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**SUMMARY WITH CRITICAL APPRAISAL**

# Fluoroquinolones for the Treatment of Urinary Tract Infection: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines


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## Abbreviations

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| APN | acute pyelonephritis |
| CFU | colony-forming unit |
| ESBL | extended-spectrum beta-lactamase |
| ESBL-EC | extended-spectrum beta-lactamase *E. coli* |
| HTA | Health Technology Assessment |
| INR | international normalized ratio |
| NICE | National Institute for Health and Care Excellence |
| RCT | randomized controlled trial |
| SOGC | Society of Obstetricians and Gynaecologists of Canada |

## Context and Policy Issues

The urinary tract is an anatomic unit extending from the urethra to the kidneys.[1] In most cases, a urinary tract infection (UTI) is caused by bacteria ascending from the urethra to the bladder.[1] Pathogens spreading to the kidneys can lead to renal parenchymal infection.[1] In some cases, UTIs can result from bloodstream-mediated infection.[1] Depending on the sites of infection, UTIs include urethritis, cystitis, and pyelonephritis.[1] Globally, the prevalence of community-acquired UTIs can be as high as 0.7% and the leading risk factors include age, history of UTIs, sexual activity and diabetes.[2] *Escherichia coli* is a common pathogen and resistance to antibiotics may develop depending on the geographic locations.[2] The diagnosis of UTIs involves history taking, urinalysis and urine culture.[1] Asymptomatic UTIs does not warrant antibiotic treatment and can be treated with self-care, such as hydration.[3] Symptomatic UTIs need to be treated with antimicrobial therapy.[1] The choice of antimicrobial agent depends on factors such as sites of infection, types of pathogens, patient characteristics, and drug availability.[3] For example, fosfomycin and pivmecillinam are recommended first-line therapies when available because of preserved pathogen susceptibility.[1] Catheter-associated UTIs that are related to the use of catheters in the hospitals or in the communities need specialist care.[4]

Fluoroquinolones are broad-spectrum antibiotics and can be used for both Gram-positive and Gram-negative bacteria.[5] For example, fluoroquinolones are considered one of the first-line antibiotics for acute uncomplicated cystitis.[1] In general, fluoroquinolones are well-tolerated.[5] However, the use of fluoroquinolones in UTIs is not recommended in children because of potential adverse effects, such as arthralgia and arthropathy.[6,7] Fluoroquinolones are also contraindicated during pregnancy because of potential damage to fetal development.[3]

More recently, the molecule configurations of fluoroquinolones have been modified to produce new generations of antibiotics.[5] For example, sitafloxacin is the newest-generation fluoroquinolone.[8-12] The most frequently used fluoroquinolones include ciprofloxacin, levofloxacin, norfloxacin, ofloxacin, and gatifloxacin.[13,14]

With increasing availability of newer-generation drugs and a broad spectrum of antibiotic effectiveness, the role of fluoroquinolones in UTI treatment may have changed. The purpose of this review is to examine the clinical effectiveness, cost-effectiveness and evidence-based guidelines regarding the use of fluoroquinolones for the treatment of UTIs.

## Research Questions

1. What is the clinical effectiveness of fluoroquinolones for the treatment of urinary tract infections?
2. What is the cost-effectiveness of fluoroquinolones for the treatment of urinary tract infections?
3. What are the evidence-based guidelines regarding the use of fluoroquinolones for the treatment of urinary tract infections?

## Key Findings

Three systematic reviews of critically low quality, nine good-quality randomized controlled trials, one fair-quality randomized controlled trial, one good-quality non-randomized study, six fair-quality non-randomized studies, and nine guidelines were included (one of which was an updated version of another). No economic evaluations were identified. There was evidence for the following fluoroquinolones: ciprofloxacin, gatifloxacin, levofloxacin, lomefloxacin, norfloxacin, rufloxacin, ofloxacin, flerofloxacin, sitafloxacin, and finafloxacin.

There was considerable heterogeneity in study design, definition and classification of urinary tract infections (UTIs) among the included studies. In one randomized controlled trial, ceftazidime was more effective than ciprofloxacin in patients with acute obstructive pyelonephritis. However, ertapenem was significantly more effective than fluoroquinolones in complicated UTIs in one non-randomized study.

When patients with pyelonephritis or complicated UTIs were considered, sitafloxacin and levofloxacin were similarly effective as ceftrizxone and plazomicin respectively. However, ceftolozane-tazobactam was significantly more effective than levofloxacin in one non-randomized study.

In terms of adverse events, there were cases of acute psychosis reported among patients treated with fluoroquinolones, penicillins, or trimethoprim-sulfamethoxazole for UTIs.

Based on good to high-quality evidence, the guidelines provide detailed recommendations in the use of fluoroquinolones for the treatment of UTIs.

In clinical guidelines, fluoroquinolones are not recommended for children and pregnant women due to the potential adverse effects. A guideline by the National Institute for Health and Care Excellence (NICE) recommends ciprofloxacin for pyelonephritis for non-pregnant women and men aged 16 years and over. In the other three guidelines, both ciprofloxacin and levofloxacin are recommended for acute pyelonephritis.

Fluoroquinolones are not recommended as first- or second-line therapy for catheter-associated UTIs or lower UTIs in NICE guidelines. In a German guideline, fluoroquinolones are not recommended for the treatment of acute uncomplicated cystitis in otherwise healthy premenopausal women, unless there is no alternative. Fluoroquinolones are not recommended for uncomplicated cystitis in a European guideline. For recurrent UTIs, there are conflicting recommendations in the guidelines. In a NICE guideline, fluoroquinolones are not recommended for people aged 16 years and over or children under 16 years. However, fluoroquinolones are recommended in a Canadian and a German guideline.

## Methods

### Literature Search Methods

A limited literature search with the fluoroquinolones concept appearing in title or subject headings, was conducted on key resources including Ovid MEDLINE, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to the main search to limit the retrieval by study type. A second broader search with main concepts appearing in the title, abstract or subject heading was also included. Methodological filters were applied to this search to limit retrieval to systematic reviews and guidelines. For both searches, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and March 26, 2019.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1. Randomized controlled studies (RCTs) or systematic reviews (SRs) were included for effectiveness or harms outcomes. Non-randomized studies with no comparator were only included if they contained information on harms outcomes.

**Table 1: Selection Criteria**

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| **Population** | Patients with urinary tract infections |
| **Intervention** | Fluoroquinolones |
| **Comparator** | Q1-Q2: Any antibiotic comparator<br>Q3: No comparator |
| **Outcomes** | Q1: Clinical effectiveness; harms (e.g., Clostridium difficile infections, tendonitis or joint disorders, hypoglycemic coma; neuropsychiatric adverse events, liver toxicity, aortic dissection, retinal detachment)<br>Q2: Cost-effectiveness<br>Q3: Guidelines |
| **Study Designs** | Health technology assessments, Systematic Reviews, Meta-Analyses, Non-Randomized Studies, Randomized Controlled Trials, Economic Evaluations, and Guidelines |

### Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Primary studies that were already captured in an included systematic review were excluded, as were guidelines with unclear methodology.

### Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using the AMSTAR 2 checklist,[15] randomized and non-randomized studies were critically appraised using the Downs and Black checklist,[16] and guidelines were assessed with the AGREE II instrument.[17] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

## Summary of Evidence

### Quantity of Research Available

A total of 442 citations were identified in the literature search. Following screening of titles and abstracts, 404 citations were excluded and 38 potentially relevant reports from the electronic search were retrieved for full-text review. Nine potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 19 publications were excluded for various reasons, and 28 publications met the inclusion criteria and were included in this report. These comprised three systematic reviews, nine randomized controlled trials (RCTs), seven non-randomized studies, and nine evidence-based guidelines (one of which was an updated version of another). Appendix 1 presents the PRISMA[18] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

### Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

#### *Study Design*

One of three included SRs was published in 2018;[19] two others in 2014.[13,14] Cattrall et al. only included RCTs on the treatment of acute pyelonephritis.[19] The search date was not reported.[19] Grigoryan et al. searched articles published before July 2017 and included trials, SRs, and observational studies for the treatment of acute cycstitis.[14] Mostafa et al. searched for articles published before July 2013 in several databases and found case reports or case series reporting the cases of antibiotic-associated psychosis during the treatment of UTIs.[13] There were no overlap in the primary studies included in the SRs.

One of the nine included RCTs was published in 2019,[9] two in 2018,[20,21] three in 2017,[10,22,23] one in 2016,[24] and three in 2015.[25-27] Connolly et al., Vente et al., Mospan et al., and Wagenlehner et al. were double-blind RCTs,[20,21,24,26] while the others were open-label RCTs. Among the RCTs, there was considerable heterogeneity in study design, populations, interventions, comparators, and outcomes.

One of the seven non-randomized studies was published in 2019,[28] one in 2018,[29] one in 2017,[30] two in 2016,[31,32] one in 2015,[33] and one in 2014.[34] Six non-randomized studies were retrospective[28-32,34] and the other was prospective.[33]

There were no relevant economic evaluations identified.

