Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Review article: Medical guidelines | Published 04 May 2020 | doi:10.4414/smw.2020.20236
Cite this as: Swiss Med Wkly. 2020;150:w20236

Guideline of the Swiss Society of Gynaecology and Obstetrics (SSGO) on acute and recurrent urinary tract infections in women, including pregnancy

Betschart Cornelia[a], Albrich Werner C.[b], Brandner Sonja[c], Faltin Daniel[d], Kuhn Annette[e], Surbek Daniel[f], Geissbühler Verena[g]

[a] Department of Gynaecology, University Hospital Zurich, Switzerland
[b] Division of Infectious Diseases / Hospital Epidemiology, Cantonal Hospital St Gallen, Switzerland
[c] Frauenzimmer Bern AG − Office for Urogynaecology, Bern, Switzerland
[d] Centre of Perineology, Dianuro, Geneva, Switzerland
[e] Department of Gynaecology, University Hospital Bern, Switzerland
[f] Department of Obstetrics, University Hospital Bern, Switzerland
[g] Department of Obstetrics and Gynaecology, Cantonal Hospital Winterthur, Switzerland

Summary

Acute and recurrent urinary tract infections (UTIs) are common auto-infectious diseases transmitted from the intestinal tract. They affect the urinary tract either through recurrence or through persistence. The incidence of UTIs increases with age and comorbidities. In this guideline from the Swiss Society of Gynaecology and Obstetrics (SSGO), diagnosis and treatment of UTIs are grouped into uncomplicated and complicated cases. This is to our knowledge the first guideline that specifically considers UTIs in pregnancy and breastfeeding, and the prevention of UTIs in the context of urogynaecological diagnosis and surgery. Recommendations are based on observational, retrospective or randomised controlled studies. The level of evidence was rated according to recommendations made by the Oxford Centre of Evidence-based Medicine.

In non-pregnant women and women <65 years with dysuria, pollakiuria and suprapubic pain, no urine diagnostic testing is needed. If the clinical presentation is unclear, urinary tests such as midstream urine stix or urine analysis should be used, and in cases of unclear or recurrent infections, a urine culture.

Routine screening for asymptomatic bacteriuria (ASB) should not be carried out, and antibiotic treatment should be avoided in cases of incidentally detected ASB. As an exception, screening for bacteriuria should be carried out in patients prior to urogynaecological surgery where urinary drainage by catheter is necessary or probable. In pregnancy, systematic screening for ASB is not recommended, because most women with ASB do not develop complications during follow-up, and contamination of urine samples collected in pregnancy is common.

Patients should be advised that most UTIs are self-limiting, that the symptoms can be relieved with non-steroidal anti-inflammatory drugs (NSAIDs) and that the same time is required to eradicate the bacteria using antibiotics or NSAIDs. For non-pregnant women with uncomplicated UTIs, a 48-hour-delayed antibiotic prescription is recommended, supplemented by NSAIDs for pain relief. If antibiotics are needed after 48 hours, or in case of direct antibiotic administration in pregnant women, the shortest possible course of treatment should be carried out.

There is increasing interest in alternatives or complementary treatments to antibiotic therapy, especially for recurrent UTIs. Different recommendations and alternative medications are summarised.

This short and comprehensive guideline provides quick answers for every day clinical questions concerning UTIs, especially for obstetricians and gynaecologists.

Keywords: *urinary tract infection*, *pyelonephritis*, *recurrent urinary tract infection*, *urinalysis*, *antibiotic therapy*, Escherichia coli

Correspondence:
Verena Geissbühler, MD, Department of Gynaecology, Head of clinic for urogynaecology, Obstetrics and Gynaecology, Brauerstrasse 15, CH-8401 Winterthur, verena.geissbuehler[at]ksw.ch

Background

The Quality Assurance Committee of the SSGO (Swiss Society of Gynaecology and Obstetrics) releases guidelines on current topics to ensure quality and the timely implementation of medical innovations. In human medicine, the number of infections caused by antibiotic-resistant bacteria has increased. The urinary tract pathogen *Escherichia coli*, which is often encountered in general and gynaecological practices, accounts for almost one third of resistant bacteria. Further, new Swiss data confirm that the resistance rate of *E. coli* to various antibiotics is increasing [1].

As most guidelines on urinary tract infections (UTIs) (table 1) do not specifically consider the treatment of women and do not include the treatment of pregnant women, the Quality Assurance Committee of the SSGO declared an expert recommendation focusing on female UTIs in both pregnant and non-pregnant women to be an urgent need. A guideline was also required in the light of the strategy of the Federal Office of Public Health to reduce antibiotic resistance.

UTIs in men are less frequent, but can be more serious than in women owing to functional and anatomical differences in the urogenital tract. Thus, diagnosis and treatment differ between men and women. UTIs in men are not a topic of this guideline.

Scope and aims

In this guideline on the management of UTIs, we report on the diagnosis and treatment of UTIs and recurrent UTIs in women and during pregnancy, with antibiotic and non-antibiotic options. The guideline also covers antibiotic therapy prior to interventions and operations in gynaecology.

Guideline assembly and conflicts of interest

The expert panel comprises members of the SSGO, including gynaecologists, obstetricians and urogynaecologists, and an infectiologist. This guideline meets the following requirements: it addresses UTIs and recurrent UTIs in pregnant and non-pregnant women, it is presented in a compressed, easy-to-understand text form, with practice recommendations for in- and outpatients including evidence-based recommendations (the search strategy is described below), and is regularly updated every 3 to 4 years. The members of the Quality Assurance Committee of the SSGO are gynaecologists working in private practices, in academia, and in regional and teaching hospitals. They have various specialisations and sub-specialisations in obstetrics and gynaecology. In addition, a representative of the Swiss Patient Organisation (SPO) is also a permanent committee member. The expert panel addresses UTIs, a day-to-day problem of Ob/Gyn practitioners nation- and worldwide, in the form of a consensus document and not as a systematic review. The committee discussed the management of UTIs during a series of meetings. A manual literature search was performed to reference statements on diagnostics and treatments where appropriate. A review of the literature, including the Pubmed, Embase and Cochrane Library databases, as well as conference proceedings of the relevant professional societies, was carried out to rate the level of evidence (LoE) and to search existing guidelines. The search for evidence used keywords (MeSH terms) grouped into the following syntax: (urinary tract infection) OR (recurrent urinary tract infection) AND (controlled) AND (randomised controlled trial [Publication Type] OR (randomised AND controlled AND trial [Title / Abstract]). Keywords used alone and/or in combination included the following: women, pregnancy, national, international guidelines, urodynamics, gynecologic surgery, pelvic floor surgery, antibiotics, phytotherapy, D-mannose, *E. coli*. The search was restricted to articles in English, German, French, Italian and Spanish that were published up to the end of December 2019. We assessed the LoE according to the recommendations from the Oxford Centre of Evidence-based Medicine (OCEBM, Levels of Evidence working Group. 2011, https://www.cebm.net/2016/05/ocebm-levels-of-evidence/).

The discussions about the recommendations took place in parallel in the Quality Assurance Committee and in the Swiss Working Group of Urogynaecology. The first and the last author of this publication were responsible for finalising the decisions, which were taken by consensus.

All authors declared no conflict of interests; no companies were involved; regular meetings of the members of the SSGO were financed according to the regulations of the society with no extra compensation.

