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Management of Bacterial Urinary Tract Infections in Adult Patients with Diabetes Mellitus

Ruby Meiland,[1] *Suzanne E. Geerlings*[2] and *Andy I.M. Hoepelman*[1,3]

1 Department of Medicine, Division Acute Medicine & Infectious Diseases, University Medical Center Utrecht, Utrecht, The Netherlands
2 Department of Internal Medicine, Vrije Universiteit Medical Center, Amsterdam, The Netherlands
3 Eijkman-Winkler Laboratory for Microbiology, University Medical Center Utrecht, Utrecht, The Netherlands

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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 than in the general population. The mechanisms that 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 diabetes. Because of the frequent (asymptomatic) upper tract involvement and the possible serious complications, many experts recommend a 7- to 14-day oral antibacterial regimen for bacterial cystitis in these patients, with an antibacterial agent that achieves high concentrations both in the urine and in urinary tract tissues. The recommended treatment of acute pyelonephritis does not differ from that in patients without diabetes. Clinical trials specifically dealing with the treatment of UTIs in patients with diabetes, comparing the optimal duration and choice of antibacterial agent,

are needed. In addition, new approaches to preventive strategies must prove their value in this specific patient group.

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 subtle conditions such as age over 65 years, treatment with immunosuppressive drugs, the presence of HIV infection and last, but not least, diabetes mellitus also predispose to an enhanced susceptibility for the development of a UTI with a complicated course.[3,4]

Diabetes is the most common endocrine disease. Besides organ complications as retinopathy, nephropathy and neuropathy, patients with diabetes also more frequently experience (complicated) infections compared with patients without diabetes. In a large study of patients with bacteraemia, it was demonstrated that two thirds of the patients had diabetes; 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 diabetes. Furthermore, it is important to realise that most of the research described in this article has been performed in female patients who have a higher prevalence of UTIs than men. Firstly, this article briefly describes specific aspects of the epidemiology, pathogenesis, clinical presentation and consequences of asymptomatic and symptomatic UTIs in adult patients with diabetes, 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.

1. Epidemiology

The majority of the infections in patients with diabetes are localised in the urinary tract.[5] An autopsy study in 1940 showed that approximately 20% of patients with diabetes had a serious infection of the urinary tract. The authors stated that this prevalence was five times higher than found in studies of patients without diabetes.[6] Although different studies show a wide range, nearly all investigators report that the prevalence of asymptomatic bacteriuria in women with diabetes is three to four times higher than in women without diabetes.[7,8] In men, results are more consistent with a frequency between 1 to 2% found, and no difference between men with diabetes and those without.[9] The frequency of symptomatic infections in women with diabetes 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 the probability 20- to 30-fold under the age of 44 years, and 3- to 5-fold over the age of 44 years.[11] Furthermore, complications of an upper UTI are more likely to occur in patients with diabetes. For example, emphysematous pyelonephritis is seen almost exclusively in patients with diabetes and, although uncommon, half the patients with papillary necrosis have diabetes.[12]

2. Pathogenesis of Urinary Tract Infections

2.1 General

UTIs almost exclusively arise 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 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 *Escherichia coli* (the most common uropathogen), many of the same principles may be applicable to other Gram negative uropathogens, for example *Klebsiella* spp.[14] Type 1 fimbriae mediate the adherence of *E. coli* to glycoprotein receptors (uroplakins) on the uroepithelial cells, whereas P fimbriae bind to glycolipid receptors in the kidney.[15]

2.2 Patients with Diabetes

The increased frequency of UTIs in patients with diabetes is most likely because of several factors (table I). Suggested host-related mechanisms are: (i) the presence of glycosuria; (ii) defects in neutrophil function; and (iii) 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 patients with diabetes than in patients without glycosuria.[8,17]

The data on impaired neutrophil function are contradictory.[22,23] Moreover, the incidence of UTIs is not increased in other groups of patients with neutrophil defects or neutropenia.[24] 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.[25] Therefore, we investigated urinary cytokine excretion in patients with diabetes and found lower urinary interleukin (IL)-8 and IL-6 concentrations ($p = 0.1$ and $p < 0.001$, respectively) in women with diabetes than in nondiabetic controls. A lower urinary leucocyte cell count correlated with lower urinary IL-8 and IL-6 concentrations ($p < 0.05$).[18] 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 diabetes is increased, compared to the adherence to uroepithelial cell of women without diabetes.[19] Thus, it seems that this increased adherence plays an important role in the pathogenesis of UTIs in women with diabetes.

