

# Common errors in diagnosis and management of urinary tract infection. I: Pathophysiology and diagnostic techniques

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### The problem

Urinary tract infection (UTI) is one of the most common diseases, occurring from the neonate up to geriatric age groups. Forty to 50% of adult women have a history of at least one UTI [1]. UTI is a major cause of Gram-negative sepsis in hospitalized patients and after renal transplantation [2]. General practitioners, paediatricians, urologists, and nephrologists are frequently consulted because of symptoms suggestive of UTI, but there are large differences in the management of such patients with respect to definition of UTI, diagnosis, and treatment. In particular, the clinical relevance of low-count bacteriuria and asymptomatic UTI as well as the potential indications for antimicrobial therapy continue to be controversial.

UTI defines a condition in which the urinary tract is infected with a pathogen causing inflammation. There is consensus that most uropathogenic microorganisms such as *Escherichia coli* colonize the colon, the perianal region, and in females the introitus vaginae and the periurethral region. Facultatively they may further ascend to the bladder and/or to the kidneys. If structures of the urinary tract are invaded, accurate diagnosis and treatment are necessary in order to ensure optimal management and to prevent further complications. UTI results from the interaction between uropathogen and the host. The microorganisms may have particular uropathogenic properties, explaining the occurrence of infection in an otherwise normal urinary tract. On the other hand, non-uropathogenic strains can induce acute infection in the presence of urological abnormalities, or when the host's defence mechanisms are impaired: in paediatric patients and old age, pregnancy, diabetes, and in

the immunocompromized patient including renal transplant recipients.

Although general guidelines exist for UTI concerning diagnosis and classification, there is a wide variation in clinical practice. There are both errors that are frequently committed and mysteries that are still unsolved. Active management is important because under some circumstances UTI may cause permanent renal scarring. Imaging procedures are a cornerstone for critical evaluation of UTI, but avoidance of investigative routines will allow a marked saving in terms of costs and in terms of unnecessary radiation and psychological stress to the patient. The prevention of recurrent UTI requires careful patient evaluation to recognize potential complicating factors including anatomical abnormalities of the urinary tract. The underlying complicating factors (reversible or permanent) influence antimicrobial treatment with respect to duration of treatment, likelihood of antibiotic resistance, and necessity of prophylaxis respectively.

### The spectrum of urinary tract infection—definitions

#### *Significant bacteriuria*

Traditionally, the concept of significant bacteriuria for the diagnosis of UTI was based on the notion that the quantitative bacterial count allowed distinction between infection and contamination. The utility and consistency of the criterion of  $\geq 10^5$  colony-forming units per millilitre (c.f.u./ml) of clean-catch urine for the diagnosis of UTI has been validated repeatedly. In children, rapid and reliable diagnosis of UTI is mandatory. Here, UTI is defined as bacterial count  $\geq 10^4$  c.f.u./ml urine, accompanied by microscopical examination of the urine to exclude vaginal contamination (because such contamination frequently results in false-positive culture tests).

#### *Low-count bacteriuria*

Investigators have found that only one-half of women with symptoms of acute lower UTI met the criterion of  $\geq 10^5$  c.f.u./ml. Studies by Kunin *et al.* [3] and

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Arav-Boger *et al.* [4] suggested that low-count bacteriuria might be an early phase of UTI. The majority of patients with bacterial counts between  $10^2$  and  $10^4$  c.f.u./ml has micro-organisms typical for UTI (*E. coli*, *Staphylococcus saprophyticus*, and enteric Gram-negative bacteria). Symptoms may arise during a transitional phase when the urethra is the primary site of colonization and inflammation. According to this concept bacteria may enter the bladder transiently, but—as a result of urodynamic and other host defence mechanisms—they are not able to grow sufficiently to achieve the high densities that are observed in well-established UTI. Several theories have been proposed to explain the phenomenon of low-count bacteriuria. First, it is likely that symptomatic bacteriuria of  $<10^5$  c.f.u./ml reflects ongoing UTI, and therefore the microbiological criterion should be reduced to  $>10^2$  c.f.u./ml in symptomatic patients. Second, a low number of bacteria in the urine may be the result of increased urine output due to high fluid intake. Third, low-count bacteriuria may be produced by slow growth of some uropathogens such as *S. saprophyticus*. Thus, one major common error in the diagnosis of UTI is to underestimate the significance of low-count bacteriuria. Particularly in men, low bacterial counts with uropathogens may be clinically meaningful, because contamination is uncommon in males.

