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SWAB Guidelines for Antimicrobial Therapy of Complicated Urinary Tract Infections in Adults

- Dr. S.E. Geerlings (coordinator, SWAB), Internal Medicine/Infectious Diseases specialist, Department of Internal Medicine, Division of Infectious Diseases, Academic Medical Center, Amsterdam
- Dr. C. van Nieuwkoop (VIZ, NIV), Internal Medicine, Emergency Medicine and Infectious Diseases specialist, Department of Internal Medicine, Hagaziekenhuis, the Hague
- E. van Haarst (NVU), Urologist, Department of Urology, St. Lucas Andreas Hospital, Amsterdam
- Dr. M. van Buren (NFN), Internal Medicine and Nephrology specialist, Department of Internal Medicine, Hagaziekenhuis, the Hague
- Dr. B.J. Knottnerus (NHG), General Practitioner, Department General Practice, Academic Medical Center, Amsterdam
- Dr. E. E. Stobberingh (NVMM), Medical microbiologist, Lab Medical Microbiology, Maastricht Univerisity Medical Center, Maastricht
- Prof. dr. C.J. de Groot (NVOG), Gynaecologist, Department of Obstetrics and Gynaecology, Vrije Universiteit Medical Center, Amsterdam
- Prof. dr. J.M. Prins (SWAB), Internal Medicine/Infectious Diseases specialist, Department of Internal Medicine, Division of Infectious Diseases, Academic Medical Center, Amsterdam

VIZ: Vereniging voor Infectieziekten (Dutch Society for Infectious Diseases); NIV: Nederlandse Internisten Vereniging (Netherlands Society of Internal Medicine); NVU: Nederlandse Vereniging voor Urologie (Dutch Society for Urology); NFN: Nederlandse Federatie voor Nefrologie (Netherlands Federation for Nephrology); NVMM: Nederlandse Vereniging voor Medische Microbiologie (Dutch Society of Medical Microbiologists); NVOG: Nederlandse Vereniging voor Obstetrie en Gynaecologie (Dutch Society for Obstetrics and Gynaecology); NHG: Nederlandse Huisartsen Genootschap (Dutch College of General Practitioners).

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SUMMARY OF RECOMMENDATIONS

WHAT IS OPTIMAL EMPIRICAL ANTIMICROBIAL AGENT?	
	In patients suspected of having a complicated UTI, a urine culture and susceptibility test should always be performed.
	Amoxicillin, co-amoxiclav, trimethoprim and trimethoprim-sulfamethoxazole (TMP-SMX) are not suitable for the empirical treatment of complicated UTI.
	The combination of amoxicillin + an aminoglycoside, a 2nd generation cephalosporin + an aminoglycoside or a 3rd generation cephalosporin intravenously can be recommended as empirical treatment of complicated UTI.
	Ciprofloxacin can only be recommended when the whole treatment is given orally, when patients do not require hospitalization or when the patient has an anaphylaxis for beta-lactam antibiotics, provided that the local resistance percentages are < 10%.
	Ciprofloxacin and other fluoroquinolones are not suitable for the empirical treatment of complicated UTI in patients from the urology department or when patients have used fluoroquinolones in the last 6 months.
	If the prevalence of fluoroquinolone resistance is thought to exceed 10%, an initial 1-time intravenous dose of a long-acting antimicrobial, such as a 3rd generation cephalosporin or an aminoglycoside, is recommended while resistance data are pending.
	If the prevalence of fluoroquinolone resistance is thought to be higher than 10% and the patient has contra indications for 3rd generation cephalosporins or an aminoglycoside, ciprofloxacin can be prescribed as an empirical treatment in women with an uncomplicated pyelonephritis.
	In the event of hypersensitivity to penicillin, a 3rd generation cephalosporin can still be prescribed, with the exception of systemic anaphylaxis in the past.
	In patients with a UTI with systemic symptoms empirical treatment should cover ESBL in the initial treatment only in patients who are colonised with ESBL-producing micro-organisms. The resistance pattern of the ESBL strain should guide empirical therapy.
	When the results of the urine culture are known, therapy must be adjusted and if possible narrowed down. If the clinical condition of the patient allows it and if the patient does not vomit, oral therapy can be prescribed.
	If the patient no longer has symptoms, there is no indication for follow-up cultures.

What is the optimal treatment duration?
Women with acute uncomplicated pyelonephritis should be treated for 7 days when treated with ciprofloxacin.
Women with acute uncomplicated pyelonephritis should be treated for 10-14 days when treated with TMP-SMX or a beta-lactam.
Women with acute complicated pyelonephritis or other complicated UTIs should be treated for 10-14 days.
Men with complicated UTIs should be treated for 14 days.

WHAT IS THE OPTIMAL TREATMENT OF UTI IN MEN?
For the treatment of a UTI without systemic symptoms in young men (<40 years) with no medical history and no previous lower urinary tract symptoms, see the recently updated Guideline for Urinary Tract Infections of the Dutch College of General Practitioners (NHG). First choice is nitrofurantion with a treatment duration of 7 days.
For all men with a UTI with systemic symptoms we refer to the general treatment guidelines.
In chronic bacterial prostatitis there is no need for empirical antimicrobial treatment and treatment should be guided by the resistance pattern of the cultured micro-organism. First choices are quinolones and TMP-SMX.
The duration of antibiotic treatment of chronic bacterial prostatitis should be at least 4 weeks.

WHAT IS THE OPTIMAL TREATMENT OF UTI IN PREGNANT WOMEN?
Nitrofurantoin (2 dd 100 mg) is the first choice and co-amoxiclav (3 dd 500/125 mg) is the second choice drug for the treatment of cystitis during pregnancy. Nitrofurantoin must not used in the last 30 days before delivery.
A 3rd generation cephalosporin (4 dd 1000 mg cefotaxime or 1 dd 2000 mg ceftriaxone) is the drug of first choice for the treatment of pyelonephritis during pregnancy.
The treatment duration of cystitis and pyelonephritis during pregnancy should be at least 5 days, and 10-14 days, respectively.
Antepartum pyelonephritis should be treated in a hospital setting and treatment should be started intravenously.

Screening and treatment of asymptomatic bacteriuria at 16-20 weeks gestation for better maternal and neonatal outcome is not recommended until new evidence is available. Exceptions are women with urinary tract anomalies and/or medical conditions including diabetes mellitus, renal transplant, sickle cell disease and neurological problems.

When Group B streptococcus (GBS) is present in the urine, which is a symptom of severe maternal GBS colonization, consultation with the gynaecologist is advised, because antibiotic prophylaxis during delivery is necessary.

IS SYSTEMIC ANTIMICROBIAL PROPHYLAXIS NECESSARY IN PATIENTS WITH A URINARY CATHETER?

It is not recommended to prescribe antibiotic prophylaxis in patients with short-term or long-term urinary catheters, or in those who catheterize themselves intermittently over prolonged periods and, as a result, there is no need to screen for bacteriuria in these patients.

IS ANTIMICROBIAL PROPHYLAXIS INDICATED AT THE TIME OF CATHETER REMOVAL OR REPLACEMENT?

Prophylactic systemic or local antimicrobials should **not** be administered routinely to patients at the time of catheter placement to reduce CA-UTI, or at the time of catheter removal or replacement to reduce CA-bacteriuria.

WHAT IS THE OPTIMAL MANAGEMENT IN PATIENTS WITH A CA-UTI?

When the patient with a catheter has only local symptoms and has no signs of a systemic infection, it is recommended to wait for the results of the cultures.

If there is a systemic infection, the patient should be treated as described in the General section for patients with a complicated UTI.
A patient who has had an indwelling catheter for a prolonged period or was catheterized intermittently must be treated empirically with a regimen including an aminoglycoside, to cover less common uropathogens like *Pseudomonas, Serratia, Providencia,* and

	Acinetobacter.
	For patients with a urinary catheter in place for at least 10 days the best empirical treatment which covers enterococci is the combination of co-amoxiclav with gentamicin. Excluding enterococci makes a third-generation cephalosporin with gentamicin the most adequate recommendation.
	If an indwelling catheter has been in place for more than 2 weeks at the onset of CA-UTI and cannot be removed, the catheter should be replaced to hasten resolution of symptoms and to reduce the risk of subsequent CA-bacteriuria and CA-UTI.

WHAT ARE THE APPROPRIATE TREATMENT DURATIONS FOR PATIENTS WITH CA-UTI?
See general treatment guidelines for the treatment duration of CA-UTI with systemic symptoms.
A 5-day antimicrobial regimen may be considered for women who develop a CA-UTI without upper tract and systemic symptoms.

WHAT IS THE OPTIMAL STRATEGY FOR URINARY TRACT INFECTIONS AND ASYMPTOMATIC BACTERIURIA IN PATIENTS WITH DIABETES MELLITUS?
It is not necessary to treat ASB in women with diabetes and, therefore, screening is not indicated.
A 7-day regimen of nitrofurantoin is recommended in diabetic women with cystitis.
For the treatment of diabetic men or diabetic women with a pyelonephritis or a UTI with systemic symptoms we refer to the sections "Men" and "Empirical treatment".

WHAT ARE THE BEST STRATEGIES FOR URINARY TRACT INFECTIONS AND ASYMPTOMATIC BACTERIURIA IN PATIENTS WITH A RENAL TRANSPLANTATION?
No recommendation can be made about screening and treatment of ASB in renal transplant patients. Experts are of the opinion that it may be appropriate to screen and start treatment for bacteriuria in the early postoperative period and up to 6 months post

	transplant.
	Prophylaxis given for *Pneumocystis jiroveci* with low-dose TMP-SMX reduces the risk of early UTI and is recommended for the first 6-9 months after renal transplantation.

	Treatment of UTI in renal transplant patients should be according to the general guidelines for treatment of complicated UTI, but in the first 3 months after transplantation empirical treatment with the combination of amoxicillin and ciprofloxacin is recommended.
	No recommendation can be made about changing immunosuppressive drugs from one class to another to prevent a recurrence of UTI.
	In the choice of antibiotics for treatment of recurrent UTI the increased risk for ESBL-related infections should be considered. Therefore, earlier culture results and fluoroquinolone use in the last < 30 days have to be checked.
	Removal of the urinary catheter should be done as soon as appropriate.
	In case of a UTI the JJ stent should be removed if possible and the urine must be cultured.
	In patients with recurrent UTI further investigations for anatomical abnormalities, bladder dysfunction or infection of the native kidneys should be initiated.
	It is important to note that several antimicrobial agents can interact with immunosuppressants, especially with calcineurine-inhibitors. Therefore, interactions have to be checked.

WHAT IS THE OPTIMAL TREATMENT IN PATIENTS WITH POLYCYSTIC KIDNEY DISEASE?	

	PET scan can be useful to identify a cyst infection. PET scan is considered positive when increased Fludeoxyglucose (FDG) uptake is demonstrated in at least one cyst.
	For the diagnosis of a cyst infection the following criteria should be used: - cyst infection is considered as definite in the presence of a cyst aspiration showing evidence of infection (neutrophils debris and/or micro-organism). - cyst infection is considered likely in the presence of all of the following features: fever (temperature >38.5°C for >3 days), abdominal pain (particularly a palpable area of renal or liver tenderness), increased C-reactive protein (CRP; >50 mg/L), and the absence of any significant recent intracystic bleeding or other causes of fever.
	Duration of treatment in case of a pyelonephritis in patients with autosomal dominant polycystic kidney disease is not different from that in other patients with a complicated

	UTI.
	In case of a cyst infection, it is recommended to start initially with ciprofloxacin, but to use the culture results to tailor treatment.
	A period of 4-6 weeks is recommended for the treatment of an infected cyst.
	In case of large (> 5 cm) infected cysts, early drainage is advised in combination with antibiotic treatment

	WHAT ARE THE POSSIBLE PREVENTION METHODS IN PATIENTS WITH RECURRENT UTI?
	For recurrent UTI in men or in patients with a catheter we refer to the section on UTI in men or in patients with a catheter.
	A differentiation must be made between persistence, relapse and reinfection of the UTI.
	In a persistent UTI the cause must be evaluated. In a relapse of the UTI the treatment can given for a longer period.
	All women can usually self-diagnose and self-treat a recurrent UTI.
	The use of ascorbic acid (vitamin C) is not recommended in the prevention of UTIs.
	In premenopausal women with recurrent UTI the following prophylaxis can be recommended to decrease the number of recurrent episodes: - daily or postcoital low dose antimicrobial therapy - cranberry products - *Lactobacillus crispatus* intravaginal suppository
	In postmenopausal women with recurrent UTI the following prophylaxis can be recommended to decrease the number of recurrent episodes: - daily or postcoital low-dose antimicrobial therapy - estrogens locally - oral capsules with *L rhamnosus GR-1* and *L. reuteri RC-14*
	Methenamine hippurate can be used for a maximum of 1 week to prevent UTI in patients without renal tract abnormalities.

WHAT ARE REASONABLE QUALITY INDICATORS (FOR INTERNAL QUALITY IMPROVEMENT) FOR EMPIRICAL ANTIMICROBIAL TREATMENT IN PATIENTS WITH A UTI?

Reasonable process quality indicators for empirical antibiotic therapy in patients with UTI to use in the Internal Medicine and Urology department are:

- Performance of urine culture.

- Prescription of treatment in accordance with guidelines.

- Tailoring of treatment on the basis of culture results.

- Switching to oral treatment when possible.

An additional four indicators to use only in the Internal Medicine department are:

- Treatment durations must follow the guidelines for the different patient groups.

- Prescription of treatment for men in accordance with guidelines.

- Replacement of catheters in patients with UTI.

 - Adaptation of the dosage on the basis of renal function.

It is recommended by the current Guideline committee that these process indicators may be used as internal Quality Improvement indicators in local QI projects. It is not recommended to use these indicators as performance indicators to compare hospitals.

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INTRODUCTION

The Dutch Working Party on Antibiotic Policy (SWAB; Stichting Werkgroep Antibiotica Beleid), established by the Dutch Society for Infectious Diseases (VIZ), the Dutch Society of Medical Microbiologists (NVMM) and the Dutch Society for Hospital Pharmacists (NVZA), coordinates activities in the Netherlands aimed at optimalization of antibiotic use, containment of the development of antimicrobial resistance, and limitation of the costs of antibiotic use. By means of the evidence-based development of guidelines, SWAB offers local antibiotic and formulary committees a guideline for the development of their own, local antibiotic policy.

PURPOSE AND SCOPE OF THE 2013 UPDATE OF THE GUIDELINES FOR THE TREATMENT OF COMPLICATED URINARY TRACT INFECTIONS

The objective of these guidelines is to update clinicians with regard to important advances and controversies in the antibiotic treatment of patients with complicated urinary tract infections (UTIs).

The guidelines described here cover the empirical antimicrobial therapy of adult patients (for this guideline ≥ 12 years) with a complicated UTI admitted to a hospital (emergency room or ward) in the Netherlands. Uncomplicated UTIs are treated predominantly by the general practitioner. For the relevant guidelines, see the recently updated Standard for Urinary Tract Infections of the Dutch Society of General Practitioners (NHG). We have tried to adhere to this standard insofar as possible. Urethritis and epididymitis are not included in this guideline. The Guidelines give a general therapy advice for all UTI with systemic symptoms because, at first presentation of a patient, it is not always possible to differentiate between an acute prostatitis, pyelonephritis or urosepsis. In addition, this differentiation has no consequences for the choice of empirical antimicrobial therapy. Apart from these general guidelines, we give specific advice for certain groups of patients separately.

KEY QUESTIONS

1. What is the optimal empirical treatment strategy concerning the choice of drug, also for patients with an increased risk for Extended-Spectrum Beta-Lactamase (ESBL)-producing Enterobacteriaceae?
2. What is the optimal duration of treatment?
3. What is the optimal treatment of urinary tract infection in men?
4. What is the optimal treatment of urinary tract infection in pregnant women? Is screening and treatment of asymptomatic bacteriuria in pregnant women recommended?

5. Is systemic antimicrobial prophylaxis necessary in patients with a urinary catheter? Is antimicrobial prophylaxis indicated at the time of catheter removal or replacement? What is the optimal management in patients with a catheter associated (CA)-UTI? What are the appropriate treatment durations for patients with CA-UTI?

6. What is the optimal treatment of urinary tract infection in diabetic patients? Is screening and treatment of asymptomatic bacteriuria in diabetic patients recommended?

7. What is the optimal treatment of urinary tract infection in renal transplant patients?

8. What is the optimal treatment of urinary tract infection in patients with polycystic kidney disease?

9. What are the optimal prevention methods in patients with recurrent UTI (rUTI)?

10. What are reasonable quality indicators for antibiotic therapy in patients with a UTI?

WHAT IS NEW IN THIS GUIDELINE COMPARED TO THE GUIDELINES OF 2006?

The Guideline committee has decided to add the following chapters:
1. Recommendations for patients with an increased risk for infection with Extended-Spectrum Beta-Lactamase (ESBL)-producing Enterobacteriaceae

2. Patients with renal transplantation.

3. Prevention methods in women with recurrent urinary tract infections.

4. Quality indicators for the antimicrobial treatment of a complicated UTI.

The Guideline committee has decided to remove the sections on:
1. Patients with bladder residual problems as a result of an obstructive or neurological disorder; these patients are discussed in the chapter on patients with a urinary catheter.

2. Patients with pyocystis; this is not a prevalent disease, therefore it is not necessary to describe it in a guideline.

DEFINITION OF COMPLICATED UTI

Differentiation between uncomplicated and complicated urinary tract infections (UTIs) has implications for the therapy, because the risks of complications or treatment failure are increased for patients with a complicated UTI.

The Guideline committee decided to use the following definition: an uncomplicated UTI is cystitis in a woman who is not pregnant, is not immunocompromised, has no anatomical and functional abnormalities of the urogenital tract, and does not exhibit signs of tissue invasion and systemic infection (1), (2).

All other UTIs are considered to be complicated UTIs. Exceptions for men are described in the section: What is the optimal treatment of urinary tract infections in men?

For the definition of uncomplicated pyelonephritis we follow the definition used in the recent updated guideline of the Infectious Disease Society of America (IDSA) for the treatment of uncomplicated UTI (also uncomplicated pyelonephritis) (3):

"Acute uncomplicated pyelonephritis is defined as pyelonephritis limited to premenopausal, nonpregnant women with no known urological abnormalities or comorbidities. It should be noted that women who are postmenopausal or have well-controlled diabetes without urological sequelae may be considered by some experts to have uncomplicated UTI, but a discussion of specific management of these groups is outside the scope of the present guideline and the IDSA guideline" (3).

