Pathogenesis and management of bacterial urinary tract infections in adult patients with diabetes mellitus

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Abstract

Urinary tract infections (UTIs) are more common and tend to have a more complicated course in patients with diabetes mellitus (DM). The mechanisms, which potentially contribute to the increased prevalence of both asymptomatic and symptomatic bacteriuria in these patients are defects in the local urinary cytokine secretions and an increased adherence of the microorganisms to the uroepithelial cells. The need for treatment of asymptomatic bacteriuria remains controversial. No evidence is available on the optimal treatment of acute cystitis and pyelonephritis in patients with DM. Because of the frequent (asymptomatic) upper tract involvement and the possible serious complications, many experts recommend a 7–14-day oral antimicrobial regimen for bacterial cystitis in these patients, with an antimicrobial agent that achieves high levels both in the urine and in urinary tract tissues. Current data suggest that shorter regimens will lead to failure also in uncomplicated UTI in women. The recommended treatment of acute pyelonephritis does not differ from that in nondiabetic patients. Clinical trials specifically dealing with the treatment of UTIs in diabetic patients, comparing the optimal duration and choice of antimicrobial agent, are needed. Besides that, new approaches to preventive strategies must prove their value in this specific patient group.

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Keywords: Urinary tract infection; Diabetes mellitus; Treatment; Pathogenesis; Asymptomatic bacteruria

1. Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections [1]. Up to 50% of women report having had at least one UTI in their lifetime [2]. Uncomplicated UTIs occur most often in young healthy adult women and are easy to treat. However, in other patient groups, UTIs can have a complicated course, are more difficult to treat and often recur. Complicated UTIs occur most commonly in patients with abnormalities of the genitourinary tract. However, other conditions such as age over 65 years, treatment with immunosuppressive drugs, the presence of human immunodeficiency virus-infection and diabetes mellitus (DM) also predispose to an enhanced susceptibility for the development of a UTI with a complicated course [3,4].

DM is the most common endocrine disease. Besides organ complications as retinopathy, nephropathy and neuropathy, diabetic patients also suffer more frequently from (complicated) infections compared with nondiabetic patients. In a large study of bacteraemic patients, it was demonstrated that two thirds of the patients had DM; the urinary tract was the most prevalent infection site [5]. In this article we focus on UTIs, although we are aware that infections elsewhere are also very important, particularly in men with DM. Furthermore, it is important to realise that most of the research described here, has been performed in female patients, who have a higher prevalence of UTIs than men. First, this article briefly describes the specific aspects of the epidemiology, pathogenesis, clinical presentation and consequences of asymptomatic and symptomatic UTIs in adult patients with DM, followed by a more extensive description of the management of...
bacteriuria in these patients. Because of the specialised character, the treatment of the complications of UTIs will not be described.

2. Epidemiology

The majority of infections in diabetic patients are localised in the urinary tract [5]. An autopsy study in 1940 showed that approximately 20% of patients with DM had a serious infection of the urinary tract. The authors stated that this prevalence was five times higher than that found in studies with nondiabetic patients [6]. Although different studies may differ in the range of the infection, nearly all investigators report that the prevalence of asymptomatic bacteriuria (ASB) in women with DM is three to four times higher than in women without DM [7,8]. In men the results are more consistent; a frequency between 1 and 2% has been found, with no difference between diabetic and nondiabetic men [9]. The frequency of symptomatic infections in women with DM is also increased [10]. Both men and women with diabetes have an increased risk of acute pyelonephritis requiring hospital admission. In a recent study, diabetes was estimated to increase this probability 20- to 30-fold under the age of 44 and three to fivefold over the age of 44 [11]. Furthermore, complications of an upper UTI are more likely to occur in diabetic patients. For example, emphysematous pyelonephritis is seen almost exclusively in diabetic patients and, although uncommon, half of the patients with papillary necrosis have diabetes [12].

3. Pathogenesis

3.1. Pathogenesis in general

UTIs invariably result from the ascending route. Bacteria colonising the perineum and vagina can enter the bladder and further ascend to the kidneys. The most important defence mechanisms of the host, are the urine flow from the kidneys to the bladder and the intermittent voiding, resulting in complete emptying of the bladder. Patients with urinary obstruction, stasis and reflux have more difficulty in clearing bacteria and these conditions also seem to predispose to the development of a UTI, although exact data are lacking [13].