#### *Asymptomatic bacteriuria*

Asymptomatic bacteriuria is frequently detected in routine investigations. Bacterial counts  $\geq 10^5$  c.f.u./ml in two consecutive clean-catch urine samples, permit to differentiate between asymptomatic UTI and contamination ( $<10^5$  c.f.u./ml). For infections with *S. saprophyticus* and *Candida* species, the lower cutoff level of  $\geq 10^4$  c.f.u./ml is commonly accepted.

Asymptomatic bacteriuria is extremely rare in the early childhood period except in the presence of anatomical abnormalities (prevalence in males 0.001% between the age of 0 and 5 years). In females it increases up to 10% until the age of 65 years. In elderly males the percentage is even higher, if there is retention of urine due to hyperplasia of the prostate. Asymptomatic bacteriuria and leukocyturia are found in up to one-third of haemodialysis patients [5]. The decrease of urine output and lack of adequate rinsing allow the bacteria to grow.

A further common error in the diagnosis and treatment of UTI is the misinterpretation of asymptomatic bacteriuria. Additional clinical information is required to decide who should be treated and who should only be monitored. Asymptomatic bacteriuria should not be treated except in pregnancy when dilatation of the urinary tract during pregnancy allows bacteria to ascend. Acute pyelonephritis during pregnancy is associated with a high frequency of abortion.

Patients with asymptomatic bacteriuria such as haemodialysis patients evaluated for kidney transplantation should be given prophylactic treatment with antibiotics at the time when they undergo invasive

urological diagnostic procedures to prevent septic complications. Currently there is a debate whether diabetic or immunosuppressed patients with asymptomatic bacteriuria should be given antibiotics. In our clinic we do not treat diabetic patients or patients with asymptomatic bacteriuria after kidney transplantation routinely. We monitor these patients carefully at short intervals, however.

#### *Contamination*

Contamination is sometimes unavoidable and remains a pitfall in the diagnosis of UTI. Contamination is likely if only small numbers of bacteria or several bacterial species grow in urinary cultures. Lactobacilli, Corynebacteria species, Gardnerella, alpha-haemolytic streptococci, and aerobes are considered urethral and vaginal contaminants. The presence of true infection can be confirmed by urethral catheterization or better by suprapubic aspiration. True polymicrobial infection is rare, except in patients with ileal conduit, neurogenic bladder, or vesicocolic fistula, and in patients with UTI complicated by stones, chronic renal abscesses, or long-term indwelling urinary catheters. The isolation of more than one organism from a single specimen of urine must always be interpreted with caution and considering (i) whether one organism is dominant, (ii) which type of the specimen was examined (chronic catheterization *vs* midstream specimen), (iii) whether features are present which suggest true infection (presence of white blood cells) or contamination (presence of vaginal epithelial cells), and (iv) whether clinical signs, symptoms and history point to the presence of UTI. Interpretation must be cautious, however, since a recent article demonstrated that squamous cells are found in 94% of catheter samples even in the absence of bacterial contamination. In 96% of midstream urine samples squamous cells were found, but only 21% had bacterial contamination. Thus the presence of squamous cells in urine samples of women is not a good pointer to the presence of bacterial contamination [6].

#### **How to diagnose urinary tract infection?**

A proposed strategy to diagnose UTI is shown in Figures 1 and 2. The interpretation of urine analysis and culture tests is entirely dependent on the quality of the urine samples submitted for examination and the conditions of transport to the laboratory.