Complicated pyelonephritis is defined as pyelonephritis in all other patient groups.

All UTIs which are not uncomplicated are considered to be complicated UTIs.

In general, a differentiation can be made in two patient groups:

1. UTI with systemic symptoms as fever or delirium.
2. UTI in a host with an increased chance for a complicated course: i.e. all men, pregnant women, patients with anatomical or functional abnormalities of the urinary tract, with a urinary catheter, with renal diseases (polycystic kidney disease, renal stones, renal transplant patients), and/or with other concomitant immunocompromising diseases such as, for example, diabetes.

In some guidelines, older women with uncomplicated UTI are considered to have a complicated UTI and are therefore treated for a longer period than younger patients. However, in a Cochrane review, 15 studies (1644 elderly women) were identified comparing single dose, short-course (3-6 days) and long course (7-14 days) antibiotic treatment for uncomplicated symptomatic UTI in elderly women. The conclusion was that, on the basis of the evidence available at present, a duration of antibiotic treatment of 3-6 days could be sufficient for treating uncomplicated UTIs in elderly women (4), (5). Therefore, the Guideline committee decided that patients older than 65 years are not considered as patients with an increased chance of a complicated course, unless they belong to one of the other above-mentioned patient groups with an increased risk for the development of complications of a UTI.

Recurrent UTIs are recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least 3 UTIs/year or 2 UTIs in the last 6 months.

Methodology

This guideline was drawn up according to the recommendations for evidence-based development of guidelines (6), (Evidence-Based Richtlijn-Ontwikkeling (EBRO) and Appraisal of Guidelines Research and Evaluation (AGREE), www.agreecollaboration.org). The guidelines are derived from a review of literature based on the 9 key questions concerning the treatment of UTI. Studies were assigned a degree of evidential value according to the handbook of the Dutch Institute for Healthcare Improvement (Centraal Begeleidingsorgaan/Kwaliteitsinstituut voor de gezondheidszorg, CBO) (CBO. Evidence-based Richtlijnontwikkeling, handleiding voor werkgroepleden. Utrecht: CBO; 2007). Conclusions were drawn, completed with the specific level of evidence, according to the grading system adopted by SWAB (Table 1 and 2). The only exception concerns Nethmap, an annual report from which the resistance surveillance data were used. The Guideline committee cannot give Nethmap a level of evidence and decided to use an asterix (*), but is of the opinion that the results can be given substantial weight, since the surveillance data described in Nethmap cover 30% of the Dutch population. Subsequently, specific recommendations were formulated.

In order to develop recommendations for the optimal treatment of UTI, the literature was searched for the key questions. For each question a literature search was performed in the PubMed database (January 1966 to January 2012) as well as in the Cochrane Register of Controlled Trials (CENTRAL). For resistance surveillance data NethMap 2011 was used, and for the interpretation of susceptibility test results, in addition, reports of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were used. When scientific verification could not be found, the guideline text was formulated on the basis of the opinions and experiences of the members of the Guideline committee.

Preparation of the guideline text was carried out by a multidisciplinary committee consisting of experts, delegated from the professional societies for infectious diseases (VIZ), medical microbiology (NVMM), hospital pharmacists (NVZA), urology (NVU), gynaecology (NVO), nephrology (NFN) and general practice (NHG). After consultation with the members of these professional societies, the definitive guideline was drawn up by the delegates and approved by the board of SWAB.

LEVEL OF EVIDENCE

Table 1. Methodological quality of individual studies

Evidence level	Definition
A1	Systematic review of at least two independent A2 level studies
A2	Randomised controlled trial (RCT) of sufficient methodological quality and power or Prospective cohort study with sufficient power and with adequate confounding corrections
B	Comparative study lacking the same quality as mentioned in A2 (including patient-control and cohort studies) or Prospective cohort study lacking the same quality as mentioned in A2, retrospective cohort study or patient-control study
C	Non-comparative study
D	Evidence based on the opinion of members of the Guideline committee

Table 2. Levels of evidence (CBO. Evidence-based Richtlijnontwikkeling, handleiding voor werkgroepleden. Utrecht: CBO; 2007)

Evidence level	Definition
Level 1	Study of level A1, or at least two independent studies of level A2
Level 2	One study of level A2, or at least two independent studies of level B
Level 3	One study of level B or C
Level 4	Expert opinion

WHAT IS THE OPTIMAL EMPIRICAL TREATMENT STRATEGY CONCERNING THE CHOICE OF DRUG?

Search strategy

Resistance data were obtained from the report Nethmap 2011 (www.swab.nl) and from the Infectious Diseases Surveillance Information System on Antimicrobial Resistance (ISIS-AR). For other articles the databases of Pubmed and the Cochrane Library were searched.

Keywords: urinary tract infection AND treatment

Limits: Last 2 years for Pubmed (IDSA guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women were published in 2011) (3)), English, adults, humans, clinical trials, guideline, meta-analysis, RCT

Pubmed: 101 results, all titles screened, 1 abstract screened, 1 additional article included.

Cochrane Library: 35 results, all titles screened, 0 abstracts screened, 0 reviews included.

Articles on antimicrobial agents which are not available in the Netherlands, or on the treatment of uncomplicated UTIs, were excluded.

Literature overview

CAUSATIVE MICRO-ORGANISMS AND RESISTANCE

Although there is a greater diversity of causative micro-organisms in complicated UTIs than in uncomplicated UTIs, *Escherichia coli* remains in most cases of complicated UTIs the causative organism. Using the Infectious Diseases Surveillance Information System on Antimicrobial Resistance (ISIS-AR) and data selected from patients in the urology and internal medicine departments of 19 Dutch hospitals (Spoorenberg et al. submitted), we found the following causative micro-organisms: *E. coli* (45-62%), Enterococcus spp. (7-15%), *Proteus mirabilis* (6-8%), and *Klebsiella pneumoniae* (7-9%).

The most useful resistance data on the above-mentioned micro-organisms were provided by the report "Nethmap" (www.swab.nl) and ISIS-AR.

In Nethmap, information has been collected on the prevalence of resistance against antibiotics in the Netherlands in the period up to 2010. The interpretation of susceptibility test follows the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). For treatment of a UTI with systemic symptoms the antimicrobial drug must achieve high concentrations in urine, kidney tissue and prostate. Therefore, nitrofurantoin and fosfomycin are not registered for the treatment of a UTI with systemic symptoms.

On the basis of resistance data from 2009/2010 (Nethmap 2011), *E. coli* isolated from patients presenting to unselected outpatient hospital departments have high resistance percentages for amoxicillin, co-amoxiclav, trimethoprim (TMP) and of trimethoprim-sulfamethoxazole (TMP-SMX) (Table 1). For ciprofloxacin the resistance percentage was 17% for *E. coli* isolated from patients presenting to unselected outpatient hospital departments (not urology or intensive care units), but in isolates from patients from urology departments it was 25%. The most important risk factor for ciprofloxacin resistance was the use of this agent in the last 6 months (7) (odds ratio (OR) 17.5, 95% confidence interval (CI) 6.0-50.7). The resistance percentages of norfloxacin, levofloxacin and moxifloxacin are similar to those of ciprofloxacin.

For intravenous antibiotics the resistance percentages of *E.coli* isolated from patients presenting to unselected outpatient hospital departments (not urology or intensive care units) are shown in Table 1.

Table 1 Data from Nethmap (SWAB) and *the Infectious Diseases Surveillance Information System on Antimicrobial Resistance (ISIS-AR) of 32,785 (first urine) isolates from 26,711 patients (complicated UTI was defined as a urine-isolate from a hospitalised patient).

Escherichia coli Antimicrobial agent	Resistance percentages 2009/2010
amoxicillin	48%
ciprofloxacin (GP)	10%
ciprofloxacin (unselected departments)	17%
ciprofloxacin (urology)	25%
co-amoxiclav	23%
nitrofurantoin	3%
trimethoprim	33%
trimethoprim-sulfamethoxazole (TMP-SMX)	31%
cefuroxime (2nd generation cephalosporin)	13%

3rd generation cephalosporins (cefotaxime)	5%
piperacilin-tazobactam	8%
imipenem and meronepenem	0.03%
gentamicin	5%
All Enterobacteriaceae*	**2010**
ciprofloxacin	11-13%
cefuroxime	12-23%
gentamicin	5-6%
amoxicillin + third-generation cephalosporins	6-7%
co-amoxiclav + gentamicin	< 5%
cefuroxime +gentamicin	< 5%

GP = general practitioner

Other uropathogens (*K. pneumoniae, P. mirabilis)* showed (besides their intrinsic resistance) comparable resistant patterns, with the exception of co-amoxiclav for which the resistance percentages were 11-12%.

To evaluate the adequacy of the SWAB guideline for antimicrobial treatment of complicated UTI from 2006, a study was performed in the urology and internal medicine departments of 19 Dutch hospitals. Patients from these hospitals were representative for the patient population in Dutch hospitals since university, teaching and non-teaching hospitals located throughout the Netherlands participated. We considered a guideline-recommended or prescribed empirical therapy to be *adequate* if the cultured uropathogen was reported to be susceptible to the recommended or prescribed antibiotic. A guideline-recommended or prescribed empirical therapy was considered to be *inadequate* in case of resistance or inadequate coverage of the cultured uropathogen.

We evaluated all patients with a complicated UTI without other conditions (n=810). The combination of amoxicillin and gentamicin was the most adequate (inadequate treatment rate

of 6%) Second-generation cephalosporins had the highest inadequate treatment rate, i.e. 24% (inadequate coverage 16%, resistance 8%), the inadequate treatment rate for third-generation cephalosporins was 18% (inadequate coverage 16%, resistance 2%), for co-amoxiclav 14% (inadequate coverage 7%, resistance 7%) and for ciprofloxacin it was 23% (inadequate coverage 9%, resistance 14%). *Enterococcus* species usually have low virulence, and it is debatable whether they should be covered in empirical therapy. Leaving out enterococci (7% of all uropathogens) decreased the inadequate treatment rate for some regimens: third-generation cephalosporins were now adequate in 10% of cases. All other regimens remained inadequate in > 10% of patients (Spoorenberg et al., submitted).

Conclusions

Level*	*Escherichia coli* is the causative organism in most cases of complicated UTIs.
Level*	*E. coli* isolated from patients presenting to unselected outpatient hospital departments (not urology or intensive care units) have high resistance percentages to amoxicillin, co-amoxiclav, trimethoprim and trimethoprim-sulfamethoxazole (TMP-SMX).
Level*	*E. coli* isolated from patients presenting to unselected outpatient hospital departments (not urology or intensive care units) have to ciprofloxacin a resistance rate of 17%, but in isolates from patients from general practice offices this is 10% and in isolates from urology departments it is 25%. The resistance percentages of norfloxacin, levofloxacin and moxifloxacin are similar to those of ciprofloxacin.
Level*	*E. coli* isolated from patients presenting to unselected outpatient hospital departments show the following resistance percentages to intravenous antimicrobial agents: gentamicin 8%, second-generation cephalosporin 13%, all third-generation cephalosporins 5%, and "last line" antimicrobial agents: piperacilin-tazobactam 8%, imipenem and meronepenem 0.03%.
Level 3	Evaluating the SWAB guideline from 2006, the combination of amoxicillin and gentamicin is the most adequate (inadequate treatment rate of 6%). Second-generation cephalosporins had the highest inadequate treatment rate, i.e. 24%; the inadequate treatment

	rate for third-generation cephalosporins was 18%, for co-amoxiclav 14% and for ciprofloxacin it was 23%. Leaving out enterococci decreased the inadequate treatment rate, third-generation cephalosporins were now adequate in 10% of cases [(Spoorenberg submitted) C].

Other considerations

Optimal therapy for UTI with systemic symptoms depends on the severity of illness at presentation, as well as local resistance patterns and specific host factors (such as allergies). In addition, urine culture and susceptibility testing should be performed, and initial empirical therapy should be tailored and followed by (oral) administration of an appropriate antibiotic agent on the basis of the isolated uropathogen.

Collateral damage, a term describing ecological adverse effects of antimicrobial therapy, such as the selection of drug-resistant organisms and colonization or infection with multidrug-resistant organisms, has been associated with the use of broad-spectrum antimicrobial agents (3). Therefore, last line antimicrobial agents like piperacilin-tazobactam, imipenem and meropenem are not recommended as first choice empirical therapy.

EMPIRICAL TREATMENT: DRUG OF CHOICE

In the recent updated IDSA guidelines for the treatment of uncomplicated UTI, it is recommended that the resistance percentages of causative micro-organisms must be below 20% to consider an agent suitable for empirical treatment of a lower UTI and must be below 10% for treatment of an upper UTI. Considering the resistance percentages of amoxicillin, co-amoxiclav, TMP and TMP-SMX, we can conclude that these agents are not suitable for the empirical treatment of pyelonephritis in a normal host and, therefore, also not for treatment of all other complicated UTIs. The same applies to ciprofloxacin and other fluoroquinolones in patients from the urology departments.

Therefore, patients with a UTI with systemic symptoms requiring hospitalization should be initially treated with an intravenous antimicrobial regimen, such as an aminoglycoside, with or without amoxicillin or a second generation cephalosporin; or a third generation cephalosporin or extended-spectrum penicillin, with or without an aminoglycoside. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results (3). These recommendations are not only suitable for pyelonephritis but for all complicated UTIs.

In view of the high degree of resistance, in particular among patients admitted to the department of urology, fluoroquinolones are not automatically suitable as empirical antimicrobial therapy, especially when the patient has used ciprofloxacin in the last 6 months (7). Therefore, this agent can only be recommended as empirical treatment when the patient is not seriously ill and it is considered safe to start initial oral treatment or if the patient has had an anaphylactic reaction to β-lactam antibiotics.

Oral ciprofloxacin (500 mg twice daily, with or without an initial 400-mg dose of intravenous ciprofloxacin) is an appropriate choice for therapy in patients not requiring hospitalization when the prevalence of resistance of community uropathogens to fluoroquinolones is not known to exceed 10%. If the prevalence of fluoroquinolone resistance is thought to exceed 10%, an initial 1-time intravenous dose of a long-acting antimicrobial, such as 1 g of ceftriaxone or an aminoglycoside, is recommended (3) while resistance data are pending. However, a study in women with uncomplicated pyelonephritis showed there were no differences in the clinical success rates of women with a ciprofloxacin susceptible *E. coli* compared to those with a ciprofloxacin resistant *E. coli* (8). After a follow-up of 4-7 days, and 14-21 days after completion of therapy, the clinical success rates were 87.0% vs. 76.9% (P=0.14) and 98.6% vs. 94.9% (P=0.18) for the ciprofloxacin susceptible and ciprofloxacin resistant groups, respectively. Therefore, it seems that in women with uncomplicated pyelonephritis, even in higher percentages of ciprofloxacin resistance, ciprofloxacin can be prescribed as an empirical treatment (8).

Because there is only a small chance that cross-hypersensitivity exists between penicillin derivatives and cephalosporins (9), the Guideline committee is of the opinion that in the event of hypersensitivity for penicillin derivatives (a rash but not a systemic anaphylactic reaction), a 3rd generation cephalosporin can still be prescribed. If β-lactam antibiotics have caused anaphylaxis in the past, a fluoroquinolone is recommended.

If the clinical condition of the patient allows it and if the patient does not vomit, then oral therapy can be prescribed (10), (11). If the patient no longer has symptoms, there is no indication for follow-up cultures.

When to cover ESBL in the empiric regimen?

In the SWAB guidelines for antibacterial therapy of adult patients with sepsis (SWAB 2010) the following recommendations are made:

1. In (departments of) hospitals with a high prevalence of Extended-Spectrum Beta-Lactamase (ESBL)-producing Enterobacteriaceae, a carbapenem with anti-pseudomonal activity (imipenem/meropenem) should be chosen as empirical antibacterial therapy if an infection caused by ESBL-producing bacteria is suspected. As no critical prevalence level has been identified, risk factors of ESBL infection should be used to target empirical therapy on an individual patient basis.

2. In patients with community-acquired and nosocomial sepsis and prior use of cephalosporins or quinolones within 30 days before presentation and/or colonized with ESBL-producing micro-organisms, the antibacterial regimen should also be active against ESBL-producing micro-organisms. This can be achieved by the addition of an aminoglycoside to the regimen or by the use of a carbapenem.

The background of these recommendations is the assumption that inadequate empirical coverage will result in a delay of start of effective therapy, and a resulting excess mortality. For patients with bacteremia caused by ESBL-producing Enterobacteriaceae this assumption proved to be correct (12). However, in this meta-analysis the increased relative risk for mortality was not corrected for confounding. In general, mortality is low in patients with UTI, and for UTI patients no excess mortality could be demonstrated for ESBL compared to non-ESBL producing strains (13), (14). In a Dutch study on antibiotic treatment and outcome in patients with ESBL-producing Enterobacteriaceae bacteremia, urosepsis and intra-abdominal infections were major sources of bacteremia. After correcting for confounding, adequacy of antibiotic treatment within 24 hours was not associated with increased 30-day mortality (WC Rottier et al.. Submitted).

For these reasons, the Guideline committee recommends to cover ESBL in the initial treatment only in patients who are colonized with ESBL-producing micro-organisms. In that case, the resistance pattern of the ESBL strain should guide empirical therapy.

WHAT IS OPTIMAL EMPIRICAL ANTIMICROBIAL AGENT?	
Recommendation	In patients suspected of having a complicated UTI, a urine culture and susceptibility test should always be performed.
Recommendation	Amoxicillin, co-amoxiclav, TMP and TMP-SMX are not suitable for the empirical treatment of complicated UTI.
Recommendation	The combination of amoxicillin + an aminoglycoside, a 2nd generation cephalosporin + an aminoglycoside or a 3rd generation cephalosporin intravenously can be recommended as empirical treatment of complicated UTI.
Recommendation	Ciprofloxacin can only be recommended when the whole treatment is given orally, when patients do not require hospitalization or when the patient has an anaphylaxis for beta-lactam antibiotics, provided that the local resistance percentages are < 10%.
Recommendation	Ciprofloxacin and other fluoroquinolones are not suitable for the empirical treatment of complicated UTI in patients from the urology department or when patients have used fluoroquinolones in the last 6 months.
Recommendation	If the prevalence of fluoroquinolone resistance is thought to exceed 10%, an initial 1-time intravenous dose of a long-acting antimicrobial, such as a 3rd generation cephalosporin or an aminoglycoside, is recommended while resistance data are pending.
Recommendation	If the prevalence of fluoroquinolone resistance is thought to be higher than 10% and the patient has contra indications for 3rd generation cephalosporins or an aminoglycoside, ciprofloxacin can be prescribed as an empirical treatment in women with an uncomplicated pyelonephritis.
Recommendation	In the event of hypersensitivity to penicillin, a 3rd generation cephalosporin can still be prescribed, with the exception of systemic anaphylaxis in the past.
Recommendation	In patients with a UTI with systemic symptoms empirical treatment should cover ESBL in the initial treatment only in patients who are colonised with ESBL-producing micro-organisms. The resistance pattern of the ESBL strain should

	guide empirical therapy.
Recommendation	When the results of the urine culture are known, therapy must be adjusted and if possible narrowed down. If the clinical condition of the patient allows it and if the patient does not vomit, oral therapy can be prescribed.
Recommendation	If the patient no longer has symptoms, there is no indication for follow-up cultures.

