CHAPTER

22 Cystitis and Urethritis

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Bacteriuria, which is bacteria in the urine, is often (but not necessarily) a sign of infection. Therefore, it is important to put the results from bacterial urine culture into the context of the patient, including clinical symptoms, results of other laboratory tests, as well as methodology used.

Urine samples can be obtained in different ways. In adults, the most common sampling is clean-catch voided urine. In infants up to 1 year of age, however, suprapubic bladder aspiration is recommended, whereas for toddlers it is more common to collect with a urine collecting bag. From patients with an indwelling urinary catheter the urine sample has to be obtained through the catheter. These differences in modes of collection of urine samples inevitably result in differences in the type and number of bacteria isolated.

DEFINITIONS

Urinary tract infections (UTIs) in general can be symptomatic or asymptomatic. Symptomatic UTI can be divided into infections restricted to the lower urinary tract (bladder and urethra) to the upper urinary tract (kidney) or infections with systemic involvement, which is urosepticemia. The focus of this chapter is on infections of the lower urinary tract.

Symptomatic Urinary Tract Infection

Acute Cystitis and Urethritis

Cystitis is defined as an inflammation of the urinary bladder. Urethritis is an inflammation of the urethra. Both are most commonly caused by a bacterial infection; in which case, they are also referred to as lower UTIs.

Classic symptoms of lower UTIs are dysuria, urinary frequency, and suprapubic pain sometimes in combination with hematuria, but normally without fever. The extent of symptoms varies between different patients and can be very mild to severe. Other diseases can mimic lower urinary tract bacterial infections like vaginitis, interstitial cystitis, and pelvic inflammatory disease.

Asymptomatic Bacteriuria

Asymptomatic bacteriuria (ABU) refers to bacteriuria in patients with no clinical UTI symptoms. For women $\geq 10^5$ colony forming units (CFU) per mL in two consecutive clean-catch urine samples is required for the diagnosis of asymptomatic bacteriuria, whereas for men only one clean-catch urine sample with $\geq 10^5$ CFU per mL is required—or a single catheterized urine specimen with one single bacterial strain of $\geq 10^2$ CFU per mL in women or men.[1]

CLASSIFICATION

Acute cystitis and urethritis can be classified as uncomplicated verus complicated UTI, nosocomial versus community-acquired UTI, and sporadic versus recurrent UTI.

Uncomplicated UTI occurs in persons with normal urinary tract, whereas complicated UTI occurs in individuals with functional or structural changes, implying deteriorated voiding predisposing for bacteriuria.

Nosocomial UTI are infections that occur 48 hours or more after admission to the hospital or as a result of health care, whereas community-acquired UTI are UTIs not included in the previous group.

Sporadic UTI include a single UTI treated with antibiotics during 6 months or maximum two UTIs needing antibiotics during 1 year, whereas recurrent UTI comprise at least two antibiotic treated UTIs during 6 months or three or more antibiotic treated UTI during 1 year.

Recurrent UTI can be further divided into relapse or reinfection. Relapse infection includes a recurrent infection with the same bacteria as the previous UTI, whereas a reinfection is caused by different bacteria than in the previous infection. Superinfection is a new infection during antibiotic treatment and where the new bacterial strain is resistant to the used antibiotic.

ETIOLOGY

By far the most common bacterial uropathogen is Escherichia coli, causing more than 80% of UTIs among female ambulatory patients. In men and hospitalized patients, E. coli is

still the most commonly isolated bacteria, but with a lower frequency. Other common uropathogenic bacteria include Klebsiella pneumoniae, Proteus mirabilis, enterococci, Streptococcus agalactiae, and Staphylococcus saprophyticus.[2,3] S. saprophyticus is the only urinary pathogen with a seasonal variation, being most common during the late summer and early autumn months.[4]

In patients with long-term indwelling catheters, bacteriuria is almost inevitably found after about 14 days. Initially, a single species of bacteria is found but later a polymicrobial flora is common, with a wide variety of infecting microorganisms found. In patients with long-term catheters Proteus mirabilis, Providencia stuartii, Morganella morganii, Klebsiella pneumoniae, E. coli, and Pseudomonas aeruginosa are most commonly isolated. In patients with short-term catheters, staphylococci are also common. Although staphylococci seldom cause symptomatic UTIs, they contribute to bacterial biofilm formation.[5,6]

Unusual causes of urethritis and cystitis include urethritis caused by Neisseria gonorrhoeae and Chlamydia trachomatis. They have a distinct pathogenesis and symptoms that can be similar to acute cystitis. They are usually described among sexually transmitted diseases. Adenoviruses (mainly type 11) cause epidemic hemorrhagic cystitis in children, especially in boys, but may cause endemic cystitis as well.[7] Other infectious causes, which are much less common, include Herpes simplex virus; atypical bacteria, like Mycoplasma genitalium and Ureaplasma urealyticum; Mycobacteria; fungi and parasites; Trichomonas spp.; and Schistosoma haematobium. There are also noninfectious forms of cystitis and urethritis—for example, traumatic cystitis, interstitial cystitis, eosinophilic cystitis, and hemorrhagic cystitis—which are described elsewhere.