One of the nine guidelines was published in 2019[35] (and was an update of an earlier version published in 2015[3]), five in 2018,[4,36-39] two in 2017,[40,41] and one in 2015.[3] The European consensus-based guidelines were published by the European Association of Urology.[3,35] For this report, the characteristics of the 2015 version of the guideline were included, and this version was critically appraised, however if the recommendations changed between the 2015 and 2019 versions then the 2019 recommendations were reported. Multiple databases were searched to identify SRs, meta-analyses of RCTs, high-quality reviews, and controlled studies.[3] The levels of evidence were graded according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence.[3] The guideline by Kranz et al.[36] published in 2018 was an update to the 2010 German AWMF (Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften) S3

guideline. Several databases were searched to identify SRs and RCTs.[36] The recommendations were made based on consensus and the levels of evidence were rated with Oxford criteria.[36] The National Institute for Health and Care Excellence (NICE) searched for SRs, RCTs and comparative studies in multiple databases and produced four guidelines.[4,37-39] The articles were systematically reviewed, but the methods to generate recommendations were unclear without the reporting of evidence levels in the four guidelines.[4,37-39] The Society of Obstetricians and Gynaecologists of Canada (SOGC) published a guideline in 2017.[40] For this guideline, PubMed and the Cochrane Library databases were searched to identify SRs, RCTs, and observational studies and the recommendations were made based on consensus.[40] The recommendations and the levels of evidence were made according to the guidelines by the Canadian Task Force on Preventive Health Care.[40] The guideline by Kranz et al. published in 2017 was developed under the aegis of the German Urological Society.[41] The Cochrane Library, MEDLINE, and Embase databases were searched to identify SRs and RCTs.[41] The recommendations were consensus-based.[41] The levels of evidence were graded according to the 2009 criteria of the Oxford Centre for Evidence-based Medicine.[41]

### *Country of Origin*

The SR by Cattrall et al. was conducted in the UK.[19] The SRs by Grigoryan et al. and Mostafa et al. were conducted in the US.[13,14]

The RCTs were led by authors based in the US (three studies),[20,24,26] Thailand (two studies),[9,10] Germany,[21] France,[22] China,[23] Ukraine,[25] and India.[27]

Two of the non-randomized studies were conducted in the US,[30,32] two in Taiwan,[31,34] one in the UK,[28] one in Germany,[29] and one in Switzerland.[33]

Two German guidelines were authored by the same first author, but published by different medical associations.[36,41] Four guidelines were authored by the National Institute for Health and Care Excellence in the UK.[4,37-39] The Canadian guideline was published by the Society of Obstetricians and Gynaecologists of Canada.[40] One guideline was published by the European Association of Urology[3] and updated in 2019.[35]

### *Patient Population*

The SRs included patients with acute pyelonephritits,[19] women with cyctitis,[14] and patients with antibiotic-associated psychosis.[13]

In the RCTs, patients with acute pyelonephritis or complicated UTIs,[9,20,21,23,26] acute uncomplicated pyelonephritis,[10,22] complicated UTIs,[24] acute obstructive pyelonephritis,[25] or uncomplicated UTIs[27] were recruited. In addition to patients with pyelonephritis or complicated UTIs, Vente et al. also included patients with uncomplicated UTIs.[21]

In the non-randomized studies, patients with suspected UTIs (elderly),[28] UTIs and a positive urine culture,[29] *Escherichia coli* pyelonephritis,[30] community-acquired complicated UTIs,[31] or a diagnosis of UTIs,[32-34] were studied.

For all nine guidelines, the intended users were health practitioners.[3,4,36-41] The target populations in the guidelines were patients with uncomplicated UTIs,[35,36,41] recurrent UTIs,[35,39] pyelonephritis,[35,37] catheter-associated UTIs,[4,35] lower UTIs,[35,38] recurrent UTIs,[35,39,40] and UTIs (not otherwise specified).[3]

The definitions of “complicated” or “uncomplicated” UTIs were not the same or not reported across publications.

### *Interventions and Comparators*

In the included SRs, intervention with fluoroquinolones was compared to other antibiotics, including other types of fluoroquinolones. In the SRs, several fluoroquinolones (ciprofloxacin,[13,14,19] gatifloxacin,[13,19] levofloxacin,[19] lomefloxacin,[19] norfloxacin,[19] rufloxacin,[19] ofloxacin,[13] and flerofloxacin[13]) were compared with non-fluoroquinolone antibiotics (trimethoprim- sulfamethoxazole,[13,19] loracarbef,[19] nitrofurantoin,[14] fosfomycin,[14] β-Lactams,[13,14] and metronidazole[13]).

In the RCTs, the fluoroquinolone interventions were: sitafloxacin,[9,10] levofloxacin,[20,24,26,27] finafloxacin,[21] ciprofloxacin,[25] and norfloxacin.[27] The fluoroquinolone interventions were compared with the following non-fluoroquinolone antibiotics: ceftriaxone,[9] plazomicin,[20] ciprofloxacin,[21,24] ertapenem,[10] ceftazidime,[25] co-trimoxazole,[27] or ceftolozane/ tazobactam.[26] In two RCTs, different dosing regimens of the same fluoroquinolones were compared. Specifically, in one RCT, five days of treatment with ofloxacin or levofloxacin was compared with ten days of treatment,[22] and in another five days of treatment with intravenous levofloxacin was compared with seven- to 14-days of treatment (intravenous then oral levofloxacin; different routes compared in this study).[23]

In the non-randomized studies, treatment with fluoroquinolones (i.e., ciprofloxacin,[28-30,32-34] levofloxacin,[31,34] norfloxacin,[34] or ofloxacin[34]) was compared to treatment with the following non-fluoroquinolone antibiotics: cephalexin,[28] co-amoxiclav,[28] nitrofurantoin,[28] piperacillin with tazobactam,[29] gentamicin,[29] cefuroxime,[29] cefpodoxime,[29] ceftazidime,[29] trimethoprim–sulfamethoxazole,[30,34] ceftriaxone,[31,32] ertapenem,[31] first-generation cephalosporins (including cefazolin or cephalexin),[32] penicillins (including ampicillin/sulbactam, amoxicillin/clavulanate, or piperacillin/tazobactam),[32] nitrofurantoin,[33] or fosfomycin.[33]

In the guidelines, any antibiotic treatment was considered.[3,4,35-41]

### *Outcomes*

The outcomes considered in the SRs were clinical success in the treatment of acute pyelonephritis,[19] symptom cure, symptom resolution, recurrence of cystitis, treatment duration[14], psychosis[13] and adverse events.[19]

In the RCTs, the outcomes were clinical success rates,[9,24,25] microbiological eradication,[10,20,21,25,27] microbiological recurrence,[10,20] clinical relapse,[10,20] early response,[21] susceptibilities of pathogens,[21,26] cure rates,[22] symptom-free cure,[10] clinical effectiveness rates,[23] treatment failure,[27]adverse events,[9,20] composite cure,[26] and adverse drug reactions.[27]

In non-randomized studies, the outcomes of interest were re-consultation and represcription,[28] hospitalization for UTIs,[28] sepsis,[28] acute kidney injury,[28] death,[28] antimicrobial resistance,[29] multi-drug resistence,[29] subsequent symptomatic UTIs,[30] antibiotic susceptibilities,[31] time to defervescence,[31] interaction with warfarin measured by international normalized ratio (INR),[32] gut microbiota composition,[33] and treatment failure.[34]

The outcomes identified in the guidelines included clinical and bacterial cure, and adverse effects.[3,4,35-41]

## Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

### Systematic reviews

Strengths common to the three SRs were that the population, intervention, comparator, and outcome components were clearly stated, systematic literature searches were conducted, and included studies were described in detail.[13,14,19] Only Mostafa et al. explained the selection criteria for study design and only case reports were eligible for inclusion.[13] Cattrall et al. and Mostafa et al. selected studies in duplicate.[13,19] Cattrall et al. and Grigoryan et al. assessed the risk of bias of the primary studies with published checklists and accounted for risk of bias when interpreting the results,[14,19] while Mostafa et al. did not.[13] Cattrall et al. explained the heterogeneity between the primary studies.[19] Conflicts of interest were declared by authors in the SRs by Grigoryan et al. and Mostafa et al.,[13,14] but not declared in the SR by Cattrall et al.[19] The review protocols of the three SRs were not published a priori.[13,14,19] Limitations common to all three reviews were that the data in the primary studies were not extracted in duplicate, the excluded studies were not listed, and the sources of funding for the primary studies were not reported.[13,14,19] Due to the more than one flaw in the critical domains of the AMSTAR 2 checklist, the quality of the three SRs was considered critically low.

