Optimization of the antibiotic policy in the Netherlands: SWAB guidelines for antimicrobial therapy of urinary tract infections in adults

SWAB Urinary Tract Infections Guidelines Committee

1. Drs. M.L. Terpstra (coordinator)
2. Prof. dr. S.E. Geerlings (chair)
3. Dr. C. van Nieuwkoop (Dutch Society for Internal Medicine, NIV)
4. Dr. E.P. van Haarst (Dutch Society for Urology, NVU)
5. Dr. H. Boom, (Dutch Federation for Nephrology, NFN)
6. Dr. B.J. Knottnerus (Dutch College of General Practitioners, NHG)
7. Drs. W. Rozemeijer (Dutch Society for Medical Microbiology, NVMM)
8. Prof. dr. C.J. de Groot (Dutch Society for Obstetrics and Gynaecology, NVOG)
9. Prof. dr. C.M.P.M. Hertogh (Dutch Association of Elderly Care Physicians, Verenso)
10. Dr. P.D. van der Linden (Dutch Society for Hospital Pharmacists, NVZA)
10. Prof. dr. J.M. Prins (Dutch Working Party on Antibiotic Policy, SWAB)

Sections that are changed compared to the 2013 version of the guidelines are highlighted in yellow.

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Secretariat SWAB
p/a
Leids Universitair Medisch Centrum
Afd. C5-P
Postbus 9600
2300 RC Leiden
secretariaat@swab.nl
www.swab.nl

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RECOMMENDATIONS

WHAT IS THE OPTIMAL EMPIRICAL ANTIMICROBIAL AGENT?	
Recommendation	In patients suspected of having UTI with systemic symptoms, 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 UTI with systemic symptoms.
Recommendation	The combination of a 2nd generation cephalosporin + an aminoglycoside, a 3rd generation cephalosporin or amoxicillin + an aminoglycoside intravenously can be recommended as empirical treatment of UTI with systemic symptoms. Empirical treatment should be continued until the susceptibility of the pathogen is determined.
Recommendation	Empirical treatment with ciprofloxacin is only recommended when treatment is started orally, when patients do not require hospitalization or when the patient had an anaphylactic reaction on beta-lactam antibiotics, provided that the local resistance percentages are < 10%.
Recommendation	Ciprofloxacin and other fluoroqinolones are not suitable for the empirical treatment of UTI with systemic symptoms in patients from the urology department or when patients have used fluoroquinolones in the last 6 months.
Recommendation	When the results of the urine culture are known, therapy must be adjusted and if possible narrowed. If the patient is clinically stable, able to tolerate oral medication and if an adequate oral antibiotic can be given, the patient should get oral treatment.
Recommendation	If symptoms have resolved after treatment, follow-up cultures are not recommended.
Recommendation	New antibiotic agents such as ceftazidime-avibactam, ceftolozane-tazobactam and fosfomycin for injection are currently not recommended in the empiric treatment of UTI with systemic symptoms.
Recommendation	We recommend empirical therapy against *Enterobacterales* resistant to 3rd generation cephalosporins in patients with UTI with systemic symptoms and prior (1 year) colonization or infection with

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	such micro-organisms. The resistance pattern of the strain should guide empirical therapy.

WHAT IS THE OPTIMAL TREATMENT DURATION?	
Recommendation	Non-pregnant women with UTI with systemic symptoms should be treated for 7 days when treated with ciprofloxacin.
Recommendation	Non-pregnant women with UTI with systemic symptoms should be treated for 10-14 days when treated with TMP-SMX or a beta-lactam[1].
Recommendation	Men with UTI with systemic symptoms should be treated for 14 days[1].

[1] In patients where a shorter treatment duration is desired due to relative-contraindications, 7 days of treatment may be considered if the patient is hemodynamically stable and afebrile for at least 48 hours.

WHAT IS THE OPTIMAL TREATMENT OF UTI IN MEN?	
Recommendation	For the treatment of a UTI without systemic symptoms men 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 nitrofurantoin 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 fluoroquinolones 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 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

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	cystitis during pregnancy. Nitrofurantoin must not be used within 30 days before delivery.
Recommendation	A 3rd generation cephalosporin (4 dd 1000 mg cefotaxim or 1 dd 2000 mg ceftriaxon) is the drug of first choice for the treatment of UTI with systemic symptoms during pregnancy.
Recommendation	The treatment duration of cystitis during pregnancy should be 5 days.
Recommendation	The treatment duration of UTI with systemic symptoms during pregnancy should be 10-14 days.
Recommendation	Antepartum UTI with systemic symptoms should be treated in a hospital setting and treatment should be started intravenously.
Recommendation	Screening of asymptomatic bacteriuria at 16-20 weeks gestation for better maternal and neonatal outcome is not recommended.
Recommendation	When ASB is diagnosed, it should be treated as a cystitis regardless of the pregnancy term.
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 recommended, because antibiotic prophylaxis during delivery is necessary.
Recommended	If symptoms have resolved after treatment of urinary tract infection, follow up cultures are not recommended.

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.
Recommendation	There is no need to screen for bacteriuria in patients with short- or long-term urinary catheters, or in those who catheterize themselves intermittently over prolonged periods.

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IS ANTIMICROBIAL PROPHYLAXIS INDICATED AT THE TIME OF CATHETER PLACEMENT, REPLACEMENT OR REMOVAL?	
Recommendation	In patients with either short- or long term urinary catheters, prophylactic systemic or local antimicrobials should **not** be administered routinely at the time of catheter placement, replacement or removal.

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 such as *Pseudomonas aeroginosa., Serratia spp., Providencia spp., and Acinetobacter spp.*
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 an aminoglycoside. Excluding enterococci makes a third-generation cephalosporin with an aminoglycoside 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?
Recommendation	See general treatment guidelines for the treatment duration of CA-UTI with systemic symptoms.

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Recommendation	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 IN PATIENTS WITH DIABETES MELLITUS?	
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?	
Recommendation	Screening and treatment of ASB in renal transplant recipients >2 months after renal transplantation is not recommended.
Recommendation	No recommendation can be made about screening and treatment of ASB in renal transplant patients <2 months after renal transplantation.
Recommendation	Treatment of UTI in renal transplant patients should be according to the general guidelines for treatment of UTI with systemic symptoms, but in the first 3 months after transplantation empirical treatment with a combination that also covers *Pseudomonas aeruginosa* and enterococci can be considered.
Recommendation	Due to its nephrotoxicity, aminoglycosides should be used with caution.
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 in the last 12 months have to be checked.
Recommendation	Removal of the urinary catheter should be done as soon as appropriate.

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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?	
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 °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	If a cyst infection is probable, as described in the diagnostic algorithm in figure 1, a PET scan may be considered. PET scan is considered positive when increased Fludeoxyglucose (FDG) uptake is demonstrated in at least one cyst.
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 UTI with systemic symptoms.
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.

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WHAT IS NEW IN THIS GUIDELINE COMPARED TO THE GUIDELINES OF 2013?

We no longer use the definitions: complicated UTI, uncomplicated pyelonephritis and complicated pyelonephritis.

Unfortunately, there is no international consensus on the definition and classification of UTI. The guidelines of the Dutch Association of Urology follow the definitions of the European Association of Urology, and distinguishes uncomplicated and complicated UTI. Because the group of patients with a complicated UTI is very heterogeneous, including women with an uncomplicated pyelonephritis, men with a cystitis and all patients with a urosepsis, these Urology guidelines contain a broad subclassification.

The Guideline committee of the current SWAB guidelines decided to use the following definitions, which are in line with the definitions used in the Standard for Urinary Tract Infections of the Dutch College of General Practitioners (NHG):

1. Cystitis: a UTI without signs of tissue invasion or systemic symptoms.
2. A UTI with systemic symptoms (such as: fever, delirium) or other signs of tissue invasion (flank pain).
3. A UTI in specific patient populations: men, pregnant women, patients with diabetes, patients with a urinary catheter, renal transplant recipients and patients with autosomal dominant polycystic kidney disease (ADPKD).

However, studies including patients with UTI have used different definitions and inclusion criteria. Therefore, in the literature overviews provided in each chapter, we use the nomenclature from the cited manuscript. However, in the recommendations, our own definitions are followed.

Treatment of cystitis is described in the Standard for Urinary Tract Infections of the Dutch College of General Practitioners (NHG). Treatment of UTI with systemic symptoms is described in Chapter 1 and 2 of the current SWAB Guidelines. Chapter 3-8 describes treatment of UTI in the mentioned specific patient populations.

Furthermore:

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1. In Chapter 1 (optimal treatment), we added literature and recommendations on the new antimicrobials agents ceftazidime-avibactam and ceftolozane-tazobactam. These antimicrobials are currently not recommended as empiric treatment for UTI with systemic symptoms.

2. In chapter 1 (optimal treatment), we follow the recommendations of the recently updated SWAB Sepsis 2019 Guidelines for treatment of ESBL. These Guidelines recommend empirical therapy against *Enterobacterales* resistant to 3rd generation cephalosporins in patients with UTI with systemic symptoms and prior (1 year) colonization or infection with such micro-organisms.

3. In Chapter 2, (treatment duration), the recommended treatment duration for women with UTI with systemic symptoms treated with TMP-SMX or a beta-lactam is still 10-14, and in men with UTI with systemic symptoms it is still 14 days. However, since there are indications that 7 days may be sufficient also for these antimicrobials and also in men, we added a footnote to this recommendation stating that in patients for whom a shorter treatment duration is desired due to relative-contraindications, 7 days of treatment may be considered if the patient is hemodynamically stable and afebrile for at least 48 hours.

4. In Chapter 3 (men), we no longer make a distinction between 'young' and 'old' men (>40) with cystitis, since this cut-off is arbitrary and young men with a cystitis and no comorbidity are usually treated by general practitioners (Standard for Urinary Tract Infections of the Dutch College of General Practitioners (NHG). In these NHG Guidelines, no distinction is made between ' young' and 'old' men either.

5. In Chapter 4 (pregnancy), we no longer recommend to screen for ASB during pregnancy in risk (e.g. diabetes) populations.

6. In Chapter 4 (pregnancy), we no longer recommend follow up cultures after treatment of UTI during pregnancy when symptoms have resolved.

7. In chapter 7 (renal transplant recipients), we no longer recommend to treat ASB in all patients <6 months after transplantation, and only make recommendations about the treatment of ASB >2 months after transplantation. There is insufficient evidence to

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make recommendations about the treatment (yes or no) of ASB <2 months after transplantation.

8. We have adopted a diagnostic algorithm for the diagnosis of cyst infection in APDKD.

The Guideline committee has decided to remove the sections on:

1. Antibiotic allergy, since this is beyond the scope of these Guidelines and the SWAB Guidelines on Antibiotic Allergy will be published in 2021.
2. Prophylactic strategies, with the exception of certain specific questions were confusion may exist in clinical practice (such as use of antibiotics during catheter exchange)
3. Prostatic syndrome, which usually does not have a bacterial aetiology and is not a UTI.
4. Asymptomatic bacteriuria (ASB), which is not a UTI and there is a general consensus that ASB does not require treatment. An exception is made in chapters on specific patient populations where there is still discussion on treatment of ASB.
5. The chapter on recurrent UTI has been removed, as recurrent UTI is extensively discussed in the recently updated Standard for Urinary Tract Infections of the Dutch College of General Practitioners (NHG): https://richtlijnen.nhg.org/standaarden/urineweginfecties, and the Dutch Society for Urology (NVU) Guidelines for Urinary tract Infection: https://www.nvu.nl/en-us/kwaliteit/richtlijnen/actuelerichtlijnen.aspx
6. The chapter on quality indicators has been removed, as this subject is not specific for UTI. A set of quality indicators has been developed by van den Bosch et al [1, 2] which is applicable to infectious diseases in general. These indicators are further described in the SWAB Guidelines for Antimicrobial Stewardship.

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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.