#### *The dipstick test*

Because many cases of UTI present acutely there is a need for a rapid diagnostic procedure. The biochemical reagent strip test (dipstick test) is the generally accepted screening test for UTI. Chemical test strips usually operate by detection of a leukocyte esterase and a nitrate reductase activity. A negative dipstick test is usually sufficient to exclude true infection. Pyuria is a characteristic feature of inflammation and is easily detected by a positive test for leukocyte esterase activ-

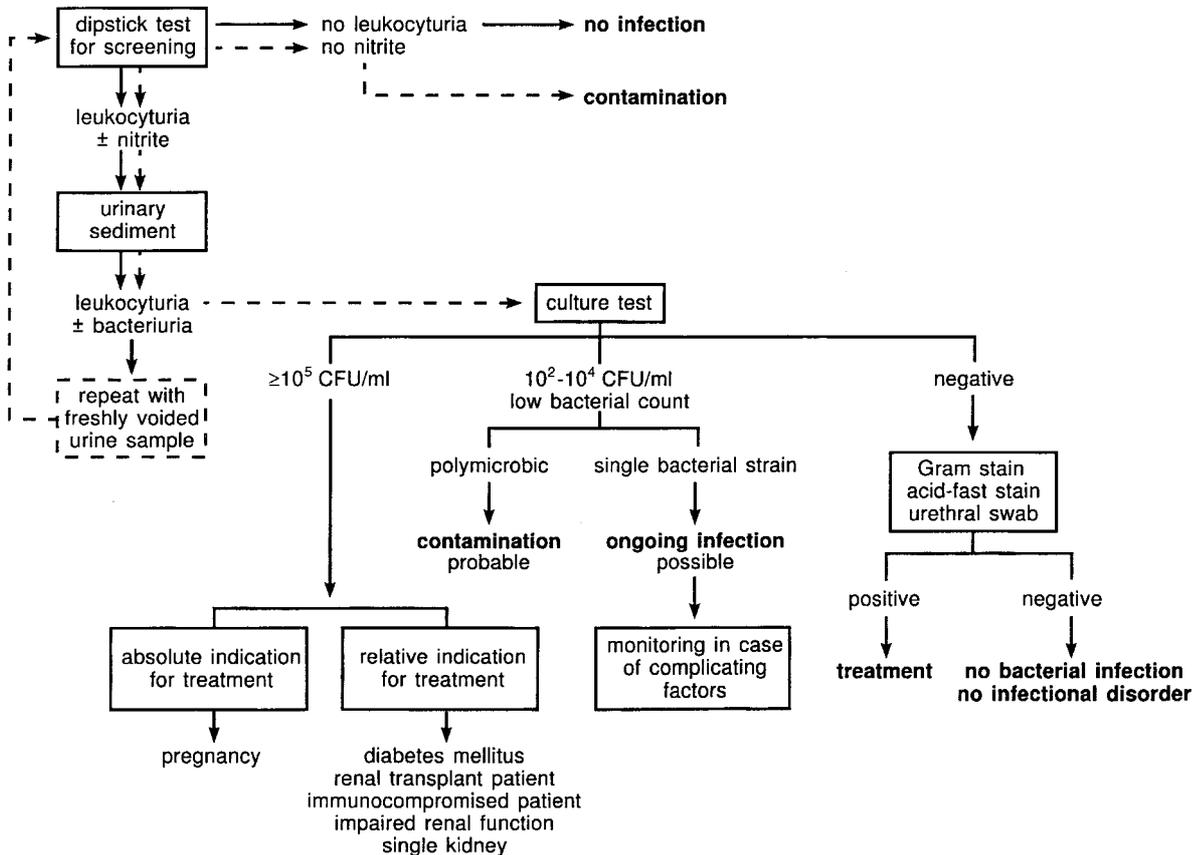


Fig. 1. Diagnostic algorithm for asymptomatic UTI. CFU/ml, colony-forming units per millilitre of urine.

ity. In practice, erythrocytes and leukocytes are lysed in the urine at pH-values  $> 6.0$ , at low urinary osmolality or when analysis is delayed. Consequently, false-negative results by microscopy are more frequent than false-positive results by dipstick. The presence of leukocyturia does not always correlate with bacteriuria. The leukocytes may originate from sites of inflammation other than the urinary tract, particularly the female genital tract. Moreover, leukocyturia may continue even if bacteriuria has cleared spontaneously or after treatment. The nitrite test depends on the detection of nitrite in the urine which is formed from nitrate by many uropathogens. The presence of nitrite is highly specific for bacteria, but several uropathogens do not reduce nitrate to nitrite, and therefore its utility is restricted to Enterobacteriaceae which give a positive test result. A urine pH of  $\geq 7.5$  suggests UTI. Also some foodstuff contains nitrate/nitrite and can therefore influence the urinary nitrite test, i.e. giving positive test results although UTI is not present.