### RCTs

There were strengths identified in the RCTs based on the Downs and Black checklist.[16] The study objectives, outcome measurement, interventions, main findings, and random variability of the outcomes (if applicable) were described.[9,10,20-27] No significant changes in medical practice were declared.[9,10,20-27] The lengths of follow-up were the same for different groups.[9,10,20-27] The compliance and outcome measurement was measured similarly between different groups.[9,10,20-27] Different groups of patients were recruited from the same populations and during similar periods of time.[9,10,20-27] All patients were randomized to different groups and loss to follow-up was taken into account in the analysis.[9,10,20-27] Except for in the study by Pasiechnikov et al., patient characteristics were described.[9,10,20-24,26,27] Except for Mospan et al., adverse effects were considered in the RCTs.[9,10,20-24,26,27] The characteristics of the patients lost to follow-up were described in two RCTs.[9,20] Connolly et al. and Vente et al. concealed the intervention allocation.[20,21] Sample sizes were calculated before the start of the trial in five studies.[9,20,23,26,27]

### Non-randomized studies

There were strengths identified in the non-randomized studies. The study objectives, outcome measurement, patient characteristics, interventions, main findings, and random variabilities of main outcomes were described.[28-34] No significant difference between the health care the patients received and the standard of care was declared.[28-34] The lengths of follow-up time were similar between different groups.[28-34] The quality of outcome measurement and compliance was similar between groups.[28-34] Different groups of patients were recruited during the same periods of time.[28-34] Except for in the study by Bischoff et al.,[29] the distributions of principal confounders in different groups were described.[28,30-34] Except for Bischoff et al. and Lee et al.,[29,34] the actual probability values were reported.[28,30-33] Ahmed et al., Bischoff et al., Fox et al., and Lee et al. adjusted for the confounders in the analysis.[28-30,34] Lin et al. and Saum et al. considered loss to follow-up in the analysis.[31,32]

There were limitations identified in the non-randomized studies. The description of the patients lost to follow-up, blinding of patients or outcome assessors, randomization, allocation concealment, and sample size estimation were not available in all non-randomized studies.[28-34]

**Guidelines**

There were strengths identified in the guidelines. In all of the included guidelines, the objectives, health questions, and target populations were described.[3,4,36-41] The involvement of relevant professional groups, target users, systematic literature searches, the consideration of both benefits and side effects, the links between evidence and recommendations, and external review, were described.[3,4,36-41] The recommendations were specific and unambiguous and different options were presented if available.[3,4,36-41] The key recommendations were easily identifiable.[3,4,36-41] Except for the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the European Association of Urology (EAU) guidelines,[3,40] the views of patients were explicitly sought.[4,36-39,41] The criteria for selecting the evidence were stated in the four NICE guidelines, SOGC guideline, Kranz et al. (2017).[4,37-41] Except for Kranz et al. (2018),[36] the strengths and limitations of the body of evidence were described.[3,4,37-41] The methods for formulating the recommendations were described in the NICE guidelines and the SOGC guideline.[4,37-40] The procedures for updating the guideline was reported in Kranz et al. (2017).[41] Facilitators and barriers to guideline application, advice on implementation, and resource implications were described in the four NICE guidelines.[4,37-39] It was reported that the views of the funding body did not influence the contents of Kranz et al. (2018), Kranz et al. (2017) and the EAU guideline.[3,36,41] Competing interests of the guideline development members were declared in the four NICE guidelines, Kranz et al. (2017) and the EAU guideline.[3,4,37-39,41] Monitoring or auditing criteria were not mentioned in any of the guidelines.

## Summary of Findings

### *Clinical Effectiveness of Fluoroquinolones*

**Systematic reviews**

In the SR by Cattrall et al.,[19] there was considerable heterogeneity between primary studies regarding outpatient treatment of pyelonephritis. The clinical success rates were not statistically different among cefaclor, ciprofloxacin, and norfloxacin at weeks 4 to 6.[19] Relatively high rates of adverse effects were observed in one trial of ciprofloxacin and trimethoprim-sulfamethoxazole, 24% and 33% respectively, compared to the results in other included primary studies.[19]

In the SR by Grigoryan et al.[14], in adult women with uncomplicated cystitis, trimethoprim-sulfamethoxazole, nitrofurantoin, or fosfomycin were the drugs compared in the primary studies.[14] Fluoroquinolones were effective for clinical and microbiological outcomes, but it was concluded that they should be reserved for more invasive infections in order to avoid inducing bacterial resistenance.[14] For men with acute UTIs, the results in the observational studies showed antibiotic therapy, including ciprofloxacin, for seven to 14 days was effective.[14] The authors concluded that options of antibiotics for women with diabetes without voiding abnormalities were similar to those for women without diabetes.[14]

In the SR by Mostafa et al., a systematic search was conducted for cases of acute psychosis that occurred during UTI treatment.[13] Acute psychosis was considered a potential adverse effect of antibiotic treatment of UTIs, although the mechanism remained

unknown.[13] Three classes of antibiotics were implicated: fluoroquinolones, penicillins, and trimethoprim-sulfamethoxazole.[13]

**RCTs**

In one RCT, oral sitafloxacin was noninferior to intravenous ceftriaxone followed by oral cefdinir to treat acute pyelonephritis and complicated UTIs.[9] However, for the same population, oral sitafloxacin was associated with lower resistance rates.[9] In the other RCT in which sitafloxacin was examined, patients with non-bacteremic acute pyelonephritis caused by extended-spectrum b-lactamase-producing (ESBL) *Escherichia coli* were randomized to receive sitafloxacin (fluoroquinolone) or ertapenem (non-fluoroquinolone) following carbapenem (non-fluoroquinolone).[10] Sitafloxacin (following carbpenem) was well-tolerated and was not significantly different from ertapenem based on clinical cure and microbiological eradication.[10]

Compared to levofloxacin, plazomicin was not significantly different in microbiological and clinical success and overall safety in patients with complicated UTIs or acute pyelonephritis.[20]

Among patients with acute obstructive pyelonephritis, ceftazidime was associated with significantly higher clinical or microbiological cure rates than ciprofloxacin after drainage, percutaneous nephrostomy or urethral stenting.[25]

Compared to co-trimoxazole, levofloxacin and norfloxacin were equally effective for the treatment of uncomplicated UTIs based on bacterial cure rates.[27]

Compared to levofloxacin, the combination of ceftolozane and tazobactam was associated with significantly better responses in a composite of microbiological eradication and clinical cure in patients with complicated lower UTIs or pyelonephritis with similar adverse event profiles.[26]

There were two RCTs in which different routes or treatment durations of fluoroquinolones were compared.[21,23] First, compared to intravenous short-course (5-day intravenous) levofloxacin, the conventional combination of intravenous and oral levofloxacin regimen (i.e. seven to 14 days of intravenous and oral treatment) was similarly effective in clinical and microbiological efficacy, tolerance, and safety among patients with complicated UTIs or acute pyelonephritis.[23] From a clinician perspective, the short-course regimen was a more convenient alternative.[23]

The need for antimicrobial treatment was not significantly different between patients treated with a 10-day intravenous ciprofloxacin regimen or a 5-day intravenous levofloxacin regimen among male patients with complicated UTIs.[24]

In patients with acute uncomplicated pyelonephritis, clinical and microbiological cure were not significantly different between those treated with 5- or 10-days of ofloxacin or levofloxacin.[22]

Lastly, compared to ciprofloxacin, finafloxacin was more “active” by demonstrating early and rapid activity against uropathogens based on the numbers of colony-forming units in urine culture, including fluoroquinolone-resistant and/or multi-resistant pathogens or ESBL producers.[21]

**Non-randomized studies**

Compared with nitrofurantoin, the use of ciprofloxacin, cephalexin, or co-amoxiclav was associated with lower rates of treatment failure, defined by re-consultation and re-prescription, in older people with UTIs.[28] The risks of UTI-related hospitalization or death were not significantly different between patients treated with nitrofurantoin and those treated with ciprofloxacin, cephalexin, or co-amoxiclav.[28]

When ciprofloxacin, piperacillin with tazobactam, gentamicin, cefuroxime, cefpodoxime, and ceftazidime were compared to each other, cephalosporins were the best choice based on antibiotic resistance for UTI patients without any of the seven risk factors identified by Bischoff et al.[29] In UTI patient with any risk factors, piperacillin with tazobactam was an equal or better option than fluoroquinolones, cephalosporins or gentamincin with respect to antibiotic resistance.[29]

Compared to ciprofloxacin, seven-day trimethoprim/sulfamethoxazole treatment was similarly effective for pyelonephritis based on the occurrence of subsequent symptomatic UTIs.[30]

In Lin et al., ceftriaxone, levofloxacin, and ertapenem all had good clinical response in the treatment of complicated UTIs.[31] However, ertapenem was associated with significantly better bacterial susceptibility, sooner defervescence and shorter hospital stays.[31]

In patients with UTIs using warfarin, the authors of a non-randomized study concluded that ciprofloxacin, first-generation cephalosporins, and penicillins were preferred because of significantly less interaction with warfarin, compared to ceftriaxone that was associated with significantly higher peak international normialized ratio (INR), significantly greater change in INR, and significantly greater percentage change in INR.[32]

When gut microbiota were considered as outcome, ciprofloxacin was associated with a significant global impact compared to nitrofurantoin in patients with uncomplicated UTIs.[33]

In patients with UTIs treated with oral fluoroquinolones, norfloxacin, or ofloxacin there were significantly lower composite treatment failure rates, compared to patients treated with ciprofloxacin or trimethoprim–sulfamethoxazole.[34]

### *Cost-effectiveness of Fluoroquinolones*

No relevant evidence regarding the cost-effectiveness of fluoroquinolones for the treatment of UTIs was identified; therefore, no summary can be provided.