Table 1: National and international guidelines on urinary tract infections addressing UTIs in adults. Guidelines for children, immunocompromised patients or patients with urinary catheters are not listed.

Guideline	Country, region	Year of release	Gender
American Urological Association (AUA)/Canadian Urological Association (CUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU): Guideline on recurrent uncomplicated urinary tract infections in women (2019) [2]	USA, Can	2019	Women, not pregnant
Guideline Harnwegsinfekt (HWI) – Society of Infectious disease [3] Available in German and French	CH	2020	Women
Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM): " Brennen beim Wasserlassen" [4] Available in German	D	2018	Women, men
Urinary tract infection (2): antimicrobial prescribing. NICE guideline (NG109) [5]	UK	2018	Women, men
Executive summary of the diagnosis and treatment of urinary tract infection: guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC) [6]	E	2018	Women, men
European Association of Urology (EAU): Guidelines on urological infections [7]	EU	2018, update 2019	Women, men, including prostatitis
Interdisziplinäre S3 Leitlinie. Epidemiologie, Diagnostik, Therapie, Prävention und Management unkomplizierter, bakterieller, ambulant erworbener Harnwegsinfektionen bei erwachsenen Patienten [8] Available in German	D, A, CH	2011, update 2017	Women, men
Recurrent urinary tract infection. Urogynaecology Committee; Family Physicians advisory Committee [9]	Can	2010	Women, men
International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases [10]	EU, USA	2011	Women
The American College of Obstetricians and Gynecologists (3): " Treatment of Urinary Tract Infections in Nonpregnant women" [11]	USA	2008	Women, not pregnant

Epidemiology and definitions

Female acute UTIs are amongst the most common bacterial infections seen by gynaecologists. Half of all women experience UTIs, and at least a quarter of these experience a recurrence. UTIs heal spontaneously at a high rate of 50–70%, and only 0.4–2.6% of uncomplicated UTIs develop into pyelonephritis if left untreated [12, 13].

Urinary tract infections can be categorised in uncomplicated or complicated UTIs or asymptomatic bacteriuria (ASB) (table 2). Recurrent UTIs, at least two infections within 6 months or three infections within a year, can be uncomplicated or complicated. Urine itself is not sterile. Between 1% and 3% of young women and 14–22% of postmenopausal, community-dwelling women have ASB [14].

Diagnostics

Uncomplicated urinary tract infections do not require diagnostic tests. The following tests are available for cases with an unclear clinical presentation:

Midstream urine stix: sensitivity 75%, specificity 82% for leucocyte esterase (proof of leucocytes in urine) [15].

Urine analysis is reliable only if the sample is not contaminated, i.e., <10 squamous cells/high power field. Midstream urine samples, if collected correctly, have a sensitivity of 95% and a specificity of 70% for UTI [16].

Urine culture is indicated in complicated or recurrent UTI, or if there are strong clinical signs of an infection but antibiotics are not effective [17]. Urine samples collected after bladder catheterisation are considered pathological if a single uropathogen species has $\geq 10^2$cfu/ml; midstream urine samples are considered to show relevant growth if there are $\geq 10^5$ cfu/ml.

Imaging: if there are ≥3 UTIs per year, cystoscopy is recommended to rule out intravesical pathology; if there are ≥2 pyelonephritis episodes per year, a kidney computed tomography (CT) scan (contrast CT) is recommended.

Treatment of acute urinary tract infections

Antibiotic-free approach

At least half of acute uncomplicated UTIs heal spontaneously, although symptoms persist longer than when treated with antibiotics [18]. Requests by the patient for a speedy relief of symptoms are common. In this new treatment guideline, a delay in antibiotic administration for 48 hours is recommended for uncomplicated UTIs and patients under 65 years of age. Pain relief should primarily be by the use of antibiotic-free treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs) with a phytotherapeutic agent or D-mannose [2, 5, 8]. Uva-ursi extract has been advocated as a phytotherapeutic agent for the relief of symptoms of acute cystitis, although a recent randomised placebo-controlled trial did not show a reduction in antibiotic use [19]. Ibuprofen 3 × 400 mg vs ciprofloxacin 2 × 250 mg for 3 days had an equally good effect on UTI symptoms after 4 days without any significant difference in the rates of recurrence [20]. Both medications are contraindicated in pregnancy.

However, two recent studies challenge the efficacy and safety of NSAIDS. A study from Switzerland reported inferiority of diclofenac to norfloxacin by day 4 and a higher risk of pyelonephritis, even though it reduced antibiotic use in women with an uncomplicated lower UTI [21]. Another recent study from Scandinavia reported that in patients with uncomplicated UTI, ibuprofen 600 mg three times daily was inferior to pivmecillinam, which is not available in Switzerland. All cases of secondary pyelonephritis occurred in the ibuprofen group [22]. Compared with fosfomycin, initial treatment with ibuprofen substantially reduced antibiotic use in women aged 18–65 with mild to moderate symptoms of UTI, but was less effective for symptom relief, and there were more cases of pyelonephritis [23]. Therefore, close clinical observation or follow-up for potential signs of pyelonephritis are indicated if lower UTIs are treated with NSAIDs. In addition, the NSAID treatment regimen should be discussed with women who want to avoid antibiotics or who are open to a delayed prescription.

An antibiotic prescription could be given to specific patients, such as those who plan to travel. Physicians should enquire about allergies.

Table 2: Categories of UTI.

	Uncomplicated UTI	Complicated UTI	Asymptomatic bacteriuria
Patients	Women without anatomical or functional abnormalities of the genitourinary tract	Pregnancy, risk factors such as poorly controlled diabetes mellitus, hospital-acquired infections, kidney disease, previous kidney transplant, urolithiasis, anatomical, functional abnormality (genital prolapse), immunosuppressants, indwelling catheter, postoperative (predisposing factors)	Any person, pregnant or non-pregnant
Clinical signs	UTI (dysuria, pollakiuria, suprapubic pain), pyelonephritis (as UTI with addition of flank or groin pain, fever)	Recurrent UTI with risk factors (see above), previously treated with NSAIDs and/or antibiotics, pyelonephritis.	No clinical signs
Diagnostics	Not required for first episode of UTI; Recommended for pyelonephritis and recurrence: urine analysis, culture Suspected pyelonephritis: ultrasound	Urine analysis, urine culture Suspected pyelonephritis: kidney ultrasound, postvoid residual urine, in pregnancy also measure cervical length Fever >38.3°C and hospitalised patients: blood cultures (2×)	Not required except before urological interventions with risk or probability of vesical mucosa lesions/damage
Microbiology	*E. coli* (>80%) (also ESBL), *Proteus mirabilis, Klebsiella* spp, *Staphylococcus saprophyticus, Enterococcus faecalis*	*E. coli* (also ESBL), *Enterococcus faecalis, Enterobacterales, Pseudomonas aeruginosa*	Any kind of bacteria in an amount of $\geq 10^5$ bacteria per ml

ESBL = extended spectrum beta-lactamase; NSAID = nonsteroidal anti-inflammatory drug

Antibiotic therapy in uncomplicated and complicated UTIs

If symptoms persist after 48 hours, starting an antibiotic is indicated. Also, ascending pain indicates a possible upper urinary infection and calls for the direct administration of antibiotics. Antibiotics may also be promptly prescribed to persons over 65 years of age, because this group of patients is more susceptible to urosepsis or UTI-associated comorbidities. As revealed by a national Danish study, the implementation of the new antibiotics guideline with avoidance of or delayed antibiotic administration led to an increase in pyelonephritis and urosepsis in UTI patients over 65 years of age [24].