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 has been thought for a long time that uropathogenic *E. coli* are non-invasive pathogens. However, a recent study in mice has shown that type-1 fimbriated *E. coli* can not only lead to exfoliation, but can also invade the uroepithelial cells, replicate and form quiescent intracellular reservoirs which can serve as a possible source for recurrent UTIs.[26] Because we found lower urinary cytokine levels in women with diabetes,[18] 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.[27] Future studies will have to provide the evidence for this phenomenon.

Table I. Host factors associated with an increased risk for symptomatic or asymptomatic urinary tract infections (UTIs) in women with diabetes mellitus

General
sexual intercourse[17]
history of (recurrent) UTIs[8]
obstruction, urine stasis, reflux, instrumentation of urinary tract[13]a
Associated with (complications of) diabetes
peripheral neuropathy[8]
macroalbuminuria[8]
longer duration of diabetes[8]
glycosuria (*in vitro*)[16]
decreased urinary cytokine secretion[18]
increased adherence of *Escherichia coli* to uroepithelial cells[19]
Genetic factors[a]
secretor status[20]
blood group[20]
history of UTIs in mother[21]

a Not studied specifically in patients with diabetes.

2.3 Associated Risk Factors

Factors that have been proposed to constitute an enhanced risk for UTIs in patients with diabetes include age, metabolic control, duration of diabetes, diabetic cystopathy, more frequent hospitalisation and instrumentation of the urinary tract, recurrent vaginitis and vascular complications.[10,28] However, different studies show conflicting results. Moreover, most of them do not differentiate between patients with type 1 (insulin-dependent) and type 2 (non-insulin–dependent) diabetes.

We have determined the risk factors for the prevalence of asymptomatic bacteriuria and the incidence of symptomatic UTIs in a large cohort of 636 women with diabetes. We found that women with type 1 diabetes with a longer duration of diabetes, or the presence of peripheral neuropathy and macroalbuminuria, had an increased risk of asymptomatic bacteriuria. In women with type 2 diabetes, a higher age, macroalbuminuria and a recent symptomatic UTI predisposed for asymptomatic bacteriuria. There was no association between how well the diabetes was controlled and the presence of asymptomatic bacteriuria.[8] Equally to healthy women, the most important risk factor for the development of a symptomatic UTI for women with type 1 diabetes was recent sexual intercourse. For women with type 2 diabetes, the most important risk factor for a symptomatic UTI was the presence of asymptomatic bacteriuria.[17,29] Thirty-four percent of the women with type 2 diabetes and asymptomatic bacteriuria developed a symptomatic UTI compared with 19% of the women without asymptomatic bacteriuria.[30]

It has been suggested that diabetic cystopathy and peripheral neuropathy are associated with the pathogenesis of UTIs in patients with diabetes.[10] However, others and we could not find a correlation between the presence of peripheral neuropathy and a bladder residue after micturition with the presence of asymptomatic bacteriuria.[8,31,32]

3. Bacteriology

The bacteria isolated from diabetic patients with a UTI are similar to those found in nondiabetic patients with a complicated UTI.[33] As in uncomplicated UTIs, *E. coli* causes the majority of infections. However, other species 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 patients with diabetes patients and in 68% of the UTIs in patients without diabetes.[34] Non-*E. coli* uropathogens found in patients with diabetes include *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., Group B streptococci and *Enterococcus faecalis*.[7,12,28] Some authors found that patients with diabetes are more likely to be infected with a resistant uropathogen.[34,35] However, we could not confirm this finding in our cohort of diabetic women with asymptomatic bacteriuria (unpublished data).