Prof dr. Johan W. Mouton was part of the Committee for the 2020 update of the SWAB guidelines for antimicrobial therapy of urinary tract infections. Regretfully he passed away on the 9th of July 2019.

PURPOSE AND SCOPE OF THE 2020 UPDATE OF THE GUIDELINES FOR THE TREATMENT OF URINARY TRACT INFECTIONS

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

In the 2020 version of these guidelines, we no longer use the term ‘complicated UTI’ and ‘uncomplicated and complicated pyelonephritis, as these terms may lead to confusion. Instead, we now address UTIs with systemic symptoms and UTIs in specific patient groups that may be at risk for complications. For guidelines considering the treatment of UTI without systemic symptoms in patients without risk factors for complications, see the recently updated Standard for Urinary Tract Infections of the Dutch College 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.

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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 Enterobacterales?
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?
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?

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 the 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.

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Literature search

For this 2020 update, we performed a comprehensive search for literature on the treatment of UTI published after the publication of the previous SWAB cUTI Guideline, with the help of a Medical Information Retrieval Specialist (R. Spijker). To make sure we would not miss literature published during the preparation process of the SWAB cUTI 2013, our time limit was set on 2012. We searched Cochrane Central Register of Controlled Trials (Cochrane Library), Medline (Ovid) and Embase (Ovid) for randomized controlled trials (RCTs) and systematic reviews (SRs) published between 2012 and the 20th of December 2019. Details of the search terms can be found in appendix 1.

We identified 5113 RCTs and 2442 SRs. Titles and abstracts were initially screened by M.L. Terpstra. If an article contained any eligible information for either of the chapters of these Guidelines, S.E. Geerlings and M.L. Terpstra discussed whether it should be considered for inclusion in this chapter. In case of doubt, the rest of the Committee was included in this discussion as well. General exclusion criteria were: studies on uncomplicated cystitis, studies published in a language other than English or Dutch and studies on antimicrobial agents not available in the Netherlands. Furthermore, RCTs that were already included in one of the SRs were excluded.

Eventually, a total number of 49 SRs and 10 RCTs were included in this update of the SWAB UTI Guidelines. Paragraphs from the SWAB 2013 Guidelines with data from RCTs that are discussed in one of the SRs/meta-analysis that have been added in this update were removed, to avoid discussing the same data twice.

For resistance surveillance data NethMap 2018 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), 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.

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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

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Chapter 1. WHAT IS THE OPTIMAL EMPIRICAL TREATMENT STRATEGY CONCERNING THE CHOICE OF DRUG IN GENERAL AND IN CASE OF ESBL?

Content:

1. Causative micro-organisms, resistance and ESBL
2. Empirical treatment: drug of choice and treatment in case of colonization with ESBL

Search strategy

Resistance data were obtained from the report NethMap 2018 (www.swab.nl) and from the Infectious Diseases Surveillance Information System on Antimicrobial Resistance (ISIS-AR, https://www.rivm.nl/isis-ar). The interpretation of susceptibility test follows the guidelines of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

For the 2020 update, a literature search was performed as previously described (page 13). After screening of titles and abstracts, 11 additional systematic reviews published since 2013 were included that discussed empiric treatment of UTI. We identified 2 additional RCTs that were not included in one of these systematic reviews.

Literature overview

CAUSATIVE MICRO-ORGANISMS AND RESISTANCE

Although there is a greater diversity of causative micro-organisms in UTI with systemic symptoms and UTI in risk populations than in cystitis, *Escherichia coli* remains the most common causative organism. ISIS-AR data (available at www.ISIS-web.nl, data retrieved on the 3th of July 2019 [3]) reported the following causative micro-organisms: *E. coli* (47%), *Enterococcus faecalis* (11%), *Proteus species* (8%), and *Klebsiella pneumoniae* (9%) (table 1). Resistance data from 2018 are displayed in table 2 (unselected departments excluding the intensive care unit and the urology department) and for the urology department in table 3.

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Table 1: Causative micro-organisms of urinary tract infections

Causative micro-organism	Number of isolates
Escherichia coli	20222 (46,6%)
Enterococcus faecalis	4640 (10,7%)
Klebsiella pneumoniae	3956 (9,1%)
Proteus species	3309 (7,6%)
Pseudomonas aeruginosa	2214 (5,1 %)
Staphylococcus aureus	1084 (2,5%)
other gram-negative rods*	4908 (11,3 %)
other gram-positive cocci**	3075 (7,1%)

Number of isolates of uropathogens found in first urine cultures (non-catheter) from adult, in-hospital, non-ICU patients in 2018. Data were retrieved on the 3th of July 2019 from 41 Dutch laboratories participating in ISIS-AR.

* *Acinetobacter* spp., *Citrobacter* spp., *Enterobacter* spp., *Hafnia* spp., *Klebsiella oxytoca, Morganella* spp., *Providencia* spp., *Serratia* spp., *Stenotrophomonas maltophilia*

** *Enterococcus faecium, Enterococcus* spp, *Groep B ß-haemolytic streptococci, Groep G ß-haemolytic streptococci* and *Streptococcus dysgalactiae equisimilis*

Table 2. Resistance percentage in unselected hospital departments.

	Escherichia coli				*Klebsiella pneumoniae*				*Proteus species*			
	totaal	% S	% I	% R	totaal	% S	% I	% R	totaal	% S	% I	% R
amoxicillin / ampicillin	18442	55,7	1,1	43,2	3571	0,2	0,1	99,7	2980	67,8	2,4	29,8
amoxicillin / clavulanic acid	18442	64,0	1,7	34,3	3569	74,8	2,0	23,3	2979	87,1	2,8	10,1
cefuroxim	18175	86,9	0,2	13,0	3541	83,3	0,1	16,6	2927	92,2	0,0	7,8
cefotaxime*	16610	93,4	0,2	6,4	3174	89,4	0,4	10,2	2654	97,5	0,1	2,4
ciprofloxacin	18441	84,7	2,1	13,2	3571	84,5	3,4	12,0	2989	89,6	0,8	9,6
cotrimoxazole	18435	77,3	0,1	22,6	3570	84,5	0,3	15,2	2987	72,3	0,5	27,2
gentamicine	17386	95,1	0,5	4,4	3356	95,6	0,0	4,4	2895	91,1	1,5	7,5

Resistance percentage in 2018 of first isolates of urine cultures (non-catheter) from hospitalized adult patients in unselected hospital departments excluding ICU and urology. Data were retrieved on the 27th of September 2019 from 42 Dutch laboratories participating in ISIS-AR.

* ESBL percentage in *E. coli* 5,7% and in *K. pneumoniae* 9,8%

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Table 3. Resistance percentage in urology department.

	Escherichia coli				*Klebsiella pneumoniae*				*Proteus species*			
	totaal	% S	% I	% R	totaal	% S	% I	% R	totaal	% S	% I	% R
amoxicillin / ampicillin	1785	52,2	0,0	47,8	387	0,0	0,0	100,0	322	67,1	0,0	32,9
amoxicillin / clavulanic acid	1785	60,2	0,6	39,2	387	72,9	0,8	26,4	322	89,4	0,0	10,6
cefuroxim	1758	85,2	0,0	14,8	381	80,3	0,0	19,7	308	88,0	0,0	12,0
cefotaxime*	1685	91,6	0,1	8,2	365	87,9	0,3	11,8	302	96,0	0,3	3,6
ciprofloxacin	1785	73,5	1,9	24,6	387	77,5	3,6	18,9	323	83,6	2,5	13,9
cotrimoxazole	1784	71,1	0,1	28,8	387	81,4	0,3	18,3	323	72,4	0,0	27,6
gentamicine	1641	93,7	0,3	6,0	365	95,3	0,0	4,7	304	93,1	1,0	5,9

Resistance percentage in 2018 of first isolates of urine cultures (non-catheter) from hospitalized adult patients in the urology department. Data were retrieved on the 27th of September 2019 from 42 Dutch laboratories participating in ISIS-AR.
* ESBL percentage in *E. coli* 7,9 % and in *K. pneumoniae* 11,1%.

Conclusions

Level*	*Escherichia coli* is the causative organism in most cases of complicated UTIs [3].
Level*	*E. coli* isolated from patients at unselected hospital departments (excluding intensive care units and the urology department) have high resistance rates to amoxicillin, co-amoxiclav, trimethoprim and trimethoprim-sulfamethoxazole (TMP-SMX) [3].
Level*	In *E. coli* isolated from patients at unselected hospital departments (excluding intensive care units and the urology department), the resistance rate of ciprofloxacin is 13.2.% and in isolates from urology departments 24.6% [3].
Level*	*E. coli* isolated from patients at unselected hospital departments show the following resistance percentages to intravenous antimicrobial agents: gentamicin 4.4%, second-generation cephalosporin cefuroxime

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	13.0%, third-generation cephalosporin cefotaxim 6.4%, and the “last resort” antimicrobial agent meropenem 0% [3].
Level*	In urine isolates from unselected departments (excluding the intensive care unit and the urology department) Extended Spectrum Beta-lactamase (ESBL) percentages were 5.7% for *E.coli* and 9.8% for *Klebsiella pneumoniae* [3].

EMPIRICAL TREATMENT: DRUG OF CHOICE

In the 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 [4]. For treatment of a UTI with systemic symptoms, the antimicrobial drug must achieve high concentrations in urine, kidney tissue and the prostate. Therefore, nitrofurantoin and fosfomycin are not registered for the treatment of a UTI with systemic symptoms.

Considering the resistance percentages of amoxicillin, co-amoxiclav, trimethoprim (TMP) and trimethoprim/sulfamethoxazole (TMP-SX), 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 UTI with systemic symptoms. The same applies to ciprofloxacin and other fluoroquinolones in patients from the urology departments.

This does not apply to patients with a cystitis treated by their general practitioner (discussed in the NHG Guidelines), as in a lower UTI higher resistance percentages (<20% instead of <10%) are accepted to consider an agent suitable for empirical treatment.

Patients with a UTI with systemic symptoms requiring hospitalization should be initially treated with an intravenous antimicrobial regimen, such as a secondgeneration cephalosporin + an aminoglycoside, a 3rd generation cephalosporin or alternatively amoxicillin + 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[4]. These recommendations suitable for all UTI with systemic symptoms (pyelonephritis, acute bacterial prostatitis, urosepsis syndrome).

In view of the high degree of resistance, in particular among patients admitted to the department of urology, fluoroquinolones are not suitable as empirical antimicrobial therapy, especially when the patient has used ciprofloxacin in the last 6 months, which is the most

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important risk factor for ciprofloxacin resistance [5]. 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.

When the prevalence of resistance of causative uropathogens to fluoroquinolones does not exceed 10%, 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.

Interestingly, a study in women with uncomplicated pyelonephritis empirically treated with ciprofloxacin (changed to appropriate therapy at day 4 when necessary) showed there was no difference in the clinical success rate of women with a ciprofloxacin susceptible *E. coli* compared to those with a ciprofloxacin resistant *E. coli* [6]. 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 theory women with uncomplicated pyelonephritis caused by *E. coli*, even in higher percentages of ciprofloxacin resistance, ciprofloxacin can be prescribed as an empirical treatment [6]. But in practice, it is not known at the moment of the start of empirical treatment whether the UTI is caused by *E. coli.*

Oral therapy can be prescribed if the clinical condition of the patient allows it and if the patient does not vomit [8, 9]. If symptoms have resolved after treatment, follow-up cultures are not recommended.

New studies and antibiotic agents

Ceftazidime-avibactam

In the recent years, several systematic reviews have been published about the use of ceftazidime-avibactam in complicated UTI [10-16]. In these reviews, results from three RCTs were discussed [17-19]: two used ceftazidime-avibactam as empiric therapy and one study included patients with known ceftazidime-resistant uropathogens or *Pseudomonas aeruginosa.* In these studies, the comparative agents were predominantly carbapenems. Results are promising: a meta-analysis of the two studies administrating ceftazidim-avibactam as empiric therapy reported that ceftazidime-avibactam has a better clinical treatment success

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rate compared to alternative antibiotics (in both studies carbapenems) (n=1095, OR=2.14, 95% CI: 1.06-4.13, p=0.03) [11].