Uncomplicated UTIs can be treated empirically. In urgent cases with clear symptoms, pharmacists (in Switzerland) are allowed to provide medication, including antibiotics from the specialty list.

The therapy options for simple UTIs and pyelonephritis are summarised in table 3 and for complicated UTIs in table 4 [25], taking into account antibiotic resistance in Switzerland (www.anresis.ch). The Swiss Centre for Antibiotic Resistance provides resistance data obtained by passive surveillance, which overestimates the true resistance rate. The actual resistance patterns of uropathogens in primary care in Switzerland (2019) are reported by Plate et al. [26]. In this study, *E. coli* showed low resistance rates to the recommended first-line antibiotics. Further, resistance to trimethoprim/sulphamethoxazole was significantly lower than reported by ANRESIS, making trimethoprim/sulfamethoxazole a suitable and cheap alternative for the empirical treatment.

The quinolone resistance rates of *E.coli* have increased from 1% to 21% in the past 10 years, and its resistance against third and fourth generation cephalosporins has increased from 1% to 9%. The resistance rates of *E. coli* to fosfomycin and nitrofurantoin remain very low. Therefore, consistent with the guidelines of the Infectious Disease Society of America and the European Society for Microbiology and Infectious Disease from 2011, fosfomycin and nitrofurantoin, as well as cotrimoxazole, can still be recommended as a first choice therapy.

Table 3: Antibiotic therapy for uncomplicated UTIs and pyelonephritis in non-pregnant women.

	Level of resistance in Switzerland for community-acquired *E. coli*, www.anresis.ch	Dosage	Duration of treatment	Remarks
Uncomplicated UTIs, first choice				
Nitrofurantoin	1.0%	2 × 100 mg/day	5 days	Not effective for pyelonephritits, low tissue absorption Minimal development of resistance, minimal "collateral damage" Severe side effects rare (pulmonary fibrosis, liver insufficiency, neuropathy) GFR ≥60ml/min
Fosfomycin	1.5%	1 × 3 g	Single dose	Not effective for pyelonephritits Administered in the evening 2−3 hours before or after meal Mainly gastrointestinal side effects
Trimethoprim/ sulfamethoxazole	23.5%	2 × 800/160 mg/day	3−5 days	Side effects: nausea, vomiting, diarrhoea, rare rash (Stevens-Johnson syndrome), jaundice, iatrogenic lupus, leuco- and thrombocytopenia Lowers levels of oral contraceptives
Uncomplicated UTIs, second choice				
Ciprofloxacin	19.0%	2 × 500 mg/day	3 days	
Amoxicillin or amoxicillin/clavulanic acid	14.2%	2 × 1 g/day	7 days	
Uncomplicated pyelonephritis				
Trimethoprim/ sulfamethoxazole	23.5%	2 × 800/160 mg/day	(7−)14 days	
Ciprofloxacin	19.0%	2 × 500 mg/day	7 days	Empirical use only if resistance rate in *E. coli* <10% Absorption reduced by milk products
Ceftriaxone (third generation cephalosporin)	9.1%	2 g/day intravenously	7−14 days	Hospitalisation or outpatient intravenous therapy

Table 4: Antibiotic therapy for complicated UTIs in non-pregnant women.

	Level of resistance in Switzerland for community-acquired *E. coli*, www.anresis.ch	Dosage	Duration of treatment	Remarks
Amoxicillin/clavulanic acid *(first choice)*	14.2%	2 × 1 g/day or 3 × 625 mg/day	5−7 days	–
Cefuroxime (second generation cephalosporin) *(Second choice)*	11.7%	2 × 500 mg	3−5 days	–
Trimethoprim/ sulfamethoxazole *(third choice)*	23.5%	2 × 800/160 mg/day	3−5 days	–
Fosfomycin *(third choice)*	1.5%	1 × 3 g every 2−3 days	3 cycles	–

The guideline of the Swiss Society of Infectious Disease dating from February 2020 classified fosfomycin as a second choice drug owing to its lower efficacy compared with nitrofurantoin shown in the study by Huttner et all [27].

The proportion of treatment failures is high and patients should be informed. In a randomised clinical trial that included 513 women with uncomplicated UTIs, clinical resolution at 28 days occurred in 70% of patients treated for 5 days with nitrofurantoin vs 58% of patients who received a single dose of fosfomycin. This is a statistically significant difference; however, nitrofurantoin was given at a dose of 100 mg three times daily, which is not the recommended dosage in Switzerland (100 mg twice daily) [27]. Nevertheless, fosfomycin 3 g, as a single dose, is a convenient, well tolerated and efficient therapy; considering the resistance rate, it is better than trimethoprim/sulfamethoxazole. In clinical practice it is still, in our opinion, a valuable first-choice option. Lopes-Montesinos and Horcajada [28] reviewed the use of oral and intravenous fosfomycin to treat complicated UTIs. Because some bacteria are multidrug-resistant, they evaluated fosfomycin as an antibiotic with enormous potential; randomised studies are under way. Doesschate et al. [29] conducted a double-blind placebo-controlled randomised non-inferiority trial (FORECAST) comparing fosfomycin with ciprofloxacin in complicated UTIs. They demonstrated non-inferiority of oral fosfomyin 3 g every 24 hours compared with oral ciprofloxacin 500 mg every 12 hours for 10 days, both given after at least 48 hours of intravenous treatment. When complicated UTI was treated with multiple-dose fosfomycin, clinical resolution occurred in two of three treatment episodes [30].

A study of the treatment of ASB showed that patients who were not treated had less recurrence than patients treated with antibiotics, and that the resistance rate of the *E.coli* was lower. In contrast to previous opinions, asymptomatic diabetic patients should not be treated [31]. In cases of acute pyelonephritis, antibiotic therapy for 7 days has proven to be as effective as the 14 days of therapy used previously [32] (LoE Ib). Complicated UTIs should be treated with a 7- to 10-day antibiotic regimen.

Alternative approaches to conventional treatment

As a result of increasing levels of antibiotic resistance, especially to trimethoprim/sulfamethoxazole and quinolones, and increasing awareness of the detrimental effects of antibiotics on the microbiome, antibiotic-free therapies are becoming increasingly important. Alternative options should be recommended to all patients with recurrent infections.

The following recommendations reduce the frequency of recurrence:

- Adequate fluid intake (additional 1.5 to 2 litres/day), check that urine is clear and postcoital micturition within an hour. The latter recommendation has not been tested in studies, but there is empirical evidence supporting it [33] (LoE IV).
- Avoid contraceptive spermicides (LoE III).
- Correct anal hygiene, cleaning from front to back (LoE III).
- No intravaginal rinses or disinfectants (LoE III).
- Avoid getting cold and cold drinks (LoE IIb).

