

INTRODUCTION

Urinary tract infection (UTI) is defined as an inflammatory response of the urothelium to microorganism (usually bacterial) invasion. UTIs are one of the most common bacterial infections affecting men and women of all ages. It is the third most common infection after respiratory and gastro-intestinal infections¹. UTI can be classified in various ways: community or hospital acquired, cystitis or pyelonephritis and uncomplicated or complicated. In this article we will review the various aspects of complicated urinary tract infection (cUTI).

DEFINITION OF COMPLICATED URINARY TRACT INFECTION (CUTI)

In general any UTI except that in a young, otherwise healthy, immunocompetent, non-pregnant female with an anatomically and functionally normal urinary tract

should be considered a cUTI. A detailed classification of the clinical syndromes of uncomplicated and cUTI is given in Table 1².

It may be noted that UTI in males, elderly, childhood, pregnancy, diabetes mellitus, recent urinary instrumentation may actually only be acute uncomplicated cystitis, and not necessarily always cUTI.² However, one must always have a high index of suspicion in these cases. The anatomical site of infection per se is not the deciding factor. In fact even pyelonephritis may be uncomplicated if it satisfies the factors mentioned above.

RISK FACTORS FOR CUTI

The risk factors for cUTI can be divided under host and organism related factors.

HOST RELATED**Male sex**

Males are generally resistant to UTI. This is because of the presence of an elongated urethra, and the antibacterial nature of prostatic secretions.³ Hence UTI in a male should raise the doubt of some underlying abnormality.

Age

Infections in childhood suggest certain abnormalities of the genitourinary tract. Vesicoureteral reflux, urethral valves, ureteropelvic obstruction, or ureterovesical obstruction are all conditions where there is a tendency for an increased incidence of urinary tract infections, and also increased severity⁴. Postmenopausal women with recurrent urinary infection are also more likely to have increased residual urine volume, cystoceles and prior genitourinary surgery thus making them more prone to cUTIs.

Cannulated urinary tract

Patients with indwelling catheters (urethral, suprapubic, nephrostomy) or a ureteral double J stent are prone to infection with resistant organisms. It is difficult to distinguish benign colonization from frank infection.

Diabetes

Diabetics are more susceptible to cUTI. Also complications such as perirenal, intra renal abscesses, carbuncles, lobar nephronia, emphysematous pyelonephritis and secondary obstruction due to renal papillary necrosis are more common in diabetics.

Chronic kidney disease

CKD patients have reduction in renal blood flow, urinary volume and reduced immune response. There is also decrease in concentrating ability of urine, reduction

Table 1: Clinical syndromes of uncomplicated and complicated UTI

Uncomplicated UTI

- Acute uncomplicated cystitis in young women
- Recurrent acute uncomplicated cystitis in young women
- Acute uncomplicated pyelonephritis in young women
- Acute uncomplicated cystitis in adults with other complicating factors

Male sex, Elderly, Pregnancy, Diabetes mellitus, Recent urinary tract instrumentation, Childhood UTI

- Asymptomatic bacteriuria

Complicated UTI

- Structural abnormality/obstruction
- Functional abnormality: neurogenic bladder, vesicoureteral reflux
- Foreign bodies: indwelling catheter (AUTI), ureteral stent, nephrostomy tube.
- Others conditions Renal failure, renal transplantation, immunosuppression, multidrug-resistant uropathogens, health care-associated (includes hospital-acquired/nosocomial place) infection, prostatitis-related infection, upper tract infection in an adult other than a healthy young woman, other functional or anatomic abnormality of urinary tract)

608 of substances in urine inhibiting bacterial growth and decreased delivery of antibiotics in the urinary tract all of which predispose them to cUTI⁵.

Urolithiasis

Stones cause injury to the urothelium and give bacteria a place to establish colonization. Certain stones are a direct result of infection especially magnesium ammonium phosphate or calcium carbonate and these stones themselves promote persistence of infection.

Pregnancy

Factors in pregnancy predisposing to cUTI are gravid uterus causing relative obstructive uropathy, high progesterone levels leading to reduced ureteral/bladder motility, voiding dysfunction and venous congestion. Hence UTI during pregnancy is considered as cUTI unless proved otherwise⁶. Appropriate treatment of UTI in pregnancy is imperative to prevent IUGR and pre-term labour. Screening of urine during pregnancy for pyuria and bacteriuria is done to detect UTI early.

Voiding dysfunction

Conditions like neurogenic bladder, spinal cord injury, myogenic atony, spina bifida, sacral agenesis lead to incomplete emptying of the bladder and encourage bacterial growth. These conditions lead to high pressure voiding which cause a reduction in blood supply to the urinary tract, impairing immune response of the host.