EPIDEMIOLOGY

UTIs are among the most common bacterial infections.[3,8] Prevalence is different depending on the age and gender of the patient. The overall risk in childhood before puberty is 3% to 5% in girls and 1% to 2% in boys.[9,10] In the neonatal period, the incidence of bacteriuria is about 1%, and this is also the only period when UTI is more prevalent in males than females.[11] After 1 year of age the incidence of UTIs reaches 2% in boys and 8% in girls.[12] During the reproductive period, the gender difference becomes even more pronounced and UTIs are some 50-fold more common in women as compared to men. Approximately 20% of women between 24 and 64 years old have at least one episode of dysuria each year, most of these being caused by bacterial infections.[13] Almost half of all women will experience at least one episode of UTI during their lifetime[8] and about 25% of these have recurrent infections. In the United States alone, UTIs account for approximately 11 million office visits and 1.7 million emergency room visits each year, resulting in almost half a million hospitalizations at a cost of $3.5 billion.[8,14,15] This figure probably underestimates the true incidence because many lower tract UTIs resolve without medical attention.

ROUTE OF INFECTION

UTIs are most commonly ascending infections caused by bacteria mainly from the intestinal tract or vagina. Hematogenous spread of infections to the urinary tract is rare and restricted to a few pathogens, such as S. aureus and Mycobacterium tuberculosis, which cause primary infections elsewhere in the body. Lymphatic spread from sites of infection elsewhere, bacterial spread through a fistula from the bowel, and retrograde infection from the prostate or kidney are very unusual but may also occur.

The perineum is a couple of square centimeters area of skin between the anal and urogenital regions. This is also a place that is highly colonized by bacteria from the gastrointestinal tract and vagina, and from where the bacteria may reach the urinary tract.[16] In the majority of cases, the bacteria are cleared off from the bladder. Sometimes, they persist and colonize the urinary tract causing asymptomatic bacteriuria or even symptomatic UTI.[16] The short female urethra is an insufficient anatomic barrier to the entry of bacteria, which may be massaged easily into the bladder. This may explain the association of UTIs and bacteriuria with sexual activity.[17] Bacteria may also be introduced into the bladder during catheterization of the urethra. Single catheterization of the bladder in ambulatory patients results in a 1% incidence of subsequent UTI.[18] Finally, voiding dysfunction in children is also clearly associated with recurrent UTI[19] and complex treatment of the dysfunction resulted in a substantial decrease of the frequency of UTI attacks.[20] All these observations suggest that ascendance of bacteria from perineum to the urethra and urinary bladder is the most common route of UTI.

PATHOGENESIS

Bacterial Factors in the Pathogenesis of Urinary Tract Infection

How do harmless commensal bacteria from the perineum become urinary pathogens? It is believed that some bacterial clones from the gut can acquire specific virulence characteristics, which increase their ability to adapt to new niches. These virulence and fitness properties are frequently encoded in specific genetic elements called pathogenicity islands. Virulence factors are here defined as proteins or macromolecular structures that contribute to causing disease, whereas fitness factors offer a competitive advantage during infection, but are not required for virulence. A combination of virulence and fitness factors form a specific type that could be called uropathogenic bacterium. However, despite many common features, there is no single profile that would cause UTI.[21,22] Uropathogenic bacteria use a multistep scheme of pathogenesis that consists of adhesion, colonization, invasion, survival, and host damage.[23] Bacterial factors can accordingly be described as adhesion and colonization factors, survival and immune escape factors, and toxins (for details, see Chapter 21).

Host Factors in the Pathogenesis of Urinary Tract Infection

The urinary tract is located in a fragile region in close proximity to the outside environment. Around 2 L of urine a day, produced by the kidneys, are emptied close to the rectum, the area highly colonized by bacteria. Still, the urinary tract is very resistant against infection. It was observed by urologists more than 100 years ago that, despite extensive instrumentation (e.g., frequent catheterization), and even without aseptic precautions, some individuals never or very seldom developed UTI.[24,25] This observation has later been confirmed experimentally, showing that bacteria introduced to the urinary bladders of healthy volunteers were rapidly eliminated.[26] In accordance, only very high concentrations of bacteria, or a combination of bacteria and an irritant substance such as paraffin or turpentine, were needed to establish UTI in experimental animals.[27,28]

In order to successfully colonize the urinary tract and cause infection, bacteria must overpower the specific anatomic organization of the urinary tract as well as chemical defense components of urine and the urinary tract mucosa. Moreover, recognition of uropathogens by human urinary epithelium leads to a strong inflammatory response.