### *Guidelines Regarding Fluoroquinolones*

In the European Association of Urology guideline updated in 2019, ciprofloxacin, levofloxacin, and ofloxacin are not recommended in uncomplicated cystitis (strong evidence).[3] Ciprofloxacin and levofloxacin are recommended for initial empirical oral therapy in uncomplicated pyelonephritis (no evidence level).[3,35] Ciprofloxacin is recommended for complicated pyelonephritis in women if the local resistance pattern remains less than 10% and the patients have contraindications for third-generation cephalosporins or an aminoglycoside.[35] It is advised not to use fluoroquinolones empirically in patients from urology departments or those exposed to fluoroquinolones in the last six months.[35]

In the guidelines by Kranz et al. (2018), fluoroquinolones and cephalosporins are not recommended for the treatment of acute uncomplicated cystitis in otherwise healthy premenopausal women, unless there is no alternative (Oxford criteria and recommendation rating: Ia-A).[36] However, ciprofloxacin and levofloxacin are recommended for acute pyelonephritis in otherwise healthy premenopausal women (V-A)).[36] Norfloxacin and ofloxacin are recommended for long-term continuous prophylaxis and post-coital single-dose prophylaxis for recurrent UTIs in otherwise healthy premenopausal women (Ib-B).[36] In the guidelines by Kranz et al. (2017), the recommendations for fluoroquinolones are the same to those in Kranz et al. (2018), except ciprofloxacin and norfloxacin are recommended for continuous long-term prophylaxis of recurrent UTIs (no evidence levels) in Kranz et al. (2017)[41] and norfloxacin and ofloxacin recommended for the same indication in Kranz et al. (2018).[36]

In 2018, NICE published four guidelines about the treatment of UTIs.[4,37-39] For the antimicrobial treatment of pyelonephritis, fluoroquinolones are not recommended as first- or second-line therapy, except for ciprofloxacin which is listed as first-choice oral and intravenous antibiotic for non-pregnant women and men aged 16 years and over (no evidence level).[37] For catheter-associated UTIs or lower UTIs, fluoroquinolones are not included as first- or second-line therapy, except for ciprofloxacin listed as first-choice intravenous antibiotic (no evidence level).[4,38] For recurrent UTI, fluoroquinolones are not recommended for any patients (no evidence level).[39]

In contrast, in the Canadian guideline (by the SOGC), quinolones are recommended as one of the antibiotics used for daily prophylaxis for women with two recurrent UTIs in six months or three recurrent UTIs in 12 months.[40]

## Limitations

The primary limitation of this report is that UTIs were diagnosed and categorized differently across the included publications, which leads to difficulty drawing conclusions across studies. In some instances, UTIs were evaluated based on a group of diagnostic codes in the databases,[28,34] whereas customized definitions were used in trials.[21,27] When UTIs were studied retrospectively, the organs involved were not always reported or known.[34] The classification of UTIs could be based on anatomical locations or disease severity.[24,26] UTIs were often categorized into complicated and uncomplicated.[3] However, the complicating factors were not always clearly reported.[22,23] This means that UTIs of different severities or complicating factors might have been considered the same.

No economic evaluation studying the cost-effectiveness of fluoroquinolones for the treatment of UTIs was identified.

When antibiotics were considered for clinical use, pathogen susceptibility was an important factor to consider.[3,36,39] However, few trials considered pathogen susceptibility in the trial design.[10]

In addition, there were conflicts between recommendations in the evidence-based guidelines. Fluoroquinolones were recommended for recurrent UTIs in a Canadian guideline[40] and not recommended in a NICE guideline.[39] As concluded in the SR by Cattrall et al., there was considerable heterogeneity between the RCTs on fluoroquinolones for the treatment of UTIs.[19] This might lead the authors to draw conclusions from studies on populations with different underlying characteristics, such as complicating factors.

## Conclusions and Implications for Decision or Policy Making

Three SRs of critically low quality, nine good-quality RCTs, one fair-quality RCT, one good-quality non-randomized study, six fair-quality non-randomized studies, and eight guidelines were included. There was considerable heterogeneity in study design, UTI definition and classification among the included studies.

### *Clinical Effectiveness*

#### Pyelonephritis

In a SR by Cattrall et al., ciprofloxacin and norfloxacin were comparable to cefaclor in clinical success of treating pyelonephritis.[19] However, ciprofloxacin was associated with higher rates of adverse effects.[19]

In the primary studies, sitafloxacin was well-tolerated and not significantly different from ertapenem as subsequent treatment for non-bacteremic acute pyelonephritis after initial carbapenem.[10] In an RCT, 5- and 10-day regimens of ofloxacin or levofloxacin were similarly effective for acute uncomplicated pyelonephritis.[22] In a non-randomized study, 7-day ciprofloxacin treatment was not significantly different from 7-day trimethoprim/sulfamethoxazole treatment.[30] However, in another RCT, ceftazidime was associated with significantly higher clinical or microbiological cure rates than ciprofloxacin after drainage in patients with acute obstructive pyelonephritis.[25]

#### Complicated UTIs

In an RCT, 10-day and 5-day intravenous ciprofloxacin were similarly effective in treating men with complicated UTsI.[24] In a non-randomized study, ceftriaxone, levofloxacin, and ertapenem all had good clinical response in the treatment of complicated UTIs.[31] However, ertapenem was associated with significantly better bacterial susceptibility, sooner defervescence and shorter hospital stays.[31]

#### Pyelonephritis and complicated UTIs

In RCTs, oral sitafloxacin was non-inferior to intravenous ceftriaxone.[9] Levofloxacin and plazomicin were similarly effective and safe.[20] Short-course intravenous levofloxacin was similarly effective as the conventional intravenous and oral levofloxacin regimen.[23]

However, the combination of ceftolozane and tazobactam was significantly more effective than levofloxacin with similar adverse event profiles in one non-randomized study.[26]

#### Uncomplicated UTIs

Levofloxacin and norfloxacin were equally effective as co-trimoxazole.[27] When gut microbiota considered as outcome, ciprofloxacin was associated with a significant global impact compared to nitrofurantoin in patients with uncomplicated UTIs.[33]

#### Lower UTIs (cystitis)

In the SR by Grigoryan et al., fluoroquinolones were effective, but there was concern about the pathogen resistance and the authors concluded that they should be reserved for more invasive infections.[14]

#### UTIs, unspecified

In an RCT, finafloxacin was more active than ciprofloxacin against uropathogens.[21] In non-randomized studies, norfloxacin, or ofloxacin were associated with significantly lower

composite treatment failure rates, compared to ciprofloxacin or trimethoprim–sulfamethoxazole.[34] Ciprofloxacin, cephalexin, or co-amoxiclav were associated with lower rates of re-consultation and re-prescription in older people than nitrofurantoin, though with similar risks of UTI-related hospitalization or death.[28]

However, cephalosporins were the best choice for UTI patients without any of the seven risk factors identified by Bischoff et al.[29] In UTI patients with any risk factors, piperacillin with tazobactam was an equal or better option than fluoroquinolones, cephalosporins or gentamincin.[29]

In UTI patients using warfarin, ciprofloxacin, first-generation cephalosporins, and penicillins were preferred because of significantly less interaction with warfarin, compared to ceftriaxone.[32]

**Adverse events**

In the SR by Mostafa et al., fluoroquinolones, penicillins, and trimethoprim-sulfamethoxazole were associated with reported cases of acute psychosis during UTI treatment.[13]

*Guidelines*

**Pyelonephritis**

In clinical guidelines, a NICE guideline recommend ciprofloxacin for pyelonephritis for non-pregnant women and men aged 16 years and over.[37] In Kranz et al. (2017 and 2018), levofloxacin is also recommended for acute pyelonephritis in otherwise healthy women.[36,41] In a European guideline, ciprofloxacin and levofloxacin are recommended for initial empirical oral therapy in uncomplicated pyelonephritis.[3,35]

**Complicated UTIs**

In a European guideline, ciporfloxacin is one of the antibiotics recommended for complicated UTIs if the fluoroquinolone resistance pattern remains less than 10% in the target patient groups and the patients have contraindications for third-generation cephalosporins or an aminoglycoside.[35] It is advised to avoid using fluoroquinolones as empirical treatment for patients in the urology departments or those exposed to fluoroquinolones in the last six months.[35]

**Catheter-associated UTIs**

Fluoroquinolones were not recommended in a NICE guideline.[4]