However, clinical experience with this new agent is limited and another recent systematic review raised some questions considering the safety of this agent. In this study, all adverse events in studies using ceftazidime/avibactam for different indications were pooled and analyzed [16]. The meta-analysis included a total of 8 trials with 3988 patients with intra-abdominal infections, pneumonia or complicated UTI, the main comparator was carbapenem. Even though there was no difference in the occurrence of adverse events (AEs), serious adverse events (SAEs) were more common in the ceftazidime-avibactam arm (RR 1.14, 95% CI 1.00-1.54, p=0.05, I^2=0%). More detailed data concerning the nature of these SAEs were not available. Separate analyses of the three complicated UTI studies did not show a significant higher risk of SAEs compared to alternative antibiotics (predominantly carbapenems) (RR 1.51, 95% CI 0.91-2.50, p=0.11, I^2 = 4%).

Ceftolozane-tazobactam

We identified 4 systematic reviews evaluating the treatment with ceftolozane-tazobactam in complicated UTI [11, 14, 20, 21]. Results from these reviews were based on data from one large RCT, the Assessment of the Safety Profile and Efficiency of Ceftolozane/Tazobactam in Complicated Urinary Tract Infections (ASPECT-cUTI) study [22]. In this double-blind non-inferiority trial, 1038 patients were included from 25 countries. Ceftolozane-tazobactam 1500 mg 3dd was compared to levofloxacin 750 mg 1dd. The composite cure, defined as both clinical cure and microbiological eradication at test of cure, was higher in the ceftolozane-tazobactam group, respectively 76.9% vs. 68.4% (95% CI 2.3-14.6), which demonstrates superiority at the 5% significance level. The incidence of AEs and SAEs was similar between the two groups. Two serious adverse events (*Clostridium difficile* infection) in the ceftolozane-tazobactam group were deemed to be related to study treatment.

Ertapenem

We identified one RCT that compared ertapenem (1g 1dd) to ceftriaxone (2g 1dd) as initial parenteral treatment of 261 patients with complicated UTI[23]. Patients received at least 3 doses of intravenous therapy before being switched to oral therapy, which was in most cases ciprofloxacin. In this non-inferiority trial, the microbial response rates and clinical cure rates were similar in the two groups. The overall incidence of drug-related adverse events was also similar in both treatment groups. Authors conclude that ertapenem is highly effective and safe for the treatment of complicated UTI.

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Fosfomycin for Injection (ZTI-01)

In 2019, a RCT was published comparing 6 g q8h fosfomycin for injection (ZTI-01) to 4.5 g IV piperacillin-tazobactam (PIP-TAZ) q8h for a fixed 7-day course (no oral switch) in 465 hospitalized patients with suspected or microbiologically confirmed complicated UTI/acute pyelonephritis [24]. Patients with concomitant bacteremia could receive up to 14 days of treatment.

In the microbiologic modified intent-to-treat (m-MITT) population, ZTI-01 met the primary objective of noninferiority compared with PIP-TAZ, with overall success rates (defined as clinical care plus microbiologic eradication) of 64.7% (119/184 patients) vs 54.5% (97/178 patients), respectively; treatment difference was 10.2% (95% confidence interval [CI]: −0.4, 20.8). Clinical cure rates at test of cure (day 19–21) were high and similar between treatments (90.8% [167/184] vs 91.6% [163/178], respectively). ZTI-01 was well tolerated. Most treatment-emergent adverse events, including hypokalemia and elevated serum aminotransferases, were mild and transient.

Conclusions

Level 2	In women with uncomplicated pyelonephritis empirically treated with ciprofloxacin (changed to appropriate therapy at day 4 when necessary) clinical success rates of women with a ciprofloxacin susceptible *E.coli* are comparable to those with ciprofloxacin resistant *E.coli:* 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 [[6] A2].
Level 3	The chance of cross-hypersensitivity between penicillin derivatives and cephalosporins is low [[7] C].
Level 1	Empiric treatment of complicated UTI with ceftazidime-avibactam results in a better clinical treatment success when compared to carbapenems [[10-16] A1].
Level 1	A meta-analysis including studies using ceftazidime-avibactam for different indications reported a higher risk of SAEs in the ceftazidim-

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	avibactam group than in the comparator group, which were predominantly carbapenems (RR 1.14, 95% CI 1.00-1.54, p=0.05, I^2=0%) [[15] A1]. Separate analyses of the three complicated UTI studies did not show a significant higher risk of SAEs (RR 1.51, 95% CI 0.91-2.50, p=0.11, I^2 = 4% [[15] A1].
Level 2	Ceftolozane-tazobactam in the empiric treatment of complicated UTI is superior to levofloxacin in both clinical cure and microbiological eradiation [[11, 14, 21] A2]
Level 2	Ceftolozane-tazobactam is not associated with more adverse or serious adverse events than levofloxacin in patients with cUTI [[22] A2]
Level 2	Ertapenem is not inferior to ceftriaxone in the initial parenteral therapy of complicated UTI on the basis of its clinical and microbiological efficacy as well as safety profile [[23] A2].
Level 3	Intravenous fosfomycin (ZTI-01) is noninferior to piperacillin-tazobactam in overall treatment success (clinical cure plus microbiologic eradication) for complicated UTI/acute pyelonephritis. Overall success occurred in 64.7% of ZTI-01 and 54.5% of piperacillin-tazobactam patients (treatment difference of 10.2%, 95% CI [−0.4, 20.8]). Clinical cure rates at test of cure (day 19–21) were high and similar between treatments (90.8% [167/184] vs 91.6% [163/178], respectively) [[24] B].

Colonization with extended spectrum beta-lactamase (ESBL-) producing organisms

The recently updated 2019 SWAB sepsis guideline elaborates on the current available literature on risk factors for colonization and infection with extended spectrum beta-lactamase (ESBL-) producing organisms, and when the antibiotic regimen should cover ESBL. A comprehensive overview of literature behind the recommendations can be found in the 2019 SWAB sepsis guideline. The complicated UTI Guideline committee has decided to adopt the recommendations from this guideline.

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We therefore recommend empirical therapy against ESBL producing bacteria only in patients with prior (1 year) colonization or infection with such organisms. The resistance pattern of the earlier cultured ESBL strain should guide empirical therapy.

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 [4]. Therefore, last line antimicrobial agents like piperacilin-tazobactam, imipenem, meropenem, ertapenem, ceftazidime-avibactam, ceftolozane-tazobactam or fosfomycin iv may be effective against complicated UTI, but are not recommended as first choice empirical therapy.

Since the Guideline committee recommends to cover ESBL only in case of previous colonization, resistance pattern of the previously cultured ESBL strain can guide empirical therapy.

Aminoglycosides, EUCAST

In the 2020 update of the EUCAST Guidance Document on Implementation and Use of the Revised Aminoglycoside Breakpoints [25], aminoglycoside monotherapy is discouraged and MIC breakpoints for *Pseudomonas aeruginosa* are no longer provided for gentamicin.

In the chapter Empiric treatment of UTI with systemic symptoms in these guidelines, we make no specific recommendation for antibiotic therapy covering *Pseudomonas aeruginosa,* but we added resistance percentages of *Pseudomonas aeruginosa* in table 4. Nevertheless, when a clear suspicion of a *Pseudomonas aeruginosa* infection is present, we recommend not to use gentamicin.

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Table 4: Resistance patterns

	Pseudomonas aeruginosa			
	totaal	% S	% I	% R
ceftazidim	2834	97,4	0,0	2,5
ciprofloxacin	2933	91,1	0,3	8,5
meropenem	2926	96,5	2,5	1,0
piperacilline/tazobactam	2680	95,4	0,0	4,6
tobramycin	2665	99,4	0,0	0,6

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WHAT IS OPTIMAL EMPIRICAL ANTIMICROBIAL AGENT?	
Recommendation	In patients suspected of having a UTI with systemic symptoms, 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 UTI with systemic symptoms.
Recommendation	The combination of a 2nd generation cephalosporin + an aminoglycoside, a 3rd generation cephalosporin or amoxicillin + an aminoglycoside intravenously can be recommended as empirical treatment of UTI with systemic symptoms. Empirical treatment should be continued until the susceptibility of the pathogen is determined.
Recommendation	Empirical treatment with ciprofloxacin is only recommended when treatment is started orally, when patients do not require hospitalization or when the patient had an anaphylactic reaction on beta-lactam antibiotics, provided that the local resistance percentages are < 10%.
Recommendation	Ciprofloxacin and other fluoroqinolones are not suitable for the empirical treatment of UTI with systemic symptoms in patients from the urology department or when patients have used fluoroquinolones in the last 6 months.
Recommendation	When the results of the urine culture are known, therapy must be adjusted and if possible narrowed. If the patient is clinically stable,

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	able to tolerate oral medication and if an adequate oral antibiotic can be given, the patient should get oral treatment.
Recommendation	If symptoms have resolved after treatment, follow-up cultures are not recommended.
Recommendation	New investigated antibiotic agents such as ceftazidime-avibactam, ceftolozane-tazobactam and fosfomycin for injection are currently not recommended in the empiric treatment of UTI with systemic symptoms.
Recommendation	We recommend empirical therapy against Enterobacterales resistant to 3rd generation cephalosporins in patients with UTI with systemic symptoms and prior (1 year) colonization or infection with such micro-organisms. The resistance pattern of the strain should guide empirical therapy.

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Chapter 2. WHAT IS THE OPTIMAL TREATMENT DURATION OF ANTIMICROBIAL TREATMENT OF UTI WITH SYSTEMIC SYMPTOMS?

Search strategy

The literature search described on page 13 yielded 9 additional systematic reviews and 5 RCTs that discussed the treatment duration of febrile UTI. None of the systematic reviews included data from randomized controlled trials published after 2013; all included studies in these reviews were already described in the previous 2013 SWAB cUTI guideline. Data from the 5 RCTs were added to the Guidelines and taken into considerations in the updated recommendations.

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 [26]. 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 [4]. These trials have already been reviewed [4, 27-32] and will be briefly discussed in this chapter.

Fluoroquinolones

Talan et al. clearly demonstrated that a 7-day course of ciprofloxacin is sufficient in young, healthy women with acute pyelonephritis [33]. This double-blind, multicenter 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 healthy women with 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.

More recently, two RCTs have been published that showed similar efficacy of 7 and 14 days of ciprofloxacin in women with UTI with systemic symptoms. The first trial [34], included 156 women. Cure rates for the 7-day regimen (n=73) and for the 14-day regimen (n=83) were 97.3% and 96.4%, respectively (difference -0·9%; 90% CI -6·5 to 4·8; p=0·004; non-inferiority confirmed). In this study patients with diabetes and/or known functional abnormalities were also included. The second study [35] was a double-blind, non-inferiority RCT performed in 35 primary care centers and 7 hospital emergency departments in the Netherlands and included

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200 men and women with febrile UTI. In this study immunocompromised patients and patients with diabetes were also included. In women, the short-term clinical cures rates for the 7- and 14-day arms were 47 of 50 (94%) versus 54 of 58 (93%), respectively. The difference in cure rate was 0.9% (90% CI, –6.9 to 8.7, $P_{\text{non-inferiority}} = 0.011$, non-inferiority confirmed).

Additionally, several studies have been published showing the efficacy of a shorter treatment duration of levofloxacin [36, 37]. In 2019, a meta-analysis was published [38] including three RCTs evaluating 750 mg levofloxacin per day for 5 days as compared to conventional therapy (either levofloxacin 500 mg for 7-14 days or ciprofloxacin 400 mg iv/500 mg orally for 10 days) in both men and women with complicated UTI/acute pyelonephritis. Similar microbiologic eradication rate were found for both regimens; RR: 1.03; 95%CI: 0.97–1.10, I^2=0%.