Anatomic Properties of the Urinary Tract

The draining system of the urinary tract is covered with urothelium, a firm carpet of epithelial cells. Urothelium is transitional epithelium consisting of three to seven layers of cells: the basal layer of stem cells, one or more intermediate layer(s), and the superficial layer, usually referred to as umbrella or facet cells. Normal human bladder urothelium is arranged in an increasing complexity from base to surface. Urothelial cells of all layers are connected by interdigitations of cytoplasmic processes and by desmosomes. Adjacent surface cells, in addition, are linked by tight junctions. This organization enables the urothelium to withstand frequent changes in bladder volume with changes in pressure on the bladder wall.[29]

The urothelium is exposed to large changes in hydrostatic pressure with the surface superficial cells and is in contact with urine varying in pH, osmolality, and containing a number of cytotoxic substances. Therefore, cell membranes of umbrella cells need a unique lipid and protein composition that contributes to the low permeability of the membrane and that controls the passage of water, ions, solutes, and large macromolecules across the mucosal surface of the cell into the underlying tissue. The apical surface of umbrella cells is folded and contains specialized uroplakin membrane domains, which undergo active reorganization.[30,31] During the initial phase of bladder filling, the apical membrane unfolds. In the latter phase of filling, the cytoplasmic vesicles are inserted to the apical membrane to accommodate the increasing bladder volume. Emptying of the bladder is then accompanied by endocytosis of the cytoplasmic vesicles and folding of the apical membrane.[32,33] In addition to the highly specialized urothelium, a mucous layer on the surface of the urinary bladder has been described.[34,35] This layer seems to be very thin, and substantially differs from the mucus in the gastrointestinal tract. It consists mainly of glycosaminoglycans and is most likely membrane-bound rather than secreted.[36]

Urine flow, regular bladder emptying, and the valve mechanisms of the urinary tract have traditionally been considered the most important protective mechanisms maintaining this area free of microbes. Accordingly, studies in patients with anomalies of the urinary tract indicate their importance in the protection against bacteria.[37] Functional abnormalities of the lower urinary tract directly influence the entry of uropathogens into the urinary tract and may lead to recurrent UTIs, mainly in children.[19,20] For premenopausal women a new sexual partner, increased frequency of intercourse, and use of spermicides are recognized as risk factors.[38] In postmenopausal women the loss of estrogen results in change of the vaginal flora, with decreased growth of lactobacilli, as well as thinning of the vaginal epithelium and decreased amounts of glycogen which contribute to the risk of recurrent UTIs.

Mucosal Antimicrobial Mechanisms

Although regular urine flow and valve mechanisms of the urinary tract protect the urinary tract against the excessive growth of bacteria, they are not enough to completely eliminate pathogens. This has been demonstrated using an in vitro model of the urinary bladder[26] as well as mathematical simulation.[39] In accordance, the mucosa of the urinary bladder has been shown to possess antimicrobial properties in vitro.[40] Only a combination of mechanical and chemical antimicrobial factors may explain the high efficiency of the urinary tract in eliminating bacteria. Although chemical antimicrobial mechanisms of the urinary tract mucosa have so far not been systematically analyzed, a number of molecules inhibiting the growth of bacteria in the urinary tract or killing bacteria have been identified: Tamm-Horsfall protein, secretory IgA, antimicrobial proteins, and peptides, namely lactoferrin, β-defensin 1 and 2, and cathelicidin.

Recognition of the Presence of Bacteria

The first cell layer in contact with invading bacteria is the urothelium. The presence of uropathogenic bacterium induces a robust immune response already after a short contact with urothelial cells. After sensing the presence of uropathogenic bacteria, epithelial cells react in different ways. They produce substances toxic to bacteria, like nitric oxide, cathelicidin, and β-defensin-2.[41–43] Exfoliation of superficial umbrella cells is also an important protective mechanism, which helps clearing bacteria from the bladder.[44] Despite the effective first line of epithelial defence, uropathogens may sometimes persist or even multiply and invade the host. Therefore, the epithelium possesses efficient tools in order to engage the help of professional

immune system cells. Epithelial cells in the urinary tract and kidney, in response to pathogens, produce a number of chemokines and proinflammatory cytokines.[45] Chemokines attract professional immune system cells, and cytokines activate them. Out of a number of chemokines, interleukin 8 seems to be of crucial importance because of its chemoattraction of neutrophils.[46,47] Cytokine-mediated upregulation of adhesion molecules and cytokine receptors facilitates the process of migration of immune cells. Amongst them, the CXCR1 receptor on renal epithelial cells has been shown to facilitate transepithelial migration of neutrophil granulocytes and bacterial clearance during UTI.[48] Neutrophils accumulate in the inflamed tissue and kill bacteria by different mechanisms: either phagocytosis or the release of the toxic content of their granules.[49] The influx of neutrophils is followed by an influx of other professional immune cells, namely monocytes/macrophages and lymphocytes, which are predominantly important in later stages of infection.