**Lower UTIs (cystitis)**

Fluoroquinolones are not recommended as first- or second-line therapy in a NICE guideline.[4] In the guideline by Kranz et al. (2018), fluoroquinolones were not recommended for the treatment of acute uncomplicated cystitis in otherwise healthy premenopausal women, unless there was no alternative.[36] Fluoroquinolones should be avoided from the treatment of uncomplicated cystitis in the updated European guideline.[35]

**Recurrent UTIs**

In a NICE guideline, fluoroquinolones were not recommended for people aged 16 years and over or children under 16 years.[39] However, fluoroquinolones were recommended for daily prophylaxis in women in a Canadian guideline.[40] Norfloxacin and ofloxacin are

recommended for long-term continuous prophylaxis and postcoital single-dose prophylaxis for recurrent UTIs in otherwise healthy women in the premenopause.[36]

**Overall Summary**

There was evidence to show that fluoroquinolones were similarly effective or more effective than conventional options, such as trimethoprim–sulfamethoxazole, to treat UTIs in patients with specific characteristics, such as non-pregnant women with pyelonephritis. It was also identified that the use of fluoroquinolones in children and pregnant women should be avoided because of the potential adverse effects. However, there are challenges to policy-making in guiding the use of fluoroquinolones in clinical practice. The use of antibiotics requires attention to pathogen susceptibilities, potential impact on pathogen resistance, drug routes, infection sites, patient compliance and other factors.[39] Providing recommendations can be challenging. There are relatively new fluoroquinolones to be compared with commonly-used ones, particularly ciprofloxacin that was examined in several RCTs, or other classes of antibiotics. For example, sitafloxacin was not mentioned in the clinical guidelines. There are also conflicts between the recommendations in the guidelines or clinical studies. For example, fluoroquinolones are not recommended by the NICE,[39] but are recommended in Canadian and German guidelines for daily prophylaxis against recurrent UTIs.[36,40] These challenges are related to the limitations in this review, including considerable heterogeneity in study design and UTI definitions, and insufficient information on pathogen susceptibilities. Further research on the use of existing and new fluoroquinolones in different types of well-defined UTIs can help address these issues in order to support the decision making in clinical care. Economic evaluations on the cost-effectiveness of fluoroquinolones are needed.

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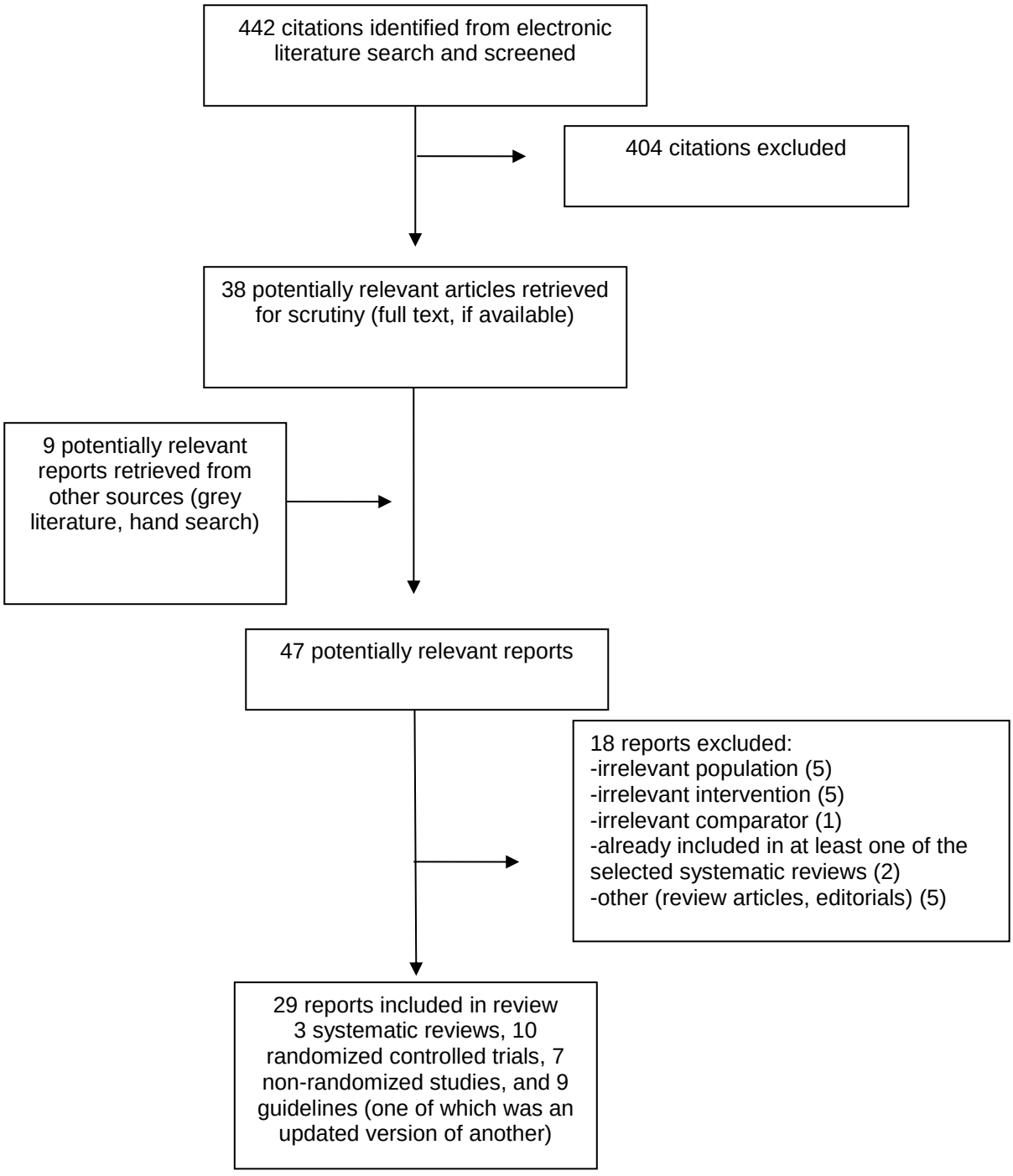
## Appendix 1: Selection of Included Studies



# Appendix 2: Characteristics of Included Publications

## Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

| First Author, Publication Year, Country | Study Designs and Numbers of Primary Studies Included | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| Cattrall et al. 2018,[19] UK | 5 RCTs in the USA or Europe conducted between 1992 and 2002<br><br>N in total = 1003<br><br>MEDLINE, Embase+ Embase classic and CENTRAL searched | Patients with acute pyelonephritis<br><br>Pyelonephritis "*defined as a bacterial infection of the renal pelvis and kidney, not including prostatitis or renal abscess*" (p. 2286)<br><br>*E. coli*: the most common infecting organism, 56.4 to 92.5% of pyelonephritis cases<br><br>Exclusion criteria: pregnancy, "*being male, urinary catheterisation within our definition of complicated pyelonephritis*", "*complicated pyelonephritis, defined as known diabetes/metabolic disease or known structural/functional urological abnormalities*" (p. 2286) | Oral antibiotics compared to each other:<br>**cefaclor** (500 mg three times daily 14 days minimum),<br>**ciprofloxacin** (500 mg twice daily 7 days or 7–10 days or 10 days),<br>**gatifloxacin** (400 mg once daily 7–10 days),<br>**levofloxacin** (250 mg once daily 7–10 days),<br>**lomefloxacin** (400 mg once daily 14 days),<br>**norfloxacin** (400 mg twice daily 14 days minimum),<br>**rufloxacin** (200 mg once daily 14 days),<br>**loracarbef** (400 mg twice daily 14 days minimum),<br>**trimethoprim-sulfamethoxazole** (160/800 mg twice daily 14 days) | Outcomes identified:<br>1) clinical success 5 to 9 days post-treatment and 4 to 6 weeks after treatment<br>2) adverse events<br><br>**Clinical success**<br>Clinical or microbiological cure, defined differently in the primary studies |
| Grigoryan et al. 2014,[14] US | Total: 27 trials (6463 patients), 6 systematic reviews, and 11 observational studies (252 934 patients) for diagnosis or treatment of acute cystitis<br><br>10 trials comparing fluoroquinolones with other first-line agents<br><br>PubMed and the Cochrane database searched for English-language studies up to July 21, 2014 | Young healthy women with acute cystitis, women with diabetes and acute cystitis, and men with acute cystitis | **Treatment Regimens for Uncomplicated Acute Cystitis in Adult Women**: Trimethoprim-Sulfamethoxazole, Nitrofurantoin, Fosfomycin, Fluoroquinolones (compared with other first-line agents in 10 trials), β-Lactams<br><br>**Treatment of UTI in Other Patient Populations**: 2 lengths of ciprofloxacin therapy compared in one RCT | 1) Diagnosis of UTIs<br>2) Treatment of UTIs: symptom cure, symptom resolution, recurrence, and treatment duration |

## Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

| First Author, Publication Year, Country | Study Designs and Numbers of Primary Studies Included | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| | | | Other Approaches to Treating Uncomplicated Acute Cystitis in Women: antimicrobial sparing methods<br><br>Delayed Therapy and Ibuprofen Therapy: delayed antibiotic therapy or anti-inflammatory agents (ibuprofen) | |
| Mostafa et al. 2014,[13] US | 14 articles, N = 15 cases<br><br>MEDLINE (PubMed; National Center for Biotechnology Information, US National Library of Medicine, Bethesda, MD), PsychINFO (via Ovid; American Psychological Association, Washington, DC), and Thomson Reuters' (formerly Institute for Scientific Information) Web of Knowledge (Science Citation Index and Social Sciences Citation Index; Thomson Reuters, Charlottesville, VA) in July 2013 | 15 cases of antibiotic associated psychosis during treatment of UTIs<br><br>Age range: from 18 to 88 years (mean age, 50.8 y) | **Antibiotics identified**<br>Ciprofloxacin (N = 5)<br>Ofloxacin (1)<br>Gatifloxacin (1)<br>Fleroxacin (1)<br><br>Oxacillin (1)<br>Metronidazole (1)<br>Amoxicillin (2)<br>TMP-SMZ (7)<br><br>More than one antibiotic might have been used in the same case | Psychosis: "*defined by the following symptoms: hallucinations, delusions, disorganization (in thinking and/or behavior), and catatonia*" (p. 484)<br><br>Delirium not included<br><br>Follow-up lengths: 2 to 10 days |

RCT = randomized controlled trial; TMP-SMZ = trimethoprim-sulfamethoxazole; UTI = urinary tract infection.