WHAT IS THE OPTIMAL TREATMENT DURATION OF ANTIMICROBIAL TREATMENT OF PYELONEPHRITIS, FEBRILE URINARY TRACT INFECTION OR UROSEPSIS?

Search strategy

Databases were Pubmed and the Cochrane Library.

Keywords: [urinary tract infection OR urosepsis OR pyelonephritis] AND treatment duration

Limits: English, adults, humans, clinical trials, guideline, meta-analysis, RCT, review, last 25 years.Pubmed: 245 results, all titles screened, all abstracts screened, 20 articles included.

Cochrane Library: no results.

Articles about antimicrobial agents which are not available in the Netherlands, or on the treatment of uncomplicated UTIs, were excluded.

Optimal treatment duration in women

Traditionally, the standard antimicrobial treatment duration of acute pyelonephritis in women was 6 weeks until 1987 when Stamm et al. showed that a 2-week regimen is equally effective (15). Since then, based on additional trials, current guidelines advocate a standard duration of about 2 weeks, whereas in special groups this can be limited to 5-7 days when using oral fluoroquinolones (3). These trials have already been reviewed (3), (16) and will be briefly discussed in this chapter.

Talan et al. clearly demonstrated that a 7-day course of ciprofloxacin is sufficient in young, healthy women with acute pyelonephritis (17). This double-blind, multicenter randomized controlled trial (RCT) compared a 7-day regimen of oral ciprofloxacin 500 mg twice daily (n=128 included in the analysis) with a 14-day regimen of TMP-SMX 160/800mg twice daily (n=127 included in the analysis) for treatment of otherwise healthy women with mild to moderate pyelonephritis. Ciprofloxacin therapy had significantly higher microbiological (99% vs. 89%, respectively) and clinical (96% vs. 83%, respectively) cure rates (95% CI for difference, 0.04-0.16; P=0.004) compared to the TMP-SMX regimen, but this was mainly explained by differences in baseline resistance. Bacteremia (all *E. coli*) was present in 5.5% of the patients. The median age in this study was 24 (range 18-58) years and all patients had uncomplicated acute pyelonephritis.

The results of another trial showed similar efficacy between 7 and 14 days ciprofloxacin in women with acute uncomplicated and complicated (diabetes and/or known structural or functional abnormalities of the urinary tract) pyelonephritis. However, only 4 women with a complicated pyelonephritis were included. Among 156 women [median age 43 (range 18-89) years], 27% with bacteremia] cure rates for the 7-day regimen (n=73) and for the 14-day regimen (n=83) were 97.3% and 96.4%, respectively (18).

Additional evidence for a one-week regimen of fluoroquinolones as an effective and safe treatment for healthy young women was provided by another study (19), (20). These articles describe one double-blind, randomized multicenter trial, which included both men and women with complicated UTI (without fever) and acute pyelonephritis (mean age 39 years). A total of 1109 subjects (39% men, 61% women) were enrolled; 619 with confirmed diagnosis of acute pyelonephritis or complicated UTI. Subjects received either levofloxacin 750 mg intravenously or orally once daily for 5 days or ciprofloxacin 400 mg intravenously and/or ciprofloxacin 500 mg orally twice daily for 10 days. At end of therapy, eradication rates in the modified intent-to-treat population were 79.8% for levofloxacin and 77.5% for ciprofloxacin-treated subjects (95% CI, -8.8% to 4.1%). In the microbiologically evaluable population, eradication rates were 88.3% for levofloxacin and 86.7% for ciprofloxacin-treated subjects (95% CI, -7.4% to 4.2%). However, it is not possible to draw conclusions about men from this study, because most men did have a UTI without fever. Subgroup analysis of predominantly women with acute pyelonephritis (19) lend additional support that an oral 5-day regimen of once-daily levofloxacin 750 mg or a 10-day regimen of ciprofloxacin twice daily is effective for mild to moderate pyelonephritis, even in those with bacteremia or complicating factors like obstruction or the presence of a urinary catheter.

The finding that a one-week regimen of fluoroquinolones is both efficacious and safe for treatment of mild to moderate acute pyelonephritis was further supported by a randomized controlled open label study (majority of patients were female) demonstrating similar outcomes (clinical and bacteriological cure rate of 93-94%) when comparing levofloxacin 250 mg once daily for 7-10 days (n=89), ciprofloxacin 500 mg twice daily for 10 days (n=58) and lomefloxacin 400 mg once daily for 14 days (n=39). The mean age in this study was 41 years. The authors noted that in severe invasive infections, such a low dose of levofloxacin may result in marginal tissue and blood concentrations (21).

A population-based cohort of 1084 non-pregnant women (18-65 years) with acute pyelonephritis in an ambulatory care setting showed that, independent of the drug administered (either a fluoroquinolone or TMP-SMX), an increased chance of treatment failure was present whenever the treatment lasted less than 10 days. Furthermore, treatment outcomes were affected by the subject's age. At age 20 years, treatment with a fluoroquinolone resulted in a reduced probability of treatment failure compared with TMP-SMX (OR, 0.56; 95% CI, 0.33-0.97). At age 60 years, there was no difference in the probability of treatment failure (OR, 1.61; 95% CI, 0.82-3.16) (22).

Optimal treatment duration in men

There is an apparent lack of studies on optimal treatment duration of acute pyelonephritis or febrile UTI in men. We found only one study directly comparing different treatment durations

in men (23). In this open, prospective and randomized trial, 72 men with community-acquired febrile UTI (without a chronic indwelling catheter) were treated with ciprofloxacin 500 mg twice daily for two or four weeks. All responded successfully with resolution of fever and symptoms. There was no significant difference in bacteriological cure rate 2 weeks post-treatment between patients treated for 2 or 4 weeks (89% vs. 97%, 95% CI for difference in proportions –3% to 19%), nor after 1 year (59% versus 76%, 95% CI –5% to 39%). The cumulative clinical cure rate after 1 year was 72% and 82%, respectively (95% CI –10% to 30%). Recurrences after 1 year comprised asymptomatic bacteriuria (ASB) (48%), symptomatic lower UTI (23%) and another episode of febrile UTI (29%). A tendency towards more recurrences in the 2-week group could be attributed to a larger proportion of men with urological lesions requiring surgical interventions (26% vs. 12%) in that group. The results should be interpreted with some caution given the wide confidence interval for the differences in cure rate; however, this study suggests a 2-week course of ciprofloxacin 500 mg twice daily may be an adequate treatment for febrile UTI in men.

Another Swedish study provided additional support for a 2-week regimen of oral fluoroquinolones in men (24). In this randomized, double-blind trial, adult men and women with a presumptive diagnosis of acute pyelonephritis (defined as febrile UTI) were randomly assigned to receive a 14-day course of oral treatment with either norfloxacin 400 mg twice daily or cefadroxil 1g twice daily. Of 197 patients enrolled, 16 (29.5%) men were treated with norfloxacin and 12 (21.1%) with cefadroxil. In this subgroup, a 14-day regimen of norfloxacin was highly effective, regardless the presence of bacteremia or complicating factors such as diabetes mellitus or urinary tract abnormalities, with significantly higher bacteriological cure rate than with cefadroxil, both at 3-10 days (100% vs. 73%, respectively) and up to 2 months after cessation of treatment (88% vs. 75%, respectively).

The same results in men were obtained from a third Swedish trial which used step-down treatment; initial intravenous treatment with cefuroxime was followed by either norfloxacin 400 mg twice daily (n=83, 42% men) or ceftibuten 200 mg twice daily (n=85) for 10 days (25). The clinical and bacteriological cure rates were 96% and 89% for the norfloxacin group versus 89% and 75% for the ceftibuten group.

Conclusions

Level 3	A 5-day course of therapy with levofloxacin, administered at a dose of 750 mg once daily, is noninferior to a 10-day course of therapy with ciprofloxacin for the treatment of acute pyelonephritis or complicated UTI in women [(19) A2; (20) A2].
Level 2	Levofloxacin 250 mg once daily for 7-10 days, ciprofloxacin 500 mg twice daily for 10 days and lomefloxacin 400 mg once daily for 14 days result in similar clinical and bacteriological cure rates of 93-94% [(21) B]. Ciprofloxacin 7 and 14 days in women with acute uncomplicated and complicated (n=4) pyelonephritis showed similar cure rates [(18) A2].
Level 2	A 7-day ciprofloxacin regimen is associated with greater bacteriologic and clinical cure rates than a 14-day TMP-SMX regimen in the treatment of acute uncomplicated pyelonephritis in women, especially in patients infected with TMP-SMX resistant strains [(17) /id} A2] and in young women (aged ≤ 20 years) [(22) B].
Level 3	An increased chance of treatment failure is present in non-pregnant women when the treatment lasts less than 10 days, independent of the drug administered [(22) B].
Level 2	No difference was found in clinical or microbiological cure rate in men with community-acquired febrile UTI after treatment of ciprofloxacin 500 mg twice daily for 2 or 4 weeks [(23) B].
Level 2	The bacteriological cure rate was significantly higher in adult men and women with febrile UTI who were treated with a 14-day course norfloxacin 400 mg twice daily compared to cefadroxil 1g twice daily [(24) B]. After initial intravenous treatment with cefuroxime, the clinical and bacteriological cure rates were higher in patients with a febrile UTI treated with norfloxacin (2 x 400 mg) (42% men) compared to treatment with ceftibuten 2x 200 mg for 10 days [(25) B].

Other considerations

There are no published studies on the efficacy of amoxicillin, co-amoxicilav or TMP-SMX less than 14 days for the treatment of acute pyelonephritis. Therefore, when these agents are used for the treatment of acute pyelonephritis, the standard treatment duration should be 14 days according to Stamm et al. (15).

It should be emphasized that the above-mentioned conclusions on treatment durations less than 14 days are based upon studies that almost exclusively included young (≤ 50 years or premenopausal) women without any comorbidities. Thus, in patients with complicated disease, those with comorbidities, the elderly and in men, the standard duration of therapy remains 14 days.

A prospective observational cohort study from the Netherlands, including consecutive non-pregnant adults with febrile UTI study visiting primary health care centers (PHCs) and emergency departments (EDs), in which the treatment duration was determined by the treating physician, with a mean treatment duration of 10-14 days, supported this treatment duration (26). Median age was 63 [IQR 42-77] years, 34% was male and 58% had comorbidity, all characteristics were comparable between both groups. Bacteremia was present in 10% of the outpatients and 27% of the inpatients. During follow-up, 8 (5%) of PHC group were hospitalized because of suspected deteriorating sepsis, progressive illness or persistent symptoms; none of them required ICU admission nor were there any attributable deaths. Clinical cure rates at 30 days were high in both groups (90% in PHC and 89% in the ED group, respectively) and persistent at least until 3 months follow-up. Thus, the outcome of this group of patients treated with oral ciprofloxacin on an outpatient basis suggests that selected adults with febrile UTI can be safely treated **at home** using a 10-14 day regimen of oral fluoroquinolones, including men, the elderly, and patients with comorbidity or bacteremia.

Currently, there is an ongoing trial among elderly and more complicated cases with pyelonephritis that compares 7 and 14 days of ciprofloxacin (27). The data of this trial are expected in 2013.

Since levofloxacin and other fluoroquinolones are also active against gram-positive micro-organisms, and are therefore unnecessarily broad, the Guideline committee is of the opinion that only ciprofloxacin can be recommended for the treatment of a UTI.

Finally, the results of the mentioned RCTs with fluoroquinolones (17), (21), (19), (20), (18) are in contrast with those of Carrie et al. (22), which showed that failure rate was increased when treatment duration was shorter than 10 days. However, because this study (which evaluates healthcare claims) has a lower level of evidence than the RCTs, the Guideline committee has decided to follow the recommendations of the IDSA guideline (3) and will

recommend a treatment duration of 7 days for ciprofloxacin, and 10-14 days for TMP-SMX or beta-lactams.

What is the optimal treatment duration?	
Recommendation	Women with acute uncomplicated pyelonephritis should be treated for 7 days when treated with ciprofloxacin.
Recommendation	Women with acute uncomplicated pyelonephritis should be treated for 10-14 days when treated with TMP-SMX or a beta-lactam.
Recommendation	Women with acute complicated pyelonephritis or other complicated UTIs should be treated for 10-14 days.
Recommendation	Men with complicated UTIs should be treated for 14 days.

WHAT IS THE OPTIMAL TREATMENT OF URINARY TRACT INFECTIONS IN MEN?

Search strategy

"Anti-Infective Agents"[Mesh]) OR "Anti-Infective Agents"[Pharmacological Action])) OR (antibiotic*))) AND (((("Prostatitis"[Mesh])) OR (prostatitis[tiab])) AND ("bacterial infections"[MeSH Terms] OR bacterial infection[Text Word])

Limits: English, Clinical trials.

Pubmed: 23 results, 5 additional articles included.

Literature overview

With the exception of cystitis in healthy young men, lower UTIs in men are considered to be complicated UTIs (28), (29).

Therefore, UTIs in men can be divided into three groups:

1. **Cystitis**

   It seems likely that men, like women, can acquire an uncomplicated cystitis. In these cases the typical complaints of frequency and dysuria are the predominant symptoms. In young men (< 40 years) with a UTI without signs or symptom of systemic disease, with no medical history and no previous lower urinary tract symptoms (LUTS) the presence of a structural or functional disorder is unlikely. Without a history or findings at physical examination that suggest a complicating factor, the UTI may be considered as uncomplicated (28), (30), (31). In the hospital setting, this group of patients will be encountered only occasionally. Therefore, this rare group will not be discussed in this guideline and we refer to the updated Guideline for Urinary Tract Infections of the Dutch College of General Practitioners (NHG).

2. **UTI with systemic symptoms (including acute prostatitis)**

   Since it not always possible in clinical practice to differentiate between acute prostatitis, pyelonephritis and urosepsis, the Guideline committee has decided to use the term UTI with systemic symptoms.

3. **Chronic bacterial prostatitis**

   Chronic bacterial prostatitis is not an acute disease and usually presents with more-prolonged (≥ 3 months) urogenital symptoms. It may be difficult to differentiate this condition from non-bacterial prostatitis. It may result in recurrent UTIs, with identical cultures. With increasing bacterial resistance in the urological population, especially against the quinolones, empiric antibiotic treatment should be avoided. Because urogenital pain is too often treated with antibiotics (32), we need to emphasize that a positive culture is the mainstay of the diagnosis and will give direction to the proper treatment. This guideline will address only acute and chronic bacterial prostatitis.

Prostatitis syndrome

Prostatitis is a group of diseases or syndromes, most of which do not have a bacterial etiology. It is estimated that no more than 10% of what is generally referred to as prostatitis, is a bacteriological prostatitis (33), (34), (35). Clinical distinction of the groups is rather difficult. The traditional classification of prostatitis recognizes acute and chronic bacterial prostatitis, non-bacterial prostatitis and prostatodynia. Over the years this classification has been adjusted, indicating the latter two groups as Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) type III A and B, respectively (36) and adding a fourth group of asymptomatic prostatitis.

Choice of drug

As the result of the physical properties of the prostate, as well as their pharmacological properties (high lipid solubility, low protein binding), fluoroquinolones, and to a lesser extent trimethoprim, achieve the highest concentrations in the prostate (37), (38). Nitrofurantoin has insufficient tissue penetration in the prostate (39), (40). No data are available for other agents.

Acute bacterial prostatitis

In probably more than half of men with a UTI there is a coexistence of a prostato-vesiculitis (41), (42). Besides the symptoms of a concurrent cystitis, a prostatitis is characterized by urogenital pain or annoyance. In a prospective study in 70 adult men with fever and symptoms or signs of a UTI and a positive urine culture, the prostate-specific antigen (PSA) and prostatic volume were measured and a digital rectal examination was performed, and were re-established on follow-up (41). The PSA was elevated in 83% of patients, but rapidly decreased. The mean prostatic volume decreased by 31% during follow-up.

Chronic bacterial prostatitis

Chronic bacterial prostatitis may give rise to recurrent lower UTIs. In an open randomized trial in 109 male patients with recurrent UTIs, 4-6 weeks treatment with norfloxacin was more effective than treatment with TMP-SMX: bacteriological eradication was estimated shortly after finishing therapy, and occurred in 93% in the norfloxacin group and in 67% in the TMP-SMX group (43). However, these differences were due to differences in resistance rate of the causative micro-organisms, which were 3% for norfloxacin and 33% for TMP-SMX. No differences were found in clinical success and microbiological eradication rates after 4 weeks treatment with levofloxacin versus ciprofloxacin (44), levofloxacin vs. prulifloxacin (45) or lomefloxacin vs. ciprofloxacin (46).

In an old (1978) randomized study of 29 men with culture-proved bacterial prostatitis, TMP-SMX, 2 tablets twice daily for 90 days, and minocycline-hydrochloride (a tetracycline) 100 mg twice daily for 28 days, seemed equally effective in controlling symptomatic recurrence during the 12 months after cessation of therapy. However, unacceptable systemic side effects were seen in the patients receiving minocycline 100 mg twice daily. Alteration of the dose to 4 x 50 mg abolished this problem (47).

Duration of treatment of chronic prostatitis

In a double-blind trial, 42 men with documented recurrent UTIs (rUTIs), which can be considered as chronic bacterial prostatitis, and an active UTI due to a member of the *Enterobacteriaceae* family that was susceptible to TMP-SMX, were randomized to receive 2 weeks TMP-SMX plus 4 weeks placebo, or 6 weeks TMP-SMX (48). All patients were periodically evaluated until week 12. In the 2-week treatment group, 6 patients were cured, and 13 had a reinfection or relapse. In the 6-week treatment group, 13 patients were cured, and 6 had a reinfection or relapse (P=0.019). Another double-blind trial randomized 30 men with chronic bacterial prostatitis to receive TMP-SMX 480 mg bid for 10 days or 6 weeks (42). Cure rates were higher in the 6-week group (9/15) than in the 10-day group (3/15), although the difference was not significant (P=0.06).