SYMPTOMS

The symptoms of a UTI substantially differ depending on age and type of infection. The symptoms in infants and young children are very nonspecific and UTIs are usually diagnosed first in the stage of upper urinary tract involvement, or septicemia. The signs may involve tachypnea, dyspnea, as well as icterus in neonates and poor feeding, fever, and vomiting in infancy. Therefore, UTIs must always be excluded in unwell children or children with unexplained fever. After infancy, the classic symptoms of lower UTIs—dysuria, urgency, and frequency—are more usual. Adults with urethritis and cystitis typically have frequent and urgent voiding of small volumes of urine and dysuria and nocturia is common. Sensation of lower abdominal discomfort also is a frequent symptom. The urine may be turbid or even bloody in one third of cases.[50] Some infections may progress after 1 or 2 days to develop a clinical picture of upper UTI, including flank or abdominal pain, fever, and vomiting, but acute cystitis very seldom progresses to cause septicemia. On the contrary, the infection may resolve spontaneously even without antimicrobial therapy. Still it cannot be justified to withhold antimicrobial therapy.[51,52]

Studies localizing bacteria by laboratory or imaging techniques have demonstrated a poor correlation between clinical manifestations and localization results. Moreover, UTIs often are asymptomatic in the elderly[53]; and other diseases may also manifest by frequency, urgency, nocturia, and incontinence in this age group. Likewise, patients with neurogenic bladders, a long-term indwelling catheter, or intermittent catheterization usually have unspecific or no symptoms referable to the bladder when a UTI develops.[5] Therefore, there should be a low threshold for microbiologic examination of the urine in these patient groups.

DIAGNOSIS

Examination of urine specimens for bacteriuria and leukocyturia are the primary laboratory investigations in suspected UTI.

Diagnostic Pitfalls

Diagnosis of cystitis and urethritis, as well as other types of UTIs, relies on the detection of bacteria and leucocytes in urine. There are two major pitfalls in the bacteriuria assessment: contamination of urine and confusion with asymptomatic bacteriuria. These problems are more obvious in certain groups of patients—namely children, the elderly, and patients with indwelling catheters—because of nonspecificity of symptoms and difficulty of collection of clean urine samples.

Studies comparing clean-voided urine samples with samples obtained by suprapubic bladder puncture showed contamination rate of 25%.[54] In infants where alternative urine sampling, mainly urine bags and catheterization, are common, the situation is even more difficult. Contamination rates reach 63% in bag specimens and 9% in catheter specimens.[55] Clean-catch sampling of infants is time- and skill-demanding and prepuce flushing in boys may lead to paraphimosis. Therefore, bladder puncture is often the recommended method to collect urine samples in infants younger than 1 year of age when the correct diagnosis is essential. In older children and adults, urine samples should if possible be cultured from clean-catch, midstream urine to avoid contamination.

Another problem is confusion of a true UTI with asymptomatic bacteriuria. Asymptomatic bacteriuria is a common condition[16,56] and, in the majority of cases, no treatment is recommended because antibiotic treatment may increase the risk for development of symptomatic infection.[57] However, in an infant presenting with high fever and bacteriuria, the differential diagnosis between pyelonephritis and asymptomatic bacteriuria with another systemic infection (e.g., adenovirus infection) is very difficult.

Similarly, in the elderly, diseases that are not related to the urinary tract may also manifest by frequency, urgency, nocturia, and incontinence,[53] therefore making the differential diagnosis between lower UTI and asymptomatic bacteriuria troublesome.

The present cut-off levels of significant bacteriuria were defined in a series of classic studies in the 1950s by Ed Kass.[58,59] As in many biologic systems, the numbers of bacteria in urine of patients with UTIs are a continuum and any cut-off is accompanied with a given sensitivity and specificity. The number of bacteria in urine may be influenced by incubation time in the urinary bladder as well as the doubling time of the bacteria. Therefore, a small bladder (e.g., low age), low incubation time (e.g., frequency), and slowly growing bacteria may negatively influence the bacterial numbers in urine specimens. Kass suggested that a threshold of $\geq 10^5$ bacteria per mL of urine reliably distinguished contaminated specimens from true bacteriuria in asymptomatic women, and accurately diagnosed women with acute pyelonephritis. Many clinicians subsequently adopted this single criterion to diagnose cystitis, although Kass had not, in fact, studied women

with lower tract symptoms.[50] Later, it has become apparent that cystitis with significant bacteriuria and cystitis with lower bacterial counts have a similar pathogenesis and may represent different stages of the same disease.[60,61] Approximately 40% of women who experience symptoms of cystitis have midstream urine cultures containing less than 10^5 bacteria per mL.[50,62] Similarly, a pediatric study of 366 infants found that 20% of children with proven symptomatic UTI had less than 10^5 bacteria per mL urine from both suprapubic aspiration and bag specimen.[63] Handling of the urine sample may also significantly influence the result of urine cultures. Only a few hours of room temperature incubation can result in significant multiplication of bacteria and false-positive results.