#### The clean-catch urine specimen

In general, patients with symptoms suggesting UTI should have a clean-catch specimen sent for urine analysis and culture test. Since the bacterial count of early morning specimens is usually greater than that of specimens obtained at other times, it has become

common practice to collect the first urine of the day. This sample is the most concentrated and bacteria in the bladder have had time to multiply overnight. At the time samples are obtained in the office more dilute urine and bacterial washout due to multiple voids yield markedly lower colony counts. Because the first urine portion flushes out urethral contaminants, collection of midstream specimens is the standard procedure. In women, collection of midstream specimens requires far greater care and co-operation than in men. It is necessary to spread the labiae and the introitus vaginae should be cleaned with water- or saline-soaked swabs. Soaps or antiseptics should not be used because they are bactericidal and result in misleadingly low bacterial counts. Obviously, a suitable sterile container for urine collection is mandatory. In uncircumcised men, the foreskin should be pulled back to avoid contamination resulting from potential colonization of the preputial sac. Problems occur in the interpretation of urine analysis particularly in the elderly because of technical difficulties of sample collection. High false-positive test rates are found in elderly females [7]; if they are incapable of providing midstream clean-catch urine specimens, the procedure should be assisted by a nurse.

#### Alternative procedures

Urine collected by suprapubic aspiration is generally considered as the diagnostic gold standard since

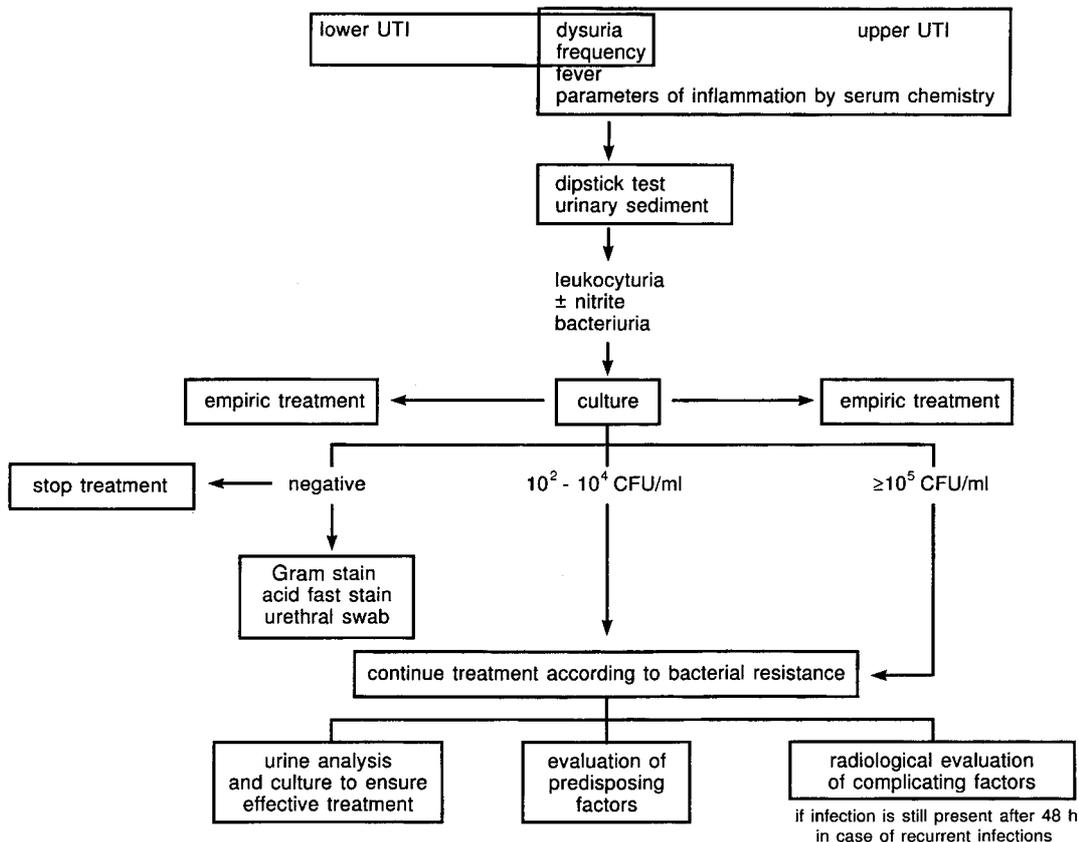


Fig. 2. Diagnostic algorithm for symptomatic UTI. CFU/ml, colony-forming units per millilitre of urine.