It has been shown that cure rates will drop with extended follow-up of 6 months or longer (49).

Observational studies of the treatment of <u>chronic</u> bacterial prostatitis with quinolones showed at 6-months follow-up eradication rates for 2 weeks therapy with ofloxacin of 67% (n=21) (Pust et al. 869-71) and with ciprofloxacin of 60% (n=15) (Weidner, Schiefer and Dalhoff 280-83); for 4 weeks therapy with norfloxacin of 64% (n=16) (Schaeffer and Darras 690-93), 72% (n=89) (Naber 18-27) or 76% (n=65) (Naber, Busch, and Focht 143-49) and with levofloxacin of 63% (n=93) (Naber 18-27), and for treatment during 6 months with norfloxacin of 60% (n=42) (50). Guidelines and reviews on prostatitis recommend a treatment duration of at least 4 weeks. This is based on experience and expert opinion and is supported by the above-mentioned clinical studies (28).

Conclusions

Level 4	Young men (< 40 years) without signs or symptoms of systemic disease, with no medical history and no previous lower urinary tract symptoms, can have an uncomplicated cystitis when typical complaints of frequency and dysuria are the predominant symptoms. Without a history or findings at physical examination that suggest a complicating factor, the UTI may be considered as uncomplicated [(28) D, (30) D, (31) C].
Level 3	In men with a UTI there is often a concurrent prostatitis [(41) C; (42) B].
Level 3	In the prostatitis syndrome, no more than 10% is a bacterial prostatitis. [(33) C; (34) C; (35) C].
Level 3	Of all antibiotic drugs fluoroquinolones, and to a lesser extent TMP/SMX, achieve the highest concentrations in the prostate. Nitrofurantoin has insufficient tissue penetration in the prostate [(38) D, (39) D; (40) C].
Level 3	Observational studies of the treatment of chronic bacterial prostatitis with quinolones for at least 4 weeks therapy showed with different quinolones at 6-months follow-up eradication rates of 60-76% [(51) C; (52) C; (46) C; (53) C; (46) C; (50) C].
Level 3	In men with culture-proved bacterial prostatitis, TMP-SMX, 2 tablets twice daily for 90 days, and minocycline-hydrochloride 100 mg twice daily for 28 days, seemed equally effective in controlling symptomatic recurrence during the 12 months after cessation of therapy [(47) B].
Level 2	No differences were found in clinical success and microbiological eradication rates after 4 weeks treatment with levofloxacin vs ciprofloxacin [(44) A2; levofloxacin vs prulifloxacin (45) B; or lomefloxacin vs ciprofloxacin (46) B].
Level 2	Men with recurrent UTIs, who can be considered as having chronic bacterial prostatitis and an active UTI, who were treated 10-14 days with TMP-SMX more often had a reinfection or relapse compared to patients who were treated for 6 weeks with TMP-SMX [(48) B; (42) B].

Other considerations

An acute prostatitis warrants empiric treatment. In patients without a urologic history and without a recent antibiotic treatment, when an outpatient treatment is considered, oral

treatment with quinolones could be started. All other patients with acute prostatitis should be admitted to the hospital to be treated intravenously. Treatment recommendations are as in general febrile UTIs.

The distinction between the different diagnoses of the prostatitis syndrome is primarily based on the symptoms, and originally on the classic four-glass test of Meares-Stamey (54). In this test urine is collected in fractions, interrupted by a transrectal prostatic massage to express prostatic fluid into the urethra. Separate analysis of each fraction was or is considered to be helpful to find proof for and to localize the infection.

Localization studies such as the classic four-glass test are rather elaborate examinations, while the interpretation of the results is unclear. In the prostatic expression or in the subsequent urine fraction of asymptomatic men bacteria or leucocytes may be found, while not all of the cultured bacteria are considered to be uropathogens and the interpretation of leukocytes in the specimen is not unequivocal (55), (56), (57). As a result, this test is nowadays used only in studies and is seldom used in daily urological practice (58).

In addition to urine cultures and urinalysis, it is encouraged to use the National Institute of Health-Chronic Prostatitis Symptom Index (referred to as the NIH-CPSI), a validated specific symptom score for this syndrome, in order to classify patients properly (59).

For chronic bacterial prostatitis prolonged antibiotic therapy of at least 4 weeks is recommended [(28)].

WHAT IS THE OPTIMAL TREATMENT OF UTI IN MEN?	
Recommendation	For the treatment of a UTI without systemic symptoms in young men (<40 years) with no medical history and no previous lower urinary tract symptoms, see the recently updated Guideline for Urinary Tract Infections of the Dutch College of General Practitioners (NHG). First choice is nitrofurantion with a treatment duration of 7 days.
Recommendation	For all men with a UTI with systemic symptoms we refer to the general treatment guidelines.
Recommendation	In chronic bacterial prostatitis there is no need for empirical antimicrobial treatment and treatment should be guided by the resistance pattern of the cultured micro-organism. First choices are quinolones and TMP-SMX.
Recommendation	The duration of antibiotic treatment of chronic bacterial prostatitis should be at least 4 weeks.

WHAT IS THE OPTIMAL TREATMENT OF URINARY TRACT INFECTIONS IN PREGNANT WOMEN?

Search strategy

Databases were Pubmed and the Cochrane library.

Keywords: [urinary tract infection OR urosepsis OR pyelonephritis] AND pregnancy AND treatment

Limits: English, adults, humans, clinical trials, guideline, meta-analysis, RCT, review, last 10 years.

143 publication since Cochrane review

Literature overview

Asymptomatic bacteriuria (ASB) is the presence of significant bacteriuria without the symptoms of a UTI. The prevalence of ASB is 2-10% in pregnant women. ASB during pregnancy can lead to serious complications for both mother and child. The incidence of ASB is similar in both pregnant and non-pregnant women (60). Pregnant women with ASB, however, develop pyelonephritis more often, probably due to the anatomic and physiologic changes that occur during pregnancy, which may facilitate bacterial growth and ascent of bacteria to the kidneys (61). If left untreated, 20-40% of pregnant women with ASB will develop pyelonephritis (60), (62), (63), (64), (65).

Other possible adverse effects, such as preterm delivery and delivering a low birth weight infant, are less well established. Preterm delivery is the main cause of neonatal mortality and morbidity worldwide. The causal mechanisms remain unknown. One of the hypotheses is that endotoxins released by bacteria cause uterine contractions leading to preterm delivery.
UTIs, including pyelonephritis, are among the most common health problems during pregnancy. They occur in up to 20% of pregnancies in some disadvantaged populations (66). Pyelonephritis is an acute episode diagnosed in 1.4% of pregnant women. It can have serious complications of sepsis and acute respiratory and renal insufficiency, and death.

Choice of drug

Antibiotic treatment in pregnancy is effective for the cure of UTIs and complications are rare (67). In a recent study, dispensing nitrofurantoin during the first trimester was not associated with increased risk of major malformations or other secondary adverse pregnancy outcomes when compared with the disease comparison group. However, dispensing nitrofurantoin the

last 30 days before delivery was associated with increased risk of neonatal jaundice (103 of 959 [10.8%]) compared with unexposed women (10,336 of 127,507 [8.1%], OR 1.31, 95% CI 1.02-1.70) (77).

In view of the lack of teratogenic effects described and the resistance percentages, the beta-lactam antibiotics are also a good choice for the treatment of a UTI during pregnancy. Nitrofurantoin (2 dd 100 mg) and co-amoxiclav (3dd 500/125 mg) are first-choice drugs for the treatment of cystitis during pregnancy in the guideline of the Dutch Society for Obstetrics and Gynaecology (NVOG). Nitrofurantoin must not used in the last days before delivery because of neonatal polyneuropathy, and fetal anemia in the 3rd trimester in glucose-6 phosphate dehydrogenase (G6PD) deficient women is described (68). Both regimens are in line with national guidelines for non-pregnant women, and are effective and safe. In the most recent update, single-dose regimen antibiotics for the treatment of a symptomatic UTI may be less effective than the short-course regimens (4-7 day regimen) regarding cure rates, recurrences and pregnancy complications including preterm birth (67). Short-term relief of symptoms is achieved at a similar rate by a 3-day regimen and prolonged antibiotic therapy for cystitis; however, women with cystitis treated with antibiotics for 5 days (or longer) had better eradication of uropathogens (69).

In pregnant women suspected of having pyelonephritis empirical intravenous therapy requiring antepartum hospitalization should be started (70), (71). Although there are insufficient data to recommend a specific treatment regimen for pyelonephritis in pregnancy, a 3rd generation cephalosporin (4 dd 1000 mg cefotaxime or 1 dd 2000 mg ceftriaxone) is the drug of first choice for the treatment of a pyelonephritis during pregnancy, because no adverse effects have been described (72). Intravenous antimicrobial therapy should be continued until the woman is afebrile for 24-48 hours and symptoms have improved; afterward women can be treated with oral antibacterial therapy based on the culture results. The total treatment duration should be at least 10 days. Experts recommend that after completion of therapy a urine culture should be obtained to verify resolution of the bacteriuria (www.nvog.nl), (71), (73). The incidence of recurrent pyelonephritis is decreased in women treated with antimicrobial suppression during pregnancy. However, data on evidence and safety are lacking for prophylactic treatment for the duration of pregnancy (74).

Whenever a group B streptococcus (GBS) is found in the urine culture, this is a sign of maternal colonization with GBS. Intravenous antibiotic treatment of the mother during delivery reduces the number of neonatal infections with GBS (75). As far as GBS is concerned, in the NVOG guideline Prevention of Perinatal Group B Streptococcus Disease published in 1998, screening is not recommended; however, in the event of severe maternal

GBS colonization (and therefore GBS in the urine) consultation with the gynaecologist is advised and in all cases administration of antibiotic prophylaxis during delivery is necessary (76).

Conclusions

Level 1	Antibiotic treatment of urinary tract infections during pregnancy results in reduction of new UTIs and pregnancy complications [(67) A1].
Level 2	Nitrofurantoin during the first trimester is not associated with increased risk of major malformations or other secondary adverse pregnancy outcomes. However, dispensing nitrofurantoin the last 30 days before delivery is associated with increased risk of neonatal jaundice (10.8%) compared with unexposed women (8.1%) [(77) A2]
Level 3	In pregnant women suspected of having pyelonephritis empirical intravenous therapy requiring antepartum hospitalization results in good clinical outcome [(70) C, (71) D].
Level 1	A urine culture positive for group B streptococcus (GBS) is a sign of severe maternal GBS colonization, and consultation of a gynaecologist is advised, and in all cases administration of antibiotic prophylaxis during delivery is necessary [(76) A1; (78) A2].

Other considerations

Treatment of ASB is similar to that of cystitis (79), but it is currently recommended not to screen for ASB (www.nvog.nl). An RCT is currently being conducted to accumulate evidence for screening and treatment of ASB at 20 weeks gestation for better maternal and neonatal outcome, and cost-efficacy (trial number NTR3068).

Antibiotic treatment is effective in reducing the risk of pyelonephritis in pregnancy (65).

Due to the higher incidence of side effects of co-amoxiclav compared to nitrofurantoin, the Guideline committee recommends to use nitrofurantoin as the first and co-amoxiclav as the second choice empirical agent in pregnant women with a cystitis.

Women with urinary tract anomalies and medical conditions including diabetes mellitus, sickle cell disease and neurological problems are at increased risk for acquiring

pyelonephritis in pregnancy. Therefore, experts recommend to culture the urine of these women at 16-20 weeks of gestation.

WHAT IS THE OPTIMAL TREATMENT OF UTI IN PREGNANT WOMEN?	
Recommendation	Nitrofurantoin (2 dd 100 mg) is the first choice and co-amoxiclav (3 dd 500/125 mg) is the second choice drug for the treatment of cystitis during pregnancy. Nitrofurantoin must not used in the last 30 days before delivery.
Recommendation	A 3rd generation cephalosporin (4 dd 1000 mg cefotaxime or 1 dd 2000 mg ceftriaxone) is the drug of first choice for the treatment of pyelonephritis during pregnancy.
Recommendation	The treatment duration of cystitis and pyelonephritis during pregnancy should be at least 5 days, and 10-14 days, respectively.
Recommendation	Antepartum pyelonephritis should be treated in a hospital setting and treatment should be started intravenously.
Recommendation	Screening and treatment of asymptomatic bacteriuria at 16-20 weeks gestation for better maternal and neonatal outcome is not recommended until new evidence is available. Exceptions are women with urinary tract anomalies and/or medical conditions including diabetes mellitus, renal transplant, sickle cell disease and neurological problems.
Recommendation	When Group B streptococcus (GBS) is present in the urine, which is a symptom of severe maternal GBS colonization, consultation with the gynaecologist is advised, because antibiotic prophylaxis during delivery is necessary.

URINARY TRACT INFECTIONS IN PATIENTS WITH A CATHETER

Search strategy

Databases were Pubmed and the Cochrane Library.

Keywords: urinary tract infection AND catheter or bacteriuria AND catheter

Limits: Last 3 years for Pubmed (guideline Catheter-associated UTI was published in 2009), English, adults, humans, clinical trials, guideline, meta-analysis, RCT

Pubmed: 36 results, all titles screened, 3 abstracts screened, 3 additional articles included

Cochrane Library: 12 results, all titles screened, 2 abstracts screened, 2 reviews included

Articles about special catheters as prevention methods or after certain procedures (for example, after operations/interventions) were excluded.

Some parts are used from the original text of the Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America (80).

Background and definitions

Catheter-associated (CA) infection refers to infection occurring in a person whose urinary tract is currently catheterized or has been catheterized within the past 48 hours. UTI refers to significant bacteriuria in a patient with symptoms or signs attributable to the urinary tract and no alternate source. Asymptomatic bacteriuria (ASB) refers to significant bacteriuria in a patient without symptoms or signs attributable to the urinary tract. Bacteriuria is a non-specific term that refers to UTI and ASB combined. In the literature about urinary catheters, CA-bacteriuria is comprised mostly of CA-ASB. The urinary catheter literature is problematic in that many published studies use the term CA-bacteriuria without providing information on what proportion of infections are CA-ASB, and some studies use the term CA-UTI when referring to CA-ASB or CA-bacteriuria (80).

Every patient with an indwelling catheter develops bacteriuria. In general it is not infection but colonization. In that case the patient will not have the complaints of a UTI. Patients (male and female) with an indwelling catheter can best be categorized into three groups:

1. Catheter in place for $\leq$ 10-14 days
2. Catheter in place for a longer period (mostly months-years)
3. Catheter over a prolonged period with intermittent catheterization

IS SYSTEMIC ANTIMICROBIAL PROPHYLAXIS NECESSARY IN PATIENTS WITH A URINARY CATHETER?

Literature overview

Results of studies included in a Cochrane review about <u>short-term</u> urinary catheter use provide evidence that antibiotic prophylaxis, compared to giving antibiotics when clinically indicated, reduced the rate of symptomatic UTI [RR 0.20 (95% CI 0.06-0.66)] in female patients with abdominal surgery and a urethral catheter for 24 hours. Receiving antibiotics the first 3 postoperative days, or from postoperative day 2 until catheter removal, reduced the rate of bacteriuria (fivefold) and other signs of infection such as pyuria and gram-negative isolates in patients' urine in surgical patients with bladder drainage for at least 24 hours postoperatively. There is also some evidence that prophylactic antibiotics reduced bacteriuria in non-surgical patients (81)

Results of studies included in a Cochrane review about <u>long-term</u> urinary catheter use show that no eligible studies are present to address the following questions in terms of effectiveness, complications, quality of life and cost-effectiveness: Is indwelling urethral catheterization better than suprapubic catheterization? Is indwelling urethral catheterization better than intermittent catheterization? Is suprapubic catheterization better than intermittent catheterization? Is giving antibiotics when microbiologically indicated better than giving antibiotics when clinically indicated?
For patients using intermittent catheterization, the limited evidence available suggests that antibiotic prophylaxis reduces the number of episodes of bacteriuria (asymptomatic and symptomatic). For patients using urethral catheterization no data were available (82).

To answer the question whether antibiotic prophylaxis is better than giving antibiotics when clinically indicated (having a symptomatic UTI), the evidence available is not sufficient as a basis for determining practice. For patients using intermittent catheterization the data were inconclusive. For patients using indwelling urethral catheterization, only a single crossover trial with 34 elderly inpatients investigated this issue and results show fewer episodes of symptomatic UTI in the prophylaxis (norfloxacin) group (1 in 276 catheterization weeks vs. 12 in 259 weeks) (83).

Conclusions

Level 1	Antibiotic prophylaxis decreases fivefold the incidence of bacteriuria in patients with a short-term indwelling catheter [(81) A1].

Level 1	No eligible studies are present to answer the questions what the best catheterization method is: indwelling urethral, suprapubic or intermittent, in terms of effectiveness, complications, quality of life and cost-effectiveness [(82) A1; (80) D].
Level 1	Antibiotic prophylaxis decreases fivefold the incidence of bacteriuria in patients who catheterize themselves intermittently over prolonged periods [(82) A1].
Level 1	Antibiotic prophylaxis decreases the incidence of symptomatic UTI in patients with a short-term indwelling catheter (RR 0.20 (95% CI 0.06-0.66) [(81) A1].
Level 3	Antibiotic prophylaxis decreases the incidence of symptomatic UTI in patients with a long-term indwelling catheter [(83) B].

Other considerations

Antibiotic prophylaxis sometimes seems effective but, on the other hand, will result in the development of resistance of the commensal flora (84). Differences in the incidence of symptomatic UTIs between groups of patients who did and did not receive antibiotic prophylaxis were small. Therefore, the Guideline committee does not recommend antibiotic prophylaxis. As a result there is no need to screen for bacteriuria in patients with a short or long-term urinary catheter.

IS SYSTEMIC ANTIMICROBIAL PROPHYLAXIS NECESSARY IN PATIENTS WITH A URINARY CATHETER?	
Recommendation	It is not recommended to prescribe antibiotic prophylaxis in patients with short-term or long-term urinary catheters, or in those who catheterize themselves intermittently over prolonged periods and, as a result, there is no need to screen for bacteriuria in these patients.

IS ANTIMICROBIAL PROPHYLAXIS INDICATED AT THE TIME OF CATHETER REMOVAL OR REPLACEMENT?