The essential step in the pathogenesis of UTIs, is the adherence of uropathogens to the bladder mucosa. Adhesins (fimbriae) are therefore important virulence factors. Although virulence factors have been characterised best in *E. coli* (the most common uropathogen), many of the same principles may be applicable to other Gram-negative uropathogens, for example klebsiellae [14]. Type 1 fimbiae mediate the adherence of *E. coli* to glycoprotein receptors (uroplakins) on the uroepithelial cells, whereas P fimbiae bind to glycolipid receptors in the kidney [15].

3.2. Pathogenesis in patients with DM

The increased frequency of UTIs in diabetic patients is likely due to several factors (Table 1). Suggested host-related mechanisms are (a) the presence of glycosuria; (b) defects in neutrophil function and (c) increased adherence to uroepithelial cells. Our in vitro studies indeed showed that glycosuria enhances the growth of different *E. coli* strains [16], however, this was not confirmed by in vivo studies which failed to show a higher prevalence of bacteriuria among diabetic patients with glycosuria compared with patients without, glycosuria [8,17].

The data on impaired neutrophil function are contradictory [18,19]. Moreover, the incidence of UTIs is not increased in other groups of patients with neutrophil defects or neutropenia [20]. Local cytokine secretion might be of importance. Cytokines are small proteins, which play an important role in the regulation of host defences against systemic and local bacterial infections [21]. Therefore, we investigated urinary cytokine excretion in diabetic patients and found lower urinary IL-8 and IL-6 concentrations (*P* = 0.1 and *P* < 0.001, respectively) in diabetic women than in nondiabetic controls. A lower urinary leukocyte cell count correlated with lower urinary IL-8 and IL-6 concentrations (*P* < 0.05) [22]. This might contribute to the increased incidence of UTIs in this patient group.

Most interestingly, we have found that the adherence of type 1-fimbriated *E. coli* to uroepithelial cells of women with DM is increased, compared with the adherence to uroepithelial cell of women without DM.

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<th>Table 1</th>
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<td>Host factors associated with an increased risk for symptomatic or asymptomatic UTIs in women with DM</td>
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<tr>
<td><strong>General</strong></td>
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<tr>
<td>Sexual intercourse [17]</td>
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<tr>
<td>History of (recurrent) UTIs [8]</td>
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<tr>
<td>Obstruction, urine stasis, reflux, instrumentation of urinary tract [13]a</td>
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<tr>
<td><strong>Associated with (complications of) DM</strong></td>
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<tr>
<td>Peripheral neuropathy [8]</td>
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<td>Macroalbuminuria [8]</td>
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<td>Longer duration of DM [8]</td>
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<tr>
<td>Glycosuria (in vitro) [16]</td>
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<tr>
<td>Decreased urinary cytokine secretion [22]</td>
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<td>Increased adherence of <em>E. coli</em> to uroepithelial cells [23]</td>
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<tr>
<td><strong>Genetic factors</strong></td>
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<td>Blood group [70]</td>
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<td>History of UTIs of the mother [71]</td>
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a Not studied specifically in diabetic patients.
[23]. So, it seems that this increased adherence plays an important role in the pathogenesis of UTIs in women with DM.

As part of the immune response, infection and adherence of the bacteria to uroepithelial cells stimulates cytokine and chemokine secretion, as well as exfoliation of the superficial cells. It had been thought that uropathogenic E. coli were non-invasive pathogens, however, a recent study in mice has shown that type-1 fimbriated E. coli can not only cause exfoliation, but can also invade the uroepithelial cells, replicate and form quiescent intracellular reservoirs which can serve as a possible source for recurrent UTIs [24]. Because we found lower urinary cytokine concentrations in women with DM [22], we hypothesised that in these patients, bacteria might invade uroepithelial cells more easily and, by an impaired inflammatory response, evade the innate host defences [15]. This would explain why relapses of UTIs occur often in these patients [25]. Future studies will have to provide the evidence for this phenomenon.