contamination is thus reliably ruled out. However, it is obvious that suprapubic aspiration is not a tool for routine diagnosis. It may be valuable, however, for young children from whom a clean specimen cannot be obtained. Urethral catheterization, frequently performed by urologists to obtain uncontaminated bladder urine, is not the method of choice unless there are strong clinical arguments for this procedure. It is likely to introduce pathogenic organisms into the bladder and is potentially more harmful than the diagnostic benefit it yields.

#### The role of microscopical examination of urine

UTI can readily be diagnosed by microscopical examination of urine. A standardized centrifuged urinary sediment investigated under a coverslip is recommended as the routine procedure because it is cheap and the differentiation of formed elements (red and white blood cells, bacteria) is easier in thin fluid layers than in traditional glass chambers (Bürker, Fuchs–Rosenthal, etc.). Centrifugation always leads to loss of particles and may produce inaccurate results in quantitative terms. On the other hand, in unspun samples a number of relevant elements can be missed. Thus, the results after centrifugation with a standardized procedure are more sensitive and specific. When compared with bright-field microscopy, the phase-contrast technique allows better detection of most

elements, especially of bacteria. The counts are usually given per low-power field or high-power field. Results can be also given per unit volume of urine. At the high magnification ( $\times 40$ ) the presence of 1–10 micro-organisms/high-power field is indicative of bacteriuria. The presence of  $\geq 10$  white blood cells/high-power field is indicative of pyuria.

#### How to culture urine?

Bacteria will continue to multiply in the warm medium of freshly voided urine. It is therefore mandatory that urinalysis and culture tests should be performed without delay. The average time of replication of *E. coli* is  $n$  minutes, so that the number of bacteria increases exponentially with time (e.g.  $2^n$  after  $n$  minutes). If bacterial examination is delayed by more than 2 h, specimens must be stored at  $4^\circ\text{C}$ , but for no more than 48 h. Dip-slide culture or a similar semiquantitative method of culture is generally preferable. These methods offer the advantage of reflecting the true approximate concentration of bacteria at the time the sample is taken so that storage at low temperature is unnecessary.

Occasionally, unusual or fastidious bacteria may induce UTI. These bacteria are difficult to detect without examination of the urine using Gram stain [8]. For example, *Haemophilus influenzae* and *Haemophilus parainfluenza* do not grow well in culture

media commonly used for enteric bacteria and as a result may go undetected. Other unusual organisms include *Pneumococcus*, *Campylobacter*, *Legionella pneumophila*, *Salmonella*, *Shigella*, *Corynebacterium* group D2, acid-fast bacilli (including *Mycobacterium tuberculosis* and atypical mycobacteria), and fungi (such as *Blastomyces* and *Coccidioides*). Gram and acid-fast stains should be performed for patients with urinary symptoms and pyuria when routine cultures are reported to be negative.

#### *Clinical presentation of urinary tract infection*

The clinical presentation of a patient with UTI ranges from asymptomatic bacteriuria to acute pyelonephritis (bacterial interstitial nephritis) or urosepsis. The presentation depends on the localization and the severity of the infection. It is essential to differentiate further between uncomplicated and complicated UTI in order to select the appropriate treatment strategies. It is sensible to categorize UTI according to the level of the urinary tract involved, the presence of symptoms and the presence of complications.