Hospital acquired UTI

Hospital acquired (nosocomial) UTI is always considered complicated, because of multiple factors like indwelling catheters, antibiotic overuse, selectivity of multidrug resistant uropathogens, skin break down, loss of urinary or bowel control and cross contamination from patient to patient⁷.

Immunosuppression

Immunosuppressant drugs including corticosteroids, calcineurin inhibitors, monoclonal antibodies, azathioprine, MMF suppress the immune system and predispose to cUTI.

PATHOGEN RELATED

E coli accounts for most of the infections in uncomplicated UTI. In cUTI apart from E coli, several other organisms may be causative. These include *Klebsiella* spp., *Proteus* spp., *Enterobacter cloacae*, *Serratia marcescens*, *Acinetobacter* species, *Pseudomonas aeruginosa*; and Gram-positive organisms such as Enterococci, coagulase-negative staphylococci and *Staphylococcus aureus*⁸. *Candida* species are commonly associated with urosepsis in urologic patients with hospital-acquired UTIs. Elderly patients and patients with cannulated urinary tract often have polymicrobial bacteriuria. Occasionally the patient has a focus of sepsis elsewhere, and the infection is hematogenously transported to the urinary system.

CLINICAL FEATURES

cUTI has a varied clinical presentation ranging from mild lower tract irritative symptoms such as frequency, urgency, dysuria, suprapubic discomfort, new or increased incontinence to severe systemic manifestations,

such as bacteremia, sepsis, septic shock and death. Acute pyelonephritis presents with fever, costovertebral angle tenderness and variable urinary tract symptoms. The initial step is to obtain a thorough medical history keeping in mind the factors associated with cUTI (Table 1) followed by a thorough physical examination.

MANAGEMENT

Investigations

Investigations play a vital role in the diagnosis of cUTI. The simple dipstick examination of the urine, which can be easily done in the clinic or bedside, is the first test. A positive leucocyte esterase dipstick test is a highly sensitive marker for the presence of pus cells in the urine. Presence of nitrites, which is indicative of bacteria, has a high positive predictive value of 94% for the diagnosis of UTI.⁹ In catheter associated UTI, clinical correlation is required along with the laboratory findings. Subsequently samples must be sent to the laboratory for urine-routine and microscopy examination and culture and sensitivity. As far as possible urine culture should be collected prior to administration of antibiotics to maximize the diagnostic yield and avoid false-negative results. Traditionally a growth of $\geq 10^5$ colony-forming units (CFUs)/mL of an uropathogen in a midstream, clean-catch urine is indicative of significant bacteriuria. However, a growth as low as 10^2 CFU/mL should be considered indicative of infection in the presence of suggestive symptoms of UTI. A count of at least 10^2 CFU/mL is sufficient for a microbiological diagnosis in urine specimens obtained by intermittent catheterization. When the urine is collected by suprapubic aspiration any quantitative count is considered significant for the diagnosis of UTI.¹⁰

In addition hematological profiles and serum chemistries including urea, creatinine, electrolytes and liver functions must be done. Blood culture is indicated when infection at distant sites is suspected.

Imaging of the urinary tract is mandatory in cUTI. Ultrasonography is a simple, non-invasive and easily available investigation. It should preferably be performed immediately in the clinic or in the casualty. It can diagnose obstruction of the urinary tract, and can raise the suspicion of pyelonephritis and or abscess formation in the renal parenchyma. Ultrasonography often needs to be supplemented with other imaging modalities. Contrast enhanced CT scan of the kidneys and urinary tract is the investigation of choice, since it provides maximum information. However, if the patient has renal dysfunction, even plain (non-contrast) CT is useful since it can identify calculi, hemorrhage, obstruction and gas in the urinary tract¹¹. Urological assessment such as cystoscopy, retrograde pyelography or urodynamic testing may also be indicated.

Treatment

The basic principles which guide the treatment of cUTIs are discussed below. The first of these is to minimize the effects of obstruction or any other anatomic abnormality. Second, aggressive use of antibiotics is mandatory. This means appropriate use of broad-spectrum drugs in appropriate dosages. Some patients may have renal