Literature overview

Fever and/or bacteremia can occur at the time of removal or replacement of a urethral catheter in a patient with CA-bacteriuria. In addition, CA-bacteriuria can occur after a catheter has been removed, although the frequency of occurence is not known. In a study of catheterized and bacteriuric women in long-term care facilities, Warren et al. reported an incidence of 2.1/100 resident days of fever within 24 hours of catheter replacement compared with 1.1/100 days without replacement (85). These episodes of fever generally resolved promptly, even without antibacterial therapy.

Several studies evaluating the risk of bacteremia with catheter removal or replacement have been performed. In a study of 115 men and women who were chronically catheterized Jewes et al. reported bacteremia following 20 of 197 (10%) of urethral catheter changes and 5% of suprapubic catheter changes: all bacteremic episodes were asymptomatic and patients were afebrile (86). Other prospective studies in geriatric populations with long-term catheters and bacteriuria have found an approximately 4% rate of transient bacteremia in patients who had removal or replacement of their indwelling catheters, and none were clinically symptomatic (87), (88), (80).

Studies have evaluated the effectiveness of antimicrobial prophylaxis in preventing CA-bacteriuria in patients who are having a catheter placed or removed. In a randomized double-blind, placebo-controlled trial in 162 elderly hospitalized patients who needed indwelling urethral catheterization, single-dose aztreonam vs. placebo 3 hours before catheterization resulted in no CA-UTI at 7 days in 89% of the patients in the aztreonam group vs. 46% in the placebo group (89). Concerns about this study include the unexpectedly high rates of CA-UTI in the first week of catheterization, short follow-up, and absence of data on antimicrobial resistance in infection episodes. In another randomized, double-blind, placebo-controlled study of 48 patients across specialties with a urethral catheter in situ for 2-7 days, patients (15% with CA-bacteriuria) assigned to a 48-hour course of either ciprofloxacin or placebo tablets starting 2 hours before catheter removal reported no difference in the rates of CA-bacteriuria by 2 weeks after removing the urethral catheter, i.e. 16% vs. 13%, respectively (90). On the other hand, results of a survey in two Dutch district hospitals which investigated the impact of concurrent administration of antibiotics on the incidence of CA-UTI, showed that 61% of catheterized patients received antibiotics at some stage during bladder drainage. The use of antibiotics within 48 hours prior to catheter removal reduced the risk of bacteriuria fivefold. Multivariate analysis of patients who were catheterized for 3-14 days indicated that,

apart from the duration of catheter employment, the use of antibiotics was the only variable significantly and independently associated with the development of bacteriuria.. Patients with bacteriuria at the time of catheter removal were more likely to have a febrile illness compared to those who remained free of CA-UTI (91).

Also a more recent prospective randomized non-blinded trial of 239 patients undergoing elective abdominal surgery in which patients were randomized to 3 doses of TMP-SMX or no treatment at urinary catheter removal showed significantly fewer CA-UTI (4.9% vs. 21.6%, P<0.001) and CA-bacteriuria (16.5% vs. 41.2%; P<0.001) in the treatment group (92).

There are no published studies of prophylactic antimicrobials in preventing CA-bacteriuria or CA-UTI in patients whose catheters are being replaced, or in preventing bacteremia in patients whose catheters are being removed or replaced.

In a double-blind, placebo-controlled randomized trial from the Netherlands the effect of single-dose prophylaxis using TMP-SMX (960 mg) (n=46) or ciprofloxacin (500 mg) (n=43) vs. placebo (n=51) before urinary catheter removal on bacteriuria (primary outcome) and UTI in surgical patients with scheduled bladder drainage for 3-14 days was assessed. Bacteriuria was determined directly after catheter removal, and UTI 12-14 days after catheter removal. After 12-14 days, incidences of bacteriuria were 19%, 19% and 33% for patients receiving ciprofloxacin, TMP-SMX and placebo, respectively. However, the incidences of symptomatic UTI were 3%, 0% and 3% for patients receiving ciprofloxacin, TMP-SMX and placebo, respectively (93).

Conclusions

Level 1	The incidence of fever and bacteremia following catheter (indwelling and suprapubic) changes is increased, but these episodes generally resolved promptly, even without antibacterial therapy [(80) A1; (85) C; (86) C; (87) C, (88) C].
Level 3	Single-dose aztreonam vs. placebo before catheterization decreased the incidence of CA-UTI at 7 days [(89) A2].
Level 1	Studies show a decrease in the incidence of bacteriuria, but report contradictory results regarding the effect of antibiotic prophylaxis after urinary catheter removal on the incidence of UTI [(93) A2 (negative result); (90) B (negative result); (92) A2 (positive result); (91) C (positive result)].

Other considerations

Based on these observations, the contradictory results on the most important outcome, namely symptomatic UTI, and concerns about rising antimicrobial resistance, prophylactic antimicrobials are not routinely recommended for catheter placement, removal or replacement. This recommendation is also supported by the low rate of serious complications in the large number of patients undergoing long-term intermittent catheterization with clean technique in the setting of chronic bacteriuria.

IS ANTIMICROBIAL PROPHYLAXIS INDICATED AT THE TIME OF CATHETER REMOVAL OR REPLACEMENT?	
Recommendation	Prophylactic systemic or local antimicrobials should **not** be administered routinely to patients at the time of catheter placement to reduce CA-UTI, or at the time of catheter removal or replacement to reduce CA-bacteriuria.

WHAT IS THE OPTIMAL MANAGEMENT IN PATIENTS WITH CA-UTI?

Literature overview

In patients with short-term catheter the most prevalent cultured micro-organism is *E. coli,* In patients with suprapubic catheterization the most prevalent cultured micro-organism is *Staphylococcus epidermidis* (94).

In patients with a long-term indwelling catheter, in addition to more common *Enterobacteriaceae*, also *Serratia, Providencia, Acinetobacter*, enterococci, yeasts and staphylococci are often cultured (28), (95).

Recently two Dutch studies were performed, one in the urology and internal medicine departments of 19 Dutch hospitals (mentioned above, Spoorenberg et al. submitted), and the other at primary care centers and in emergency rooms (26). The most common isolated pathogens in, respectively, 174 and 62 patients with a urinary catheter in place for at least 10 days were *E. coli* (25-39%), Klebsiella sp (10-12%), enterococci (5-10%), *P. mirabilis* (9-12%) and *P. aeruginosa* (8-9%) (26).

In this patient group the combination of co-amoxiclav with gentamicin was the most adequate (inadequate treatment rate of 3%). Excluding enterococci decreased the inadequate treatment rates for the regimens of a cephalosporin combined with gentamicin or a fluoroquinolone, making a third-generation cephalosporin with gentamicin the most adequate recommendation (inadequate treatment rate of 2%) (Spoorenberg et al. submitted).

Therefore, patients with a catheter need recommendations other than those described in the general treatment recommendations for a complicated UTI. Patients with a urinary catheter have an increased risk to have a fluoroquinolone-resistant micro-organism (OR 3.1, 95% CI 0.9-11.6) (7).

A prospective RCT evaluated whether long-term urinary catheters should be replaced prior to treatment of CA-UTI (96). Twenty-one male and 33 female elderly nursing home residents with long-term indwelling urinary catheters (time since last replacement, 2.5-5 weeks) and CA-UTI were randomized to indwelling catheter replacement or no replacement before initiating antimicrobial therapy with a fluoroquinolone. Patients who underwent catheter replacement had significantly decreased polymicrobic CA-bacteriuria 28 days after antimicrobials were discontinued (P=0.02), a shorter time to improved clinical status at 72 hours after the initiation of therapy (P<0.001), and a lower rate of CA-UTI within 28 days after therapy (P=0.015). These findings support catheter replacement prior to antimicrobial treatment for CA-UTI if the catheter has been in place for at least 2 weeks and cannot be discontinued.

In another study it was shown that when a symptomatic UTI is present, pyuria disappears faster during intermittent compared to suprapubic or indwelling catheterization (97).

Conclusions

Level 3	In patients with short-term use of catheter the most prevalent cultured micro-organism is *E. coli.* In patients with suprapubic catheterization the most prevalent cultured micro-organism is *Staphylococcus epidermidis* [(94) C].
Level 3	In patients with long-term catheter *E. Coli* is the most prevalent pathogen, but enterococci, staphylococci, *Pseudomonas, Serratia, Providencia, Acinetobacter* and yeasts are also frequently cultured [(95) C; (26) C; Spoorenberg submitted, B].
Level 3	Patients with a urinary catheter have an increased risk to have a fluoroquinolone-resistant micro-organism [(7) B].
Level 3	For patients with a urinary catheter in place for at least 10 days the best empirical treatment which covers enterococci was the combination of co-amoxiclav with gentamicin. Excluding enterococci made a third-generation cephalosporin with gentamicin the most adequate recommendation [Spoorenberg submitted, B].
Level 3	When the indwelling catheter is changed at the time of treatment of a symptomatic UTI, a higher percentage of patients has disappearance of the bacteriuria and a more rapid recovery from the symptoms [(96) A2].
Level 3	When a symptomatic UTI is present, pyuria disappears faster during intermittent compared to suprapubic or indwelling catheterization [(97) B].

Other considerations

Catheter-associated UTIs are often polymicrobial and caused by multiple-drug resistant uropathogens. Urine cultures are recommended prior to treatment in order to confirm that an empiric regimen provides appropriate coverage and to allow tailoring of the regimen based on antimicrobial susceptibility data (80).

In patients with long-term catheter and systemic symptoms, empirical treatment with fluoroquinolones or gentamicin is warranted to cover less common micro-organisms such as *Pseudomonas, Serratia, Providencia, Acinetobacter*. However, a study from the Netherlands demonstrated that patients with a urinary catheter have an increased risk to have a

fluoroquinolone-resistant micro-organism, which only leaves the aminoglycosides for empirical treatment in this patient group. *Enterococcus* species usually have low virulence, and it is debatable whether they should be covered in empirical therapy. Therefore, the Guideline committee decided to give recommendations with and without the coverage of enterococci.

As earlier antimicrobial treatment remains the strongest predictor for resistant causative micro-organisms (7), in a patient with a catheter who only has local symptoms we recommend to wait for the results of the cultures.

The Guideline committee is of the opinion that the faster disappearance of pyuria with intermittent catheterization is not important enough to recommend intermittent catheterization for all patients with a symptomatic UTI.

WHAT IS THE OPTIMAL MANAGEMENT IN PATIENTS WITH A CA-UTI?	
Recommendation	When the patient with a catheter has only local symptoms and has no signs of a systemic infection, it is recommended to wait for the results of the cultures.
Recommendation	If there is a systemic infection, the patient should be treated as described in the General section for patients with a complicated UTI. A patient who has had an indwelling catheter for a prolonged period or was catheterized intermittently must be treated empirically with a regimen including an aminoglycoside, to cover less common uropathogens like *Pseudomonas, Serratia, Providencia,* and *Acinetobacter.*
Recommendation	For patients with a urinary catheter in place for at least 10 days the best empirical treatment which covers enterococci is the combination of co-amoxiclav with gentamicin. Excluding enterococci makes a third-generation cephalosporin with gentamicin the most adequate recommendation.
Recommendation	If an indwelling catheter has been in place for more than 2 weeks at the onset of CA-UTI and cannot be removed, the catheter should be replaced to hasten resolution of symptoms and to reduce the risk of subsequent CA-bacteriuria and CA-UTI.

WHAT ARE THE APPROPRIATE TREATMENT DURATIONS FOR PATIENTS WITH CA-UTI?

Literature overview

There is a wide spectrum of conditions represented in patients with complicated UTI, including those with CA-UTI, such as an uncomplicated cystitis, pyelonephritis, pyelonephritis with abscess, prostatitis, and bacteremia. There are no published trial data that provide treatment outcomes for these different types of patients with CA-UTI and, thus, the optimal duration of antimicrobial treatment for CA-UTI is not yet known. In published reviews the recommended treatment durations for complicated UTI range from 7-21 days (80), depending on the severity of the infection.

In an RCT, Harding et al. demonstrated that women with lower tract CA-UTI within 14 days after catheter removal had similar resolution rates with single-dose therapy or 10 days of therapy with TMP-SMX with better outcomes in women aged ≤ 65 years (98). For patients with lower tract symptoms alone, resolution rates with single-dose therapy or 10 days of therapy were similar: 11 of 14 (79%) and 13 of 16 women (81%), respectively. Infection was resolved more often in women aged ≤ 65 years than in older women: 62 of 70 (89%) vs. 24 of 39 women (62%) (P<0.001). Bacteriuria resolved spontaneously more frequently in younger women: 14 of 19 (74%) compared with 1 of 23 older women (4%) (P< 0.001). Single-dose therapy resolved infection in 31 of 33 patients (94%) who were aged ≤ 65 years (98). In women with upper tract CA-UTI, 10 days of treatment with TMP-SMX led to resolution in 6 of 9 women (67%) (98).

In a study of 46 men and women with neurogenic bladders managed by intermittent catheterization, a 10-day course of an antimicrobial to which the infecting strain was susceptible (most received TMP-SMX) was no more effective than a 3-day course in treating episodes (29 in each group) of CA-bacteriuria, about half of which were CA-UTI (41% in the 3-day group vs. 55% in the 10-day group) (99). Rates of cure, persistence, and relapse were similar in the two treatment groups.

Another randomized, double-blind, placebo-controlled trial was performed comparing 3-day and 14-day regimens of ciprofloxacin, 250 mg twice daily, for the treatment of mild CA-UTI in 60 patients with spinal cord injury, most using intermittent catheterization. Patients with pyelonephritis or symptoms of systemic infection were excluded (100). Microbiological cure, but not clinical cure, at long-term follow-up was significantly better among patients who received therapy for 14 days than among patients who received therapy for 3 days. Microbiological and symptomatic relapse were significantly more common in the 3-day treatment group. The authors concluded that for patients with spinal cord injury, treatment of CA-UTI for 14 days leads to improved clinical and microbiological outcomes, compared with

short-course therapy. Since there was no difference in clinical outcomes between the two treatment groups at long-term follow-up, it seems likely that the optimal treatment duration in such patients lies somewhere between 3 and 14 days.

In another multicenter, double-blind, randomized, non-inferiority study of 619 patients with acute pyelonephritis or complicated UTI, levofloxacin 750 mg intravenously or orally once daily for 5 days was compared with ciprofloxacin 400 mg intravenously and/or ciprofloxacin 500 mg orally twice daily for 10 days (20). A detailed description of the types of complicated UTI in the treatment groups was not provided, but 68 (11%) patients were catheterized. Clinical success rates post-treatment were similar (81% vs. 80%, respectively), as were microbiologic eradication rates (80% vs. 80%, respectively). Microbiologic eradication was lower in subjects with a catheter vs. those without a catheter, but among catheterized patients the microbiologic eradication rate was higher in the levofloxacin group (79%) than in the ciprofloxacin group (53%) (95% CI 3.6-47.7%). Clinical outcomes in catheterized subjects were not reported..

Conclusions

Level 3	In 6 of 9 (67%) women with upper tract CA-UTI 10 days of TMP-SMX treatment led to resolution [(98) C].
Level 3	Women with lower tract CA-UTI within 14 days after catheter removal had similar resolution rates with single-dose therapy or 10 days of therapy with TMP-SMX, with better outcomes in women aged less than 65 years [(98) B].
Level 3	Men and women with neurogenic bladders managed by intermittent catheterization have similar rates of cure, persistence, and relapse after a 10-day or 3-day course of an antimicrobial to which the infecting strain was susceptible [(99) B].
Level 3	In patients with spinal cord injury, treatment of mild CA-UTI for 14 days leads to improved clinical and microbiological outcomes, compared with short-course (3 days) therapy [(100) A2].
Level 3	In patients with acute pyelonephritis or complicated UTI and a catheter the microbiologic eradication rate was higher in the levofloxacin group 750 mg intravenously or orally once daily (79%) than ciprofloxacin 500

	mg orally twice daily for 10 days (53%) (95% CI, 3.6% to 47.7%). Clinical outcomes in catheterized subjects were not reported [(20) A2].

Other considerations

It is desirable to limit the duration of treatment, especially for milder infections and infections that respond promptly to treatment, to reduce the selection pressure for drug-resistant flora, especially in patients on long-term catheterization. The sample size for the above-mentioned study (20) was for all patients with a complicated UTI and not for the subgroup of patients with a CA-UTI. Only the microbiologic eradication rate was mentioned in this subgroup, which was higher in the levofloxacin than in the ciprofloxacin group. However, the Guideline committee has the opinion that the clinical resolution of symptoms is a more important endpoint.

Concerning the treatment duration, the Guideline committee considers CA-UTI with systemic symptoms to be a complicated UTI and refers to the recommendations as described in the chapter on treatment duration. Shorter durations of treatment are preferred in appropriate patients to limit development of resistance. Therefore, the Guideline committee is of the opinion that a shorter course, such as a 5-day regimen commonly used in women with uncomplicated lower UTI, is also reasonable in women with mild CA-UTI without upper tract and systemic symptoms.

Regimens should be adjusted as appropriate depending on the culture and susceptibility results and the clinical course.

	WHAT ARE THE APPROPRIATE TREATMENT DURATIONS FOR PATIENTS WITH CA-UTI?
Recommendation	See general treatment guidelines for the treatment duration of CA-UTI with systemic symptoms.
Recommendation	A 5-day antimicrobial regimen may be considered for women who develop a CA-UTI without upper tract and systemic symptoms.

URINARY TRACT INFECTIONS AND ASYMPTOMATIC BACTERIURIA IN PATIENTS WITH DIABETES MELLITUS

For all articles databases were Pubmed and the Cochrane Library.

Keywords first search: diabetes mellitus AND urinary tract infection AND treatment;

Limits: Last 7 years for Pubmed (SWAB guideline for the treatment of complicated UTI was published in 2005), English, adults, humans

Pubmed: 142 results, all titles screened, 10 abstracts screened, 6 additional articles included.

Cochrane Library, keywords urinary tract infection and diabetes mellitus: 3 results, no abstracts screened, no additional articles included.

Keywords second search: diabetes mellitus AND asymptomatic bacteriuria

Limits: Last 10 years for Pubmed (IDSA guideline for screening and treatment of ASB was published in 2005), English, adults, humans

Pubmed: 36 results, all titles screened, 4 abstracts screened, 4 additional articles included.

Cochrane Library: 5 results, 3 abstracts screened, 1 additional article included.

Literature overview

Epidemiology

In a systematic review and meta-analysis on asymptomatic bacteriuria (ASB) in diabetic patients, 22 studies were included. ASB was present in 439 of 3,579 (12.2%) patients with diabetes mellitus (DM) and in 121 of 2,702 (4.5%) healthy control subjects. ASB was more common both in patients with type 1 DM (OR 3.0 [95% CI 1.1-8.0]) and type 2 DM (3.2 [2.0-5.2]) than in control subjects. The point prevalence of ASB was higher in both women (14.2 vs. 5.1%; 2.6 [1.6-4.1]) and men (2.3 vs. 0.8%; 3.7 [1.3-10.2]) (101).