#### *Lower vs upper urinary tract infection*

Differentiation between lower and upper UTI is important because renal involvement is associated with more severe complications. The clinical presentation of a patient gives important hints to distinguish between lower and upper UTI. Usually, no alterations of acute phase reactants are found in patients with lower UTI and body temperature is below 38°C. Upper UTI causes elevation of inflammatory parameters such as C-reactive protein or leukocytosis and fever. Diagnostic procedures to accurately localize UTI are invasive and not without risk (bladder and/or ureteral catheterization). A variety of non-invasive methods have been proposed to distinguish between lower (urethra, bladder) and upper (kidney) UTI, particularly recent contributions of renal nuclear medicine [9]. In clinical practice monitoring of bacteriuria may help to differentiate at least retrospectively between lower and upper UTI. For example, if bacteriuria is gone after 1-day or short-term (3 days) treatment, the diagnosis of lower UTI is likely. In a recent publication urinary excretion of N-acetyl-beta-glucosaminidase (NAG), a lysosomal enzyme present in the proximal convoluted tubule, has been used to differentiate between lower and upper UTI. Urinary NAG excretion was significantly higher in patients with upper than lower UTI or healthy adults [10].

#### *Symptomatic vs asymptomatic urinary tract infection*

Based on clinical signs and symptoms one can distinguish between asymptomatic (asymptomatic bacteriuria) and symptomatic UTI (dysuria, frequent voiding, flank pain, fever). 'Symptomatic abacteriuria', i.e. bacterial infection with low counts of uropathogens may present as the so-called urethral syndrome. Other causes of 'symptomatic abacteriuria' include infection with

*Chlamydia*, *Mycoplasma*, *Trichomonas*, *Gonococci*, *Candida* or *Mycobacteria*. Similar symptoms can also arise from urological bladder problems including tumours. Renal abscess formation without drainage into the urinary tract, complete ureteral obstruction, urinary tract tuberculosis, Schistosomiasis, antimicrobial treatment or use of antiseptic agents (incorrectly obtained urine samples) can also present as 'symptomatic abacteriuria'.

#### *Complicated vs uncomplicated urinary tract infection*

Persistent or recurrent UTI in adults with anatomically and functionally normal urinary tracts leads rarely, if ever, to renal damage. Therefore, it is important to distinguish between complicated and uncomplicated UTI. Complicated UTI implies infections of urinary tracts which are anatomically or functionally altered (urodynamics or voiding are abnormal). Associated conditions complicating UTI are summarized in Table 1. Uncomplicated infections occur mainly in otherwise healthy females with structurally normal urinary tract and intact voiding mechanisms. In contrast, complicating factors put individuals of both genders at a higher risk of developing progressive renal damage, bacteraemia, and urosepsis.

Complicated UTI is a clear contraindication against short-term treatment (<7 days). In such patients antibiotic therapy is recommended for 2–6 weeks. Furthermore, for accurate treatment of UTI it is important whether the complicating factor could be eliminated during therapy (for example removal of a stone) or whether it persists (for example indwelling urinary catheter).

### **How does urinary tract infection develop: interaction between microbe and host**

#### *The pathogen: the commensal flora*

UTI is frequently caused by organisms which are normal commensals in the distal urethra and adjacent sites. The most common route of infection is by ascension. The well-recognized gender difference in the prevalence of UTI is clearly related to the short length

**Table 1.** Factors complicating urinary tract infection

Disorders of urine transport
Anatomical
Neurogenic
Associated diseases
Polycystic kidney disease
Analgesic abuse
Sickle-cell anaemia
Immunosuppression (incl. transplantation)
Miscellaneous
Diabetes mellitus
Pregnancy
Prostatitis
Indwelling urinary catheter

of the female urethra. Uropathogens are part of the normal faecal flora. These bacteria colonize the perianal region and then ascend in females to the introitus vaginae which is a reservoir for several uropathogens, particularly if the vaginal flora is not intact. Colonization spreads to the periurethral area, urethra, and bladder, strongly depending on sexual activity. Even during voiding, however, there is sufficient turbulence in the female urethra to allow backflow of organisms into the bladder. The role of normal vaginal flora in the defence against genital colonization with potentially pathogenic adhering *E. coli* has been demonstrated in several studies. The reported vaginal colonization rate of *E. coli* varies from 6 to 26% [11,12].