Nowadays, bacterial counts of 10^4 or sometimes even 10^3 CFU per mL, depending of the infecting microorganism, are regarded as significant in patients with clinical UTI symptoms. Therefore, the number of bacteria in urine must be interpreted in a complex view together with other laboratory tests and in the whole clinical context.

Another laboratory sign of UTI is leukocyturia or pyuria.[64] The finding of pyuria is unfortunately not specific for urethritis and cystitis. Both systemic inflammation and asymptomatic bacteriuria may be accompanied by the presence of leukocytes in urine. Despite its limitations, pyuria together with other tests serves as one of the indications of infection of the urinary tract.[65]

Urine Culture

Conventional microbiologic quantification of bacteriuria is performed by inoculating a predefined urine volume, mostly 1 or 10 μl, onto appropriate agar plates, incubating at 37°C overnight, then identifying the bacterial species and estimating the number of bacterial colonies.[66] Susceptibility testing can be performed either directly from the urine or by subculturing from bacterial colonies. Bacterial species and recommendation of appropriate antibiotic usage can therefore be presented within 24 hours. Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) is a novel technique for rapid identification of bacterial pathogens, possibly also directly from infected urine. Although it gives high accuracy, conventional culture is still needed for bacterial susceptibility testing.[66a]

Another way of monitoring bacterial growth, especially in the outpatient clinical settings, is the dip slide test. The dip slide consists of a plastic paddle with culture agar on each side that is immersed in urine and then incubated at 37°C overnight. The method allows semiquantitative measurements; however, the accuracy is limited, mainly because of the relatively high inoculums and the small agar surfaces. There are several drawbacks with the method, one being the absence of antibiotic susceptibility testing. Another limitation is the risk of over-interpretation of mixed bacterial cultures, especially gram-negative bacteria and, conversely, the risk of not being able to see and evaluate weak bacterial growth like that often seen for group B streptococci.[67,68]

Microscopic Examination of Urine

Urine can be examined microscopically for the presence of bacteria and leukocytes. Microscopic examination is simple and faster than urine culture. The Gram staining is useful both for analysis of bacterial type, gram-negatives or -positives, morphology, rod or cocci, as well as for quantitative analysis. The presence of one or more bacteria per oil immersion field in uncentrifuged urine correlates with $\geq 10^5$ bacteria per mL on culture with a sensitivity and specificity over 90%.[69] However, this method does not detect low count infections, nor does it give possibility for species identification or antibiotic resistance.

More than 95% of patients with symptomatic UTIs have significant leukocyturia.[70] However, pyuria is also found in several other diseases not related to UTI. Because examination of centrifuged urine sediment is not reproducible, quantitative analysis of a fresh, uncentrifuged specimen of urine is recommended.[64] The most common method is counting under the microscope using a hemocytometer chamber. A count of 10 or more leukocytes per mL is considered abnormal. Most women with symptomatic lower UTI have more than 60 leukocytes per mL.[71] As mentioned before, leukocyturia must be carefully evaluated together with other symptoms and signs because it lacks specificity for symptomatic UTIs. In addition, the accuracy of microscopic evaluation of the urine for leukocytes is no better than that of rapid esterase test on a dipstick. Moreover, laboratory facilities are needed, and results are delayed. Therefore, the role of microscopy for white cells for the diagnosis of UTI was recently questioned.[72]

Rapid Diagnostic Tests

Several methods are being used for the rapid detection of bacteriuria and leukocyturia. Such methods may be very useful in a clinical setting when a fast diagnosis is essential. Optimally, rapid tests have low cost, high sensitivity, and high specificity. Therefore, they are useful as screening methods for groups at risk, such as pregnant women. Moreover, in the laboratory these tests may also help select which specimens require further microbiologic investigation. Two biochemical tests have been devised: the nitrite and leukocyte esterase tests.

The nitrite test is based on the bacteria's ability to reduce nitrate to nitrite. It is rapid to perform and evaluate and easy to interpret.[72,73] A test strip is immersed in urine and a color change is observed within 2 minutes, if positive. The test has high specificity, but low sensitivity, which implies that positive results indicate prevalence of bacteria, whereas negative results do not rule out bacteriuria because high bacterial concentrations are needed. Likewise, some common uropathogenic bacteria will not be positive in the test. S. saprophyticus and enterococci do not reduce nitrate to nitrite and Pseudomonas reduce nitrite further to ammonia and nitrogen—therefore, none of these bacteria will be positive. False-positive results can be obtained after having

eaten phenazopyridine, whereas high levels of vitamin C can give false-negative test results. The Leukocyte esterase test is a simple and rapid test for leukocytes.[74] It has high specificity and sensitivity and gives similar results as microscopy of urine sediment. When granulocytes are available, the test strip rapidly turns purple with intensity corresponding to the leukocyte concentration. It is important to remember that negative results in either or both tests do not exclude bacteriuria and that especially a positive leukocyte esterase test can be due to reasons other than bacterial infection.