Other antibiotics

In 2018, two studies were published that compared 7 vs 14 days of antibiotic treatment in which the antibiotic was chosen by the treating physician [39, 40]. The first study included 54 men and women with acute pyelonephritis treated with non-fluoroquinolone antibiotics and requiring hospitalization. Patients with diabetes or acute kidney injury were also included. Eligible patients should have clinically improved following empirical or culture-guided antibiotic treatment and should be afebrile for >48 hours at the time of randomization. Patients were randomized at day 7. If the patient was allocated to the intervention arm, then the antibiotic treatment was stopped and he/she was discharged home. In those allocated to continued treatment (control arm), the same antibiotic regimen was continued until day 14, and then they were discharged. The antibiotic regimen was in 76% of the patients aminoglycoside based. In this study, the difference (90% CI) in retreatment rate between the trial arms was −3.7% (−15.01% to 6.15%). The upper bound of the CI for the difference in favor of the continued treatment arm (6.15%) was well below the prespecified margin of 15%, establishing non-inferiority of 7 days of treatment as compared to continued treatment. Non-inferiority criterion was also met in a per-protocol analysis (difference in retreatment rate −3.85% [−15.53% to 6.04%]). In a posthoc subgroup analysis, there was no evidence to suggest that the treatment effect differed by characteristics such as age, gender, diabetes, urinary pathogen, presence of bacteremia, and use of an aminoglycoside.

The second study by Yahav et al. [40] was a large randomized, multicenter, open-label, noninferiority trial including 604 patients with gram-negative bacteremia. Patients had to be afebrile and hemodynamically stable for >48 hours to be included in this study. Most included patients had a UTI: 173 men and 320 women. Patients received 7 vs. 14 days of covering

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antibiotic, which was defined as an antibiotic matching the in-vitro susceptibility of the gram-negative pathogen in blood. Type of empirical or directed antibiotic treatment was again chosen by the treating physician, just as the decision to switch to oral therapy. For the iv treatment, the antibiotic regimens were cephalosporins (+- 50%), beta-lactam/beta-lactamase inhibitors (+- 25%), aminoglycosides (12,5%), carbapenems (6%) and quinolones (5%). Oral treatment consisted of quinolones (75%), beta-lactams (17%) and trimethoprim (8%). The primary composite outcome of mortality, clinical failure, readmissions, or extended hospitalization at 90 days occurred in 140 of 306 patients in the short-duration group (45.8%) compared with 144 of 298 in the long-duration group (48.3%) (RD, –2.6% [95% CI, –10.5% to 5.3%]), establishing noninferiority. No significant difference between the study arms was documented for all predefined subgroups, including patients with UTI. Noninferiority criteria were met in all subgroups, except for the (small) subgroups of patients receiving inappropriate empirical antibiotic treatment and those with bacteremia caused by a MDR pathogen.

Optimal treatment duration in men

Literature on the optimal treatment duration of acute pyelonephritis or febrile UTI in men is relatively scarce and in older studies men were usually excluded.

One study did directly compare different treatment durations in men [41]. 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%). These 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

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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.

Several previously mentioned studies also included men. In the RCT performed in the Netherlands comparing 7 days to 14 days of ciprofloxacin [35], 90 men were included. In this study, the clinical cure rate through the 10- to 18-day post-treatment visit differed significantly between those treated for 7 or 14 days: respectively 86% vs. 98%, difference in cure rate: –11.2 (90% CI, –20.6 to –1.8) $p_{superiority}$ = 0.025, inferiority was confirmed. However, long-term clinical cure rates met the criteria for non-inferiority, indicating that there was no difference in the need for antibiotic retreatment for UTI during 70-84 days follow-up post treatment.

Another previously mentioned study [40] that also included men initially did not provide a subanalysis of this group. Nevertheless, in a response letter [42] additional data including only the men with a gram-negative bacteremic UTI were provided. This analysis included 91 men in the short arm (7 days) and 82 men in the long arm (14 days). Also in this subgroup analysis, no significant difference was found in any of the endpoints (among others: 90-day all-cause mortality, readmissions, suppurative complications, new clinically or microbiologically documented infections <90 days) between 7 or 14 days of treatment. It is important to note that to be included in this study patients had to be afebrile and hemodynamically stable for >48 hours.

Conclusions

Level 2	A 7-day ciprofloxacin regimen is associated with greater bacteriological 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 [[33] A2].
Level 1	A treatment duration of 7 days with ciprofloxacin is non-inferior to 14 days of treatment in women with UTI with systemic symptoms [[34] A2; [35] A2] .

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Level 1	A 5-day course of therapy with 750 mg levofloxacin once daily in men and women results in a similar clinical success rate compared to either levofloxacin 500 mg daily for 7–14 days or ciprofloxacin 400 mg IV or 500 mg oral, twice daily for 10 days: RR: 1.04; 95%CI: 0.99–1.10, I2=0%; [[38] A1].
Level 3	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% [[43] B]
Level 2	Intravenous levofloxacin 750 mg once daily for 5 days is noninferior to a 7-14 day regimen of levofloxacin 500 mg once daily starting intravenously and switched to an oral regimen (based on mitigation of clinical symptoms) [[44] A2].
Level 3	In women with acute uncomplicated pyelonephritis, 5 days of treatment with either ofloxacin 200 mg bid or levofloxacin 500 mg qd results in similar clinical cure rates compared to 10 days of treatment when the microorganism involved is susceptible [[45] B].
Level 3	Stopping the effective non-fluoroquinolone antibiotics following clinical improvement at day 7 is non-inferior to continued treatment until day 14 in patients with acute pyelonephritis requiring hospitalization [[39] B].
Level 2	In patients with gram-negative bacteremia achieving clinical stability before day 7, an antibiotic course of 7 days is noninferior to 14 days [[40] A2].
Level 3	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 [[41] B].
Level 3	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 [[46] B] After initial intravenous treatment with cefuroxime, the clinical and bacteriological cure rates were higher in patients with a febrile UTI

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	treated with norfloxacin (2 x 400 mg) (42% men) compared to treatment with ceftibuten 2x 200 mg for 10 days [[47]. B]
Level 2	In men with community-onset febrile UTI, treatment with ciprofloxacin for 7 days results in a lower clinical cure rate through the 10- to 18-day post-treatment visit when compared to 14 days of treatment (respectively 86% vs. 98%, difference in cure rate: –11.2 (90% CI, –20.6 to –1.8) $p_{superiority}$ *= 0.025, inferiority confirmed),* while long-term clinical cure rates are similar [[35] A2]
Level 2	In men with gram-negative bacteremic UTI that achieved clinical stability before day 7, an antibiotic treatment course of 7 days was non-inferior to 14 days [[42] A2]

Other considerations

Studies with fluoroquinolones in women consistently show comparable efficacy for 5-7 days as compared to 10-14 days of treatment. There are very few published studies on the efficacy of amoxicillin, co-amoxicilav or TMP-SMX for less than 14 days in the treatment of acute pyelonephritis. Even though the previously mentioned study in gram-negative bacteremic patients [40] did also include patients treated with these antibiotics, a subgroup analysis per administered antibiotic was not provided. In addition, while no differences in relapse of bacteremia or readmissions were found, data on recurrence of UTI were not provided.

Nevertheless, results of the study of Yahav are promising and the Guideline Committee suggests that in certain patient populations where a short-course of treatment is desired due to relative-contraindications, a treatment duration of 7 days with amoxicillin, co-amoxicilav or TMP-SMX can be considered if the patient is hemodynamically stable and afebrile for at least 48 hours. Examples of these relative contra-indications may be interactions with other drugs or side effects of the antibiotic therapy. Also, when no options for oral therapy because of the resistance pattern of the uropathogen are present, a shorter treatment duration may be considered to shorten the length of stay. In this situation, the risks of a prolonged hospital stay should be taken into account in the decision to continue or stop antibiotic treatment at day 7.

Results considering the treatment duration in men are conflicting. Whilst Yahav et al. [42] showed that in men with a gram-negative bacteremic UTI 7 days of treatment is non-inferior to

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14 days of treatment, the study conducted by van Nieuwkoop et al.[35] showed that 7 days of treatment results in a lower initial clinical cure rate, while the long-term clinical cure rate is similar. Therefore, also here the Guideline Committee suggests that, when the patient is hemodynamically stable and afebrile for at least 48 hours, a shorter treatment duration (e.g. 7 days) may be considered in patients when a short-course treatment is desired. Again, examples of these relative contra-indications may be interactions with other drugs, side effects of the antibiotic therapy, or the lack of a suitable oral agent necessitating a prolonged hospital stay.

What is the optimal treatment duration?	
Recommendation	Non-pregnant women with UTI with systemic symptoms should be treated for 7 days when treated with ciprofloxacin.
Recommendation	Non-pregnant women with UTI with systemic symptoms should be treated for 10-14 days when treated with TMP-SMX or a beta-lactam[1].
Recommendation	Men with UTI with systemic symptoms should be treated for 14 days[1].

[1] In patients where a shorter treatment duration is desired, 7 days of treatment may be considered if the patient is hemodynamically stable and afebrile for at least 48 hours.

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Chapter 3. WHAT IS THE OPTIMAL TREATMENT OF URINARY TRACT INFECTIONS IN MEN?

From the literature search as described on page 13, all studies considering the treatment of bacterial urinary tract infection in men were included. Studies on the prostatic syndrome, a group of diseases or syndromes usually without a bacterial etiology [48-50], were excluded. We identified one new SR and no additional RCTs. The SR was added to the literature overview.

Literature overview In this guideline, UTIs in men are divided into three groups:

1. **Cystitis**

   It is 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 men with a UTI without signs or symptoms 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 [51-53]. 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 for all men with probable cystitis 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 uropathogens. With increasing bacterial resistance in the urological population, especially against the fluoroquinolones, empiric antibiotic treatment should be avoided. Because urogenital pain is too often treated with antibiotics [54], 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.

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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 [55, 56]. Nitrofurantoin has insufficient tissue penetration in the prostate [57, 58]. No data are available for other agents.

Acute bacterial prostatitis

In probably more than half of all men with a UTI there is a coexistence of a prostato-vesiculitis [59, 60]. Besides the symptoms of a concurrent cystitis, a prostatitis is characterized by urogenital pain or discomfort. 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 [59]. 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 [61]. 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 [62], levofloxacin vs. prulifloxacin (45) or lomefloxacin vs. ciprofloxacin [63]. This comparable efficiency of different fluoroquinolones was also reported in a systematic review from 2013 [64].

In an old (1978) randomized study of 29 men with culture-proven 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 [65].

Duration of treatment of chronic prostatitis

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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 *Enterobacterales* family that was susceptible to TMP-SMX, were randomized to receive 2 weeks TMP-SMX plus 4 weeks placebo, or 6 weeks TMP-SMX [66]. 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 [60]. 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 [67]. Observational studies of the treatment of chronic bacterial prostatitis with quinolones showed at 6-months follow-up eradication rates for 2 weeks therapy with ofloxacin of 67% (n=21) [68] and with ciprofloxacin of 60% (n=15) [69]; for 4 weeks therapy with norfloxacin of 64% (n=16) [70], 72% (n=89) [63] or 76% (n=65) [71] and with levofloxacin of 63% (n=93) [63] and for treatment during 6 months with norfloxacin of 60% (n=42) [70]. 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 [72].

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Conclusions

Level 4	Men 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 [[72] D, [52] D, [53] C].
Level 3	In men with a UTI there is often a concurrent prostatitis [[59] C; [60] B]
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 [[55] D, [57] D; [58] 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% [70] C; [73] C; [63] C;[71] C; [63] C; [74] 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 [65] B.
Level 1	No differences were found in clinical success and microbiological eradication rates after 4 weeks of treatment with levofloxacin vs ciprofloxacin; levofloxin vs prulifloxacin; or lomefloxacin vs. ciprofloxacin. [[62] A2; [[63] B; [75] B; [64]] A1]
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 [[60, 66], 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, when the local resistance percentages of the causative uropathogens are < 10%. All other patients with acute prostatitis should be admitted

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to the hospital to be treated intravenously. Treatment recommendations are the same as for general febrile UTIs.