Defensive properties of the commensal flora against colonization by bowel organisms include production of inhibitors against potential pathogens, aggregate formation of commensal species with microbes of the same specimen or with potential pathogens, colonization of epithelial surfaces, and competition with potential pathogens for sites of adhesion. The quantitative relationship of vaginal *E. coli* with phases of the menstrual cycle also points to hormonal determinants of vaginal colonization with *E. coli*. Local trauma, such as sexual intercourse or urethral massage, promotes invasion of the urinary tract. Therefore, in the presence of colonization of the introitus vaginae by uropathogens, women may suffer from recurrent UTI, while in their absence UTI is rare even in sexually active women. Repeated or prolonged administration of antibiotics may also result in urethral and vaginal colonization by uropathogenic bacteria and predispose to UTI. A vaginal pH of 5 or less protects against vaginal colonization and urogenital infections: *Lactobacillus* usually colonizes the vagina, generates an acidic vaginal pH and interferes with the adhesion of *E. coli*, one of the most common uropathogens in otherwise normal women. Weekly vaginal instillation of *Lactobacillus casei* for 1 year in premenopausal women can lower the rate of UTIs by approximately 80% [13] but fails to prevent urogenital infections completely. It is also likely that use of soaps to clean the genital tract alters the milieu and the respective flora. In addition, compared to other contraceptive methods, the use of diaphragms, cervical caps, or spermicides for contraception is associated with a higher incidence of UTI [11,12].

In females with recurrent UTI, hormonal factors are thought to influence bacterial attachment to epithelial cells. Genitourinary mucosal cells have oestrogen receptors [14]. Adherence changes during the menstrual cycle and is maximal during peak oestrogen stimulation. Administration of oestrogens changes the quality and quantity of the mucopolysaccharide layer lining the bladder and urethra and increases lower urinary tract visceral smooth-muscle tone and contractility. Oestrogen deficiency in postmenopausal women is associated with a higher risk of UTI. The mucosa atrophies, *Lactobacillus* disappears from the vaginal flora, vaginal pH increases, and the vagina is then predominantly colonized by Enterobacteriaceae,

especially *E. coli*. In a controlled trial [15] intravaginal administration of oestriol reduced the incidence of UTI in postmenopausal women with recurrent UTI. *Lactobacillus* reappeared after 1 month in 61% and mean vaginal pH decreased from 5.5 to 3.8 ( $P < 0.001$ ). Thus, topically applied vaginal oestriol can prevent recurrent UTI in postmenopausal women.

#### *Inflammation in the urinary tract: host/parasite interaction*

Frequency and severity of UTI are determined by the balance between local uroepithelial defence mechanisms and pathogenicity of uropathogenic microorganisms. Specific virulence factors allow bacteria to survive and to replicate in the host. Virulence factors of *E. coli* and *Proteus mirabilis* are well established (Table 2) and include synthesis of aerobactin and enterobactin (iron-binding proteins with extremely high affinity to iron, which is necessary for replication of uropathogens) as well as production of haemolysin and expression of fimbriae. Mannose-sensitive fimbriae (type 1-fimbriae) have been found on pathogenic and non-pathogenic *E. coli* species, whereas mannose-resistant fimbriae (P-fimbriae) have been detected on uropathogenic species only. P-fimbriae are called pyelonephritis-associated pili because they can attach specifically to epithelial receptors of the urogenital tract and can further ascend from the bladder up to the kidneys [16,17]. Abnormalities of the urinary tract (vesico-ureteral reflux) or diagnostic procedures (cystoscopy, micturation urography, bladder lavage) favour ascension of pathogenic bacteria.

*Escherichia coli* species have P-fimbriae (>90%). These virulence factors are usually not present in *E. coli* causing lower UTI in girls and women, but are obligatory in lower UTI in males, whose urinary tract is relatively resistant to infections (longer urethra in males, presence of bactericidal secretion of the prostate). Predominantly in young women, *S. saprophyticus* can also cause acute cystitis or pyelonephritis. Compared to *S. aureus* and *S. epidermidis*, *S. saprophyticus* displays not only the strongest attachment to uroepithelial cells, but also has additional invasive properties, resulting in penetration into the respective cells. A possible role of  $\alpha_1$ -microglobulin in mediating bacterial attachment was found by Wassall *et al.* [18]. The adhesion of *Pseudomonas aeruginosa* B4 to a model surface was strongly associated with the presence

**Table 2.** Bacterial virulence factors

Expression of fimbriae (pili)
Synthesis of aerobactin and enterobactin
Production of haemolysin
Glycocalyx-mediated adherence
Somatic antigen expression
Urease production
Motility
Resistance to serum bactericidal activity

of  $\alpha_1$ -microglobulin, which may be acting as a mediator of bacterial adhesion.