3.3. Associated risk factors

Factors that have been proposed as constituting an enhanced risk for UTIs in diabetics include age, metabolic control, duration of DM, diabetic cystopathy, more frequent hospitalisation and instrumentation of the urinary tract, recurrent vaginitis and vascular complications [10,26]. However, different studies show conflicting results. Moreover, most of them do not differentiate between patients with DM type 1 and type 2. We have determined the risk factors for the prevalence of ASB and the incidence of symptomatic UTIs in a large cohort of 636 diabetic women. We found that women with DM type 1 with a longer duration of diabetes, or the presence of peripheral neuropathy and macroalbuminuria had an increased risk of ASB. In women with DM type 2, a greater age, macroalbuminuria and a recent symptomatic UTI predisposed for ASB. There was no association between the diabetes regulation and the presence of ASB [8]. For healthy women, the most important risk factor for the development of a symptomatic UTI for women with DM type 1 was recent sexual intercourse. For women with DM type 2, the most important risk factor of a symptomatic UTI was the presence of ASB [27,17]. Thirty-four percent of the women with DM type 2 with ASB developed a symptomatic UTI compared with 19% of the women without ASB [28].

It has been suggested that diabetic cystopathy and peripheral neuropathy are associated with the pathogenesis of UTIs in diabetic patients [10]. However, we, along with other groups, could not find a correlation between the presence of peripheral neuropathy and a bladder residue after micturition or with the presence of ASB [8,29,30].

4. Bacteriology

The bacteria isolated from diabetic patients with a UTI are similar to those found in nondiabetic patients with a complicated UTI [31]. As in uncomplicated UTIs, E. coli causes the majority of infections. However, other strains are relatively more frequently cultured in these patients. For example, one study reported E. coli to be the causative uropathogen in 47% of the UTIs in diabetic patients and in 68% of the UTIs in nondiabetic patients [32]. Non-E. coli uropathogens found in patients with DM, include Klebsiella spp, Enterobacter spp, Proteus spp, Group B Streptococci and Enterococcus faecalis [7,12,26]. Some authors found that diabetic patients are more likely to be infected with a resistant uropathogen [32,33]. However, we could not confirm this finding in our cohort of diabetic women with ASB. A total of 135 E. coli were isolated from women with DM (mean age 57 ±14 years) and compared with 5907 routine isolates of E. coli obtained from female patients visiting an outpatient department (mean age 52 ±17). The resistance rates of E. coli isolated from diabetic patients and the routine isolates of E. coli to trimethoprim-sulphamethoxazole (TMP-SMX) were 19 and 23%, respectively, to amoxycillin 16 and 32%, to nitrofurantoin 1 and 3%, to ciprofloxacin 0 and 4%, to ofloxacin 0 and 5%, and to norfloxacin 1 and 4% (Meiland et al., unpublished information).

5. Consequences of asymptomatic bacteriuria

Recently, a large study among 796 sexually active, nonpregnant women without DM (age 18–40 years old), identified ASB as a strong predictor of a subsequent symptomatic UTI [34]. In other studies of nondiabetic patients, it was suggested that ASB can lead to recurrent UTIs, progressive renal impairment, hypertension and an increased mortality [35] although most authors agree that ASB per se in a healthy individual causes no harm [36,37]. However, despite the high prevalence of ASB among women with DM, little is known about the consequences in this specific population [12,7]. In the study mentioned earlier, we have shown that women with DM type 2 with ASB at baseline had an increased risk of developing a UTI during the 18-month follow-up, compared with women with DM type 2 without ASB at baseline (17% without ASB versus 27% with ASB P = 0.02). In contrast, we did not find a difference in the incidence of a symptomatic UTI between DM type 1 women with and without ASB. However, a more interesting finding was that women with DM type 1 and
ASB had tendency to a faster decline in renal function than those without ASB (relative increase in creatinine 4.6% versus 1.5%, \( P = 0.2 \)) [28]. If longer follow-up studies, such as ongoing in our centre, show that ASB contributes to the development of diabetic nephropathy, this would have important consequences. Diabetes now accounts for 35% of all new cases of end-stage renal disease in the United States, and persons with DM make up the fastest growing group of renal dialysis and transplant recipients [38,39].