Table 2: Sequelae of Complicated UTI

- Urosepsis
- Acute kidney injury
- Structural damage to the kidney
 - Abscess: intrarenal or perinephric
 - Emphysematous pyelonephritis
 - Acute papillary necrosis
- Pregnancy: IUGR, preterm delivery
- Rare long term renal complications
 - Xanthogranulomatous pyelonephritis
 - Malakoplakia

impairment and the drug doses need to be adjusted accordingly. It is always necessary to not only cover Gram-positive and Gram-negative bacteria, but also to choose the specific drugs based upon the culture and sensitivity patterns available in the given hospital or area. A delay in initiating appropriate broad spectrum antimicrobial agent for severe cUTI is associated with increased mortality. Empiric anti-fungal therapy with azoles or amphotericin may be indicated in diabetics or patients with indwelling urinary catheter. Once the cultures and sensitivities are available, appropriate adjustments must be made. A very effective modality is to use combination therapy. This is especially true when antibiotics from different classes are used together, because they work on different sites in the bacterium. Oral antimicrobial therapy is often appropriate for treatment. Parenteral therapy is indicated if patients are unable to tolerate oral therapy, have impaired gastrointestinal absorption, have hemodynamic instability, or if the infecting organism is known or suspected to be resistant to oral agents. The duration of therapy should be seven days for individuals with lower tract symptoms, and 10 to 14 days for individuals presenting with upper tract symptoms or sepsis syndrome. Patients with chronic urological devices should receive as short a duration of therapy as possible to limit antimicrobial pressure leading to resistance emergence.

The diagnosis of renal abscess needs drainage of the pus. Emphysematous pyelonephritis an emergency. It occurs almost exclusively in diabetics, and is characterized by the finding of air in the renal parenchyma, identified by CT, ultrasound, or abdominal radiographs. Intervention is always required, and even if instituted in a timely fashion there is a high mortality rate.

Sequelae of cUTI

Unless treated appropriately in time, cUTI can have many serious sequelae (Table 2). The most worrying is urosepsis. This is more likely in immunocompromised patients though all patients are at risk. In fact many patients may present with urosepsis. It more common with Gram-negative organisms and may be associated with multiple organ failure and death. Another serious sequela of cUTIs is renal failure. This may be acute kidney injury or acute kidney injury superimposed on pre-existing chronic

kidney disease. This deterioration in renal function may improve or may persist requiring renal support therapy. Pre-existing renal insufficiency (including post-transplant cases) and urinary tract obstruction are predisposing conditions.

Xanthogranulomatous pyelonephritis and malakoplakia are relatively uncommon late complications, but almost always result in renal loss.

PREVENTION

Since cUTI has a high morbidity and sometimes mortality one must take steps to prevent its occurrence. Training of the nursing staff for appropriate care of the indwelling urinary catheter is mandatory. Prolonged urinary catheterisation must be avoided. Wherever possible, underlying genitourinary abnormalities should be diagnosed and corrected. Chemoprophylaxis is indicated to prevent recurrent symptomatic infection or deterioration in renal function for selected patients with persistent genitourinary abnormalities.

CONCLUSION

Complicated UTI is an important health problem, because of an increase in the number of patients who are at risk. The average age of citizens is increasing, as is the likelihood of contacting those diseases that are associated with aging. Hence it is important for the medical community to diagnose this condition early, and to treat aggressively to not only shorten the disease course, prevent the occurrence of harmful sequelae and also to minimize antimicrobial resistance.

REFERENCES

1. Laupland KB, Ross T, Pitout JDD, *et al.* Community-onset urinary tract infections: a population-based assessment. *Infection* 2007; 35:150–3.
2. Hooton T. Urinary tract infection in adults. In: *Comprehensive clinical nephrology Fifth Ed.* Eds. Johnson RJ, Feehally J, Floege J, Saunders, an imprint of Elsevier Inc. 632–43.
3. Fair WR, Couch J, Wehner N. Prostatic antibacterial factor. Identity and significance. *Urology* 1976; 7:169–77.
4. Koff SA. Clues to neonatal genitourinary problems. *Postgrad Med* 1977; 62:93–101.
5. Kamińska W, Patzer J, Dzierzanowska D. Urinary tract infections caused by endemic multi-resistant Enterobacter cloacae in a dialysis and transplantation unit. *J Hosp Infect* 2002; 51:215–20.
6. McLaughlin SP, Carson CC. Urinary tract infections in women. *Med Clin North Am* 2004; 88:417–29.
7. Gaynes R, Edwards JR. Overview of nosocomial infections caused by gram-negative bacilli. *Clin Infect Dis* 2005; 41:848–54.
8. Nicolle LE. Complicated urinary tract infection in adults. *Can J Infect Dis Med Microbiol* 2005; 16:349–60.
9. Lammers RL, Gibson S, Kovacs D, *et al.* Comparison of test characteristics of urine dipstick and urinalysis at various test cutoff points. *Ann Emerg Med* 2001; 38:505–12.
10. Nicolle LE. Urinary tract infections in adults. In: *Brenner and Rector's The Kidney* 1356–82.
11. Craig WD, Wagner BJ, Travis MD. Pyelonephritis: radiologic-pathologic review. *Radiographics* 2008; 28:255–277; quiz 327–328.