The following medications or solutions reduce the frequency of recurrence and can be recommended during the acute phase of a UTI, *but not during pregnancy*:

- D-mannose for prophylaxis; D-mannose binds to bacterial pili and thereby reduces the adherence of *E. coli* to the urothelium. A study of women with recurrent UTIs compared the effect of prescribing D-mannose, nitrofurantoin or a placebo over a 6-month period. This showed that D-mannose (2 g/day) and nitrofurantoin (50 mg/day) were equally effective, but the former had significantly fewer side effects [34] (LoE Ib).
- Topical oestrogen reduces UTIs in postmenopausal women [35]. A randomised study of 93 postmenopausal women with recurrent UTIs comparing the use of intravaginal oestrogen (0.5 mg for the first 2 weeks, then twice weekly) over 8 months with the use of a placebo, showed a significant reduction in UTI frequency: 0.5 versus 5.9 episodes per patient per year [36] (LoE Ib). A study also showed beneficial effects of localised oestrogen in premenopausal women using combined contraception [37] (LoE III). Localised oestrogen should not be the first-choice recommendation for patients with oestrogen-dependent gynaecological carcinomas, but in cases where alternative therapies have not been effective, there is clinical evidence and safety data supporting low doses of oestriol (50 µg/g) [38].
- Cranberry capsules (or juice) contain proanthocyanidine, which inhibits the adherence of the fimbriae of *E.coli* to the urothelium. The studies are inconsistent and there is no clear evidence to support its use in UTIs [39] (LoE III). Overall, the clinical use of cranberries remains questionable, because there is a lack of high quality evidence.
- OM-89 (Uro-Vaxom®), a lyophilised extract of 18 different uropathogenic strains of *E.coli*, reduces the frequency of UTIs by 40−50% (LoE IIa).
- Intravesical use of hyaluronic acid and chondroitin sulphate builds up the glycosaminoglycan layer of the bladder and can be used as prophylactic treatment for recurrent UTIs [40] (LoE Ia). Some health insurance providers do not cover this treatment, whereas others do; this situation is currently being discussed with the health insurance companies.
- Acidification of urine with methenamine salts occurs through the production of formaldehyde, which is bacteriostatic. There is evidence that this is carcinogenic in long term animal testing (LoE IIa). A Cochrane analysis showed beneficial results of acidification of urine in patients without urinary tract abnormalities or catheters, but not in patients with structural abnormalities [41]. Methenamine can be considered as a short-term therapy (LoE Ia).
- Utipro®plus: xyloglucan and gelatine build a biofilm reducing bacterial adherence in intestine with associated changes in the intestinal microbiome; propolis and hibiscus lead to the acidification of urine. A randomised study where two Utipro®plus capsules/day were added to ciprofloxacin, followed by one capsule/day for 15

days showed a significant reduction (−19.4%) in the frequency of recurrence of UTI compared with placebo [42] (LoE IIb).

– Angocin®: active ingredients are mustard oils (isothiocyanates) from nasturtium and horseradish root. Angocin® showed good efficacy when used for recurrent UTIs [43] (LoE Ib).
– Uva-ursi extract has been advocated for relief of symptoms of acute cystitis although a recent randomised placebo-controlled trial did not show a reduction in antibiotic use [19].
– Vaccination with extraintestinal *E. coli* (ExPEC4V) [44]. This vaccine is in phase Ib of clinical testing. It was well tolerated and no side effects were seen (LoE experim.).
– Probiotics and lactobacillus drinks are not recommended as UTI prophylaxis, probably because no optimal formulations have been identified yet. New data show beneficial outcomes from *Lactobacillus crispatus* applied as an intravaginal ovule, and also for or *L. rhamnosus* GR-1 and *L. reuteri* RC-14, which are being investigated further (LoE IIa).
– Vitamin C cannot be recommended for reducing UTIs, because the results of two studies are contradictory. At best, its only use might be as an acidifying additive (LoE III).
– Stool transplants and changes to the urinary microbiome are currently under investigation (LoE experim.)

Pregnancy

In principle, there is an increased risk of pyelonephritis and complications of pregnancy with both symptomatic UTIs and ASB. Pregnant women with ASB are at a 20- to 30-fold greater risk of developing pyelonephritis and possible subsequent complications such as urosepsis, premature birth and SGA (small for gestational age) children [45]. These older and methodologically questionable studies were the background reasoning behind the recommendation for systematic screening for ASB in pregnant women, including antibiotic therapy in cases with positive cultures. Although a new randomised controlled study showed that untreated ASB in pregnant women of a non-risk group (see details below) increases the risk of developing pyelonephritis, there was no increased risk of premature birth or other neonatal or maternal complications. These new data have been taken into consideration in a new meta-analysis and other national guidelines. The benefit of systematically screening all pregnant women for ASB is currently not proven, but bacterial screening following vaginal smears in the first trimester continues to be recommended [46, 47] (LoE 1a). Systematic screening of all pregnant women for ASB can no longer be recommended, with the exception of pregnant women at risk owing to factors such as diabetes mellitus, immunosuppression, functional or structural abnormalities of the urinary tract, previous episodes of pyelonephritis, previous premature births or late pregnancy loss.

Current data show that a single dose of antibiotic, 3 g fosfomycin, is sufficient in pregnancy [31, 48], but is not recommended in cases with an increased risk of premature birth, when more prolonged therapy should be given. Ibuprufen and chinolones like ciprofloxacin are both contraindicated in pregnancy.

Antibiotic therapy for uncomplicated UTI and pyelonephritis during pregnancy and breastfeeding is summarised in table 5.

Asymptomatic bacteriuria

It is not necessary to routinely screen non-pregnant women for asymptomatic bacteriuria, nor to treat it if incidentally discovered [49]. A study of the treatment of ASB showed that patients who were not treated had fewer recurrences than patients treated with antibiotics and that the resistance rate of *E.coli* was lower. In contrast to previous opinions, it is now recommended that asymptomatic diabetic patients should not be treated [31]. The study by Kazemier investigated the maternal and neonatal consequences of treated and untreated ASB in pregnancy [50]. The conclusion of the study was that the non-treatment of ASB in pregnant women is an option. As mentioned above, systematic screening for asymptomatic bacteriuria in pregnant women is no longer recommended, with the exception of pregnant women at risk owing to factors such as diabetes mellitus, immunosuppression, functional or structural abnormalities of the urinary tract, previous episodes of pyelonephritis, previous premature births or late pregnancy loss [51].

Testing for and treating of ASB is not recommended except for selected indications (see section below “Antibiotic prophylaxis before a urological procedure”).

Prophylaxis

Antibiotic prophylaxis is no longer indicated before surgical interventions such as hip or knee prosthesis or gynaecological operations such as hysterectomies [46]. Kidney transplant recipients are a special case [52]. More recent

Table 5: Antibiotic therapy for uncomplicated UTI and pyelonephritis during pregnancy and breastfeeding.

	Level of Resistance in Switzerland for community- acquired *E. coli*, www.anresis.ch	Dosage	Duration of treatment	Remarks
Amoxicillin/clavulanic acid *(first choice)*	14.2%	2 − 1 g/day or 3 − 625 mg/day	5−7 days	Suitable throughout whole pregnancy and breastfeeding period
Cefuroxime (second generation cephalosporin) *(second choice)*	11.7%	2 − 500 mg	3−5 days	Suitable throughout whole pregnancy and breastfeeding period
Trimethoprim/ sulfamethoxazole *(third choice)*	23.5%	2 − 800/160 mg/day	3−5 days	Contraindicated in first and third trimester; *suitable during breastfeeding*

data show that UTIs could significantly impact on graft function and long-term outcomes, and that the prevention and early treatment of UTI is of importance, especially in the first 6 months after transplantation. For information on the dosage for see reference [52].

