cases of kidney transplantation or hematopoietic progenitors, but also in autoimmune diseases with severe immunosuppressant treatment, although it is not as frequent). Mainly, it can produce asymptomatic viruria or viremia with affection of the urinary tract. The main manifestations are hemorrhagic cystitis with hematuria, interstitial nephritis, urethral or urethral stenosis, and subacute interstitial nephropathy that may progress to chronic kidney failure. Treatment requires symptomatic measures and reduction of immunosuppressant treatment if possible. Alternatives may be cidofovir, ciprofloxacin, of IgG iv.

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