For chronic bacterial prostatitis prolonged antibiotic therapy of at least 4 weeks is recommended [72].

WHAT IS THE OPTIMAL TREATMENT OF UTI IN MEN?	
Recommendation	For the treatment of a UTI without systemic symptoms in men 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 nitrofurantoin 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.

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Chapter 4. WHAT IS THE OPTIMAL TREATMENT OF URINARY TRACT INFECTIONS IN PREGNANT WOMEN?

Search strategy

From the literature search described on page 13 of these guidelines, 8 new systematic reviews were identified including data on UTI during pregnancy. One new RCT was identified, which was also discussed in one of the included systematic reviews.

Literature overview

Asymptomatic bacteriuria (ASB) is the presence of 1 or more species of bacteria growing in the urine at specified quantitative counts (≥105 colony-forming units [CFU]/mL or ≥108 CFU/L), irrespective of the presence of pyuria, in the absence of signs or symptoms attributable to urinary tract infection (UTI) [76]. The prevalence of ASB is 2-10% in pregnant women. The incidence of ASB is similar in both pregnant and non-pregnant women [77]. 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 [78]. Even though one of the systematic reviews did investigate benefit and harms of screening for ASB versus no screening, authors report that no eligible studies were found in their literature search [79].

Several systematic reviews have evaluated treatment of ASB [79-85] and a recent meta-analysis pointed out that antibiotic treatment of ASB results in a significantly reduced number of symptomatic UTI (11 RCTs, 2002, RR = 0.22,95% CI 0.12–0.40;), a reduction in risk of low birthweight (8 RCTs, n=1689, RR =0.58, 95% CI 0.36-0.94) and a reduced risk of preterm delivery (4 RCTs, n=854, RR= 0.34, 95% CI 0.18–0.66) when compared with placebo or no treatment [80]. However, it should be noted that from the 14 included RCTs in this review, 13 were published more than 30 years ago. The only recent study, published by Kazemier et al., did not find an association between ASB and preterm birth [86].

Kazemier and colleagues performed a multicentre cohort study with an embedded randomized controlled trial. In this study, women (aged ≥18 years) at eight hospitals and five ultrasound centers in the Netherlands with a singleton pregnancy between 16 and 22 weeks' gestation were screened for ASB. ASB positive women were eligible to participate in the RCT in which treatment with nitrofurantoin was compared to placebo. Women who refused to participate in the randomized controlled trial did not receive any antibiotics, but their outcomes were

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collected for analysis in the cohort study. The final cohort consisted of 4283 women, of whom 248 were ASB positive (prevalence of 5.79%). From these ASB positive women, 40 were randomly assigned to nitrofurantoin and 45 to placebo for the randomized controlled trial, whereas the other 163 asymptomatic bacteriuria-positive women were followed without treatment. In this study, untreated or placebo-treated ASB-positive women developed pyelonephritis in only five [2·4%] of 208 cases, compared with 24 [0·6%] of 4035 asymptomatic bacteriuria-negative women (adjusted OR 3·9, 95% CI 1·4-11·4). This low incidence of pyelonephritis in untreated ASB positive women is in contrast with previous published literature, in which incidence numbers of 20-40% have been reported [77, 87-90] . The pre-term delivery rate <34 weeks was similar in the ASB-positive women who were untreated or received placebo and the ASB-negative women (adjusted OR 0.7, 95% CI 0.2-2.8).

Furthermore, the embedded RCT comparing treatment with nitrofurantoin to placebo or no treatment pointed out that treatment with nitrofurantoin does not result in a significantly lower pyelonephritis rate. Even though none of the ASB positive women who received nitrofurantoin developed pyelonephritis, the risk difference compared to the ASB-positive women who were untreated or received placebo was -2.4 (95% CI -19.2-14.5) [86, 91]. The risk of pre-term birth <34 weeks was also similar between the ASB-positive women treated with nitrofurantoin and the ASB-positive women who were untreated or received placebo (risk difference: -1.5, 95% CI -15.3-18.5).

Treatment of ASB with a single-dose of antibiotics has been evaluated in several studies and two systematic reviews recently evaluated these studies [80, 92]. In the Cochrane systematic review published by Widmer et al. 13 studies were included involving 1622 women. A comparison was made between single-dose and short-course (four to seven-day) of treatment. Antibiotic agents used in these studies were ampicillin, nitrofurantoin, cephalexin, fosfomycin trometamol, fosfomycin, amoxicillin-clavulanate, amoxicillin, co-trimoxazole, trimethoprim, and other sulphonamides. Furthermore, whilst some studies compared different treatment durations of the same antimicrobial family, others used different antimicrobial agents in the single dose and short-term treatment group. A meta-analysis pointed out that cure rates were similar whether women received a single dose or a short course of any antibiotic treatment (13 studies, n=1502, RR 1.28, 95% confidence interval (CI) 0.87 to 1.88, I^2 = 56%). The quality of evidence reported by the authors was low. When data from only good quality trials using the same antimicrobial agents in the single dose and the short-term treatment duration group were pooled, cure rates where better in the short-term regimens (four- to seven-day) (2 studies, n=803, RR 1.72, 95% CI 1.27 to 2.33; I^2 = 0%).

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Choice of drug

A recent systematic review evaluated the fetal safety of nitrofurantoin and evaluated the risk of major malformations[93]. No associations were found between fetal exposure to nitrofurantoin and major malformations in the included cohort studies (five cohort studies, 9275 exposed and 149,1933 unexposed infants, RR of 1.01 (95% CI 0.81 to 1.26). However, in the case-control studies, a slight but significant teratogenic risk was reported (three case–control studies, 39,268 cases of major malformations and 129,394 controls, OR: 1.22 95% CI 1.02 to 1.45). No increased risk for cardiovascular malformations, oral cleft, or craniosynostosis was identified. However, the risk of hypoplastic left heart syndrome appeared to be increased (three case-control studies, OR: 3.07 95% CI 1.59 to 5.93). From these three studies, an overwhelming weight effect was contributed by the case–control study performed by Crider et al. [94] In this study, women were asked to recall medications they had used during pregnancy, up to 24 months after the estimated date of delivery. The American College of Obstetricians an Gynaecologist [95] pointed out that although this was a large study, it had several significant limitations. First, it was subject to recall bias because women were asked about antibiotic use after pregnancy. Second, the prescription of antibiotics was not confirmed by the medical record; approximately 35% of patients could not recall the specific product name. Third, because this was an observational study, it was not possible to determine whether the birth defect was due to the antibiotic itself, the infection for which the antibiotic was prescribed, or some other confounding factor. Lareb, the Netherlands Pharmacovigilance Centre, has also evaluated this study and classified use of nitrofurantoin during pregnancy as safe, with the exception of 30 days before delivery, since its use the last 30 days before delivery is 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) [96].

In view of the lack of teratogenic effects described and the resistance percentages of causative uropathogens, 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). As mentioned above, nitrofurantoin must not be 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 [97]. Single-dose regimen antibiotics for the treatment of a symptomatic UTI are mentioned to be less effective than the short-course regimens (4-7 day regimen) regarding cure rates,

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recurrences and pregnancy complications including preterm birth [98]. 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 [99].

In pregnant women suspected of having pyelonephritis empirical intravenous therapy requiring antepartum hospitalization should be started [100, 101]. Although there are insufficient data to recommend a specific treatment regimen for pyelonephritis in pregnancy, a 3rd generation cephalosporin (4 dd 1000 mg cefotaxim or 1 dd 2000 mg ceftriaxon) is the drug of first choice for the treatment of a pyelonephritis during pregnancy, because no adverse effects have been described [102]. Similar to non-pregnant women 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. It is recommended that the total treatment duration should be at least 10 days. 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 [103].

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 [104]. As far as GBS is concerned, in the NVOG guideline Prevention of Perinatal Group B Streptococcus Disease published in 2017, screening is not recommended; however, when a GBS is cultured in the urine, this is considered as severe maternal GBS colonization, and a consultation with the gynaecologist is recommended and in all cases administration of antibiotic prophylaxis during delivery is necessary [105].

Conclusions

Level 1	The benefits and harms of screening for ASB during pregnancy are unclear [[79] A1].
Level 2	The risk of pyelonephritis is higher in ASB-positive women (untreated or placebo-treated) than in ASB-negative women (five [2·4%] of 208 women *vs* 24 [0·6%] of 4035) [86] A2].

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Level 1	Whilst several older studies published before 1987 showed that treatment of ASB reduces the risk of pyelonephritis and preterm birth, recently a large Dutch trial in singleton low risk pregnancies reported no significant difference between ASB-positive women who received nitrofurantoin compared to untreated- or placebo treated ASB-positive women in the pyelonephritis rate (risk difference -2.4 95% CI -19.2-14.5) or pre-term delivery rate (risk difference -1.5, 95% CI -15.3-18.5) [[79, 80, 82-84] A1].
Level 1	A meta-analysis comparing 4-7 days of antibiotic treatment for ASB during pregnancy with a single dose showed, for any antibiotic used, that the no-cure rate was slightly lower for the short-course treatment than after a single dose of treatment (average risk ratio (RR) 1.28, 95% confidence interval (CI) 0.87 to 1.88; women = 1502, studies = 13; I^2 = 56%). An additional meta-analysis including only data from good quality trials, using the same antimicrobial agent in the short- and single dose treatment arm, showed that cure rates were higher after short (4-7 days) treatment compared to the a single dose of treatment (average RR 1.72, 95% CI 1.27 to 2.33; women = 803, studies = two; I^2 = 0%) [[92] A1].
Level 1	While no association was found between fetal exposure to nitrofurantoin and major malformation in cohort studies, there was a slight but significant teratogenic risk in case–control studies [[93] A1].
Level 2	Dispensing nitrofurantoin the last 30 days before delivery is associated with increased risk of neonatal jaundice (10.8%) compared with unexposed women (8.1%) [[96] A2].
Level 3	In pregnant women suspected of having pyelonephritis empirical intravenous therapy requiring antepartum hospitalization results in good clinical outcome [[101] C; [100] 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 recommended. In all cases administration of antibiotic prophylaxis during delivery is necessary [[105] A1; [106] A2].

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Other considerations

It is currently not recommended to screen for ASB (www.nvog.nl) and in the Netherlands urine cultures are generally only taken in circumstances when there is a suspicion of a UTI. Therefore, if ASB is found it is questionable whether it is truly completely asymptomatic, especially since clinical symptoms of UTI such as urgency and frequency can be difficult to distinguish from symptoms related to the pregnancy itself. For this reason the SWAB cUTI Guideline Committee follows the recommendation of the NVOG Guidelines, namely that once diagnosed, ASB in pregnant women should be treated. This is independent of the pregnancy term, and treatment of ASB is similar to that of cystitis [107].

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. In line with the recommendations in the NHG urinary tract infections, follow-up cultures after treatment are not recommended if symptoms have resolved.

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 be used in the last 30 days before delivery.
Recommendation	A 3rd generation cephalosporin (4 dd 1000 mg cefotaxim or 1 dd 2000 mg ceftriaxon) is the drug of first choice for the treatment of UTI with systemic symptoms during pregnancy.
Recommendation	The treatment duration of cystitis during pregnancy should be 5 days.
Recommendation	The treatment duration of UTI with systemic symptoms during pregnancy should be 10-14 days.
Recommendation	Antepartum UTI with systemic symptoms should be treated in a hospital setting and treatment should be started intravenously.
Recommendation	Screening of asymptomatic bacteriuria at 16-20 weeks gestation for better maternal and neonatal outcome is not recommended.