Host-specific factors associated with UTI include production of secretory immunoglobulin A interfering with adhesion, presence of Tamm–Horsfall mucoprotein (THP) causing bacterial aggregation and washout, bactericidal properties of the serum as well as urodynamic factors, i.e. bacterial washout [19–21]. THP has specific receptors for several uropathogens and the bound bacteria are washed out in the urine.

P-fimbriae and/or F-adhesins are present in 50–65% of *E. coli* strains in patients with cystitis and in 75–90% of isolates from patients with pyelonephritis, whereas they are present in only 10–15% of faecal *E. coli* from patients without UTI [22,23]. Women with recurrent UTI have frequent and persistent vaginal *E. coli* colonization [24]. Furthermore, the susceptibility to UTI in women is associated with changes in the adhesive characteristics of vaginal epithelial cells. An increased attachment of *E. coli* to vaginal epithelial cells has been demonstrated in women with recurrent UTI [25]. Non-secretors of blood group antigens, easily determined in the saliva, are also prone to recurrent UTI. This has been confirmed by recent studies [26–28].

*Escherichia coli* and other Gram-negative bacilli can be classified on the basis of somatic antigens (O antigens) present in the lipopolysaccharide component of the cell wall. Approximately 150 serotypes have been identified and a limited number have been implicated as urinary pathogens. However, a correlation between particular serotypes and parenchymal invasion has not been established. Other somatic antigen markers include the K antigens of capsular origin, located in a more exterior position relative to the O antigens of the cell wall. A correlation between K-rich strains and invasion of the renal parenchyma was found in pregnant women with bacteriuria. K-rich *E. coli* are relatively resistant to phagocytosis and to destruction by complement.

During UTI, cytokines are released into the urine or into the systemic circulation. A considerable proportion of women with bacteriuria have increased urinary interleukin (IL)-6 levels, but serum IL-6 levels are only elevated in women with acute pyelonephritis [29]. Elderly women and men with bacteriuria have also increased urinary IL-1 $\alpha$  and IL-6 [30]. In contrast, urinary and serum IL-6 concentrations are decreased in pregnant women with acute pyelonephritis [31]. Decreased cytokine and immunoglobulin production during pregnancy may explain why pregnant women are more prone to develop UTI. IL-6 is synthesized by epithelial cells of the bladder and kidney, and by peripheral mononuclear blood cells after contact with attached *E. coli* [32,33]. One could anticipate that determination of urinary IL-6 differentiates between asymptomatic bacteriuria and contamination [29], but urinary IL-6 levels did not correlate with pyuria, while urinary IL-8 concentrations did [32,34]. Recruitment of polymorphonuclear leukocytes (PMNL) into the urine seems to be associated with local production of IL-8, both by uroepithelial cells and PMNL. Four

hours after intravesical instillation of lipopolysaccharide, neutrophils infiltrate the bladder wall and mRNA for inducible nitric oxide synthase (iNOS), IL-6 and IL-10 are detected in the bladder wall but not in the kidney [35]. Such localized inflammatory response illustrates the importance of lipopolysaccharide as a mediator of the host response in UTI. These findings point to the potential use of measurements of urinary excretion of nitrate and cyclic 3'5'guanosine monophosphate (cGMP) as markers of the induction of iNOS in UTI. IL-1 $\alpha$  is present in the urine of patients with asymptomatic bacteriuria or symptomatic UTI, but IL-1 $\beta$ , tumour necrosis factor alpha (TNF- $\alpha$ ) or TNF- $\beta$  are not [30,34].

The mechanisms leading to chronic UTI have not been clarified. Uroepithelial cells and red blood cells carry specific receptor components (glycosphingolipids) for P-fimbriae. The expression is determined by the alleles of the P-blood group system. The presence of P1 antigens is associated with the risk of UTI and is more frequent in patients with symptomatic infections or renal scar formation. Scar formation is favoured when uropathogenic micro-organisms release superoxide, oxygen radicals, or proteinases, thus interfering with phagocytosis.

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