6. Clinical presentation

UTIs in diabetic patients can be either asymptomatic or symptomatic. ASB is defined as the presence of at least 10⁵ colony-forming units of the same urinary tract pathogen per millilitre in two consecutive clean voided midstream urine cultures. Several studies have shown that the presence of ASB is a predictor of symptomatic infections, in patients with DM as well as in patients without DM [17,34]. The presentation of a lower (symptomatic) UTI can be accompanied by classical symptoms as dysuria, frequency, urgency, haematuria, and/or abdominal discomfort. However, the same symptoms may be produced by inflammation in the urethra or by infective agents as Chlamydia trachomatis, herpes simplex or by a vaginitis (e.g. Candida albicans) which also occur frequently in women with DM. Therefore, a urine specimen should be checked for leukocyturia (the presence in uncentrifuged urine, of ≥ 5 leukocytes/high power field or 10 leucocytes/mm³) and bacteriuria. Upper tract involvement is common in patients with DM [9,40]. Acute pyelonephritis is a clinical syndrome characterised by fever and chills, flank pain, costovertebral angle tenderness, and other general symptoms, such as nausea and vomiting. There may or may not be symptoms of lower UTI, such as dysuria. Some patients, however, only present with symptoms of a lower UTI but nevertheless have upper tract involvement (subclinical pyelonephritis) [10]. Bilateral involvement is more common in diabetic patients [41]. Infection leads to bacteraemia relatively often in these patients. There are exceptional cases of renal abscesses, papillary necrosis and emphysematous pyelonephritis [12,42]. Renal abscess formation should be suspected in patients who do not respond to antimicrobial therapy after 72 h. Therefore, if symptoms do not resolve within this time period, ultrasonography or CT-scanning of the kidneys should be performed [10]. Papillary necrosis is also a complication of UTI in the diabetic patient, which is important to recognize. Symptoms consist of flank pain, chills, fever and renal insufficiency develops in 15% of the cases. Therefore, the diagnosis should be suspected in patients responding poorly to antimicrobial therapy. Emphysematous pyelonephritis is a necrotizing infection characterised by gas production within the renal parenchyma. The disease is seen almost exclusively in diabetic patients. Gram-negatives are the most common isolates but multiple organisms may occur. Clinical features include fever, flank pain and a palpable mass in 45% of the patients. Bacteraemia is a frequent complication of emphysematous pyelonephritis. Diagnosis is made radiographically starting with a plain abdominal film of the kidney, ureter and bladder that detects renal emphysema in 85%. Ultrasound can be useful, especially in diagnosing obstructive complications. However, CT-scanning (without contrast) is the study of choice because of its high sensitivity and because it precisely defines the localization and extension of the gas formation, which is important in determining the optimal therapeutic strategy [10].

7. Treatment

Despite the high prevalence of the disease, clinical trials specifically dealing with the treatment of UTIs in diabetic patients are rare. No randomised trials are available comparing the optimal duration and the choice of the treatment. Therefore, most recommendations for treatment of UTIs in diabetic patients are based on expert opinions more than on scientific evidence.

Discussion exists whether all UTIs in patients with DM should be considered and subsequently treated as complicated infections. Do the vast majority of UTIs in diabetic patients need to be labelled ‘complicated’ with the resulting more aggressive management? Why not be more conservative, get the data from prospective studies and not create ‘disease’ when there is none in many patients? Some authors indeed state that the term ‘complicated’ should be reserved for (diabetic) patients with therapy failure (persistent or recurrent infection) or with the presence of other conditions which in itself would lead to categorization as ‘complicated UTI’ (e.g. abnormalities of urinary tract, impaired renal function) [43,44]. However, others [33,45] mean that all UTIs in patients with DM should be treated as complicated infections, in order to avoid the development of possible dangerous complications.

7.1. Antimicrobial treatment

Few clinical trials have dealt with the outcome of treatment of ASB in patients with DM [40,9]. From these studies, the authors conclude that (1) 2 weeks of treatment is as effective as 6 weeks treatment; (2) the recurrence rate is high, even after prolonged antibiotic treatment; and (3) recurrences (4–8 weeks post-therapy) are mostly re-infections and not relapses with the same microorganism (which occur earlier). In addition, physicians should be aware of the high prevalence of
underlying structural genitourinary abnormalities among bacteriuric women with DM [40].