TREATMENT

Many countries have guidelines for the treatment of cystitis and asymptomatic bacteriuria. These guidelines take into consideration the local bacterial susceptibility pattern in the respective countries and may therefore vary between different areas.

Asymptomatic Bacteriuria in Adults

Only few patient groups run an increased risk for adverse outcomes due to asymptomatic bacteriuria, mainly pregnant women and patients undergoing urologic intervention. Pregnant women have an increased risk of developing acute pyelonephritis in the early phase of pregnancy and are also likely to experience premature delivery.[75,76] Therefore, screening during the early stage is recommended and pregnant women should be treated with antibiotics if urine culture shows significant bacterial growth.[1]

In the majority of patients who undergo urologic interventions, bacteriemia occurs, with clinical evidence of septicemia in up to 10%.[77] Therefore, in patients with urologic intervention, where mucosal bleeding is expected, antibiotic treatment should be initiated prior to such intervention.[1] Although an increased risk of symptomatic UTIs may be observed in remaining cases, screening for or treatment of asymptomatic bacteriuria is not indicated.

Cystitis in Adult Women

Uncomplicated acute sporadic cystitis in previously healthy nonpregnant women should be treated with antibiotics if the patients present themselves with typical symptoms. Recommendations differ regarding the need of verification with rapid tests or urine culture. Most countries have reached consensus that nonpregnant women with uncomplicated sporadic cystitis presenting with typical symptoms can be treated without previous urine culture or dipstick. The treatment strategy is to cover the infecting microorganism but not disturb the normal bacterial flora in the gut. The antibiotic concentrations in the urine should be high with a narrow antibacterial spectrum. If left untreated about 30% have no symptoms after about 1 week. There are currently new guidelines from the Infectious Disease Society of America (IDSA) and European Society for Microbiology and Infectious Diseases (ESCMID),[78] which will be referred to in the text. Variations may of course exist in other countries.

For women with symptoms of acute uncomplicated cystitis and absence of flank pain, fever, or other suspicions of acute pyelonephritis, and where the patient is able to take oral medication, recommended treatment is with one of the following antimicrobial agents: nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomycin, or pivmecillinam. Pivmecillinam is only available in some European countries and not licensed/available in North America.[78] Trimethoprim-sulfamethoxazole is the only of these drugs that can be used if early acute pyelonephritis is suspected. The duration of treatment depends on the choice of therapy; for nitrofurantoin and pivmecillinam 5 days is proposed whereas only 3 days for trimethoprim-sulfamethoxazole. For fosfomycin a single dose is sufficient; however, lower efficacy than some other recommended agents has been observed.[78] Both nitrofurantoin and pivmecillinam are rapidly eliminated through the urine and therapeutic concentrations are only found in the urine up to 1 day after therapy is ended. Trimethoprim on the other hand can be detected in the urine up to 2 or 3 days after the medication is stopped. Patients who are treated with nitrofurantoian should be advised not to take alkalizing agents, such as potassium citrate, because the effect of higher pH correlates to higher minimal inhibitory concentration (MIC).[79] Moreover, women with renal impairment should not be treated with nitrofurantoin because effective concentration of antibiotics in the urine is not possible to reach and toxic concentrations of antibiotics can occur in the plasma.

Quinolones should be avoided for empirical treatment of cystitis and instead used for acute pyelonephritis. Moreover, the high prevalence of resistance against fluoroquinolones has been reported in some areas. Ampicillin and amoxicillin alone should be avoided because they require close follow-up and have lower efficacy than other available agents. When the resistance prevalence to trimethoprim exceeds 20%, or if used for UTI within the previous 3 months, alternative therapy should be considered.[78]

Recurrent Cystitis in Women

The main risk factors for recurrent cystitis differ between premenopausal and postmenopausal women. In premenopausal women an association with sexual intercourse, the use of spermicides, and age of first UTI has been demonstrated. In postmenopausal women vaginal prolapse, cystocele, postvoid residue, changes in vaginal flora, and urinary incontinence are the main risk factors.[80,81]

Nitrofurantoin, trimethoprim-sulfamethoxazole (avoid if resistance prevalence >20%, or if used for UTI during the last 3 months), and pivmecillinam (if in a country where it is available) can be used for treatment.[78] However, it is important to establish a correct diagnosis and, therefore, urine culture with susceptibility testing should be performed and antibiotic treatment adjusted according to the susceptibility results. Patients with hematuria or persistent bacterial growth in spite of appropriate antibiotic treatment should undergo cystoscopy and imaging of the upper urinary tract.