## Table 3: Characteristics of Included Primary Clinical Studies

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| **RCTs** | | | | |
| Lojanapiwat et al. 2019,[9] Thailand | RCT, open-label, randomized, controlled, non-inferiority, multi-centre<br><br>No trial registration reported | 289 adult patients with acute pyelonephritis or complicated urinary tract infection (141 in the sitafloxacin group and 148 in the other group)<br><br>Complicated UTIs not defined | Oral sitafloxacin (100 mg twice daily for 7–14 days)<br><br>versus<br><br>intravenous ceftriaxone (2g several days) followed by oral cefdinir (100 mg three times per day for another 4–12 days) | Clinical success rates at the end of treatment<br><br>Adverse events<br><br>Telephone follow-up: at the test of cure (21 to 28 days after the end of treatment) |
| Connolly et al. 2018,[20] USA | RCT, multi-centre, double-blind, phase 2<br><br>NCT01096849 | 145 patients with complicated urinary tract infection and acute pyelonephritis<br><br>Complicating factors for a cUTI<br>1) an indwelling catheter (to be removed or replaced by ≤ 12 h after randomization),<br>2) urine residual volume of ≥ 100 ml, neurogenic bladder, or urinary retention in men due to previously diagnosed benign prostatic hypertrophy | Levofloxacin (750 mg once daily for 5 days)<br><br>versus<br><br>Plazomicin (10 or 15 mg/kg of body weight once daily for 5 days) | Microbiological eradication at the test of cure, 5 to 12 days after the last treatment<br><br>Microbiological recurrence and clinical relapse at long-term follow-up, 33 to 47 days after the last treatment<br><br>Adverse events |
| Vente et al. 2018,[21] Germany | Analysis of 2 RCTs, phase 2, multi-centre in Poland, Germany or Singapore<br><br>Registration: NCT00722735 and NCT01928433 (also published in Wagenlehner et al. 2018)[42] | 198 patients with uncomplicated urinary tract infections (uUTIs) and complicated urinary tract infections (cUTIs) or acute pyelonephritis (PN)<br><br>Complicating factors not defined | Finafloxacin (300 mg twice a day orally for uUTI or 800 mg once a day intravenously for cUTI/PN)<br><br>versus<br><br>ciprofloxacin (250 mg twice a day orally for uUTIs and 400 mg twice a day intravenously for cUTI/PN) | Early response at day 3<br><br>Susceptibilities of pathogens<br><br>Eradication: "*elimination or reduction of study entry pathogens to < $10^3$ CFU/ml in urine culture*" (p. 1) |
| Dinh et al. 2017,[22] France | RCT, multi-centre open-label, non- | 100 patients with acute uncomplicated | **Ofloxacin 200 mg twice daily** | **Primary outcome**<br>Cure rate at day 30 |

## Table 3: Characteristics of Included Primary Clinical Studies

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| | inferiority<br><br>No registration reported | pyelonephritis<br><br>Complicating factors not defined<br><br>Inclusion criteria: community women, aged ≥18 years old, attending the emergency department, recent (<48 h) urinary tract infection (UTI) clinical signs (dysuria, pyuria, frequency, urgency and suprapubic pain, costovertebral angle tenderness), a body temperature >38 °C, and a positive urinalysis [colony-forming units (CFU) ≥ $10^5$/mL] | **or levofloxacin 500 mg daily**<br><br>5 days versus 10 days | **Secondary outcome**<br>Cure rate at day 10<br><br>Cure: "*resolution of clinical signs related to UTI and apyrexia without the need for additional or alternative antibiotic therapy*" (p. 1444)<br><br>Follow-up: at day 5, 10, and 30 after the end of treatment |
| Malaisri et al. 2017,[10] Thailand | RCT, prospective, open-label, single-centre<br><br>Registration: NCT02537847 | 36 patients with acute pyelonephritis caused by extended-spectrum b-lactamase-producing *Escherichia coli*<br><br>Complicating factors for complicated pyelonephritis: male, age >60 years, diabetes mellitus or malignancy, receiving steroid, chemotherapy or radiation, and having anatomical/functional abnormality of the urinary system.<br><br>Inclusion criteria: hospitalized or non-hospitalized; over 18 years of age; presumptive diagnosis of acute pyelonephritis; positive urine culture of ≥ $10^5$ colony-forming units (CFU)/mL ESBL- | **Initial treatment**<br>carbapenems for 3 days, including meropenem 1 g every 8 hours, imipenem 500 mg every 6 hours, doripenem 500 mg every 8 hours, and ertapenem 1 g once daily<br><br>**Subsequent treatment assignment**<br>oral sitafloxacin 100 mg twice daily<br><br>versus<br><br>intravenous ertapenem 1 g infused over 30 min once daily<br><br>Doses subject to adjustment depending on creatinine clearance | **Primary clinical outcomes**<br>Cure vs. failure at day 10<br><br>Cure: free of symptoms<br>Failure: persistent symptoms<br><br>**Secondary clinical outcome**<br>Recurrence: new onset of clinical signs and symptoms at the end of the study or at day 30.<br><br>Bacteriological responses: quantitative urine culture at day 10 |

## Table 3: Characteristics of Included Primary Clinical Studies

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| | | EC; and voluntarily consent<br><br>Acute pyelonephritis: "*pyuria (≥10 leukocytes per high-power field (HPF) in urine analysis) combined with all of the following: fever (body temperature ≥ 38°C), urinary syndrome (dysuria, urgency, or urinary frequency), flank pain, or costovertebral angle tenderness*" (p. 557) | Total duration of antibiotic treatment: 10 days | |
| Ren et al. 2017,[23] China | RCT, prospective, open‑label, multi-centre (16), non‑inferiority<br><br>No registration reported | 317 patients with cUTI or APN: inpatients (n = 196) or outpatients (n = 121)<br><br>Complicating factors not defined<br><br>Inclusion criteria: at least 18 years old, inpatients (n = 196) or outpatients; diagnoses of cUTI or APN (females only), and provision of informed consent | **2 levofloxacin regimens**<br>intravenous levofloxacin (750 mg/150 mL) once daily for 5 consecutive days<br><br>versus<br><br>intravenous levofloxacin 500 mg/100 mL once daily and then shifted to an oral regimen of levofloxacin 500 mg tablet once daily for 7 to 14 days | **Primary outcome**<br>clinical effectiveness rate at the end of therapy<br><br>Clinical efficacy classified as complete remission, remission, non-remission, and not applicable<br><br>**Secondary outcomes**<br>Clinical effectiveness rate at the second and third hospital visits and several others<br><br>End of therapy: day 6 + 1 in the levofloxacin 750-mg group and day 8 to 15 in the levofloxacin 500-mg group). |
| Mospan et al. 2016,[24] US | Analysis of a RCT initially published in 2008, multi-centre, double-blind, noninferiority in cUTI and acute pyelonephritis.<br><br>Registration: | 427 patients with cUTIs (224 male, 203 female)<br><br>Majority: white, over the age of 60, and infected with *E. coli*<br><br>Complicating factors: Neurogenic bladder or | levofloxacin 750 mg once daily for 5 days<br><br>versus<br><br>ciprofloxacin 400 mg intravenously then 500 mg orally twice daily for 10 days | Clinical success rates: no further need for antimicrobial treatment |