The need for screening of ASB in diabetic (female) patients, with the intention to treat, depends on the question whether or not ASB per se can lead to serious complications as renal function deterioration [46]. Since such evidence is not yet available, we and several authors, [36] but not all, [10,37] believe that a restrictive policy towards the treatment of ASB is justified. A recently published randomised controlled trial sheds some new light on this. In this study of Harding et al. [47], 108 diabetic women with ASB (diagnosed by two urine cultures showing ≥10^5 CFU) were randomised to receive a 3- or 14-day course of either TMP-SMX or placebo. Ciprofloxacin was provided to patients in the antibiotic-treatment group who were infected with a resistant organism. Because the first six patients assigned to a 3-day antibiotic regimen had early relapses, this study arm was discontinued. All patients were subsequently screened every 3 months for bacteriuria, and women in the antibiotic therapy group were given further suppressive antimicrobial therapy if they were bacteriuric. Four weeks after the end of the initial course of therapy, 78% of placebo recipients had bacteriuria, compared with 20% of women who received antimicrobial agents (P < 0.001). During a mean follow-up of 27 months, 20 of 50 women in the placebo group (40%) and 23 of 55 women in the antimicrobial-therapy group (42%) had at least one episode of symptomatic UTI. The time to a first symptomatic episode was similar in the placebo group and the antimicrobial-therapy group, as were the rates of any symptomatic UTI and hospitalization for UTI. The authors concluded that treatment of ASB in women with diabetes does not reduce complications and diabetes itself should not be an indication for screening for or treatment of ASB [47].

However, in our previous paper [28] we described how women with diabetes type 1 and ASB had a tendency to a decline in renal function during the short follow-up. Since diabetes type 1 and type 2 are considered different diseases, separate analyses of these patient groups are warranted. In the study of Harding et al., all patients were analysed together and only 17(20%) had type 1 diabetes. We think therefore, that the conclusion of this very interesting study should be that it is difficult to keep these patients non-bacteriuric. Furthermore, we think that it is premature to conclude that screening and treatment of ASB in diabetic women is not needed because we should await the results of our 5 year follow-up study with nearly 200 women with type 1 diabetes, which has renal function development as primary outcome parameter [48].

For uncomplicated acute bacterial cystitis (i.e. in otherwise healthy young women), the Infectious Diseases Society of America (IDSA) recommends a 3-day course with TMP-SMX as standard therapy. Alterna-

tively, one can prescribe trimethoprim alone or a fluoroquinolone, for example ofloxacin. Other fluoroquinolones have similar effectiveness, but taking into account the higher costs and the increasing problem of resistant microorganisms, these should only be used as an alternative in communities with high rates of resistance to TMP-SMX [49]. However, the guidelines do not include complicated infections.

Few therapeutic trials have specifically been performed using diabetic patients. Because of the frequent (asymptomatic) upper tract involvement and the possible serious complications, many experts recommend a 7–14-day oral antimicrobial regimen for bacterial cystitis in diabetic patients, instead of the recommended 3-day course for uncomplicated cystitis [10,27,50]. In a recent double-blind study, the efficacy in the treatment of complicated urinary lower UTIs of a 5-day ofloxacin treatment was compared with a 10-day regimen. Four hundred and sixteen women were studied of whom an unknown percentage had DM. The authors concluded that both regimens were equally effective [51].

Although some authors state that in diabetic patients the choice of agent does not differ from the treatment in otherwise healthy patients [31,44], most authors prefer antimicrobial agents which achieve high levels not only in the urine but also in the urinary tract tissues: e.g. fluoroquinolones, TMP-SMX and amoxycillin-clavulanic acid [27,52]. This may especially hold true given the recent data indicating invasion of E. coli into the bladder cells [24]. A recent randomised, double-blind study including 85 (20%) women with DM, has shown that a 7-day regimen with ciprofloxacin or with ofloxacin resulted in a cure rate of 90 and 87%, respectively, 5–9 days after treatment of a complicated lower UTI [53]. In the group of women with DM, the success rates were comparable (87 and 85%) [51,53]. These data, the mouse data of Hultgren’s group showing a potential intraepithelial reservoir, our own data showing a very high relapse rate in ASB and the data of Nicolle’s group showing a 10% failure rate in the six women treated for ASB, in our opinion, suggest that treatment guidelines for uncomplicated UTI in diabetic women should differ from those in the IDSA guidelines (Table 2). We would recommend a 7-day regimen with an agent that pene-