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Recommendation	When ASB is diagnosed, it should be treated as a cystitis regardless of the pregnancy term.
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 recommended, because antibiotic prophylaxis during delivery is necessary.
Recommended	If symptoms have resolved after treatment of urinary tract infection, follow-up cultures are not recommended.

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Chapter 5. URINARY TRACT INFECTIONS IN PATIENTS WITH A CATHETER

The literature search described on page 13 yielded 5 additional systematic reviews and 2 RCTs.

Articles on specially treated catheters as prevention method or on UTI after certain procedures (for example, after operations/interventions) were excluded. Some parts of the following text are cited from: Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America [108].

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 [108].

Every patient with an indwelling catheter or 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 ≤ 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

The use of antibiotic prophylaxis in patients with a short-term catheter has been evaluated in a Cochrane systematic review [109]. In this review, six trials were included comparing prophylactic antibiotics in both surgical and non-surgical patients with a catheter for less than

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14 days. There was broad consistency across the trials that prophylactic antibiotics reduced the frequency of bacteriuria and in a meta-analysis of three trials (others could not be included due to heterogeneity), the risk ratio (RR) of bacteriuria was 0.20; (95% CI 0.13-0.31). However, only one of the included studies reported symptomatic UTI as an outcome measure. In this study that was published in 1985, significantly fewer cases of UTI were reported in the prophylaxis group (RR 0.20 95% CI 0.06 to 0.66, number needed to treat: 4) [109, 110].

Two systematic reviews evaluated the prophylactic use of antibiotics in long-term urinary catheter use [111, 112]. In these reviews, several prophylactic strategies are described in spinal cord injury (SCI), spina bifida or neurogenic bladder patients performing either clean intermittent or chronic indwelling catheterization. Authors from both systematic reviews conclude that although multiple RCTs have assessed prophylactic strategies in patients with long-term catheters, trials show heterogenous results and positive trials were tempered by increased antimicrobial resistance and adverse events.
A detailed overview of these preventive strategies and RCTs can be found in these SRs. In the following paragraph we highlight a few studies that are described in these reviews or that were identified in our literature search described on page 13.

The effect of discontinuing prophylactic antibiotics (TMP/SMX) was reported in two RCTs [113, 114]. These studies reported no difference in UTI risk with or without antibiotic prophylaxis. The first study [113] included patients with spinal cord injury (intermittent catheterization, reflex voiding, indwelling catheter or suprapubic catheter), the second study only intermittently catheterized neurogenic bladder patients [114]

Our literature search also identified a large RCT (n=404) from 2018 that was not included in the two previously mentioned SRs (Garcia-Arguello et al. 2017; Tradewell et al. 2018). This RCT [115] included adults performing clean intermittent self-catheterization who had suffered from at least 2 UTI or had been hospitalized for a UTI in the past 12 months. In this study, the intervention group received once-daily oral antibiotic prophylaxis with either 50 mg nitrofurantoin, 100 mg trimethoprim or 250 mg cephalexin for 12 months. The frequency of symptomatic antibiotic-treated UTI was reduced by 48% (incidence rate ratio (IRR) 0.52, 95% confidence interval (CI) 0.44 to 0.61) and the reduction in microbiologically proven UTI was similar (IRR 0.49, 95% CI 0.39 to 0.60). Development of antimicrobial resistance was seen more frequently in pathogens isolated from urine and *Escherichia coli* from perianal swabs in participants allocated to antibiotic prophylaxis.

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Another study, which was not mentioned in the previously mentioned SRs was a single crossover trial with 34 elderly inpatients using indwelling urethral catheterization. This study showed fewer episodes of symptomatic UTI in the prophylaxis (norfloxacin) group vs. placebo (1 in 276 catheterization weeks vs. 12 in 259 weeks) [116].

An alternative prophylactic regimen that has been described is weekly oral cyclic antibiotics (WOCA), in which two different high-dose antibiotics are rotated on a weekly basis, with for example amoxicillin 3000 mg, cefixime 400 mg, fosfomycin trometamol 600 mg, nitrofurantoin 300 mg, and TMP-SMX 320/1600 mg, each of them once a week. During week A, the patient receives antibiotic A, and the following week the patient is given another antibiotic B. In the previous mentioned SRs, three studies from the same study group were identified describing such strategies. Two studies, a prospective observational and a cross-sectional study including respectively 38 and 50 patients with neurogenic bladder, showed significant reductions in UTI, antibiotic use, and hospitalization with WOCA [117, 118]. A third, small prospective observational study assessing WOCA in six pregnant women with neurogenic bladder and recurrent UTI observed a significant reduction of UTI (6 UTI/patient/year before pregnancy to 0.4 during pregnancy and under WOCA; $p<0.001$) and no obstetric complications. Infant outcomes were good [119].

Furthermore, gentamicin instillation has been mentioned as treatment option to prevent UTI in patients with long-term catheters. The systematic reviews did not identity RCTs that addressed the use of gentamicin to prevent UTI in neurogenic bladder patients. However, a single retrospective quasi-experimental study assessing 22 patients with neurogenic bladder (intermittent catheterization) comparing before and after the use of intravesical gentamicin found that patients had fewer symptomatic UTI's (median 4 vs. 1 episodes; $p<0.004$) and underwent fewer courses of oral antibiotics after initiating gentamicin (median 3.5 vs. 1; $p<0.01$) [120].

Level 1	Antibiotic prophylaxis decreases fivefold the incidence of bacteriuria in patients with a short-term indwelling catheter [[121] [A1]]
Level 1	There is limited evidence on the effect of antibiotic prophylaxis on the incidence of symptomatic UTI in patients with short-term indwelling catheters. A recent systematic review [[109] A1] identified only one

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	study that reported clinical UTI as outcome measure. In this study from 1985 [[110], B] a significant decrease in symptomatic UTI was reported after antibiotic prophylaxis (n = 90, RR 0.20 (95% CI 0.06-0.66).
Level 1	In patients with spinal cord injury and neurogenic bladder with long-term catheters, prophylaxis papers described a variety of preventive strategies, but none were consistently superior to prevent UTI. Positive trials were tempered by increased antimicrobial resistance and adverse events [[111, 112] A1].
Level 3	In patients with neurogenic bladder, use of weekly oral cyclic antibiotics results in a significant reduction of UTI, antibiotic use, and hospitalization [[117-119] B].
Level 3	After initiating (once daily) gentamicin instillation, patients with neurogenic bladder (intermittent catheterization) had fewer symptomatic UTI's (median 4 vs. 1 episodes; p<0.004) and underwent fewer courses of oral antibiotics (median 3.5 vs. 1; p<0.01) [[120] B].
Level 2	In patients performing clean intermitted self-catheterization with >2 UTI or hospitalisation for >1 UTI in the past 12 months, antibiotic prophylaxis reduced the frequency of symptomatic UTI with 48% (incidence ratio 0.52, 95% CI 0.44-0.61) [[115] A2].

Other considerations

Antibiotic prophylaxis will result in the development of resistance of the commensal flora [122]. A significant decrease in symptomatic UTI was reported in patients with short-term indwelling catheters after antibiotic prophylaxis (RR 0.20 (95% CI 0.06-0.66, number need to treat 4) [109]. However, in light of the increasing antibiotic resistance and the side effects of antibiotic agents, the Guideline committee does not recommend antibiotic prophylaxis. Nevertheless, it may be considered in selected vulnerable patients. Since a clear definition of vulnerability does not exist, this decision should be based on the clinical judgement of the treating physician. For more information considering vulnerability in elderly patients, we refer to the Verenso Guidelines (https://www.verenso.nl/richtlijnen-en-praktijkvoering/richtlijnendatabase).

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Also, since every patient with an indwelling catheter or catheter develops bacteriuria, which is not infection but colonization, 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.
Recommendation	There is no need to screen for bacteriuria in patients with short- or long-term urinary catheters, or in those who catheterize themselves intermittently over prolonged periods.

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 [123]. 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 [124]. 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 [108, 125, 126].

Prior to catheterization

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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 [127]. 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.

Replacement

A recent Cochrane review studied policies on antibiotic prophylaxis at the time of catheter replacement of long-term indwelling CAD [128]. In this review only one trial was identified that compared antibiotic prophylaxis to no prophylaxis at the time of catheter replacement. In this trial, no statistically significant difference in incidence of positive urine cultures was found between giving either 1 g of intravenous meropenem 30 minutes before catheter replacement or no antibiotic. Neither was there a significant difference in the incidence of clinical infections including urosepsis. No other published studies of prophylactic antimicrobials to prevent CA-bacteriuria or CA-UTI in patients whose catheters are being replaced were found.

Removal

A meta-analysis evaluating antibiotic prophylaxis at the time of catheter removal in short-term transurethral CAD showed a reduced rate of symptomatic UTI after antibiotic prophylaxis (4.7%) compared to controls (11.0%) (7 studies, n=1520, risk ratio 0.45 (0.28-0.72) NNT 17 (12 to 30) [129]. None of the included study assessed subsequent symptomatic urinary tract infections caused by antibiotic resistant organisms as a secondary endpoint.

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 [[108] A1; [123-126] C].
Level 3	Single-dose aztreonam vs. placebo before catheterization decreased the incidence of CA-UTI at 7 days [127] A2].
Level 3	In patients with long-term catheters, 1 gram of intravenous meropenem compared to no antibiotic 30 minutes before catheter replacement does

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	not result in a lower incidence of positive urine cultures or clinical infections [[128] B]
Level 1	In patients with short-term catheters, antibiotic prophylaxis at the time of removal of the catheter reduces the incidence of symptomatic UTI: prophylaxis 4.7% vs. controls 11%, with a number needed to treat of 17 (95% CI: 12-30) [[129] A1].

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, replacement, or removal in patients with long-term catheters. 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 while having chronic bacteriuria.

In patients with short-term catheters, antibiotic prophylaxis at the time of removal results in a lower incidence of UTI. Due to the concerns of the increasing antimicrobial resistance and the fact that UTI is generally a mild condition if treated promptly, the Guideline Committee does not recommend routine antibiotic prophylaxis at removal of short-term catheters. Nevertheless, it may be considered in selected vulnerable patients. Since a clear definition of vulnerability does not exist, this decision should be based on the clinical judgement of the treating physician.

IS ANTIMICROBIAL PROPHYLAXIS INDICATED AT THE TIME OF CATHETER PLACEMENT, REPLACEMENT OR REMOVAL?	
Recommendation	In patients with either short- or long term catheters, prophylactic systemic or local antimicrobials should **not** be administered routinely at the time of catheter placement, replacement or removal.

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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* [130]. In patients with a long-term indwelling catheter, in addition to more common *Enterobacterales*, also *Serratia spp, Providencia spp, Acinetobacter spp*, enterococci, yeasts and staphylococci are often cultured [72, 131].

Two Dutch studies have been performed evaluating pathogens in urine of patients with catheters, one in the urology and internal medicine departments of 19 Dutch hospitals [132], and the other at primary care centers and in emergency rooms [133]. 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 spp* (10-12%), enterococci (5-10%), *P. mirabilis* (9-12%) and *P. aeruginosa* (8-9%) (26). In this group, inadequate coverage rate was 40 % for second generation cephalosporins, 33 % for third generation cephalosporins and 37% for fluoroquinolones. Leaving out entercoccocci decreased the inadequate coverage rates to respectively 31%, 22% and 27%. The combination of co-amoxiclav with gentamicin was the most adequate (inadequate treatment rate of 3%). Excluding enterococci also 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%) ([132] 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) [5].

A prospective RCT evaluated whether long-term urinary catheters should be replaced prior to treatment of CA-UTI [134]. 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 [135].