It has been shown that diabetic patients have an increased risk for UTI (102); (103). A recent study in primary care patients from the Netherlands demonstrated that relapses and reinfections were reported in 7.1% and 15.9% of women with DM, respectively, vs, 2.0% and 4.1% of women without DM, respectively. There was a higher risk of recurrent UTI in women with DM compared with women without DM (OR 2.0; 95% CI 1.4-2.9). Women who had had DM for at least 5 years (OR 2.9; 95% CI 1.9-4.4) or who had retinopathy (OR 4.1; 95% CI 1.9-9.1) were at risk of recurrent UTI (104). This increased recurrence rate was confirmed in one study (105), but not in another (22). In contrast, in an American study in women with DM type 1, sexual activity rather than measures of diabetes control and complications was the main risk factor for UTI. The prevalence of cystitis was similar to that in non-diabetic women participants in a national survey (106).

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In addition, diabetic patients more often develop complications: bacteremia (107) and longer hospitalization (108), (102), due to their UTI. For this reason a cystitis in a patient with DM is considered a complicated UTI.

WHAT IS THE OPTIMAL TREATMENT OF ASB AND UTI IN PATIENTS WITH DIABETES MELLITUS?

It has been demonstrated that ASB in women with DM is benign and that 20% of diabetic subjects with ASB remained bacteriuric with the original infecting organism for a long period of observation. Women infected with gram-negative organisms were more likely to have persistent bacteriuria. Many women with resolution of initial bacteriuria, with or without antibiotics, became bacteriuric again during follow-up. Treatment may reduce the overall proportion of time infected in the long term and carriage of a unique strain, but most treatment regimens were followed by subsequent recolonization. Infecting strains did not have virulence factors characteristic of uropathogenic *E. coli* (109). Furthermore, ASB in women with DM does not result in renal function decline (110). However, more women with ASB will develop a symptomatic UTI compared to those without (111). Also, in another study with male and female patients with DM type 1 and 2, the presence of ASB was associated with an increased risk of hospitalization for urosepsis as principal diagnosis (hazard ratio [95% CI] 4.4 [1.2-16.5]; P=0.004) (112).

Because in the above-mentioned prospective study (110) no evidence was found that ASB in itself can lead to a decline in renal function (in women with type 1 or type 2 DM), it is unlikely that treatment of ASB will lead to a decrease in the incidence of diabetic nephropathy. This is in accordance with a study of women with DM and with ASB in which a comparison was made between women who received antibiotic therapy and women who received placebo. In that study, no difference was seen in serum creatinine levels after a mean follow-up of 2 years (113).

Choice of drug

Because the resistance percentages for *E. coli* and other uropathogens from the urine of patients with and without DM are comparable (114), (115), the choice of antibiotic treatment is not different for diabetic patients.

Duration of therapy

No prospective trials are available in which the optimal treatment (agent choice and duration) in these patients has been investigated. Some studies show that patients with diabetes have

more complications (107), (108) related to their UTI compared to non-diabetic patients. Concerning the recurrence rate of UTI in diabetic compared to non-diabetic women, two studies using Dutch registration database containing pharmacy dispensing data from 2 different time periods show contradictory results (116), (117). In the largest study (117), the prescriptions of 10,366 women with diabetes and 200,258 women without diabetes were compared. Women with diabetes more often received a long treatment, but still had a higher recurrence rate of UTIs compared with those without diabetes.

Conclusions

Level 1	Patients with diabetes mellitus (DM) have a higher prevalence of ASB than patients without DM [(101) A1].
Level 2	Patients with DM have a higher incidence of UTIs than patients without DM [(102) B; (103) B], but this is less clear for patients with DM type 1 [(106) B]
Level 2	Patients with DM develop more complications of their UTI [(102) B; (107) B; (108) B].
Level 2	Diabetic patients with ASB more often develop a UTI compared to diabetic patients without ASB [(111) B; (112) B].
Level 2	ASB (with and without antimicrobial treatment) in women with DM does not result in renal function decline [(109) A2; (110) B]
Level 2	The resistance percentages for *E. coli* and other uropathogens from the urine of patients with and without DM are comparable [(114) B; (115) B].
Level 2	It is not clear whether the chance of therapeutic failure is increased after treatment of UTI among women with DM compared to women without DM [(117) B; (104) B; (105) B; (22) B; (116) B].

Other considerations

ASB in women with DM does not result in renal function decline and the majority of women does not develop a symptomatic UTI. In addition, because women with symptomatic UTI will present with symptoms and because of the collateral damage of treatment (resistance, side-

effects), the Guideline committee recommends not to treat ASB in women with DM. Therefore, screening for ASB is not indicated in these patients. This is in accordance with the IDSA guideline for the diagnosis and treatment of asymptomatic bacteriuria in adults (73).

Considering the resistance percentages of the causative micro-organisms, patients with UTI and DM can be treated with the same agents as those without DM; therefore, nitrofurantoin for women with DM and only cystitis seems to be a good choice. In the largest study from the Netherlands, more recurrent UTIs were demonstrated even with a treatment duration of longer than 5 days [(117). However, we do not know whether a longer treatment duration will result in a lower recurrence rate.

The Guideline committee decided to recommend (in accordance with the NHG standard) a longer duration of therapy, namely 7 days, for the treatment of a lower UTI in a woman with DM. For the treatment of a pyelonephritis in a woman with DM, we refer to the General section above.

WHAT IS THE OPTIMAL STRATEGY FOR URINARY TRACT INFECTIONS AND ASYMPTOMATIC BACTERIURIA IN PATIENTS WITH DIABETES MELLITUS?	
Recommendation	It is not necessary to treat ASB in women with diabetes and, therefore, screening is not indicated.
Recommendation	A 7-day regimen of nitrofurantoin is recommended in diabetic women with cystitis.
Recommendation	For the treatment of diabetic men or diabetic women with a pyelonephritis or a UTI with systemic symptoms we refer to the sections "Men" and "Empirical treatment".

WHAT ARE THE BEST STRATEGIES FOR URINARY TRACT INFECTIONS AND ASYMPTOMATIC BACTERIURIA IN PATIENTS WITH A RENAL TRANSPLANTATION?

Search strategy

Databases Pubmed and Cochrane Library

Search Cochrane: search terms: urinary tract infections and kidney transplantation: 1 hit, 1 review included

Search Pub Med: urinary tract infections and kidney transplantation

Limits: <10 years, adults, human studies: 327 results, all titles screened, 68 abstracts screened, 20 papers included.

Literature overview

UTIs are the most common infectious complications after renal transplantation, accounting for 45-70% of all infections. The incidence of recurrent UTI (≥ 3 year) is reported to range from 6-18% (118).

The highest incidence of UTI is in the first 3 months after transplantation, which may be related to surgical trauma, presence of urinary catheters and ureteric stents, as well as high doses of immunosuppressive drugs (119). In several retrospective cohort studies the major risk factors for UTI include female gender, time on hemodialysis, diabetes mellitus, pretransplant UTIs, indwelling bladder catheters, anatomic abnormalities of the kidney, intra-operative ureteric stenting, rejection episodes, cytomegalovirus and BK virus infection, re-transplantation, polycystic kidney disease, postmortal donor, ASB and possibly the amount and kind of immunosuppression (120), (118), (121), (122).

Vesico-ureteric reflux (VUR) to the transplanted kidney appears to be a unique risk factor for this group of patients, occurring in 47% of transplant recipients with recurrent UTIs (118). This VUR is a consequence of the kidney transplantation surgery, which causes disruption of the normal valve of the ureteric orifice.

There are conflicting results on the role of immunosuppressive drugs in the risk of UTI in renal transplant patients. In one retrospective cohort study, treatment with mycophenolate mofetil was associated with a higher incidence of UTI compared to azathioprine-based therapy (123), whereas others found an increased incidence of UTI in azathioprine-treated patients (124). Induction therapy with antithymocyte globulin compared to induction therapy with basiliximab showed to increase the risk of UTI in the first year after transplantation, with similar graft and patient survival (125), (126).

No clinical data are available on the benefit of changing immunosuppressive drugs from one class to another to prevent one recurrence of UTI; therefore, no recommendations can be made on this topic.

Especially lower UTIs in the first 6 months after transplantation (early UTI) have a higher risk of complications, because these early infections are more commonly associated with pyelonephritis, bacteremia, and relapse (127), (128). Recurrent UTI, and especially acute graft pyelonephritis (AGPN) and bacteremia, are associated with a poorer graft and poorer patient outcome (129). In a prospective study in 177 renal transplant patients, AGPN did not alter graft or recipient survival but, compared to patients with uncomplicated UTIs, patients with AGPN exhibited a significant decrease in creatinine clearance, already detected after 1 year (MDRD-GFR: AGPN: 39.5 ± 12.5; uncomplicated UTI: 54.6 ± 21.7 mL/min/1.73 m^2, P< 0.01) and still persistent (about 50%) 4 years after transplantation (130). This trend was also demonstrated in a large analysis of data from the United States Renal Data System (USRDS) in 28,942 patients (131). In that analysis, late UTI was significantly associated with an increased risk of subsequent death in Cox regression analysis (P < 0.001; adjusted hazard ratio [HR], 2.93; 95% confidence interval [CI], 2.22, 3.85); and adjusted HR for graft loss was 1.85 (95% CI, 1.29, 2.64). The association of UTI with death persisted after adjusting for cardiac and other infectious complications, and regardless of whether UTI was assessed as a composite of outpatient/inpatient claims, primary hospitalized UTI, or solely outpatient UTI.

The most frequently isolated micro-organisms in the first months after transplantation are *E. coli, P. aeruginosa* and enterococci (120), (130), (132). The risk for infection with ESBL-producing micro-organisms increases significantly with recurrent episodes of UTI, as shown in retrospective studies (133).

Asymptomatic bacteriuria

In a prospective analysis of urine cultures in 89 patients during 1 year after kidney transplantation, 151 episodes of bacteriuria were detected in 49 patients, of which 65% was ASB, 13% a lower UTI and 22% an upper UTI (Golebiewska et al. 2985-90). In a retrospective single-center study in 388 renal transplant patients bacteriuria was noted in 57% of the female and 21% of the male patients. Bacteriuria correlated positively with the dose of prednisolone and mycophenolate acid (122).

ASB can impair renal function in kidney transplant patients, probably due to cumulative inflammatory damage (132), (127).

In another retrospective study the impact of ASB on renal transplant outcome was analysed in 189 renal transplant recipients. A total of 2-5 ASB episodes were independent factors

associated with pyelonephritis, whereas more than 5 episodes was a factor associated with rejection (134). Only a few studies have addressed the problem of ASB in renal transplant recipients; however, in neither of these studies were the frequency of ASB screening or the parameters to evaluate renal function specified. In a more recent study, no benefit on graft function was demonstrated by treatment of ASB (135).

Prevention/Prophylaxis

With the use of antibiotic prophylaxis against *Pneumocytis jiroveci* pneumonia (PJP) with TMP-SMX the incidence of UTI has decreased (135).

A recent meta-analysis showed no significant difference in graft loss (risk ratio [RR] 0.99, 95% CI 0.91-1.81) with prophylactic use of antibiotics in the first 6 months after renal transplantation. However, prophylaxis lowered the risk for developing sepsis with bacteremia by 87% (RR 0.13, 95% CI 0.02-0.7) and the risk for developing bacteriuria (symptomatic or asymptomatic) by 60% (RR 0.41, 95% CI 0.31-0.56; 3 trials). Symptomatic UTI and pyelonephritis were not reported. No significant reduction was found in all-cause mortality, and adverse events rates and conflicting results were reported for the development of resistant bacteria (128). In most of the transplantation centers prophylaxis with TMP-SMX (480-960 mg once daily) for 6-12 months after the kidney transplant is used as PJP prophylaxis. This is in accordance with the recommendations of the guideline of the Kidney Disease: Improving Global Outcomes (KDIGO) from 2009 (136), because this prophylaxis showed to be beneficial also for prevention of UTI (137), (128), (138). Some studies showed a similar protection for UTI with the use of ciprofloxacin or 1 month ofloxacin prophylaxis after transplantation (139); however, this regimen does not protect against PJP.

In an RCT, trial prophylaxis with high-dose TMP-SMX (320/1600 daily in 2 gifts) decreased the incidence of UTI to 25% compared to 49% in the patients with a moderate (160/800 daily) or low dose (80/400 daily) (138).

Besides TMP-SMX prophylaxis, a good surgical technique and early removal of urinary catheters have a large impact on reducing the risk for UTI after kidney transplantation. Early removal (< 3 days) reduced the rate of UTI to 14%, compared to a rate of 74% in patients with a late removal (>7 days) of the urinary catheter (140), (141).

Recurrent UTI in renal transplant patients

Recurrent UTI (rUTI) in renal transplant patients is difficult to treat. The general recommendations for rUTI can also be applied for renal transplant patients, although none of these interventions (like cranberries or topical estragen) have been thoroughly studied in this

group of patients. Although cranberry juice may have some inhibitory effect on CYP3A activity, no interference with cyclosporine levels has been found (142).

Treatment

There is no specific literature concerning the choice of agent and duration of antibiotic treatment in renal transplant patients. Especially lower UTIs in the first 6 months after transplantation (early UTI) have a higher risk of complications, because these early infections are more commonly associated with pyelonephritis, bacteremia, and relapse (127), (128). For that reason it is recommended that all patients with UTIs in the first 6 months after renal transplantation with clinical and laboratory evidence suggestive of kidney allograft pyelonephritis, should be hospitalized and treated with intravenous antibiotics (KDIGO AmJ Transplant 2009;9(suppl 3):S59-62).

Although it seems reasonable that the immunodeficient state of the renal transplant patients plays an important role in the pathogenesis of recurrent UTI in these patients, no robust data are available on the best choice of immunosuppressive drugs in these patients, or possible benefits of switching between classes of immunosuppressive drugs.

Conclusions

Level 1	UTI are the most common infectious complications after kidney transplantation [(118) B]. The highest incidence of UTI is in the first 3 months after transplantation [(119). A1].
Level 2	Induction therapy with antithymocyte globulin compared to induction therapy with basiliximab increases the risk of UTI in the first year after transplantation, with similar graft and patient survival.. [(125) A2]
Level 1	With the use of prophylaxis with TMP-SMX for PJP the incidence of UTI has decreased [(135) A1]
Level 3	In a double-blind RCT prophylaxis with high-dose TMP-SMX (320/1600 daily in 2 gifts) decreased the incidence of UTI to 25% compared to 49% in the patients with a moderate (160/800 daily) or low dose (80/400 daily) [(138) A2].
Level 3	ASB episodes are associated with pyelonephritis and with rejection [(134) B].

Level 2	Treatment of ASB in renal transplants does not show any benefit on graft function [(134) B; (135) B].
Level 1	A meta-analysis showed no significant difference in graft loss with prophylactic use of antibiotics in the first 6 months after renal transplantation. However, prophylaxis lowered the risk for developing sepsis with bacteremia by 87% (RR 0.13, 95% CI 0.02-0.7) and the risk for developing bacteriuria (symptomatic or asymptomatic) by 60% (RR 0.41, 95% CI 0.31-0.56) [(128) A1].
Level 3	The most frequently isolated micro-organisms in the first 3 months after transplantation appear to be the *Escherichia Coli* , *Pseudomonas aeruginosa* and enterococci [(120) C; (130) C; (132) D].
Level 3	Early (< 3 days) removal of urinary catheters reduces the risk of UTI in the post-transplantation period [(140) C; (141) D].
Level 4	Early UTI in the first 6 months after transplantation are more commonly associated with pyelonephritis, bacteremia and relapse (127) D; (137) D].
Level 2	Recurrent UTI and acute graft pyelonephritis are associated with a poorer graft and patient outcome [(130) C; (131) B; (129) A2].
Level 3	The incidence of UTI with ESBL-producing micro-organisms increases with the number of recurrent UTI [(133) B].
Level 3	Although cranberry juice may have some inhibitory effect on CYP3A activity, no interference with cyclosporine levels has been found [(142) C].

Other considerations

In general the treatment of UTI in renal transplant patients is not different from the treatment in non-transplants; for these patients we refer to the paragraph on empirical treatment and duration of treatment.

However, in the first 3 months after transplantation *P. aeruginosa* and enterococci are more frequently isolated and empirical treatment must cover these micro-organisms (120), (130), (132). Because of the nephrotoxicity of gentamicin, the Guideline committee recommends to cover these agents with a combination of amoxicillin and ciprofloxacin.

Prevention of UTI after kidney transplantation also needs a thorough management of structural and functional urinary tract abnormalities in the pre-transplant period, which sometimes even justifies nephrectomy of the native kidneys, especially in patients with recurrent UTI in polycystic kidney disease and in patients with VUR to their native kidneys.

In the face of a relapsing UTI in a renal transplant recipient, functional or anatomic abnormalities must be excluded (e.g. stone, obstructive uropathy, poorly functioning bladder, or urodynamic disorders following complication of ureterovesical anastomosis). The most common findings include ureteral reflux, strictures at the ureterovesical junction, neurogenic bladder, and subvesical obstruction, especially in men aged over 60 years. Early removal (< 3 days) of the catheter to reduce the rate of UTI is often not possible, because the junction between ureter and bladder is not healed 3 days after the transplantation (140), (141).

Evidence to support screening recommendations in the post renal transplant period is incomplete. Experts think that it may be appropriate to screen and start treatment for bacteriuria in the early postoperative period and up to 6 months post transplant. However, continued screening for and treatment of ASB in a clinically stable renal transplant recipient beyond 6 months does not seem beneficial given the lack of impact of bacteriuria on graft survival (143). Because of these conflicting results, no clear recommendation can be made for screening and treatment of ASB in renal transplant or other solid organ transplant recipients, which is in concordance with the IDSA guidelines on the Diagnosis and treatment of ASB (73).

In case of an early UTI and presence of a JJ ureteral stent it should be assumed that, despite antibiotic treatment, the urine will (latently) remain infected as long as a corpus alienum is present in the urinary tract. This stent should be removed if possible and the urine must be cultured. In cases of recurrent pyelonephritis experts recommend to administer prolonged courses of antibiotics up to several days after removal of the stent.