Table 2
Cystitis in diabetic women-treatment guidelines

| 3-Day therapy is probably not effective [12,25,47] |
| Treat with agents that penetrate the urothelium [24] |
| TMP-SMX is the agent of choice in areas with low resistance rates (< 20%) [54,56] |
| Fluoroquinolones are effective [53] |
| β-lactam antibiotics are less effective [49] |
| Short course therapy with nitrofurantoin and fosfomycin should be evaluated |

trates epithelial cells. Both TMP-SMZ and the fluoroquinolones have proven to be effective, both are more effective than β-lactam agents [49]. In areas with a resistance rate over 20% for TMP-SMZ the primary choice would be a fluoroquinolone because low resistance rates are found at least all over Europe [54]. To prevent resistance development against the agents mentioned above, studies with both nitrofurantoin and fosfomycin are warranted. Noteworthy is the possible hypoglycaemic effect of TMP-SMX, which has been observed using (larger doses of) this agent [50,52].

In all cases of suspected pyelonephritis in diabetic patients a culture of urine before starting therapy is indicated, as well as blood cultures if the patient is severely ill [10]. The treatment of uncomplicated pyelonephritis does not differ for patients with or without DM. For treatment of mild acute pyelonephritis IDSA recommends an oral fluoroquinolone, possibly after an initial single parenteral dose of an antimicrobial. Diabetic patients are usually treated within the hospital, with a parenteral fluoroquinolone or a cephalosporin as initial therapy. In communities with a resistance rate of <15% of E. coli to TMP-SMX, TMP-SMX is considered a suitable alternative. After 48–72 h, if symptoms have resolved, oral therapy may be started. These recommendations rely on clinical practice, since all randomised studies comparing oral with intravenous therapy have excluded patients with underlying systemic illnesses as DM. The current standard duration of therapy for uncomplicated pyelonephritis in both diabetic and nondiabetic patients is 14 days [27,49,52,55]. In a recent randomised trial a 7-day oral ciprofloxacin regimen was more effective than a 14-day TMP-SMX regimen for the treatment of uncomplicated pyelonephritis, as indicated by greater bacteriological and clinical cure rates [56]. This was probably due to a high resistance rate (18%) to TMP-SMX in this study. However, this study tells us that for uncomplicated pyelonephritis, a course of 7-days treatment is enough. Although highly interesting, comparable studies will have to be performed specifically enrolling patients with DM, before such a regimen can be advised for these patients.

In patients with DM, a follow-up urine culture (2–4 weeks post-therapy) is considered useful to detect early relapses and because of the higher treatment failure [33]. Considering the text mentioned above, it is clear that clinical trials specifically dealing with the treatment of UTIs in diabetic patients, comparing the optimal duration and the choice of the therapy, are needed.

The traditional treatment of emphysematous pyelonephritis is nephrectomy of the affected kidney. Surgery has been reported to lower the mortality from 80% in patients treated with antimicrobial treatment alone, to 20% [10]. Although an increasing number of cases are reported of successful conservative management, antimicrobial therapy combined with percutaneous drainage, [57] no consensus exists whether this strategy should replace (or proceed) the standard nephrectomy.

7.2. Non-antimicrobial treatments and preventive strategies

The worldwide increasing problem of resistant uropathogens [58] calls for additional non-antimicrobial strategies, both for the treatment and for the prevention of UTIs (Table 3). General advice includes sufficient fluid intake, complete emptying of the bladder during voiding, less use of spermicides and restrictive catheter use.