Pregnancy is another situation where the significance of a prophylactic treatment of ASB is possibly of value. Studies that have a different outcome are discussed above in the sections on "Pregnancy" and "Asymptomatic bacteriuria".

Antibiotic prophylaxis before a urological procedure

Cystoscopy and urodynamic studies

Prophylactic antibiotics are not indicated before cystoscopy or urodynamic assessment unless the physician responsible makes another decision based on experience and on the individual case. Eradication of ASB is not necessary [53] (LoE IV) except when it comes to mucosal lesions/damage as in, for example, bladder biopsies, for which prophylaxis is indicated. Routine antibiotic prophylaxis should be avoided in urodynamic assessment to investigate urinary stress incontinence in cases of genital prolapse, provided that there is no significant postvoid residual urine (<100 ml). Patients with a cystocele are more likely to have microhaematuria than those without a cystocele, but this is not associated with infection. *Important:* UTIs must be excluded before any urogynaecology intervention, or treated as necessary (LoE Ib).

Antibiotic prophylaxis before or directly after urodynamic assessment or cystoscopy can be considered in cases where patients have recurrent UTIs, postvoid residual urine >100 ml, neurological bladder dysfunction, age ≥ 70 years, presence of indwelling catheter or immunocompromise. Recommended antibiotics include trimethoprim/sulfamethoxazole 800/160mg or fosfomycin 3 g sachet single dose [54] (LoE IIa).

Incontinence and prolapse operations

Single-dose antibiotic prophylaxis with a first generation cephalosporin (cefazolin, 30 minutes before skin incision) is recommended, although according to the latest review from the US Centers for Disease Control and Prevention, there is only moderate evidence supporting this [55] (LoE IIb). Extended antibiotic therapy should not be given if the postoperative recovery is without complications, and also should not be given following mesh operations (sacrocolpopexy, incontinence slings and vaginal meshes) [56]. A published decision analysis model suggests that antibiotic prophylaxis is probably not required before the insertion of mid-urethral slings [57]. Postoperative antibiotic prophylaxis after urogynaecological procedures requiring intermittent self-catheterisation is not indicated [58] (LoE IV).

Postoperative bladder atony, increased postvoid residual urine

Postoperative postvoid residual urine, catheterisation for >24 hours or repeated catheterisation, are risk factors for urinary tract infections. Nevertheless, prolonged postoperative prophylactic antibiotic therapy in these situations remains controversial and, based on current evidence, is not recommended [59]. Measuring postvoid residual urine postoperatively using ultrasound is preferable to measuring repeatedly with single-use catheters. If recurrent UTIs occur beyond the immediate postoperative period, it is necessary to establish the cause (fistula, mesh erosion) (LoE Ia).

If it is necessary to drain the bladder long-term postoperatively because of increased postvoid residual urine, suprapubic drainage is preferable to transurethral. No difference is seen in the occurrence of bacteriuria or UTIs with intermittent self-catheterisation using hydrophilic coated single-use catheters or suprapubic catheterisation [60].

Treatment and prophylaxis of recurrent UTIs

For recurrent UTIs there is a distinction between a relapse (UTI due to the same pathogen within two weeks of ending therapy) and a reinfection (new UTI more than 2 weeks after ending therapy, usually due to a different pathogen). Reinfections are twice as frequent and should be treated with the same medication for the same duration as the first infection (LoE Ia). If there are no predisposing factors, it is also possible to treat following a self-diagnosis, which is appreciated by many women. Easy to handle infection-specific Combur®-Strip tests with three fields are available.

In the case of frequent recurrence, antibiotic prophylaxis over a period of 6 months can be considered as a last resort (table 6), either to be taken continuously or only postcoitally if sexual intercourse is the cause. Continuous and postcoital low-dose antibiotic prophylaxis are equally effective in reducing recurrent UTIs.

Discussion and areas of future research

Uncomplicated UTIs are ideally treated with antibiotic treatment delayed by 48 hours if symptoms persist. This recommendation is in accordance with recent recommendations of other societies that were published as a reaction to the rise of antibiotic resistance [2, 5, 8].

Our expert opinion emphasises that primarily analgesics such ibuprofen, immunomodulations/vaccines and phytotherapeutics should be used in the treatment of uncomplicated and recurrent UTIs in order to halt antibiotic resistance. The global rise in antibiotic resistance has caused the number of national and international guidelines addressing UTIs to increase in the last 2 years: from 2011 to 2017 no UTI guidelines were published or amended, since 2018 six guidelines have been released, including our

Table 6: Continuous and postcoital prophylaxis in UTIs (according UpToDate® [61]).

	Dose	Duration
Nitrofurantoin	50−100 mg/day or 3 ×/week	6 months, then stop Postcoital: within 30 minutes following sexual intercourse
Trimethoprim/ sulfamethoxazole	40/200 mg 1 ×/day or 40/2000 mg 3 ×/week	6 months, then stop Postcoital: within 30 minutes following sexual intercourse
Fosfomycin	3 g every 7−10 days	6 months, then stop

gender-specific guideline. The recommendations given in these national and international publications with respect to antibiotic-free therapies should help to contain antibiotic resistance.

Another advantage of the antibiotic-free approach is that it reduces the recurrence rate of UTIs [49]. Similarly, treatment of ASB is obsolete. This also increasingly applies to ASB in pregnancy, although the evidence with respect to this issue is still somewhat weak.

Quinolones should be avoided in uncomplicated UTIs, because they can lead to potentially permanent side effects affecting tendons, muscles, joints, nerves, blood vessels and the central nervous system [62].

Gender-adapted and differentiated UTI treatment algorithms for men and women and pregnant women are required, and will become important in the future.

Recent basic research uses polymerase chain reaction (PCR) in urine cultures to investigate the effect of the bladder microbiome on urinary urge symptoms and UTIs [63, 64]. The bladder microbiome seems to be more complex than previously thought and this begs a reappraisal of our current testing in recurrent UTI. Future research will point out the role of bacterial survival after treatment as well as defects in urothelial barrier function that might contribute to the failure to eradicate UTI.

On a clinical level, large randomised, double-blind studies of alternative approaches to conventional treatment with long follow-up are required.

Summary

- Routine screening for ASB should not be carried out, and no treatment should be given if ASB is discovered by chance, with the exception of patients prior to urogynaecological surgery.
- Systematic screening of asymptomatic bacteriuria in pregnant women is not recommended anymore. However, ASB in risk-groups or acute UTI should be treated accordingly (table 2). Bacterial screening following vaginal smears is still recommended for all pregnant women.
- Acute UTIs should be treated as briefly as possible with UTI-specific antibiotics (table 2).
- Patients should be informed that most UTIs are self-limiting, that the symptoms can be relieved with non-steroidal anti-inflammatory drugs and that the same time is required to eradicate the bacteria using antibiotics or NSAIDs. This does not apply in pregnancy. At the moment this issue is controversial.
- If no relief of symptoms is seen in a suspected recurrent UTI, and if no leucocytes or bacteria are present in catheter urine, a hyperactive bladder or bladder pain syndrome should be considered. Repeat antibiotic treatment is not recommended in this situation, and it is recommended to refer the patient to a centre with expertise.
- Antibiotic therapy prior to or following urodynamic testing or cystoscopy is only indicated in specific cases, as discussed in this text. No endocarditis prophylaxis is necessary prior to urodynamic testing.
- Incontinence or prolapse surgery with or without mesh: moderate evidence for antibiotic prophylaxis prior to surgery using first generation cephalosporins.
- There are various conservative options to prevent UTIs: behavioural measures and antibiotic-free options should be given priority given the increasing antibiotic resistance.
- In cases with significant postvoid residual urine, the cause should be identified. If this is not possible, intermittent single-use or suprapubic drainage should be used rather than transurethral drainage, without using short or long-term antibiotic prophylaxis.
- There is no evidence that preoperatively recurring UTIs can be reduced by prolapse surgery.
- New research approaches include adaptation of the urinary microbiomes and vaccination against uropathogens.