Depending on the context, additional investigations might be indicated, such as ultrasound study of the native and transplanted kidneys, positron emission tomography (PET) or computer tomography (CT) scan, cystoscopy or micturating cystogram. One should keep in mind that the native kidneys can be a source for recurrent infections, especially in patients with pre-transplant rUTI.

Because of toxicity, the Guideline committee will not recommend high-dose TMP-SMX (320/1600 daily in 2 gifts) as prophylaxis against UTI, despite the decreased incidence of UTI (138).

WHAT ARE THE BEST STRATEGIES FOR URINARY TRACT INFECTIONS AND ASYMPTOMATIC BACTERIURIA IN PATIENTS WITH A RENAL TRANSPLANTATION?	
Recommendation	No recommendation can be made about screening and treatment of ASB in renal transplant patients. Experts are of the opinion that it may be appropriate to screen and start treatment for bacteriuria in the early postoperative period and up to 6 months post transplant.
Recommendation	Prophylaxis given for *Pneumocystis jiroveci* with low-dose TMP-SMX reduces the risk of early UTI and is recommended for the first 6-9 months after renal transplantation.
Recommendation	Treatment of UTI in renal transplant patients should be according to the general guidelines for treatment of complicated UTI, but in the first 3 months after transplantation empirical treatment with the combination of amoxicillin and ciprofloxacin is recommended.
Recommendation	No recommendation can be made about changing immunosuppressive drugs from one class to another to prevent a recurrence of UTI.
Recommendation	In the choice of antibiotics for treatment of recurrent UTI the increased risk for ESBL-related infections should be considered. Therefore, earlier culture results and fluoroquinolone use in the last < 30 days have to be checked.
Recommendation	Removal of the urinary catheter should be done as soon as appropriate.
Recommendation	In case of a UTI the JJ stent should be removed if possible and the urine must be cultured.
Recommendation	In patients with recurrent UTI further investigations for anatomical abnormalities, bladder dysfunction or infection of the native kidneys should be initiated.
Recommendation	It is important to note that several antimicrobial agents can interact with immunosuppressants, especially with calcineurine-inhibitors. Therefore, interactions have to be checked.

WHAT IS THE OPTIMAL TREATMENT IN PATIENTS WITH POLYCYSTIC KIDNEY DISEASE?

Search strategy

Polycystic Kidney Disease AND Urinary Tract Infections

Pubmed: 160 hits, all abstracts screened, 11 articles included

Cochrane Library: no hits

Literature overview

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder, with a prevalence of 1:500-1000, and accounting for 4-10% of dialysis patients (144), (145). Approximately 50-75% of patients with ADPKD will have a UTI during their lifetime, most of them presenting as an uncomplicated lower UTI (Gibson, 1998 222 /id}. The incidence of complicated upper UTI has not been well evaluated, but ranged from 32% in a retrospective cohort and up to 56% in an autopsy study (146), (147). Discrimination between an upper UTI caused by a pyelonephritis or by a cyst infection can be difficult (145), (148). Although cyst infection is reported as one of the most frequent complications of ADPKD (149), published data on this topic are relatively scarce and all data are retrospective.

In one of the largest studies in this field, a retrospective French cohort study of 389 patients with ADPKD (144), incidence rates of cyst infections were 0.01 episode per patient per year, accounting for hospitalization in 8.4% of the ADPKD patients *E. coli* was the most common causing organism, accounting for 75% of cases, which suggests an ascending mechanism for cyst infection.

A more recent retrospective study from Albania (150) demonstrated in 180 ADPKD patients that 60% had a UTI during a 1-year follow-up period. UTI were more frequent in women than in men, 43% had a cyst infection, 38% a pyelonephritis and 19% a lower UTI. Again, *E. coli* was found in 75% of the patients. Blood culture was positive in only 10% of the patients, and urine culture was negative in 40%. Urinary cultures are often negative, since the cysts may not be in communication with the collecting system.

Radiological imaging for the diagnosis of infected cysts is often of little help because the cyst changes, induced by an infection, are not very specific. PET scan can be useful to identify the infected cysts (151), although PET scan has not been evaluated in intracystic bleeding, which is the main differential diagnosis of cyst infections in these patients. In the above-mentioned study from Sallee et al. (144), ultrasound, CT scan and magnetic resonance imaging (MRI) failed to detect a likely or definite cyst infection (for definitions, see below) in

94%, 82% and 60%, respectively, and yielded negative results in more than half of the patients with a definite diagnosis of cyst infections. In contrast, PET scan proved to be helpful for the detection of cyst infection in 100% of the cases, which was also shown is smaller case series (148), (152). PET scan was considered positive when increased Fludeoxyglucose (FDG) uptake was demonstrated in at least one cyst, and the diagnosis was based on the following criteria (144):

- Cyst infection is considered as definite in the presence of a cyst aspiration showing evidence of infection (neutrophils debris and/or micro-organism).

- Cyst infection is considered likely in the presence of all of the following features: fever (temperature >38.5°C for >3 days), abdominal pain (particularly a palpable area of renal or liver tenderness), increased C-reactive protein (CRP; >50 mg/L), and the absence of any significant recent intracystic bleeding (based on the results of an abdominal CT scan), or other causes of fever.

The Guideline committee recommends to use these criteria in clinical practice.

Treatment

As far as possible, a distinction should be made between cyst infection and pyelonephritis, since most cysts are not in communication with a filtering glomerulus. As a consequence, in case of a cyst infection, the antibiotics must enter the cyst by diffusion, which is more efficient for lipid soluble drugs like fluoroquinolones and TMP-SMX. Penicillins and aminoglycosides often do not penetrate cysts. In case of large (> 5 cm) infected cysts, early drainage in combination with antibiotic treatment is advised (144). Efficacy of antibiotic treatment and infection eradication are defined by a good clinical response and at least two negative blood and/or urine cultures (144).

Conclusions

Level 3	The incidence of lower and upper UTI and cyst infections is high in patients with autosomal dominant polycystic kidney disease [(150) C, (144) C, (145) D].
Level 3	*Eschericha coli* is the most common causative organism, accounting for 75% of cases [(144) C; (150) C].
Level 3	Urinary cultures are often negative, since the cysts may not be in communication with the collecting system [(150), C].
Level 3	Ultrasound, CT scan and MRI failed to detect the infected cyst in the majority of patients [(144) C].
Level 3	PET scan can be useful to identify a cyst infection [(144) C; (151) D; (148) D; (152) D].
Level 4	PET scan is considered positive when increased Fludeoxyglucose (FDG) uptake is demonstrated in at least one cyst and the following criteria can be used for the diagnosis of a cyst infection [(144) D]: - Cyst infection is considered as definite in the presence of a cyst aspiration showing evidence of infection (neutrophils debris and/or micro-organism). - Cyst infection is considered likely in the presence of all of the following features: fever (temperature >38.5°C for >3 days), abdominal pain (particularly a palpable area of renal or liver tenderness), increased C-reactive protein (CRP; >50 mg/L), and the absence of any significant recent intracystic bleeding or other causes of fever.
Level 3	To treat a cyst infection fluoroquinolones or TMP-SMX must be used. Penicillins and aminoglycosides often do not penetrate cysts [(144) C].
Level 4	In case of large (> 5 cm) infected cysts, early drainage is advised in combination with antibiotic treatment [(144) D].
Level 4	Efficacy of antibiotic treatment and infection eradication are defined by a good clinical response and at least two negative blood and/or urine cultures [(144) D].

Other considerations

No data are available on a comparison of antimicrobial regimens for this group of patients.

For the above-mentioned reasons and the known resistance patterns of the causative uropathogens, it is recommended to start initially with ciprofloxacin, but to use the culture results to tailor treatment.

Duration of treatment in case of a pyelonephritis is not different from that in other patients with a complicated UTI. The optimal duration for treatment of infected cysts is unknown. Usually a longer period of 4-6 weeks is recommended.

WHAT IS THE OPTIMAL TREATMENT IN PATIENTS WITH POLYCYSTIC KIDNEY DISEASE?	
Recommendation	PET scan can be useful to identify a cyst infection. PET scan is considered positive when increased Fludeoxyglucose (FDG) uptake is demonstrated in at least one cyst.
Recommendation	For the diagnosis of a cyst infection the following criteria should be used: - cyst infection is considered as definite in the presence of a cyst aspiration showing evidence of infection (neutrophils debris and/or micro-organism). - cyst infection is considered likely in the presence of all of the following features: fever (temperature >38.5°C for >3 days), abdominal pain (particularly a palpable area of renal or liver tenderness), increased C-reactive protein (CRP; >50 mg/L), and the absence of any significant recent intracystic bleeding or other causes of fever.
Recommendation	Duration of treatment in case of a pyelonephritis in patients with autosomal dominant polycystic kidney disease is not different from that in other patients with a complicated UTI.
Recommendation	In case of a cyst infection, it is recommended to start initially with ciprofloxacin, but to use the culture results to tailor treatment.
Recommendation	A period of 4-6 weeks is recommended for the treatment of an infected cyst.
Recommendation	In case of large (> 5 cm) infected cysts, early drainage is advised in combination with antibiotic treatment

WHAT ARE THE OPTIMAL PREVENTION METHODS IN PATIENTS WITH RECURRENT URINARY TRACT INFECTIONS?

Search strategy

Databases were Pubmed and the Cochrane Library.

Keywords: urinary tract infection AND prevention or urinary tract infection AND prophylaxis or urinary tract infection AND self treatment.

Limits: From 1990 until now, English, adults, humans, clinical trials, guideline, meta-analysis, RCT.

Pubmed: 426 results, all titles screened, 40 abstracts screened, 12 articles included.

Cochrane Library: 22 results, all titles screened, 4 abstracts screened, 3 reviews included.

Patient groups were patients with recurrent UTI (rUTIs), not patients with an increased chance for a UTI as, for example, spinal cord injury patients or pregnant women. For these patients we refer to the guideline of the *Werkgroep Infectie Preventie (WIP) Preventie van infecties als gevolg blaaskatherisatie*. Also articles concerning non-antibiotic agents/prophylaxis were included, but only of available agents (e.g. not bacterial interference). Articles about behavioral strategies to prevent rUTI were excluded. Prevention/prophylaxis by using certain regimens during certain procedures (e.g. after operations/interventions) in patients without rUTIs or for the prevention of bacteriuria were excluded.

Prophylaxis with antimicrobial agents during catheter use, placement or removal is described in the chapter on Catheter-associated UTI, and after renal transplantation is described in the chapter Renal Transplantation. For rUTI in men or in patients with a catheter we refer to the section on UTI in men or in patients with a catheter.

Literature overview

Recurrent urinary tract infections (rUTIs) is a common health care problem and is defined in the literature by three episodes of UTI in the last 12 months, or two episodes in the last 6 months. Approximately 50-70% of women will have a UTI sometime during their lifetime and 20-30% of women who have a UTI will have a rUTI (153) (154). In general, in men and post-menopausal women it is recommended to exclude anatomical or functional abnormalities of the urogenital tract as a cause of rUTI. In pre-menopausal women the yield of most diagnostic procedures is low (155).

There are four patterns of response of bacteriuria to therapy: cure, bacteriologic persistence, bacteriologic relapse, or reinfection. Bacteriologic persistence is persistence of bacteriuria with the same microorganism after 48 hours of treatment. Relapse is an infection with the same micro-organism that caused initial infection and usually occurs within 1-2 weeks after the cessation of treatment. A relapse indicates that the infecting organism has persisted in the urinary tract. Reinfection is an infection after sterilization of the urine. Most of the time there is a change in bacterial species. Reinfection can be defined as a 'true' recurrence. Both persistence and relapse may be related to inadequate treatment. It is very important to determine whether rUTIs are relapses or reinfections and to make a differentiation between these patterns, since this has treatment consequences. Experts are of the opinion that in a persistent UTI the cause must be evaluated. In a relapse of the UTI the treatment can be given for a longer period. All recommendations in this guideline concern patients with reinfections.

The first consideration in prevention is to address modifiable behavioral practices. Other effective strategies can be divided into antimicrobial or nonantimicrobial**.**

Antimicrobial prophylaxis

Low-dose antimicrobial therapy remains an effective intervention to manage frequent, recurrent, acute uncomplicated UTI. The antimicrobial may be given as continuous daily or every-other-day therapy, usually at bedtime, or as postcoital prophylaxis. Experts suggest an initial duration of prophylaxis is 6 months; however, 50% of women will experience recurrence by 3 months after discontinuation of the prophylactic antimicrobial. When this occurs, prophylaxis may be reinstituted for as long as 1 or 2 years and remains effective.

Nineteen studies involving 1120 women were included in a Cochrane review (153)**.** During active prophylaxis the rate range of microbiological recurrence per patient-year was 0-0.9 person-year in the antibiotic group vs. 0.8-3.6 with placebo. The RR of having one microbiological recurrence was 0.21 (95% CI 0.13-0.34) favoring antibiotic, and the number-needed-to-treat (NNT) was 1.85. For clinical recurrences the RR was 0.15 (95% CI 0.08-0.28) and the NNT was 1.85. The RR of having one microbiological recurrence after prophylaxis was 0.82 (95% CI 0.44-1.53). The RR for severe side-effects was 1.58 (95% CI 0.47-5.28) and for other side-effects the RR was 1.78 (CI 1.06-3.00) favoring placebo. Side-effects included vaginal and oral candidiasis and gastrointestinal symptoms (153). One RCT compared postcoital versus continuous daily ciprofloxacin and found no significant difference in rates of UTIs, suggesting that postcoital treatment could be offered to women who have UTI associated with sexual intercourse (156).

After the publication of the Cochrane review, in a new study 317 women with rUTI were randomized to receive one sachet containing fosfomycin trometamol equivalent 3 g or placebo every 10 days during 6 months. All endpoints concerning the incidence of UTIs were in favor of the fosfomycin (157).

<u>Self-diagnosis and self treatment with antimicrobials</u>
Studies of the natural history of rUTI demonstrate substantial variability in the number of recurrences, which often cluster in time. Thus, continuous prophylaxis may result in unnecessary antimicrobial use in women who have infrequent recurrences or clustered recurrences. An alternative strategy, namely patient self-diagnosis and self-treatment (in other words women start with antimicrobial treatment, which they already have at home, when they think that they have a UTI) of recurrent UTIs, may decrease antimicrobial use and improve patient convenience. In a prospective study the accuracy of self-diagnosis and the cure rates seen with self-treatment of UTIs in 172 women (mean age 23 years) who had a history of rUTIs was determined. A total number of 88 of 172 women self-diagnosed a total of 172 UTIs. Laboratory evaluation showed a uropathogen in 144 cases (84%), sterile pyuria in 19 cases (11%), and no pyuria or bacteriuria in 9 cases (5%). Clinical and microbiological cures occurred in 92% and 96%, respectively, of culture-confirmed episodes. No serious adverse events occurred (154).

In a smaller study 34 women (mean age 36 years) were enrolled. A total of 28 women followed for 355 months had 84 symptomatic episodes and 25 had 67 UTIs. Of the 84 symptomatic episodes 78 (92%) responded clinically. Of 78 cultured episodes 11 (14%) were negative. The remaining 67 cultured documented infections were cured microbiologically 5-7 days after therapy. No adverse effects occurred (158).

In another study, 68 postmenopausal women were randomized to take a low-dose antibiotic each night (continuous group, n=37) or a single-dose antibiotic each time they experienced conditions predisposing to UTI (intermittent group, n=31). During the 12-month study, 1.4 and 1.9 UTIs/patient developed in the continuous and the intermittent groups, respectively, which was significantly lower than the incidence of UTIs in the previous 12 months in these patients (4.7 and 5.1 UTIs/patient, respectively). The incidence of gastrointestinal adverse events was significantly lower in the intermittent group compared with the continuous group (9.1% versus 30.0%) (159).

Nonantimicrobial strategies
Several nonantimicrobial strategies to prevent recurrent UTI have been developed and evaluated. In this guideline we describe the studies concerning vitamin C, cranberries, estrogens, lactobacilli and methenamine.

<u>Vitamin C</u>

Many women use vitamin C as a prevention method against UTI, but only two trials (one in non-pregnant and one in pregnant women) have been performed, with contradictory results.

In the first study the effect of ascorbic acid on urine pH was studied in spinal cord injury patients. The study was designed to compare the baseline urine pH value and the urine pH value after the administration of placebo or ascorbic acid 4 x 500 mg per day. Thirty-eight patients began the study, but only 13 patients completed the study. A significant decrease in urine pH value was not obtained. There was no clinical benefit from the use of ascorbic acid, 2 patients in the vitamin C and 1 patient in the placebo group developed a UTI during the 6th and 8th day after start (160).

In the other non-randomized trial in pregnant women, it was shown that daily intake of 100 mg ascorbic acid reduced the incidence of UTIs by 30% (161). However, it is very difficult to understand the results of this trial, because the daily vitamin C dose was very low and the endpoint very subjective.

<u>Cranberries</u>

In a Cochrane review 10 studies (n=1049, 5 cross-over, 5 parallel group) were included. Cranberry/cranberry-lingonberry juice versus placebo, juice or water was evaluated in 7 studies, and cranberry tablets versus placebo in 4 studies (one study evaluated both juice and tablets). Cranberry products significantly reduced the incidence of UTIs at 12 months (RR 0.65, 95% CI 0.46-0.90) compared with placebo/control. Cranberry products were more effective in reducing the incidence of UTIs in women with recurrent UTIs, than in elderly men and women or people requiring catheterization. The authors concluded that there is some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12-month period, particularly for women with recurrent UTIs. Its effectiveness for other groups is less certain. The large number of dropouts/withdrawals indicates that cranberry juice may not be acceptable over long periods of time. It is not clear what is the optimum dosage or method of administration (e.g. juice, tablets or capsules). Daily cranberry products (juice or tablets) decrease the frequency of recurrent infection by about 30-40%, compared with 90-95% effectiveness of antimicrobial use (162).

In a recent study it was shown that cranberry capsules are less effective than low-dose TMP/SMX in the prevention of rUTIs in premenopausal women. However, in contrast to low-dose TMP/SMX, cranberries did not result into in an increase in resistant micro-organisms in the commensal flora [(84).

<u>Estrogens</u>

Estrogen replacement restores atrophic mucosa, lowers vaginal pH, and may prevent urinary tract infections. Therefore, topical vaginal estrogen is a potential intervention to decrease recurrent episodes for postmenopausal women, but its use also remains controversial.