4. Consequences of Asymptomatic Bacteriuria

Recently, a large study among 796 sexually active, nonpregnant women without diabetes (aged 18 to 40 years) identified asymptomatic bacteriuria as a strong predictor of a subsequent symptomatic UTI.[36] In other studies of nondiabetic patients, it was suggested that asymptomatic bacteruria can lead to recurrent UTIs, progressive renal impairment, hypertension and an increased mortality,[37] although most authors agree that asymptomatic bacteriuria *per se* in a healthy individual causes no harm.[38,39] However, despite the high prevalence of asymptomatic bacteriuria among women with diabetes, little is known about the consequences in this specific population.[7,12]

In the study discussed in section 2.3, we have shown that women with type 2 diabetes with asymptomatic bacteriuria at baseline had an increased risk of developing a UTI during the 18-month follow-up compared with women with type 2 diabetes without asymptomatic bacteriuria at baseline (17% without *vs* 27% with, $p = 0.02$). In contrast, we did not find a difference in the inci-

dence of a symptomatic UTI between women with type 1 diabetes with and without asymptomatic bacteriuria. However, a more interesting finding was that women with type 1 diabetes and asymptomatic bacteriuria had a tendency to a faster decline in renal function than those without asymptomatic bacteriuria (relative increase in creatinine 4.6 *vs* 1.5%, p = 0.2).[30] If longer follow-up studies, as ongoing at the University Medical Centre Utrecht, show that asymptomatic bacteriuria 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 US, and persons with diabetes make up the fastest growing group of renal dialysis and transplant recipients.[40,41]

5. Clinical Presentation

UTIs in patients with diabetes can be either asymptomatic or symptomatic. Asymptomatic bacteriuria is defined as the presence of at least 10^5 colony forming units (cfu) of the same urinary tract pathogen per millilitre in two consecutive clean-voided midstream urine cultures. Several studies have shown that the presence of asymptomatic bacteriuria is a predictor of symptomatic infections in patients with as well as in patients without diabetes.[17,36]

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 such as *Chlamydia trachomatis*, herpes simplex or by a vaginitis (e.g. *Candida albicans* infection), which also occur frequently in women with diabetes. Therefore a urine specimen should be checked for leukocyturia (the presence, in uncentrifuged urine, of ≥5 leucocytes/high power field or 10 leucocytes/mm^3) and bacteriuria.

Upper tract involvement is common in patients with diabetes.[9,42] 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. However, some patients only present with symptoms of a lower UTI but nevertheless have upper tract involvement (subclinical pyelonephritis).[10]

Bilateral involvement is more common in patients with diabetes.[43] Infection leads to bacteraemia relatively often in these patients.

There are exceptional cases of renal abscesses, papillary necrosis and emphysematous pyelonephritis.[12,44] Renal abscess formation should be suspected in patients who do not respond to antibacterial therapy after 72 hours. Therefore, if symptoms do not resolve within this time period, ultrasonography or computed tomography (CT) scanning of the kidneys should be performed.[10] Papillary necrosis is also a complication of UTI in patients with diabetes, which is important to recognise. Symptoms consist of flank pain, chills, fever and renal insufficiency develops in 15% of patients. Therefore the diagnosis should be suspected in patients responding poorly to antibacterial therapy. Emphysematous pyelonephritis is a necrotising infection characterised by gas production within the renal parenchyma. The disease is seen almost exclusively in patients with diabetes. Gram-negative bacteria are the most common isolates but multiple organisms 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 which 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 localisation and extension of the gas formation, which is important in determining the optimal therapeutic strategy.[10]

6. Treatment

Despite the high prevalence of the disease, clinical trials specifically dealing with the treatment of UTIs in patients with diabetes 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 patients with diabetes are based on expert opinions more than on scientific evidence.

There is debate about whether all UTIs in patients with diabetes should be considered and subsequently treated as complicated infections. Do the vast majority of UTIs in patients with diabetes 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 categorisation as 'complicated UTI' (e.g. abnormalities of urinary tract, impaired renal function).[45,46] However, others[35,47] state that all UTIs in patients with diabetes should be treated as complicated infections, in order to avoid the development of possible dangerous complications.