Author contributions

CB: conception and design, analysis and interpretation of data, drafting and writing of the article, final approval, President of the Swiss Urogynaecological Society. WCA: analysis and interpretation of data, critical examination of the results to extract important information, final approval, Member of the Swiss Society for Infectious Diseases. SB: analysis and interpretation of data, critical examination of the results to extract important information, final approval, Committee Member of the Swiss Urogynaecological Society. DF: analysis and interpretation of data, final approval, Past-president of the Swiss Urogynecological Society. AK: analysis and interpretation of data, final approval, Past-president of the Swiss Urogynecological Society. DS: critically revision of the article for intellectual content, final approval, President of the Quality Assurance Committee of the SSGO (Swiss Society of Gynaecology and Obstetrics). VG: conception and design, analysis and interpretation of data, drafting the article, final approval, Committee Member of the Quality Assurance Committee of the SSGO (Swiss Society of Gynaecology and Obstetrics), Member of the Swiss Urogynaecological Society.

Financial disclosure / ethical compliance

This guideline was approved by the Swiss Society of Gynaecology and Obstetrics and their subcommittees of Urogynaecology and Fetomaternal Medicine.

This study was funded by the Swiss Society of Gynaecology and Obstetrics (SSGO).

This expert panel recommendation has been reviewed by the members of the Quality Assurance Committee of the Swiss Society of Gynaecology and Obstetrics SSGO. The Quality Assurance Committee compiles guidelines and expert letters with utmost care.

The drug manufacturer's instructions must be observed at all times, in particular the dosage instructions. To the best knowledge of the Committee, guidelines and expert letters correspond to the latest scientific insights at the time of publication. Users must take intervening changes into account.

Ethical approval: This article does not refer to any studies involving human participants or animals carried out by any of the authors.

Competing interests

All authors declare no conflict of interest.

References

1 Zanichelli V, Huttner A, Harbarth S, Kronenberg A, Huttner B; Swiss Centre For Antibiotic Resistance Anresis. Antimicrobial resistance trends in Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis urinary isolates from Switzerland: retrospective analysis of data from a national surveillance network over an 8-year period (2009-2016). Swiss Med Wkly. 2019;149:. doi: http://dx.doi.org/10.4414/smw.2019.20110. PubMed.

2 Anger J, Lee U, Ackermann A, et al. Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline. American

Urological Association (AUA) / Canadian Urological Association (CUA) / Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU). 2019. Available at: https://www.auajournals.org/PDF/rUTIguideline.

3 Huttner A, Kronenberg A, Hasse B. Harnwegsinfekt (HWI). Available at: https://ssi.guidelines.ch/guideline/2981.

4 Schmiemann G, Gebhardt K, Hummers E. Brennen beim Wasserlassen. Available at: https://www.degam.de/files/Inhalte/Leitlinien-Inhalte/Dokumente/DEGAM-S3-Leitlinien/053-001_Brennen%20beim%20Wasserlassen/053-001l_Brennen%20Wasserlassen_Langversion_29-08-18.pdf.

5 National Institute for Health and Care Excellence. (5). Urinary tract infection (2): antimicrobial prescribing. https://www.nice.org.uk/guidance/ng109.

6 de Cueto M, Aliaga L, Alós JI, Canut A, Los-Arcos I, Martínez JA, et al. Executive summary of the diagnosis and treatment of urinary tract infection: Guidelines of the Spanish Society of Clinical Microbiology and Infectious Diseases (SEIMC). Enferm Infecc Microbiol Clin. 2017;35(5):314–20. doi: http://dx.doi.org/10.1016/j.eimc.2016.11.005. PubMed.

7 Bonkat G, Bartoletti RR, Bruyère F, Cai T, Geerlings SE, Köves B, et al. EAU Guidelines on urological infections. Available at: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Urological-infections-2019.pdf. Accessed on 2020 January 4

8 Leitlinienprogramm DGU. AWMF: Interdisziplinare S3 Leitlinie: Epidemiologie, Diagnostik, Therapie, Pravention und Management unkomplizierter, bakterieller, ambulant erworbener Harnwegsinfektionen bei erwachsenen Patienten. Kurzversion 1.1.-2, 2017 AWMF Registernummer: 043/044. Available at: http://www.awmf.org/uploads/tx_szleitlinien/043-044l_S3_Harnwegsinfektionen pdf. Accessed on 2020 January 4

9 Epp A, Larochelle A, Lovatsis D, Walter J-E, Easton W, Epp A, et al.; UROGYNAECOLOGY COMMITTEE; FAMILY PHYSICIANS ADVISORY COMMITTEE. Recurrent urinary tract infection. J Obstet Gynaecol Can. 2010;32(11):1082–90. doi: http://dx.doi.org/10.1016/S1701-2163(16)34717-X. PubMed.

10 Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al.; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52(5):e103–20. doi: http://dx.doi.org/10.1093/cid/ciq257. PubMed.

11 American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 91: Treatment of urinary tract infections in nonpregnant women. Obstet Gynecol. 2008;111(3):785–94. doi: http://dx.doi.org/10.1097/AOG.0b013e318169f6ef. PubMed.

12 Christiaens TC, De Meyere M, Verschraegen G, Peersman W, Heytens S, De Maeseneer JM. Randomised controlled trial of nitrofurantoin versus placebo in the treatment of uncomplicated urinary tract infection in adult women. Br J Gen Pract. 2002;52(482):729–34. PubMed.

13 Ferry SA, Holm SE, Stenlund H, Lundholm R, Monsen TJ. Clinical and bacteriological outcome of different doses and duration of pivmecillinam compared with placebo therapy of uncomplicated lower urinary tract infection in women: the LUTIW project. Scand J Prim Health Care. 2007;25(1):49–57. doi: http://dx.doi.org/10.1080/02813430601183074. PubMed.

14 Boscia JA, Kobasa WD, Knight RA, Abrutyn E, Levison ME, Kaye D. Epidemiology of bacteriuria in an elderly ambulatory population. Am J Med. 1986;80(2):208–14. doi: http://dx.doi.org/10.1016/0002-9343(86)90011-2. PubMed.

15 Hurlbut TA, 3rd, Littenberg B. The diagnostic accuracy of rapid dipstick tests to predict urinary tract infection. Am J Clin Pathol. 1991;96(5):582–8. doi: http://dx.doi.org/10.1093/ajcp/96.5.582. PubMed.