Prevention of Recurrent Cystitis in Adult Women

Recurrent UTI is a significant problem for the individual patient and a need for prophylaxis is often called upon. A Cochrane Review demonstrated that the use of antibiotics is beneficial to reduce the number of clinical as well as microbiologic recurrent UTIs in pre- and postmenopausal women.[82] There are several possibilities for prophylaxis. Most commonly, antibiotics can be continued daily for between 4 and 12 months. However, prophylaxis should not be initiated until 1 to 2 weeks after treatment, when urine culture is negative, ensuring bacterial eradication. Low doses of nitrofurantoin, cephalexin, trimethoprim, and trimethoprim-sulfamethoxazole have been recommended.[83] Women who experience recurrent UTIs, in association with sexual activity, can be offered postcoital prophylaxis. A major advantage with single dose therapy is that it produces fewer side effects because the women only take one third of the antibiotic otherwise used, and the outcome is still similar to daily prophylaxis.[83,84] Postmenopausal women could also benefit from vaginal estrogen, because it has been demonstrated to reduce the number of UTIs.[85,86] Cranberries might reduce the incidence of UTIs in women with recurrent infections,[87] but there is no evidence on concentrations that must be used. In studies performed the withdrawal rate has been high, suggesting that cranberry products are not acceptable over long periods. Adverse events like gastrointestinal intolerance, weight gain, and drug–cranberry interactions have been reported.[88]

Acute Cystitis in Men

Bacteriuria in men is rare and, when it occurs, it is mostly associated with predisposing factors like prostate hyperplasia, prostate cancer, or urethral stricture. At least 50% of men with recurrent UTIs and more than 90% of those with febrile UTIs have prostate involvement,[89,90] which may lead to complications like chronic bacterial prostatitis or prostate abscesses. Therefore, it is important to examine the prostate to rule out prostatitis or other concurrent pathologic changes of the prostate. Ciprofloxacin or trimethoprim-sulfamethoxazole are generally recommended as first choice. For infections caused by enterococcus, with a natural resistance to trimethoprim, amoxicillin is recommended. Due to the frequent prostate engagement treatment duration should be 2 weeks.[91]

Asymptomatic Bacteriuria in Children

Children with asymptomatic bacteriuria do not present with symptoms but bacteriuria is detected by screening. There is relatively good evidence of long-term outcomes and influence of treatment from randomized controlled trials.[92–94] The conclusion from these trials was that treatment of asymptomatic bacteriuria does not influence the emergence of symptomatic UTIs, clearance of vesicoureteric reflux, kidney growth, or the progression of kidney scars. Therefore, in contrast with previous recommendations,[50] the screening for and the treatment of asymptomatic bacteriuria in children is not currently recommended.

Cystitis and Urethritis in Children

The aim of the treatment is to effectively eradicate the infection, relieve symptoms, and minimize the development of complications after a UTI. Currently, there is consensus that symptomatic cystitis/urethritis in children should be treated with antibiotics. There are many studies addressing questions regarding type and duration of antibiotic treatment.[95–97] In summary, there is no difference in outcomes between short duration (2–4 days) and longer duration (7–14 days) of treatment, so short-duration antibiotic treatment should be used for children with lower UTIs. The evidence does not provide guidance as to which antibiotic is most useful but a choice from trimethoprim, nitrofurantoin, a first-generation cephalosporin, or amoxicillin would be supported by current clinical practice. It is recommended to follow local bacterial susceptibility patterns and recommendations in the respective countries and regions.

It is also important to emphasize that infants and children with high risk of serious illness should be referred immediately to a pediatric nephrologist. This also applies for all infants younger than 3 months with a possible UTI, who are initially treated as upper UTI with parenteral antibiotics. Urine analysis including urine culture is essential in the diagnostic algorithm in both of the above-mentioned groups. For children 3 years and older, with typical lower UTIs and positive nitrite and leukocyte esterase tests, urine culture is not necessary. Oral 3- to 5-day courses of antibiotic treatment are recommended for children 3 months and older with uncomplicated lower UTI.[98] The parents or caregivers should also be advised to bring the child for reassessment if he/she is still unwell after 24 to 48 hours. If an alternative diagnosis is not made, a urine sample should be sent for culture and antibiotic sensitivity test if that has not already been carried out. If an infant or child is receiving prophylactic antibiotic medication and develops symptomatic UTI, treatment should be with a different antibiotic. The urine culture and the antibiotic resistance pattern are then especially important.