6.1 Antibacterial Treatment

Few clinical trials have dealt with the outcome of treatment of asymptomatic bacteriuria in patients with diabetes.[9,42] The authors of these studies conclude that: (i) 2 weeks of treatment is as effective as 6 weeks treatment; (ii) the recurrence rate is high, even after prolonged antibacterial treatment; and (iii) recurrences (4 to 8 weeks post-therapy) are mostly reinfections 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 diabetes.[42]

The need for screening for asymptomatic bacteriuria in (female) patients with diabetes, with the intention to treat, depends on the question of whether or not asymptomatic bacteriuria *per se* can lead to serious complications as renal function deterioration.[48] Since such evidence is not yet available, we and several other authors,[38] but not all,[10,39] believe that a restrictive policy towards the treatment of asymptomatic bacteriuria is justified. Especially since it is not known whether treatment of asymptomatic bacteriuria in women with diabetes leads to an improved outcome,[33] but also because of the possible adverse effects of the antibacterial therapy and the increasing antibacterial resistance rate. However, physicians must be aware of the potential of underlying pathology and serious complications.[42,49]

For uncomplicated acute bacterial cystitis (that is, in otherwise healthy young women) the Infectious Diseases Society of America (IDSA) recommends a 3-day course of cotrimoxazole (trimethoprim/sulfamethoxazole) as standard therapy. Alternatively, trimethoprim alone or a fluoroquinolone, for example ofloxacin, can be prescribed. Other fluoroquinolones have similar effectiveness, but considering the higher costs and the increasing problem of resistant micro-organisms, these should only be used as an alternative in communities with high rates of resistance to cotrimoxazole.[50] However, the IDSA guidelines do not include complicated infections.

Few therapeutic trials have specifically been performed among patients with diabetes. Because of the frequent (asymptomatic) upper tract involvement and the possible serious complications, many experts recommend a 7- to 14-day oral antibacterial regimen for bacterial cystitis in patients with diabetes, instead of the recommended 3-day course for uncomplicated cystitis.[10,29,51] In a recent double-blind study, the efficacy in the treatment of complicated urinary lower UTIs of a 5-day course of ofloxacin was compared to a 10-day regimen. 416 women were studied of whom an unknown percentage had diabetes. The authors con-

cluded that both regimens were equally effective.[52]

Although some authors state that in patients with diabetes the choice of agent does not differ from the treatment in otherwise healthy patients,[33,46] most authors prefer antibacterial agents which achieve high concentrations not only in the urine but also in the urinary tract tissues, for example, fluoroquinolones, cotrimoxazole and amoxicillin/clavulanic acid.[29,53] This may especially hold true given the recent data indicating invasion of *E. coli* into the bladder cells.[26] A recent randomised, double-blind study including 85 (20%) women with diabetes has shown that a 7-day regimen with ciprofloxacin or with ofloxacin both result in a cure rate of 97% 5 to 9 days after treatment of a complicated lower UTI.[54] In general, nephrotoxic antibacterial agents should be avoided whenever possible. As stated earlier in this section, evidence for either optimal duration of therapy or choice of antibacterial agent is lacking. Noteworthy is the possible hypoglycaemic effect of cotrimoxazole, which has been observed using (larger doses of) this agent.[51,53]

In all diabetic patients with suspected pyelonephritis, 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 diabetes. For treatment of mild acute pyelonephritis the IDSA recommends an oral fluoroquinolone, possibly after an initial single parenteral dose of an antibacterial. Patients with diabetes 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 cotrimoxazole, this agent is considered a suitable alternative. If symptoms have resolved after 48 to 72 hours, 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, such as diabetes. The current standard duration of therapy for uncomplicated pyelonephritis in both diabetic as in nondiabetic patients is 14 days.[29,50,53,55] In a recent randomised trial a 7-day oral ciprofloxacin regimen was more effective than a 14-day cotrimoxazole regimen for the treatment of uncomplicated pyelonephritis, as indicated by greater bacteriological and clinical cure rates.[56] This was probably the result of a high resistance rate (18%) to cotrimoxazole in this study. However, this study does indicate that in uncomplicated pyelonephritis a treatment duration of 7-days is enough. Although highly interesting, comparable studies will have to be performed specifically enrolling patients with diabetes, before such a regimen can be advised in these patients.