16 Pappas PG. Laboratory in the diagnosis and management of urinary tract infections. Med Clin North Am. 1991;75(2):313–25. doi: http://dx.doi.org/10.1016/S0025-7125(16)30456-4. PubMed.

17 Fihn SD. Clinical practice. Acute uncomplicated urinary tract infection in women. N Engl J Med. 2003;349(3):259–66. doi: http://dx.doi.org/10.1056/NEJMcp030027. PubMed.

18 Falagas ME, Kotsantis IK, Vouloumanou EK, Rafailidis PI. Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: a meta-analysis of randomized controlled trials. J Infect. 2009;58(2):91–102. doi: http://dx.doi.org/10.1016/j.jinf.2008.12.009. PubMed.

19 Moore M, Trill J, Simpson C, Webley F, Radford M, Stanton L, et al. Uva-ursi extract and ibuprofen as alternative treatments for uncomplicated urinary tract infection in women (ATAFUTI): a factorial randomized trial. Clin Microbiol Infect. 2019;25(8):973–80. doi: http://dx.doi.org/10.1016/j.cmi.2019.01.011. PubMed.

20 Bleidorn J, Gágyor I, Kochen MM, Wegscheider K, Hummers-Pradier E. Symptomatic treatment (ibuprofen) or antibiotics (ciprofloxacin) for uncomplicated urinary tract infection?--results of a randomized controlled pilot trial. BMC Med. 2010;8(1):30. doi: http://dx.doi.org/10.1186/1741-7015-8-30. PubMed.

21 Kronenberg A, Bütikofer L, Odutayo A, Mühlemann K, da Costa BR, Battaglia M, et al. Symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: randomised, double blind trial. BMJ. 2017;359:j4784. doi: http://dx.doi.org/10.1136/bmj.j4784. PubMed.

22 Vik I, Bollestad M, Grude N, Bærheim A, Damsgaard E, Neumark T, et al. Ibuprofen versus pivmecillinam for uncomplicated urinary tract infection in women-A double-blind, randomized non-inferiority trial. PLoS Med. 2018;15(5):. doi: http://dx.doi.org/10.1371/journal.pmed.1002569. PubMed.

23 Gágyor I, Bleidorn J, Kochen MM, Schmiemann G, Wegscheider K, Hummers-Pradier E. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. BMJ. 2015;351:h6544. doi: http://dx.doi.org/10.1136/bmj.h6544. PubMed.

24 Gharbi M, Drysdale JH, Lishman H, Goudie R, Molokhia M, Johnson AP, et al. Antibiotic management of urinary tract infection in elderly patients in primary care and its association with bloodstream infections and all cause mortality: population based cohort study. BMJ. 2019;364:l525. doi: http://dx.doi.org/10.1136/bmj.l525. PubMed.

25 Hasse B, Huttner A, Huttner B, Egger M, Zanetti G, Marschall J, et al. Behandlung von unkomplizierten Harnwegsinfektionen. 22 May 2014. Available at: http://www.sginf.ch/files/behandlung_von_unkomplizierten_harnwegsinfektionen.pdf

26 Plate A, Kronenberg A, Risch M, Mueller Y, Di Gangi S, Rosemann T, et al. Active surveillance of antibiotic resistance patterns in urinary tract infections in primary care in Switzerland. Infection. 2019;47(6):1027–35. doi: http://dx.doi.org/10.1007/s15010-019-01361-y. PubMed.

27 Huttner A, Kowalczyk A, Turjeman A, Babich T, Brossier C, Eliakim-Raz N, et al. Effect of 5-day nitrofurantoin vs single-dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women: a randomized clinical trial. JAMA. 2018;319(17):1781–9. doi: http://dx.doi.org/10.1001/jama.2018.3627. PubMed.

28 López-Montesinos I, Horcajada JP. Oral and intravenous fosfomycin in complicated urinary tract infections. Rev Esp Quimioter. 2019;32(Suppl 1):37–44. PubMed.

29 Ten Doesschate T, van Mens SP, van Nieuwkoop C, Geerlings SE, Hoepelman AIM, Bonten MJM. Oral fosfomycin versus ciprofloxacin in women with *E.coli* febrile urinary tract infection, a double-blind placebo-controlled randomized controlled non-inferiority trial (FORECAST). BMC Infect Dis. 2018;18(1):626. doi: http://dx.doi.org/10.1186/s12879-018-3562-2. PubMed.

30 Derington CG, Benavides N, Delate T, Fish DN. Multiple-dose oral fosfomycin for treatment of complicated urinary tract infections in the outpatient setting. Open Forum Infect Dis. 2020;7(2):. doi: http://dx.doi.org/10.1093/ofid/ofaa034. PubMed.

31 Köves B, Cai T, Veeratterapillay R, Pickard R, Seisen T, Lam TB, et al. Benefits and harms of treatment of asymptomatic bacteriuria: a systematic review and meta-analysis by the European Association of Urology Urological Infection Guidelines Panel. Eur Urol. 2017;72(6):865–8. doi: http://dx.doi.org/10.1016/j.eururo.2017.07.014. PubMed.

32 Rudrabhatla P, Deepanjali S, Mandal J, Swaminathan RP, Kadhiravan T. Stopping the effective non-fluoroquinolone antibiotics at day 7 vs continuing until day 14 in adults with acute pyelonephritis requiring hospitalization: A randomized non-inferiority trial. PLoS One. 2018;13(5):. doi: http://dx.doi.org/10.1371/journal.pone.0197302. PubMed.

33 Hooton TM, Vecchio M, Iroz A, Tack I, Dornic Q, Seksek I, et al. Effect of increased daily water intake in premenopausal women with recurrent urinary tract infections: A Randomized Clinical Trial. JAMA Intern Med. 2018;178(11):1509–15. doi: http://dx.doi.org/10.1001/jamainternmed.2018.4204. PubMed.

34 Kranjčec B, Papeš D, Altarac S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. World J Urol. 2014;32(1):79–84. doi: http://dx.doi.org/10.1007/s00345-013-1091-6. PubMed.

35 Perrotta C, Aznar M, Mejia R, Albert X, Ng CW. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. Cochrane Database Syst Rev. 2008;16(2):. doi: http://dx.doi.org/10.1002/14651858.CD005131.pub2. PubMed.

36 Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. N Engl J Med. 1993;329(11):753–6. doi: http://dx.doi.org/10.1056/NEJM199309093291102. PubMed.

37 Pinggera GM, Feuchtner G, Frauscher F, Rehder P, Strasser H, Bartsch G, et al. Effects of local estrogen therapy on recurrent urinary tract infections in young females under oral contraceptives. Eur Urol. 2005;47(2):243–9. doi: http://dx.doi.org/10.1016/j.eururo.2004.09.008. PubMed.

38 Farrell R; American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice. Committee Opinion No. 659: The use of vaginal estrogen in women with a history of estrogen-dependent breast cancer. Obstet Gynecol. 2016;127(3):e93–6. doi: http://dx.doi.org/10.1097/AOG.0000000000001351. PubMed.

39 Beerepoot MAJ, Geerlings SE, van Haarst EP, van Charante NM, ter Riet G. Nonantibiotic prophylaxis for recurrent urinary tract infections: a systematic review and meta-analysis of randomized controlled trials. J Urol. 2013;190(6):1981–9. doi: http://dx.doi.org/10.1016/j.juro.2013.04.142. PubMed.