An interesting possible preventive or treatment option is ingestion of cranberry juice. At first, the beneficial effect of cranberry juice was thought to be the result of acidification of the urine. More recently, in vitro studies have identified the inhibition of bacterial adherence to the uroepithelial cells as the most plausible mechanism of action [59]. Another possible preventive strategy is the oral or vaginal administration of lactobacilli. Lactobacilli are part of the commensal vaginal flora and are thought to protect against UTIs by competitive exclusion of uropathogens [60]. In a recent randomised trial, regular drinking of cranberry juice but not of Lactobacillus GG drink reduced the recurrence of UTIs in women with E. coli infection [61]. In addition, several investigators have studied the influence of oestrogen administration. Oestrogen deficiency in postmenopausal women has been implicated in the pathogenesis of recurrent UTI, apparently due to an increase in vaginal pH and the subsequent reduction in the number of lactobacilli [62]. Several randomised trials of oestrogen administration have been performed, mostly including small numbers of patients and with conflicting results. In a recent review, the authors conclude that oestrogen administration is of benefit in decreasing the recurrence rate of UTIs in postmenopausal women, especially if

<table>
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<td>Non-antimicrobial treatments and strategies that possibly reduce the incidence of UTIs</td>
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<tr>
<td>General preventive strategies [72]</td>
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<tr>
<td>Sufficient fluid intake</td>
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<tr>
<td>Complete emptying of bladder during voiding</td>
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<tr>
<td>Less use of spermicides</td>
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<tr>
<td>Restrictive catheter use [73]</td>
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<tr>
<td>Cranberry juice (oral) [61]</td>
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<tr>
<td>Lactobacilli (oral or vaginal) [61,74]</td>
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<tr>
<td>Oestrogen supplements in postmenopausal women (oral or vaginal) [62–64]</td>
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<tr>
<td>Vaccines (both currently withdrawn)</td>
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<tr>
<td>Urovac [68]</td>
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<tr>
<td>FimH-adhesin-based [66,67]</td>
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The strategies mentioned have been studied in nondiabetic patients.
administered vaginally [63]. A randomised, blinded study of 2763 postmenopausal women who participated in a study on coronary heart disease, reported no reduction of the frequency of UTIs in those patients with oral hormone therapy (oestrogen plus medroxyprogesterone acetate) compared with women who received a placebo [64]. All strategies mentioned have been studied in nondiabetic patients, but we think that the results will be comparable in patients with DM. A randomised study comparing oestrogens with cranberry juice in elderly nondiabetic women is currently underway. However, one should realise that cranberry juice is difficult to take (large volume), contains a lot of calories and is expensive.

Since the adherence of E. coli to the uroepithelial cell is an essential step in the pathogenesis of UTIs, prevention of this would theoretically lead to a decreased incidence of UTIs. Therefore, attention has shifted towards the development of a vaccine, based on the FimH adhesin of type 1 fimbriae of E. coli. In vitro and animal studies have shown that this vaccine can prevent adherence of E. coli to uroepithelial cells and decrease incidence of UTIs in vaccinated monkeys [65,66]. We have demonstrated that addition of vaccine-induced antiserum to uroepithelial cells isolated from diabetic women, also decreases the adherence of type-1 fimbriated E. coli to diabetic uroepithelial cells [67]. At this moment, clinical studies have been discontinued, because although safe, the vaccine proved only 30% effective in young sexually active women. In addition, another vaccine under study in women with recurrent UTIs. This vaccine is based on immunisation by vaginal suppositories containing heat-killed uropathogenic bacteria from 10 different isolates [68]. This vaccine is also no longer available.

Over the last few years, more research has been done in the area of prevention of post-operative infections in diabetic patients. Although non-randomised, these studies confirm the hypothesis that hyperglycaemia is associated with an increased risk of post-operative infection. The authors recommend optimal peri-operative glycaemic control (glucose levels <200 mg/dl) [69,44].

8. Future issues

Longer follow-up studies among diabetic patients (as are ongoing in our centre) analysing the effects of ASB on renal function should answer the question whether women with DM (especially type-I) should be kept non-bacteriuric. Furthermore, randomised therapeutic trials specifically enrolling patients with DM will have to define the best therapeutic management, focussing on the type of antimicrobial agent and optimal treatment duration. New developments on non-antimicrobial approaches must show their value in preventing UTIs in diabetic patients.

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