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Level 3	In patients with short-term use of catheter the most prevalent cultured micro-organism is *E. coli.*
Level 3	In patients with long-term catheter *E. Coli* is the most prevalent pathogen, but enterococci, staphylococci, *Pseudomonas aeroginosa, Serratia* spp.*, Providencia* spp., *Acinetobacter* spp. and yeasts are also frequently cultured [[131, 133] C; [132], B].
Level 3	Patients with a urinary catheter have an increased risk to have a fluoroquinolone-resistant micro-organism [[5] 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 an aminoglycoside. Excluding enterococci made a third-generation cephalosporin with an aminoglycoside the most adequate recommendation [[132], 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 [[134] A2].
Level 3	When a symptomatic UTI is present, pyuria disappears faster during intermittent compared to suprapubic or indwelling catheterization [[135] 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 [108].

In patients with long-term catheter and systemic symptoms, empirical treatment with fluoroquinolones or an aminoglycoside is warranted to cover less common micro-organisms such as *Pseudomonas aeroginosa., Serratia* spp., *Providencia* spp., and *Acinetobacter* spp.

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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, which is also dependent on the context of the patient (illness severity, comorbidities, contraindications against antimicrobials etc.) Therefore, the Guideline committee decided to give recommendations with and without the coverage of enterococci.

Since prior use of antibiotics is the strongest predictor for an infection caused by a resistant micro-organism,[5], we recommend to wait for culture results before treatment is started if the patient has no systemic symptoms.

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 such as *Pseudomonas aeroginosa., Serratia spp., Providencia spp., and Acinetobacter spp.*
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 an aminoglycoside. Excluding enterococci makes a third-generation cephalosporin with an aminoglycoside 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

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	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, such as an uncomplicated cystitis, pyelonephritis, pyelonephritis with abscess, prostatitis, and bacteremia. This also holds true for CA-UTI. 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 known. In published reviews the recommended treatment durations for complicated UTI range from 7-21 days [108] , depending on the severity of the infection.

In an RCT, Harding et al. investigated women with lower tract CA-UTI within 14 days after catheter removal. Asymptomatic patients (119) with catheter-acquired bacteriuria were randomly assigned to receive no therapy, a single dose (320-1600 mg) of therapy with trimethoprim-sulfamethoxazole, or 10 days (160-800 mg twice daily) of therapy. Thirty-two patients with lower tract symptoms alone received a single dose or 10 days of therapy, and 10 patients with upper tract symptoms or signs received 10 days of therapy. Single-dose therapy resolved bacteriuria in 30 of 37 patients (81%; CI, 68% to 94%); 10 days of therapy in 26 of 33 (79%; CI, 65% to 93%). 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 [81%], respectively). Ten days of therapy resolved infection in 6 of 9 (67%) patients with upper tract symptoms. In conclusion, for asymptomatic patients and patients with lower tract symptoms alone, single-dose therapy was as effective as 10 days of therapy In another 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) [114]. Rates of cure, persistence, and relapse were similar in the two treatment groups.

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In 2017 a systematic review was published evaluating the duration of treatment in spinal cord injury patients [111]. In this review, a randomized, double-blind, placebo-controlled trial is described that compared 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 [136]. Patients with pyelonephritis or symptoms of systemic infection were excluded. 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. Another study included in this systematic review was a trial that randomized 61 patients with symptomatic CA-UTI to 5 (in conjunction with catheter exchange) or 10 days (without catheter exchange) of treatment with antimicrobials guided by gram stain. The primary endpoint of the study was met, indicating that the 5-day regimen with catheter exchange was noninferior to the 10-day regimen with catheter retention on the basis of clinical cure. However, criteria for noninferiority on the basis of microbiologic response and resolution of pyuria were not met and the 5-day regimen of antibiotics was associated with higher rates of UTI recurrence than the 10-day regimen [137].

Conclusions

Level 3	In women with lower tract CA-UTI within 14 days after catheter removal, asymptomatic patients and patients with lower tract symptoms alone had similar resolution rates with single-dose therapy or 10 days of therapy with TMP-SMX [[138] 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 [[114] B].
Level 3	In patients with spinal cord injury performing clean intermittent catheterization or condom drainage, three days of treatment for a lower

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	UTI with ciprofloxacin 250 mg twice daily results in a similar clinical, but a lower microbiological cure rate and a higher relapse rate compared to 14 days of treatment [[136] (B)]
Level 3	In patients with spinal cord injury, an indwelling catheter and symptomatic CA-UTI, five days (in conjunction with CAD exchange) or 10 days (without CAD exchange) of treatment with antimicrobials guided by gram stain resulted in similar initial clinical cure rates, but higher relapse rates in the 5 days' group [[137] B]

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.

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.

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Chapter 6. URINARY TRACT INFECTIONS IN PATIENTS WITH DIABETES MELLITUS

The literature search described on page 13 yielded no additional articles on the treatment of UTI in patients with diabetes mellitus (DM). In this search, articles on asymptomatic bacteriuria (ASB) were excluded, since ASB is not a UTI and it is now generally accepted that ASB should not be treated in patients with DM [76].

Literature overview

Epidemiology

It has been shown that diabetic patients have an increased risk for UTI [139, 140]. A 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 [141]. This increased recurrence rate was confirmed in one study [142], but not in another [143]. 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 [144].

In addition, diabetic patients more often develop complications: bacteraemia [145] and longer hospitalization [139, 146], due to their UTI.

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

Choice of drug

Because the antibiotic susceptibility for *E. coli* and other uropathogens of patients with and without DM are comparable [147, 148], the choice of antibiotic treatment is not different for diabetic patients.

Duration of therapy

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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 [145, 146] 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 [149, 150]. In the largest study [150], 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, defined as longer than 5 days, but still had a higher recurrence rate of UTIs compared with those without diabetes.

Conclusions

Level 2	Patients with DM have a higher incidence of UTIs than patients without DM [[139, 140] B], but this is less clear for patients with DM type 1 [[144] B].
Level 2	Patients with DM develop more complications of their UTI [[139, 145, 146] B].
Level 2	The resistance percentages for *E. coli* and other uropathogens from the urine of patients with and without DM are comparable [[147, 148] 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 [[141-143, 149, 150] B].

Other considerations

Considering the antibiotic susceptibility of the causative micro-organisms, patients with UTI and DM can be treated with the same agents as those without DM. Nitrofurantoin is a good choice for diabetic women with cystitis.. In the largest study from the Netherlands, more recurrent UTIs were demonstrated even with a treatment duration of longer than 5 days [150]. However, we do not know whether a longer treatment duration will result in a lower recurrence rate.

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The guideline committee recommends in accordance with the NHG standard 7 instead of 5 days treatment for lower UTI in women 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 INFECTION in PATIENTS WITH DIABETES MELLITUS?	
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”.

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Chapter 7. WHAT ARE THE BEST STRATEGIES FOR URINARY TRACT INFECTIONS AND ASYMPTOMATIC BACTERIURIA IN PATIENTS WITH A RENAL TRANSPLANTATION?

Search strategy

In the literature search described on page 13, two additional systematic reviews and one randomized controlled trial were identified.

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% [151].

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 [152]. 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 [153] [151, 154] [155].

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 [151]. 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 [156], whereas others found an increased incidence of UTI in azathioprine-treated patients [157]. 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 [158, 159].

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.

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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 [160, 161]. Recurrent UTI, and especially acute graft pyelonephritis (AGPN) and bacteremia, are associated with a poorer graft and poorer patient outcome [162]. 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 [163]. This trend was also demonstrated in a large analysis of data from the United States Renal Data System (USRDS) in 28,942 patients [164]. 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 [153, 163, 165]. The risk for infection with ESBL-producing micro-organisms increases significantly with recurrent episodes of UTI, as shown in retrospective studies [166].

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 [153]. 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 [155].

ASB can impair renal function in kidney transplant patients, probably due to cumulative inflammatory damage [160, 165].

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 [167]. 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.

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Whether ASB in renal transplant recipients should be treated with antibiotics remains a subject of debate. Recently, two systematic reviews were published evaluating treatment of ASB in renal transplant recipients [80, 168]. These reviews identified two RCTs. In the first RCT, 100 patients were included and the time since transplantation was ≥12 months [169], while the second RCT included 111 patients and the time since transplantation was ≥2 months. Meta-analysis of these RCTs did not show benefit of treatment of ASB in terms of reducing incidence of symptomatic UTIs (n=200, RR=0.86, 95% CI 0.51-1.45). Furthermore, no significant differences in the rate of ASB clearance, graft loss, or change in renal function during longer-term follow-up were demonstrated.

More recently (2019), a multicentre, open-label, non-blinded prospective noninferiority randomized controlled trial compared antibiotic treatment with no treatment for ASB in renal transplant recipients in the first year after transplantation [170]. Patients were included in the first month after transplantation, after removal of urinary catheters, and were followed for 12 months. In this study, 205 renal transplant recipients were randomized to receive or not receive antibiotics if ASB would occur during follow-up. ASB occurred in 41 (42.3%) and 46 (50.5%) patients in the treatment and no treatment groups, respectively. The median time from renal transplant to study inclusion was 4 days (interquartile range [IQR] 3–7). There were no differences in the occurrence of acute graft pyelonephritis in the intention-to-treat population (12.2% [5 of 41] in the treatment group vs 8.7% [4 of 46] in the no treatment group; risk ratio, 1.40; 95% confidence interval, 0.40–4.87) or the per-protocol population (13.8% [4 of 29] in the treatment group vs 6.7% [3 of 45] in the no treatment group; risk ratio, 2.07, 95% confidence interval, 0.50–8.58). No differences were found in the following secondary endpoints either: bacteremic acute graft pyelonephritis, cystitis, graft rejection, graft function, graft loss, opportunistic infections, need for hospitalization, and mortality. The only secondary endpoint that differed between the two groups was the antibiotic susceptibility: fosfomycin (P = .030), amoxicillin-clavulanic (P < .001) resistance, and extended-spectrum β-lactamase production (P = .044) were more common in urinary isolates of renal transplant recipients receiving antibiotic treatment for AB.

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 [171].

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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 [160] [161]. 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 [172].

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 [[161] B]. The highest incidence of UTI is in the first 3 months after transplantation [[152] 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. [[158] A2]
Level 3	ASB episodes are associated with pyelonephritis and with rejection [[167] B].
Level 1	Treatment of ASB in renal transplant recipients more than two months after transplantation does not result in a reduction of incidence of symptomatic UTI (n=200, RR=0.86, 95% CI 0.51-1.45) or in a significant difference in the rate of ASB clearance, graft loss or change in renal function [[80, 168] A1.
Level 3	Treatment of ASB in renal transplant recipients without a urinary catheter, <12 months after transplantation, does not result in a decreased occurrence of acute graft pyelonephritis, bacteremic acute graft pyelonephritis, cystitis, graft rejection, graft function, graft loss,

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	opportunistic infections, need for hospitalization, or mortality, while it does result in an decreased antibiotic susceptibility [[170] B].
Level 3	The most frequently isolated micro-organisms in the first 3 months after transplantation are *Escherichia Coli*, *Pseudomonas aeruginosa* and enterococci [153, 163] C; [165] D].
Level 4	Early UTI in the first 6 months after transplantation are more commonly associated with pyelonephritis, bacteremia and relapse [[160, 173] D].
Level 2	Recurrent UTI and acute graft pyelonephritis are associated with a poorer graft and patient outcome [[163] C; [164] B; [162] A2].
Level 3	The incidence of UTI with ESBL-producing micro-organisms increases with the number of recurrent UTI [[166] B].
Level 3	Although cranberry juice may have some inhibitory effect on CYP3A activity, no interference with cyclosporine levels has been found [[171] 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 [153, 163, 165].

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 [174, 175].

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The IDSA guideline 'Clinical Practice Guideline for the management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America' [76] recommends against screening for or treating ASB in patients who have had a renal transplant >1 month prior and point out there is insufficient evidence to inform a recommendation in patients within the first month following renal transplantation. This is in somewhat in contrast to the Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice, which recommend against routinely collecting urine cultures or treating bacteriuria in asymptomatic KT recipients more than 2 months after renal transplantation.