In patients with diabetes, a follow-up urine culture (2 to 4 weeks post-therapy) is considered useful to detect early relapses and because of the higher rates of treatment failure.[35] It is clear from the discussion in this section that clinical trials specifically dealing with the treatment of UTIs in patients with diabetes, 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 antibacterial treatment alone, to 20%.[10] Although an increasing number of cases are being reported of successful conservative management, antibacterial therapy combined with percutaneous drainage,[57] no consensus exists as to whether this strategy should replace (or proceed) the standard nephrectomy.

6.2 Non-Antibacterial Treatments and Preventive Strategies

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

An interesting possible preventive or treatment option is ingestion of cranberry juice. At first, the

Table II. Non-antibacterial treatments and strategies that possibly reduce the incidence of urinary tract infections[a]

General preventive strategies[59]
sufficient fluid intake
complete emptying of bladder during voiding
decrease use of spermicides
restrictive catheter use[60]
Cranberry juice (oral)[61]
Lactobacilli (oral or vaginal)[61,62]
Estrogen supplementation in postmenopausal women (oral or vaginal)[63-65]
Vaccines
Urovac[66]
FimH-adhesin-based (under development)[67,68]

a The strategies mentioned have been studied in patients without diabetes.

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.[69] 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.[70] 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 estrogen administration. Estrogen deficiency in postmenopausal women has been implicated in the pathogenesis of recurrent UTI, apparently as a result of an increase in vaginal pH and the subsequent reduction in the number of lactobacilli.[64] Several randomised trials of estrogen administration have been performed, most including only small numbers of patients and with conflicting results. In a recent review, the authors conclude that estrogen administration is of benefit in decreasing the recurrence rate of UTIs in postmenopausal women, especially if administered vaginally.[63] A randomised, blinded study among 2763 postmenopausal women who participated in a study on coronary heart disease, reported no reduction of the frequency of UTIs in patients with oral hormone therapy (estrogen plus medroxyprogesterone) compared with women who received a placebo.[65]

All strategies mentioned in this section have been studied in patients without diabetes but we think that the results will be comparable in patients with diabetes.

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, the current development of a vaccine, based on the FimH adhesin of type 1 fimbriae of *E. coli* is very promising. *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.[67,71] We have demonstrated that addition of vaccine-induced antiserum to uroepithelial cells isolated from women with diabetes also decreases the adherence of type-1 fimbriated *E. coli* to diabetic uroepithelial cells.[68] At this moment, clinical studies with this vaccine in patients without diabetes are ongoing. In addition, another vaccine is currently being studied in women with recurrent UTIs. This vaccine is based on immunisation by vaginal suppositories containing heat-killed uropathogenic bacteria from ten different isolates.[66] If proven effective, these vaccines would be a welcome supplement of our therapeutic armamentarium.

In the last years, more research has been done in the area of prevention of post-operative infections in patients with diabetes. 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).[46,72]

7. Future Issues

Longer follow-up studies among patients with diabetes (as ongoing in our centre) analysing the effects of asymptomatic bacteriuria on renal function should answer the question whether women with diabetes should be kept non-bacteriuric. Fur-

thermore, randomised therapeutic trials specifically enrolling patients with diabetes will have to define the best therapeutic management, focussing on type of antibacterial agent and optimal treatment duration. New developments on non-antibacterial approaches, especially the current developed vaccine, must show their value in preventing UTIs in diabetic patients.

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Correspondence and offprints: Professor *Andy I.M. Hoepelman*, Department of Medicine, Division Acute Medicine & Infectious Diseases, University Medical Center Utrecht, Room F02.126, P.O. Box 85500, Utrecht, 3508 GA, The Netherlands.
E-mail: I.M.Hoepelman@digd.azu.nl