Nine studies (3345 women) were included in a Cochrane review (163). Oral estrogens did not reduce UTI compared to placebo (4 studies, 2798 women: RR 1.08, 95% CI 0.88 to 1.33). Vaginal estrogens versus placebo reduced the number of women with UTIs in two small studies using different application methods. The RRs were 0.25 (95% CI 0.13-0.50) (164) in the first study and 0.64 (95% CI 0.47-0.86) in the second study (165). Adverse events for vaginal estrogens were breast tenderness, vaginal bleeding or spotting, nonphysiologic discharge, vaginal irritation, burning and itching.

In another study the efficacy and safety of estriol-containing vaginal pessary was compared with the use of oral nitrofurantoin macrocrystal therapy for preventing UTI in postmenopausal women with rUTI. Over a period of 9 months, 86 women received an estriol-containing vaginal pessary (0.5 mg estriol) twice weekly, and 85 women received nitrofurantoin (100 mg) once daily. A total number of 124 episodes of UTI in women who received estriol-releasing pessaries and 48 episodes of UTI in women treated with nitrofurantoin were recorded (P=0.0003). Twenty-eight women (32.6%) who received estriol had no episodes of UTI versus 41 women (48.2%) in the nitrofurantoin group. There was a significant increase in the number of superficial cells in women who received estriol, whereas in the NM group, no such changes occurred (166).

Lactobacilli

Probiotics to re-establish vaginal colonization with H_2O_2-producing lactobacilli, have also being investigated. A recent double-blind placebo-controlled trial studied a *Lactobacillus crispatus* intravaginal suppository probiotic (Lactin-V; Osel) (daily for 5 days, then once weekly for 10 weeks) for the prevention of recurrent UTI. A total of 100 premenopausal women with at least one prior UTI in the last 12 months (median number lifetime UTIs was 4.5) were randomized to receive either Lactin-V or placebo after treatment with antimicrobials for acute UTI. Recurrent UTI occurred in 7/48 (15%) of women receiving Lactin-V compared with 13/48 (27%) of women receiving placebo (RR 0.5; 95% CI 0.2-1.2). High-level vaginal colonization with *L. crispatus* (≥10e6 throughout follow-up) was associated with a significant reduction in recurrent UTI only for Lactin-V (RR for Lactin-V 0.07; RR for placebo 1.1; P < 0.01) (167).

In another RCT 252 postmenopausal women with rUTIs were randomized to receive 12 months of prophylaxis with TMP-SMX 480 mg, once daily or oral capsules containing 10e9 colony-forming units of *Lactobacillus rhamnosus GR-1* and *Lactobacillus reuteri RC-14* twice daily. The mean number of symptomatic UTIs in the year preceding randomization was 7.0 in the TMP-SMX group and 6.8 in the lactobacilli group. In the intention-to-treat analysis, after 12 months of prophylaxis, these numbers were 2.9 and 3.3, respectively. The between-treatment difference of 0.4 UTIs per year (95% CI, -0.4 to 1.5) was outside the non-inferiority margin. At least 1 symptomatic UTI occurred in 69.3% and 79.1% of the TMP-SMX and lactobacilli participants, respectively; median times to the first UTI were 6 and 3 months, respectively (log rank p=0.02). However, after 1 month of TMP-SMX prophylaxis, resistance to TMP-SMX, trimethoprim, and amoxicillin had increased from approximately 20-40% to approximately 80-95% in *E. coli* from the feces and urine of asymptomatic women and among *E. coli* causing a UTI. During the 3 months after TMP-SMX discontinuation, resistance levels gradually decreased. Resistance did not increase during lactobacilli prophylaxis (168).

Methenamine salts

Methenamine salts act via the production of formaldehyde from hexamine, which acts as a bacteriostatic agent without being affected by bacterial resistance mechanisms. They are well tolerated. In vitro and in vivo studies suggest that a urinary pH below 5.5 is needed for bacteriostatic concentrations of free formaldehyde to be generated from methenamine hippurate. Therefore, urinary tract infections with urease producing *Proteus* (and possibly *Pseudomonas*), that increase urine pH through hydrolyzation of urea to ammonia, will not be affected by methenamine due to insufficient generation of formaldehyde. Acidification of urine may be achieved with additional high dose vitamin C (1-4 gram) Thirteen studies (2032 participants) were included in a Cochrane review of methenamine hippurate (169). Subgroup analyses suggested that methenamine hippurate may have some benefit in patients without renal tract abnormalities or urinary catheters (symptomatic UTI: RR 0.24, 95% CI 0.07-0.89; bacteriuria: RR 0.56, 95% CI 0.37-0.83), but not in patients with known renal tract abnormalities (symptomatic UTI: RR 1.54, 95% CI 0.38- 6.20; bacteriuria: RR 1.29, 95% CI 0.54-3.07). For short-term treatment duration (1 week or less) there was a significant reduction in symptomatic UTI in those without renal tract abnormalities (RR 0.14, 95% CI 0.05-0.38). The rate of adverse events was low.

However, in 2011 formaldehyde was officially declared carcinogenic by the National Toxicology Program (NTP). The exposure in the bladder to formaldehyde can be high if it is used at high doses for a prolonged time, but the risk of bladder cancer from use of

methenamine is a theoretical risk which has not been confirmed (National Toxicology Program, Department of Health and Human Services Report on Carcinogens, Twelfth Edition (2011) Formaldehyde).

Conclusions

Level 4	It is important to differentiate between persistence, relapse and reinfection, because this has treatment consequences.
Level 1	Continuous antibiotic prophylaxis (with different agents) for 6-12 months reduced the rate of UTI during prophylaxis compared to placebo in women with recurrent, acute uncomplicated urinary tract infection [(153) A1; (157) A2].
Level 3	No significant difference in rates of UTIs were found between postcoital versus continuous daily ciprofloxacin [(156) A2].
Level 2	Women can accurately self-diagnose and self-treat recurrent UTIs [(154) B; (158) B; (159) B].
Level 3	There is no clinical benefit from the use of ascorbic acid (vitamin C) in the prevention of UTIs in spinal cord injury patients [(160) B].
Level 3	There is clinical benefit from the use of ascorbic acid (vitamin C) in the prevention of UTIs in pregnant women [(161) B].
Level 1	The effect of daily cranberry products (juice or tablets) decreases the frequency of recurrent infection in women with rUTIs by about 30-40%. It is not clear what the optimum dosage or method of administration is [(162) A1].
Level 3	Cranberry capsules are less effective than low-dose TMP/SMX in the prevention of rUTIs in premenopausal women. However, in contrast to low-dose TMP/SMX, cranberries do not result in an increase in resistant micro-organisms in the commensal flora [(84) A2].
Level 3	Prophylaxis with *Lactobacillus crispatus* intravaginal suppository probiotic after treatment for cystitis is associated with a reduction in recurrent UTI in premenopausal women [(167) A2].

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Level 3	In postmenopausal women with recurrent UTIs, oral capsules with *L rhamnosus GR-1* and *L. reuteri RC-14* marginally did not meet the non-inferiority criteria in the prevention of UTIs when compared with TMP-SMX. However, unlike TMP-SMX lactobacilli did not increase antibiotic resistance of the commensal flora [(168) A2].
Level 1	Topical vaginal estrogen is a potential intervention to decrease the number of recurrent episodes for postmenopausal women [(163) A1].
Level 3	Use of an estriol-containing pessary is less effective than oral nitrofurantoin in the prevention of bacteriuria in postmenopausal women [(166) A2].
Level 1	Methenamine hippurate may be effective for preventing UTI in patients without renal tract abnormalities, particularly when used for short-term prophylaxis [(169) A1], but no evidence exists about long-term use or use in patients with urinary catheters and a potential health risk of prolonged exposure to formaldehyde may preclude long term administration.

Other considerations

When the patient has a persistent UTI, the cause of this persistence must be evaluated (renal abcess, etc.). Experts are of the opinion that when the patient has a relapse of a UTI, the UTI has to be treated again, but with a longer treatment duration (for example 4 instead of 2 weeks). All recommendations in this Guideline concern patients with reinfections.

The results of the above-mentioned studies show that low-dose antimicrobial prophylaxis is the most effective in the prevention of rUTIs. However, this results in increasing resistance of the commensal flora. The recently updated IDSA guideline on the treatment of uncomplicated UTI recommends to take into account this "collateral damage" (3). Furthermore, it has been shown that different antimicrobial agents have different effects. In one study the gram-negative aerobic flora was strongly affected during the administration of norfloxacin and TMP/SMX, but not during nitrofurantoin (170). These findings help in the selection of the most appropriate antimicrobial agent for prophylaxis in recurrent UTIs.

Furthermore, prophylaxis with non-antimicrobial agents might not result in an increase of antimicrobial resistance of the commensal flora (84), (168). Therefore, the use of cranberry prophylaxis oral or *Lactobacillus crispatus* intravaginal in premenopausal women and oral

capsules with *L rhamnosus GR-1* and *L. reuteri RC-14* or topical vaginal estrogen in post-menopausal women can still be recommended.

Concerning the recommendation about the use of vitamin C, it is difficult to understand the positive effect of the prevention trial in pregnant women, because the daily vitamin C dose was much lower (1 x 100 mg instead of 4 x 500 mg) than in the trial with the negative results. Moreover, the trial was not blinded and the endpoint was highly subjective (161).Therefore, the Guideline committee is of the opinion that prophylaxis with vitamin C cannot be recommended.

WHAT ARE THE POSSIBLE PREVENTION METHODS IN PATIENTS WITH RECURRENT UTI?	
Recommendation	For recurrent UTI in men or in patients with a catheter we refer to the section on UTI in men or in patients with a catheter.
Recommendation	A differentiation must be made between persistence, relapse and reinfection of the UTI.
Recommendation	In a persistent UTI the cause must be evaluated. In a relapse of the UTI the treatment can given for a longer period.
Recommendation	All women can usually self-diagnose and self-treat a recurrent UTI.
Recommendation	The use of ascorbic acid (vitamin C) is not recommended in the prevention of UTIs.
Recommendation	In premenopausal women with recurrent UTI the following prophylaxis can be recommended to decrease the number of recurrent episodes: - daily or postcoital low dose antimicrobial therapy - cranberry products - *Lactobacillus crispatus* intravaginal suppository
Recommendation	In postmenopausal women with recurrent UTI the following prophylaxis can be recommended to decrease the number of recurrent episodes: - daily or postcoital low-dose antimicrobial therapy - estrogens locally - oral capsules with *L rhamnosus GR-1* and *L. reuteri RC-14*
Recommendation	Methenamine hippurate can be used for a maximum of 1 week to prevent UTI in patients without renal tract abnormalities.

WHAT ARE REASONABLE QUALITY INDICATORS FOR ANTIBIOTIC THERAPY IN PATIENTS WITH UTI?

Literature overview

Quality indicators (QIs) must comply with high quality standards and should be constructed in a careful and transparent manner (171). Optimally, they should measure the quality in a valid and reliable manner with little inter- and intra-observer variability so that they are suitable for comparison between professionals, practices, and institutions (171). However, it should be emphasized that many of the current QIs have been constructed based on relatively weak evidence and, rather, represent current best practices.

Based on the 2006 SWAB guideline for the treatment of complicated UTIs, in 2008 we developed a set of valid QIs for the antibiotic treatment of patients with UTI (172). A multidisciplinary panel of 13 experts reviewed and prioritized recommendations extracted from this evidence-based national guideline. The content validity was assessed in 2 consecutive rounds with an in-between discussion meeting. Next, we tested the feasibility, interobserver reliability, opportunity for improvement, and case-mix stability of the potential indicators for a dataset of 341 inpatients and outpatients with complicated UTIs who were treated at the urology or internal medicine departments at 4 hospitals. The panel selected and prioritized 13 indicators. Four indicators performed satisfactorily both in the Internal medicine and Urology departments:

1. performance of urine culture

2. prescription of treatment in accordance with guidelines

3. tailoring of treatment on the basis of culture results

4. switch to oral treatment when possible ;

An additional five indicators performed satisfactorily only in the Internal Medicine department, mainly because not enough patients could be included in the Urology department:

5. selective use of fluoroquinolones

6. treatment duration at least 10 days

7. prescription of treatment for men in accordance with guidelines

8. replacement of catheters in patients with UTI

9. adaptation of the dosage on the basis of renal function.

Conclusions

Level 3	Based on the 2006 SWAB guideline for the treatment of complicated UTIs, a set of valid quality indicators was developed: Four indicators performed satisfactorily both in the Internal medicine and Urology departments and an additional five indicators performed satisfactorily only in the Internal Medicine department [(172) C].

Other considerations

All the above-mentioned QIs can be developed again from the present revision of this guideline, with the exception of "Administration of treatment for at least 10 days". Based on the latest available study results, the updated guideline recommendations concerning treatment durations are:

1. Women with acute uncomplicated pyelonephritis should be treated for 7 days when treated with ciprofloxacin.

2. Women with acute uncomplicated pyelonephritis should be treated for 10-14 days when treated with TMP-SMX or a beta-lactam.

3. Women with acute complicated pyelonephritis or other complicated UTIs should be treated for 10-14 days.

4. Men with complicated UTIs should be treated for 14 days.

Therefore, the Guideline committee decided to change the treatment duration indicator to read: Treatment duration should follow the guideline recommendations for the different patient groups.

Furthermore, because interpretation of the results of the indicator "Selective use of fluoroquinolones" was very difficult, this indicator is no longer recommended (Spoorenberg et al. abstract IDSA 2011).

Recent evaluation of these QIs among 1,964 patients with a complicated UTI in 19 Dutch hospitals revealed that the quality of antibiotic treatment showed a wide variation between departments and considerable room for improvement. Median indicator performance ranged from 26-77%, with the lowest median performance on the indicator "Prescribe treatment for men in accordance with guidelines" (26%, range between departments 5-51%), and the highest on the indicator "Perform a urine culture" (77%, range between departments 28-93%). For other indicators like "Tailor treatment according to culture results" and "Switch

from i.v. to oral therapy after 48-72 hours" there was also a wide inter-departmental range (Spoorenberg et al. abstract IDSA 2011).

Another important consideration is that QIs are increasingly used for perspectives other than internal quality improvement alone. External comparison (QIs used as performance indicators) is commonly used to compare hospitals and physicians, as minimal control measures for the Dutch Healthcare Inspectorate, but also as tools for contract negotiations between hospitals and healthcare insurers, and as transparency measures for patient and public.

The current Guideline committee is of the opinion that the above-mentioned process indicators may be used as internal Quality Improvement indicators used in local QI projects, but they were not designed as performance indicators allowing a valid comparison between hospitals.

WHAT ARE REASONABLE QUALITY INDICATORS (FOR INTERNAL QUALITY IMPROVEMENT) FOR EMPIRICAL ANTIMICROBIAL TREATMENT IN PATIENTS WITH A UTI?	
Recommendation	Reasonable process quality indicators for empirical antibiotic therapy in patients with UTI to use in the Internal Medicine and Urology department are: - Performance of urine culture. - Prescription of treatment in accordance with guidelines. - Tailoring of treatment on the basis of culture results. - Switching to oral treatment when possible. An additional four indicators to use only in the Internal Medicine department are: - Treatment durations must follow the guidelines for the different patient groups. - Prescription of treatment for men in accordance with guidelines. - Replacement of catheters in patients with UTI. - Adaptation of the dosage on the basis of renal function.
Recommendation	It is recommended by the current Guideline committee that these process indicators may be used as internal Quality Improvement

	indicators in local QI projects. It is not recommended to use these indicators as performance indicators to compare hospitals.

GUIDELINE APPLICABILITY AND DECLARATION OF INTEREST

Applicability

This guideline was developed and approved by representatives of the professional medical societies, mentioned in the introduction and methods sections and therefore represents the current professional standard in 2013. The guideline contains general recommendations. It is possible that, in individual cases, these recommendations do not apply. Applicability of the guideline in clinical practice resorts to the responsibility of every individual practitioner. Facts or circumstances may occur, in which deviation of the guideline is justified, in order to provide optimal quality of care for the patient.

Declaration of interest

The SWAB employs strict guidelines with regard to potential conflicts of interests as described in the SWAB Format for Guideline Development (www.swab.nl). Members of the preparatory committee reported the following potential conflicts of interest:

SE Geerlings: for the RCTs mentioned in the reference numbers 84 en 168 (Beerepoot et al.): Ref 84: Cranberry capsules and placebo capsules for this trial were delivered by Springfield Nutraceuticals, Oud Beijerland, The Netherlands. Ref 168: Chr Hansen A/S, Denmark has the patents for *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 and donated the placebo capsules for this trial.

E v Haarst: has received speaker fees on a national urological symposium from GlaxoSmithKline, the manufacturer of amoxicillin-clavulanic acid.

Other authors: no potential conflicts of interest declared.

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ABBREVIATIONS

ADPKD	Autosomal dominant polycystic kidney disease
AGPN	Acute Graft Pyelonephritis
ASB	Asymptomatic Bacteriuria
CA	Catheter Associated
CA-UTI	Catheter-Associated Urinary Tract Infection
CI	Confidence Interval
CMV	Cytomegalovirus
CNI	Calcineurine inhibitors
CP/CPPS	Chronic Prostatitis/Chronic Pelvic Pain Syndrome
CRP	C-reactive Protein
CT	Computer Tomography
ED	Emergency Departments
ESBL	Extended-Spectrum Beta-Lactamase
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FDG	Fludeoxyglucose
G6PD	glucose-6 phosphate dehydrogenase
GBS	group B streptococcus
GFR	Glomerular Filtration Rate
GP	General Practitioner
HR	Hazard Ratio
IDSA	Infectious Diseases Society of America (IDSA)
ISIS-AR	Infectious Diseases Surveillance Information System on Antimicrobial Resistance
KDIGO	Kidney Disease: Improving Global Outcomes
LTCFs	Long-Term Care Facilities
LUTS	Lower Urinary Tract Symptoms
MDRD	Modification of Diet in Renal Diseases
MRI	Magnetic Resonance Imaging
mTOR	mammalian Target Of Rapamycine
NHG	Nederlands Huisartsen Genootschap
NNT	Number Needed to Treat
NTP	National Toxicology Program
OR	Odds ratio
PET-scan	Positron Emission Tomography scan
PHC	Primary health care centers

PJP	*Pneumocytis jiroveci* pneumonia
PSA	Prostate-Specific Antigen
QIs	Quality Indicators
RCT	Randomized Controlled Trial
RR	Relative Risk
rUTI	recurrent Urinary Tract Infection
SWAB	Stichting Werkgroep Antibiotica Beleid
TMP-SMX	Trimethoprim-Sulfamethoxazole
USRDS	United States Renal Data System
UTI	Urinary Tract Infection
vs.	versus
VUR	vesico-ureteric reflux
WIP	Werkgroep Infectie Preventie

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