40 De Vita D, Antell H, Giordano S. Effectiveness of intravesical hyaluronic acid with or without chondroitin sulfate for recurrent bacterial cystitis in adult women: a meta-analysis. Int Urogynecol J Pelvic Floor Dysfunct. 2013;24(4):545–52. doi: http://dx.doi.org/10.1007/s00192-012-1957-y. PubMed.

41 Lee BS, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. Cochrane Database Syst Rev. 2012;10(10):. doi: http://dx.doi.org/10.1002/14651858.CD003265.pub3. PubMed.

42 Salvatorelli N, García-Larrosa A, Allegrini A, Pavone D. A new approach to the treatment of uncomplicated cystitis: results of a randomized placebo-controlled clinical trial. Urol Int. 2016;97(3):347–51. doi: http://dx.doi.org/10.1159/000445326. PubMed.

43 Albrecht U, Goos KH, Schneider B. A randomised, double-blind, placebo-controlled trial of a herbal medicinal product containing Tropaeoli majoris herba (Nasturtium) and Armoraciae rusticanae radix (Horseradish) for the prophylactic treatment of patients with chronically recurrent lower urinary tract infections. Curr Med Res Opin. 2007;23(10):2415–22. doi: http://dx.doi.org/10.1185/030079907X233089. PubMed.

44 Huttner A, Hatz C, van den Dobbelsteen G, Abbanat D, Hornacek A, Frölich R, et al. Safety, immunogenicity, and preliminary clinical efficacy of a vaccine against extraintestinal pathogenic *Escherichia coli* in women with a history of recurrent urinary tract infection: a randomised, single-blind, placebo-controlled phase 1b trial. Lancet Infect Dis. 2017;17(5):528–37. doi: http://dx.doi.org/10.1016/S1473-3099(17)30108-1. PubMed.

45 Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM; Infectious Diseases Society of America; American Society of Nephrology; American Geriatric Society. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clin Infect Dis. 2005;40(5):643–54. doi: http://dx.doi.org/10.1086/427507. PubMed.

46 Angelescu K, Nussbaumer-Streit B, Sieben W, Scheibler F, Gartlehner G. Benefits and harms of screening for and treatment of asymptomatic bacteriuria in pregnancy: a systematic review. BMC Pregnancy Childbirth. 2016;16(1):336. doi: http://dx.doi.org/10.1186/s12884-016-1128-0. PubMed.

47 Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2019;68(10):1611–5. doi: http://dx.doi.org/10.1093/cid/ciz021. PubMed.

48 Usta TA, Dogan O, Ates U, Yucel B, Onar Z, Kaya E. Comparison of single-dose and multiple-dose antibiotics for lower urinary tract infection in pregnancy. Int J Gynaecol Obstet. 2011;114(3):229–33. doi: http://dx.doi.org/10.1016/j.ijgo.2011.03.014. PubMed.

49 Cai T, Mazzoli S, Mondaini N, Meacci F, Nesi G, D'Elia C, et al. The role of asymptomatic bacteriuria in young women with recurrent urinary tract infections: to treat or not to treat? Clin Infect Dis. 2012;55(6):771–7. doi: http://dx.doi.org/10.1093/cid/cis534. PubMed.

50 Kazemier BM, Koningstein FN, Schneeberger C, Ott A, Bossuyt PM, de Miranda E, et al. Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. Lancet Infect Dis. 2015;15(11):1324–33. doi: http://dx.doi.org/10.1016/S1473-3099(15)00070-5. PubMed.

51 Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, et al. Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria: 2019 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2019;68(10):1611–5. doi: http://dx.doi.org/10.1093/cid/ciz021. PubMed.

52 Fiorentino M, Pesce F, Schena A, Simone S, Castellano G, Gesualdo L. Updates on urinary tract infections in kidney transplantation. J Nephrol. 2019;32(5):751–61. doi: http://dx.doi.org/10.1007/s40620-019-00585-3. PubMed.

53 García-Perdomo HA, López H, Carbonell J, Castillo D, Cataño JG, Serón P. Efficacy of antibiotic prophylaxis in patients undergoing cystoscopy: a randomized clinical trial. World J Urol. 2013;31(6):1433–9. doi: http://dx.doi.org/10.1007/s00345-013-1034-2. PubMed.

54 Cameron AP, Campeau L, Brucker BM, Clemens JQ, Bales GT, Albo ME, et al. Best practice policy statement on urodynamic antibiotic prophylaxis in the non-index patient. Neurourol Urodyn. 2017;36(4):915–26. doi: http://dx.doi.org/10.1002/nau.23253. PubMed.

55 Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al.; Healthcare Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection, 2017. JAMA Surg. 2017;152(8):784–91. doi: http://dx.doi.org/10.1001/jamasurg.2017.0904. PubMed.

56 Andy UU, Harvie HS, Ackenbom MF, Arya LA. Single versus multidose antibiotic prophylaxis for pelvic organ prolapse surgery with graft/mesh. Eur J Obstet Gynecol Reprod Biol. 2014;181:37–40. doi: http://dx.doi.org/10.1016/j.ejogrb.2014.07.016. PubMed.

57 Shepherd JP, Jones KA, Harmanli O. Is antibiotic prophylaxis necessary before midurethral sling procedures for female stress incontinence? A decision analysis. Int Urogynecol J Pelvic Floor Dysfunct. 2014;25(2):227–33. doi: http://dx.doi.org/10.1007/s00192-013-2180-1. PubMed.

58 Dieter AA, Amundsen CL, Edenfield AL, Kawasaki A, Levin PJ, Visco AG, et al. Oral antibiotics to prevent postoperative urinary tract infection: a randomized controlled trial. Obstet Gynecol. 2014;123(1):96–103. doi: http://dx.doi.org/10.1097/AOG.0000000000000024. PubMed.

59 Hamid R, Losco G. Pelvic Organ Prolapse-Associated Cystitis. Curr Bladder Dysfunct Rep. 2014;9(3):175–80. doi: http://dx.doi.org/10.1007/s11884-014-0249-4. PubMed.

60 Tenke P, Köves B, Johansen TE. An update on prevention and treatment of catheter-associated urinary tract infections. Curr Opin Infect Dis. 2014;27(1):102–7. doi: http://dx.doi.org/10.1097/QCO.0000000000000031. PubMed.

61 Hooton TM, Gupta K, Calderwood SB, Bloom A. Recurrent simple cystitis in women. UpToDate [Internet]. Last updated: 2019 Apr 29. Available at: https://www.uptodate.com/contents/recurrent-simple-cystitis-in-women.

62 FDA updates warning for fluoroquinolone antibiotics on risks of mental health and low blood sugar adverse reactions. 2018. Available at: https://www.fda.gov/news-events/press-announcements/fda-updates-warnings-fluoroquinolone-antibiotics

63 Mueller ER, Wolfe AJ, Brubaker L. Female urinary microbiota. Curr Opin Urol. 2017;27(3):282–6. doi: http://dx.doi.org/10.1097/MOU.0000000000000396. PubMed.

64 Gasiorek M, Hsieh MH, Forster CS. Utility of DNA next-generation sequencing and expanded quantitative urine culture in diagnosis and management of chronic or persistent lower urinary tract symptoms. J Clin Microbiol. 2019;58(1):e00204–19. doi: http://dx.doi.org/10.1128/JCM.00204-19. PubMed.