## Table 3: Characteristics of Included Primary Clinical Studies

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| | NCT00210886 | urinary retention; Intermittent catheterization; and Partial obstruction | | |
| Pasiechnikov et al. 2015,[25] Ukraine | Prospective cohort study, randomized | 241 patients with acute obstructive pyelonephritis<br><br>Inclusion criteria: isochronal absence of kidney function on intravenous urogram with simultaneous pyeloectasy of involved kidney, presence of the fever of over 38° C, tenderness in the flank, dysuria and pyuria in urine obtained from kidney drainage (more than 10 leukocytes per high-power field of urinary sediment), and informed consent | Randomization to percutaneous nephrostomy (n=124) or ureteral stenting (n = 117) first<br><br>then each group randomized to<br><br>ciprofloxacin<br><br>versus<br><br>3rd generation cephalosporin, ceftazidime | Clinical and microbiological cure rates<br><br>Microbiological cure: "*pathogen growth of less than $10^3$ CFU/ml from the urine, as well as no growth from urine cultures if bacteriuria was initially documented*"(p. 165)<br><br>Clinical cure: "*significant reduction or surcease of all symptoms and signs of disease*" (p. 165)<br><br>Adverse events<br><br>Follow-up: up to 21 days |
| Vachhani et al. 2015,[27] India | RCT, open label, parallel group<br><br>Registration: Reg. No. 2014/03/006671 | 175 patients with uncomplicated UTI<br><br>Complicating factors not defined<br><br>Inclusion criteria: 18-65 years, "*symptoms of dysuria or frequency/urgency of micturation, burning micturation, fever and urine culture showing >105 colony forming unit (CFU) per milliliter (CFU/ml)*" (p. 156) | levofloxacin 250 mg once daily (N = 60)<br><br>versus<br><br>co-trimoxazole 960 mg twice daily (N=58)<br><br>versus<br><br>norfloxacin 400 mg twice daily (N=57 ) | Bacteriological cure rate: conversion of pre-treatment positive bacterial urine culture into negative urinary culture on day 4<br><br>Treatment failure: positive culture at the end of treatment period<br><br>Adverse drug reactions: recorded at follow up visit<br><br>follow-up on day 4 |
| Wagenlehner et al. 2015,[26] Germany reanalyzed in Huntington et al. 2016,[43] USA | RCT, large, global (25 countries), phase 3<br><br>Assessment of the Safety Profile and | Adult patients (≥18 years) with cUTIs, including pyelonephritis<br><br>Definitions: "*Pyelonephritis was* | Intravenous levofloxacin (high dose, 750 mg) once daily for 7 days<br><br>versus | Primary endpoint Composite cure: "achieving clinical cure and microbiological eradication of all baseline uropathogens" |

## Table 3: Characteristics of Included Primary Clinical Studies

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| | Efficacy of Ceftolozane/ Tazobactam in Complicated Urinary Tract Infections (ASPECT-cUTI)<br><br>NCT01345929 and NCT01345955 | *defined by the presence of two or more of the following symptoms: fever (oral temperature higher than 38°C) accompanied by rigors, chills, or warmth; flank pain; costovertebral angle or suprapubic tenderness on physical examination; or nausea or vomiting. Complicated lower-urinary-tract infections included all these symptoms plus suprapubic pain, dysuria, urinary frequency or urgency, and at least one of the following: male sex with urinary retention, indwelling urinary catheter, current obstructive uropathy, or any functional or anatomical urogenital-tract abnormality*" (p. 1950) | intravenous ceftolozane/ tazobactam (1.5 g) every 8 h | (p. 1951)<br><br>Other outcomes Pathogen speciation and susceptibility testing<br><br>Clinical cure: "*complete resolution, substantial improvement (ie, reduction in severity of all baseline signs and symptoms and worsening of none), or return to preinfection signs and symptoms of complicated lower-urinary-tract infections or pyelonephritis without the need for additional antibiotic therapy*" (p. 1951)<br><br>Clinical failure: "*the presence of one or more signs or symptoms of complicated lower urinary- tract infections or pyelonephritis requiring additional antibiotics, or an adverse event leading to premature discontinuation of the study drug and the starting of additional antibiotic therapy*" (p. 1951)<br><br>Microbiological eradication: "*a test-of-cure urine culture with fewer than $10^4$ colony-forming units per mL of the baseline uropathogen*" (p. 1951) |

## Table 3: Characteristics of Included Primary Clinical Studies

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| **Non-randomized studies** | | | | |
| Ahmed et al. 2019,[28] UK | Retrospective cohort study, | 42,298 older adults with suspected UTIs, aged ≥65 years, empirically treated for a UTI with nitrofurantoin, cefalexin, ciprofloxacin, or co-amoxiclav<br><br>Propensity score matching<br><br>UTIs defined in the Clinical Practice Research Datalink (CPRD) | Ciprofloxacin, cephalexin, and co-amoxiclav compared to nitrofurantoin | Re-consultation and re-prescription: proxy for treatment failure within 14 days<br><br>Hospitalization for UTIs within 14 days<br><br>Sepsis within 14 days<br><br>Acute kidney injury within 14 days<br><br>Death within 28 days |
| Bischoff et al. 2018,[29] Germany | Retrospective cohort study, single-centre, emergency department | 137 patients with UTIs and a positive urine culture | Ciprofloxacin, piperacillin with tazobactam (Pip/taz), gentamicin, cefuroxime, cefpodoxime, and ceftazidime**,** compared to each other | Antimicrobial resistances and multidrug resistance<br><br>Multi-drug resistance (MDR): pathogens non-susceptible to at least one agent in three or more antimicrobial categories<br><br>Extensively drug-resistant (XDR): pathogens fully susceptibly to only two or less antimicrobial categories<br><br>Follow-up: cross-sectional |
| Fox et al. 2017,[30] US | Retrospective cohort study, multi-centre | 272 women ages 16 and older with *Escherichia coli* pyelonephritis<br><br>Exclusion criteria: pregnancy, dialysis dependency, *E. coli* not susceptible to the treatment prescribed, polymicrobial urine culture, or greater than 48 hours of antibiotic | TMP-SMX 7 days<br><br>versus<br><br>ciprofloxacin 7 days<br><br>dosage unspecified route unspecified | Subsequent, symptomatic urinary tract infection within 30 days |

## Table 3: Characteristics of Included Primary Clinical Studies

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| | | therapy other than TMP-SMX or ciprofloxacin | | |
| Lin et al. 2016,[31] Taiwan | Retrospective cohort study | 358 patients with community-acquired complicated urinary tract infections<br><br>Complicating factors not defined | Ceftriaxone (CRO), levofloxacin (LVX), and ertapenem (ETP). | **Effectiveness**<br>Antibiotic susceptibilities<br>Time to defervescence since admission<br>Hospitalization stay<br><br>**Follow-up time:** not specified |
| Saum et al. 2016,[32] US | Retrospective cohort study, chart review, single-centre | 120 elderly chronic warfarin patients with a diagnosis of UTIs<br><br>Inclusion criteria: admitted as an adult inpatient, a diagnosis of UTIs, and receiving warfarin for any indication prior to admission | Ceftriaxone<br><br>versus<br><br>first-generation cephalosporins (including cefazolin or cephalexin),<br><br>versus<br><br>penicillins (including ampicillin/sulbactam, amoxicillin/clavulanate, or piperacillin/tazobactam)<br><br>versus<br><br>ciprofloxacin. | **Interaction between warfarin and antibiotics used in the treatment of UTIs**<br>international normalized ratio (INR) change from baseline between each antibiotic group<br><br>**Follow-up time:** not reported |
| Stewardson et al. 2015,[33] Switzerland | Part of a prospective cohort study, single-centre<br><br>Registration: ISRCTN26797709 | 22 UTI patients and 20 non-exposure adults<br><br>UTIs not defined | **Exposure to antibiotics**<br>Ciprofloxacin 500 mg twice daily (N = 10)<br><br>Nitrofurantoin macrocrystals 100 mg twice daily (N = 10)<br><br>Fosfomycin, one 3 g dose (N = 2)<br><br>**No exposure to antibiotics**<br>Control patients without antibiotic treatment (N | Gut microbiota composition by sequencing "*stool samples collected: at baseline (time point 1); at completion of antibiotic therapy (time point 2); and 4 weeks after the second sample (time point 3)*" (p. 344.e3)<br><br>Follow-up time: 4 weeks |

## Table 3: Characteristics of Included Primary Clinical Studies

| First Author, Publication Year, Country | Study Design | Population Characteristics | Intervention and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|---|---|---|---|
| | | | = 10)<br><br>Adult household contact for each patient treated with ciprofloxacin (N = 10) | |
| Lee et al. 2014,[34] Taiwan | Retrospective cohort study, population-based, new-user incident-case cohort design | 73,675 individuals with UTI<br><br>UTI International Classification of Disease 9th Clinical Modification (ICD-9-CM) codes: 590.xx (infection of the kidney), 595.xx (cystitis) and 599.xx (other disorders of the urethra and urinary tract, including urinary tract infection of unspecified site) | Norfloxacin, ofloxacin, levofloxacin, ciprofloxacin, and trimethoprim–sulfamethoxazole<br><br>compared to one another | Treatment failure: hospitalization or emergency department visits for UTI<br><br>Follow-up: up to 42 days |

APN = acute pyelonephritis; ASPECT = Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam; CFU = colony-forming unit; CPRD = Clinical Practice Research Datalink; CRO = ceftriaxone; cUTI = complicated urinary tract infection; ESBL-EC = extended-spectrum beta-lactamase *E. coli*; ETP = ertapenem; HPF = high-power field; ICD-9-CM = International Classification of Disease 9th Clinical Modification; INR = international normalized ratio; LVX = levofloxacin; MDR = multi-drug resistance; PN = pyelonephritis; RCT = randomized controlled trial; TMP-SMX = trimethoprim/sulfamethoxazole; UTI = urinary tract infection; uUTI = uncomplicated urinary tract infection; XDR = extensively drug-resistant.