IMAGING AND FOLLOW-UP

In contrast to upper UTIs, investigations after a single cystitis/urethritis are only recommended in infants younger than 6 months of age when distinction between lower and upper UTI may be difficult. Ultrasound examination of the kidneys and urinary tract within 6 weeks is the recommended method. Further investigation (99m-technetium dimercaptosuccinic acid [DMSA] scintigraphy, micturating cystourethrography [MCUG]) is only required in cases of abnormal ultrasound finding. In infants 6 months and older, and in children, no investigations and no follow-up are required.[98,99]

In children with recurrent lower UTIs, defined as three or more episodes of cystitis/urethritis, or one episode of pyelonephritis and one or more episodes of cystitis/urethritis, much more extensive investigation should be done in order to identify and treat the underlying risk factors. For infants younger than 6 months, ultrasound during the acute infection, DMSA scintigraphy 4 to 6 months following the acute infection, and eventually MCUG are recommended. In infants and children older than 6 months with recurrent UTIs, an ultrasound within 6 weeks and DMSA 4 to 6 months following acute infection are recommended as the initial investigation.[98] Further investigation is indicated in the case of abnormal ultrasound. A careful patient history, with focus on volume and frequency of micturition and toilet habits, is highly recommended because it may reveal functional abnormalities of the urinary tract and may lead to further examinations, uroflowmetry, or more detailed urodynamic investigation.

PREVENTION OF RECURRENCE IN CHILDREN

Recurrent UTIs are associated with considerable suffering and substantially influence quality of life. Therefore, all opportunities to prevent recurrences should be explored. All underlying anatomic and functional anomalies of the urinary tract should be treated. Moreover, clinical studies have identified the following risk factors for recurrent infections in children: age under 6 months at the first infection, family history of UTI, high-grade vesicoureteric reflux, infrequent voiding, poor fluid intake, and functional stool retention, but evidence is limited.[19,100,101] Although no prospective randomized studies have, to our knowledge, been carried out to investigate strategies to influence the risk factors in order to prevent recurrent UTIs, consensus recommendations were made.[98] According to them, children who have had a UTI should be examined with focus on dysfunctional elimination syndromes and constipation. Children should be encouraged to drink an adequate amount, and they should have ready access to clean toilets when required and should not be expected to delay voiding.

Antibiotic Prophylaxis

In many national guidelines it is currently recommended to use a low-dose antibiotic treatment after a UTI until imaging of the urinary tract has been completed. Moreover, long-term low-dose antibiotic treatment has been used as a prophylaxis of recurrent UTIs regardless of the presence of the anatomic or functional abnormality in the urinary tract. Putting together infections of the upper and lower urinary tract, prophylactic antibiotic treatment reduced bacteriuria based on a meta-analysis of eight studies including 1,103 patients.[98] There is, however, no evidence of a reduction in the incidence of symptomatic UTI based on meta-analysis of five studies including 539 patients.[98] Therefore, antibiotic prophylaxis should not be routinely recommended in infants and children following a first-time lower UTI. However, antibiotic prophylaxis may be considered in infants and children with recurrent UTIs.

CATHETER-ASSOCIATED URINARY TRACT INFECTIONS

At the time of catheter insertion, microorganisms belonging to the patient´s flora can gain access to the urinary bladder. Chronic catheterization leads almost inevitably to bacteriuria. The preferred mechanism of bladder entry is extraluminal. It is speculated that bacteria migrate within the mucopurulent space between the urethra and the catheter. However, organisms can also enter the bladder intraluminally, where the bacteria migrate into the bladder as a result of manipulation of the catheter system.[102–104] Bacteria adhere to the indwelling catheter and form biofilm. Catheter-associated UTI in patients with urethral, indwelling suprapubic, or intermittent catheterization is defined by the presence of symptoms or signs compatible with UTI combined with $\geq 10^3$ cfu/mL of ≥ 1 single bacterial species in a single catheter urine specimen or in a midstream voided urine sample from a patient where the urethral catheter, suprapubic, or condom catheter has been removed. Importantly, no other source of infection should be identified.[5] Due to the variety of infecting microorganisms, with various antibiotic sensitivity patterns, liberal attitude to urine culture including susceptibility testing is advocated. To prevent catheter-associated UTIs, guidelines from many countries recommend antimicrobial coated or impregnated urinary catheters. The most common antimicrobial compounds are silver and nitrofurazone. In a recent Cochrane Review from 2008 it was concluded that silver alloy catheters significantly decreased the incidence of asymptomatic bacteriuria during the first week of catheterization, and with less effect thereafter.[102] A similar effect was observed for nitrofurazone impregnated catheters, but only during the first week of catheterization.[102] However, the effect on bacterial adhesion and persistence has recently been questioned.[103]

When a symptomatic infection occurs, a change of catheter combined with urine culture and antibiotic therapy is appropriate. But as long as the person is asymptomatic, urine culture is not needed and routine treatment is not recommended.

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