Several studies have shown that patients >2 months after renal transplantation do not benefit from treatment of ASB. However, studies considering the early post-transplantation period are scarce: we identified only RCT [170] that included patients within the first month after transplantation and unfortunately this study lacked statistical power to make a conclusion about the period < 2 months after renal transplantation. Therefore, the Guideline Committee believes that there is insufficient evidence to make recommendations about the first one to two months after transplantation.

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.
One should keep in mind that the native kidneys can be a source for recurrent infections, especially in patients with pre-transplant rUTI.

WHAT ARE THE BEST STRATEGIES FOR URINARY TRACT INFECTIONS AND ASYMPTOMATIC BACTERIURIA IN PATIENTS WITH A RENAL TRANSPLANTATION?	
Recommendation	Screening and treatment of ASB in renal transplant recipients >2 months after renal transplantation is not recommended.
Recommendation	No recommendation can be made about screening and treatment of ASB in renal transplant patients <2 months after renal transplantation.

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Recommendation	Treatment of UTI in renal transplant patients should be according to the general guidelines for treatment of UTI with systemic symptoms, but in the first 3 months after transplantation empirical treatment with a combination that also covers *Pseudomonas aeruginosa* and enterococci can be considered.
Recommendation	Due to its nephrotoxicity, aminoglycosides should be used with caution.
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 in the last 12 months 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.

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Chapter 8: WHAT IS THE OPTIMAL TREATMENT IN PATIENTS WITH POLYCYSTIC KIDNEY DISEASE?

Search strategy

The literature search described on page 13 identified one new systematic reviews and no RCTs on the treatment of UTI in patients with polycystic kidney disease. Because of the scarce literature on this topic and lack of an evidence based treatment strategy, as asked by the nephrology association, a relevant retrospective study considering a diagnostic algorithm on the management of ADPKD was also included.

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 [176, 177]. Approximately 50-75% of patients with ADPKD will have a UTI during their lifetime, most of them presenting as an uncomplicated lower UTI [177].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 [178, 179]. Discrimination between an upper UTI caused by a pyelonephritis or by a cyst infection can be difficult [177, 180].
Although cyst infection is reported as one of the most frequent complications of ADPKD [181], 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 [176], 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 [181] 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.

Another retrospective study describing the diagnostic challenges of cyst infections in APDK, analyzed a cohort of 173 ADPDK patients presenting with abdominal pain and/or fever [182]. This study reported that in cyst infection the causative bacterium was found in 52.2% of the

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cases, either in urine (21.7%), in blood (39.1%), or in both (8.7%). *E. coli* represents the most frequent pathogen, with a prevalence of 91.7%. Urine or blood cultures remained sterile in >90% of cyst hemorrhage. In this study, cyst infection was definite if confirmed by cyst puncture, and probable if 4 criteria were met: 3 days of fever, loin/liver tenderness, C-reactive protein (CRP) plasma levels >50mg/L and no CT evidence for cyst hemorrhage. Other episodes were grouped as inflammation of unknown origin. In this study, CRP cut-off at 70 mg/dl showed 92% sensitivity and 81% specificity in cyst infection diagnosis. Ultrasound, CT and magnetic resonance diagnosed cyst infections in 2.6%, 20% and 16.7% of cases, respectively.[18]FDG-PET/CT was performed in 10/23 cyst infections, with a positive yield of 4/4 in patients with a definite cyst infection, and 4/6 in patients with a probable cyst infection. One plausible explanation for negative results was that the procedure was performed at a very late stage [182]: in one patient 4 weeks post admission (this patient had recovered without antibiotic therapy) and in the second patient 6 days after antibiotic therapy ended.

It has been shown before that PET scans can been useful to identify the infected cysts [183], although PET scans have 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. [176], 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 [180, 184]. 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 [176]:

- 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.

In the previously mentioned retrospective study [182], the authors have proposed an algorithm to help clinicians discriminate cyst infection from cystic haemorrhage and non-cystic diseases in ADPKD patients presenting with suspected acute cyst complication (figure 1).

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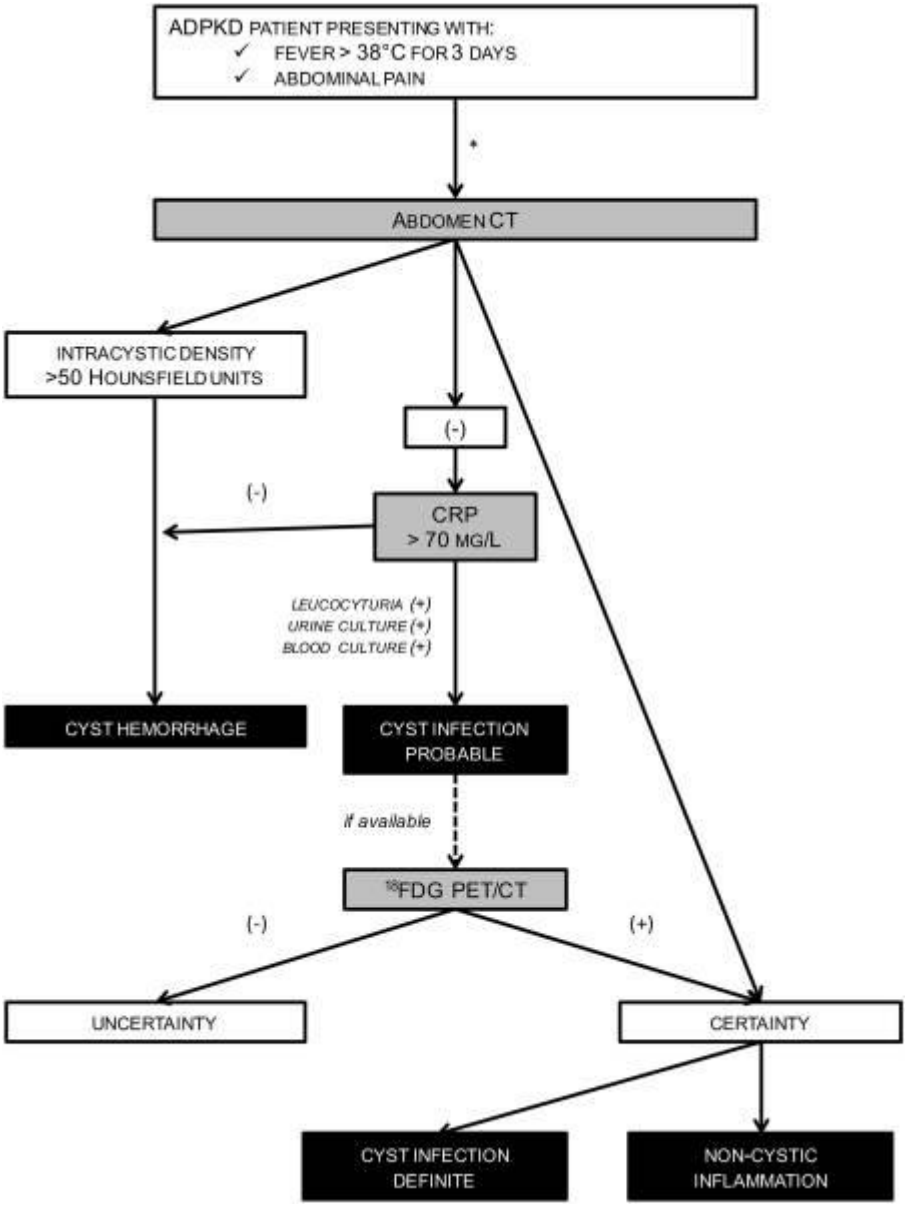

Figure 1. Diagnostic algorithm to manage patients with autosomal dominant polycystic kidney disease (ADPKD) presenting with suspected acute cyst complication [182].

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. A systematic review published in 2017 [185] concluded that no evidence-based strategy exists for the treatment of

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a cyst infection. This review provides an overview of 60 studies with in total 85 ADPKD patients with a renal cyst infection and describes treatment strategies and outcomes, yet it does not recommend certain treatment strategies. In this review, definite cyst infection was defined as the isolation of a pathogen from cyst aspirate and since no uniform criteria exist for the diagnosis of probable cyst infection, all remaining cases were included under the diagnosis of probable infection. Results described in this review are summarized in the following section.

In the 85 patients with ADPKD and renal cyst infection, 160 treatments were performed: 92 antimicrobial, 29 percutaneous and 39 surgical. Initial management often consisted of antimicrobials (79%) and quinolone-based regimens were favored (34%). Overall, 61% of patients failed initial treatment, but treatment failure has decreased over time (before the year 2000: 75%; during and after the year 2000: 51%, p= 0.03). Comparison of patients with the initial treatment outcome failure vs. success, showed that patients that failed treatment were significantly older, received a shorter initial antimicrobial treatment (median [range]: 7 days [5–14] vs. 28 days [21–44] <0.001) and pathogens other than *E.coli* were more frequently cultured (54% vs. 18%, p=0.0001). The percentage of cultured antimicrobial-resistant pathogens did not differ between patients with and without treatment failure [185].

As previously mentioned, most cysts are not in communication with a filtering glomerulus. Thus, 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. Furthermore, in case of large (> 5 cm) infected cysts, early drainage in combination with antibiotic treatment is advised [176]. Efficacy of antibiotic treatment and infection eradication are defined by a good clinical response and at least two negative blood and/or urine cultures [176].

Conclusions

Level 3	The incidence of lower and upper UTI and cyst infections is high in patients with autosomal dominant polycystic kidney disease [[176, 181] C, [177] D].
Level 3	*Eschericha coli* is the most common causative organism, accounting for > 75% of cases [; [176, 186] C [182] B].

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Level 3	Urinary cultures are often negative, since the cysts may not be in communication with the collecting system [[181] C].
Level 3	Ultrasound, CT scan and MRI failed to detect the infected cyst in the majority of patients [[176] C] [182] B].
Level 3	In ADPKD patients presenting with abdominal pain and/or fever, CRP cut-off at 70 mg/dl showed a 92% sensitivity and 81% specificity in cystic infection diagnosis [[182] B]
Level 3	PET scan can be useful to identify a cyst infection [[176] C; [180, 183, 184] D] [182] B]
Level 4	The following criteria are used for the diagnosis of a cyst infection: - Cyst infection is considered as definite in the presence of a cyst aspiration showing evidence of infection (neutrophils debris and/or micro-organism) [176] D [182] C. - Cyst infection is considered likely in the presence of all of the following features: fever (temperature >38°C [182] - 38.5°C [176] for >3 days, abdominal pain (particularly a palpable area of renal or liver tenderness), increased C-reactive protein (CRP; >50 [176] - 70 [182] mg/L), and the absence of any significant recent intracystic bleeding or other causes of fever [176] D; [182] C].
Level 4	PET scan is considered positive when increased Fludeoxyglucose (FDG) uptake is demonstrated in at least one cyst [[176] D]
Level 1	The rate of treatment failure in patients with infected cysts in APDKD is high: 51% [[185] A1] Patients that failed treatment were significantly older, received shorter initial antimicrobial treatment (median [range]: 7 days [5–14] vs. 28 days [21–44] <0.001) and pathogens other than *E.coli* were more frequently cultured (54% vs. 18%, p=0.0001). The percentage of cultured antimicrobial-resistent pathogens did not differ between patients with and without treatment failure [[185] A1].
Level 3	To treat a cyst infection fluoroquinolones or TMP-SMX must be used. Penicillins and aminoglycosides often do not penetrate cysts [[176] C].

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Level 4	In case of large (> 5 cm) infected cysts, early drainage is advised in combination with antibiotic treatment [[176] 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 [176] 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 UTI with systemic symptoms.. 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	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 °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	If a cyst infection is probable, as described in the diagnostic algorithm in figure 1, a PET scan may be considered. PET scan is considered positive when increased Fludeoxyglucose (FDG) uptake is demonstrated in at least one cyst.

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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 UTI with systemic symptoms.
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

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