## Table 4: Characteristics of Included Guidelines

| Intended Users, Target Population | Intervention and Practice Considered | Major Outcomes Considered | Evidence Collection, Selection, and Synthesis | Evidence Quality Assessment | Recommendations Development and Evaluation | Guideline Validation |
|---|---|---|---|---|---|---|
| Kranz et al., 2018[36] Germany | | | | | | |
| **Intended Users** Practitioners<br><br>**Target population** adult patients with un-complicated UTI<br><br>German AWMF S3 guideline 2017 update (previous version published in 2010) | UTI diagnosis and management<br><br>Antibiotic and non-antibiotic treatment considered | Not reported | "Systematic literature searches were conducted in MEDLINE, EMBASE, and the Cochrane Library to identify literature published in 2010–2015" (p. 271)<br><br>Evidence- and consensus-based synthesis<br><br>17 representatives of 12 medical societies and a member of a patient organization | **Oxford criteria** level of evidence (I-V) ratings<br><br>**Recommendations graded**<br>A: strong recommendation: should/should not<br>B: weak recommendation: ought to/ought not to<br>C: recommendation inconclusive: may be considered. | A interdisciplinary committee developed the guideline[44] | Reviewed by international experts |
| NICE 2018,[37] UK<br>Pyelonephritis (acute): antimicrobial prescribing | | | | | | |
| **Intended Users** Health professionals<br><br>**Target population** People with pyelonephritis, their families and carers | Acute pyelo-nephritis management<br><br>Antibiotic and non-antibiotic treatment | Clinical outcomes, such as mortality and infection, indicators of antibiotic treatment, antimicrobial resistance, and patient-reported outcomes | Databases searched: Medline; Medline in Process; Embase; Cochrane database of systematic reviews (CDSR); Database of abstracts of effectiveness (DARE) (legacy); Cochrane | Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox | A multidisciplinary committee developed the guideline | Not reported |

## Table 4: Characteristics of Included Guidelines

| Intended Users, Target Population | Intervention and Practice Considered | Major Outcomes Considered | Evidence Collection, Selection, and Synthesis | Evidence Quality Assessment | Recommendations Development and Evaluation | Guideline Validation |
|---|---|---|---|---|---|---|
| | | | Central Register of Controlled Trials (CENTRAL); Health Technology Assessment (HTA) database; Clinicaltrials.gov from 2006 to present<br><br>Regulatory agency websites searched | | | |
| NICE 2018,[4] UK<br>Urinary tract infection (catheter-associated): antimicrobial prescribing | | | | | | |
| **Intended Users** Health professionals<br><br>**Target population** People with catheter-associated urinary tract infection, their families and carers | Antibiotic use and measures to reduce antibiotic resistance | Clinical outcomes, such as mortality and infection, indicators of antibiotic treatment, antimicrobial resistance, patient-reported outcomes, and health and social care utilization | Databases searched: Medline; Medline in Process; Embase; Cochrane database of systematic reviews (CDSR); Database of abstracts of effectiveness (DARE) (legacy); Cochrane Central Register of Controlled Trials (CENTRAL); Health Technology Assessment (HTA) database; | Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox | A multidisciplinary committee developed the guideline | Not reported |

## Table 4: Characteristics of Included Guidelines

| Intended Users, Target Population | Intervention and Practice Considered | Major Outcomes Considered | Evidence Collection, Selection, and Synthesis | Evidence Quality Assessment | Recommendations Development and Evaluation | Guideline Validation |
|---|---|---|---|---|---|---|
| | | | Clinicaltrials.gov from 2006 to present<br><br>Regulatory agency websites searched | | | |
| NICE 2018,[38] UK<br>Urinary tract infection (lower): antimicrobial prescribing | | | | | | |
| **Intended Users** Health professionals<br><br>**Target population** People with lower urinary tract infection, their families and carers | Antibiotic use and measures to reduce antibiotic resistance | Clinical outcomes, such as mortality and infection, indicators of antibiotic treatment, antimicrobial resistance, patient-reported outcomes, and health and social care utilization | Databases searched: Medline; Medline in Process; Embase; PubMed; Cochrane database of systematic reviews (CDSR); Database of abstracts of effectiveness (DARE) (legacy); Cochrane Central Register of Controlled Trials (CENTRAL); Health Technology Assessment (HTA) database; Clinicaltrials.gov from 2000 to present<br><br>Regulatory agency websites searched | Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox | A multidisciplinary committee developed the guideline | Not reported |

## Table 4: Characteristics of Included Guidelines

| Intended Users, Target Population | Intervention and Practice Considered | Major Outcomes Considered | Evidence Collection, Selection, and Synthesis | Evidence Quality Assessment | Recommendations Development and Evaluation | Guideline Validation |
|---|---|---|---|---|---|---|
| NICE 2018,[39] UK<br>Urinary tract infection (recurrent): antimicrobial prescribing | | | | | | |
| **Intended Users** Health professionals<br><br>**Target population** People with recurrent urinary tract infection, their families and carers | Antimicrobial prescribing strategy for preventing recurrent urinary tract infections | Clinical outcomes, such as mortality and infection, indicators of antibiotic treatment, antimicrobial resistance, patient-reported outcomes, and health and social care utilization | Databases searched: Medline; Medline in Process; Embase; Cochrane database of systematic reviews (CDSR); Database of abstracts of effectiveness (DARE) (legacy); Cochrane Central Register of Controlled Trials (CENTRAL); Health Technology Assessment (HTA) database; Clinicaltrials.gov from 2006 to present<br><br>Regulatory agency website searched | Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox | A multidisciplinary committee developed the guideline | Not reported |
| Society of Obstetricians and Gynaecologists of Canada 2017,[40] Canada | | | | | | |
| **Intended Users** Practitioners<br><br>**Target population** Women with recurrent urinary tract | "Investigation, treatment, and prevention of recurrent urinary tract infections in women" (p. e422) | Not reported | Systematic literature searches for systematic reviews, randomized control trials/controlled clinical trials, | Guidelines developed by the Canadian Task Force on Preventive Health Care | Recommendations made according to the guidelines by the Canadian Task Force on Preventive Health Care | Reviewed by the Family Physicians Advisory Committee<br><br>Approved by the Executive and Council |

## Table 4: Characteristics of Included Guidelines

| Intended Users, Target Population | Intervention and Practice Considered | Major Outcomes Considered | Evidence Collection, Selection, and Synthesis | Evidence Quality Assessment | Recommendations Development and Evaluation | Guideline Validation |
|---|---|---|---|---|---|---|
| infections | | | and observational studies in PubMed and The Cochrane Library for articles in English<br><br>No date restrictions | | | of the Society of Obstetricians and Gynecologists of Canada |
| Kranz et al. 2017,[41] Germany | | | | | | |
| **Intended Users**<br>Practitioners<br><br>**Target population**<br>Adult patients with uncomplicated UTI<br><br>Developed under the aegis of the German Urological Society (Deutsche Gesellschaft für Urologie)<br><br>Complied with the AWMF regulations | Diagnosis, treatment, and prevention of uncomplicated urinary tract infections<br><br>Antibiotic and non-antibiotic treatment considered | Clinical cure, symptoms, microbiological cure, antibiotic sensitivity | Systematic literature search for randomized, controlled trials and systemic reviews (period: 2008–2015) in the Cochrane Library, MEDLINE, and Embase databases | Appraisal of Guidelines for Research and Evaluation (AGREE) criteria<br><br>Level of evidence according to the 2009 criteria of the Oxford Centre for Evidence-based Medicine | Recommendation grades: by the members of the guideline group<br><br>Evidence-based statements and recommendations: formulated over the course of 17 consensus/telephone conferences.<br><br>Formal consensus finding in the form of a nominal group process under the leadership of an external moderator from the AWMF | Not reported |
| European Association of Urology 2015,[3] Europe<br>Updated in 2019[35] | | | | | | |
| **Intended Users**<br>Practitioners<br><br>Target population, | Diagnosis and treatment of urologic infections<br><br>Antibiotic and | Search terms for outcomes not reported<br><br>Outcomes reported | Annual assessment of new publications since the publication of | References graded according to their level of evidence | Guidelines graded with a classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of | Some texts reviewed by external reviewers |

## Table 4: Characteristics of Included Guidelines

| Intended Users, Target Population | Intervention and Practice Considered | Major Outcomes Considered | Evidence Collection, Selection, and Synthesis | Evidence Quality Assessment | Recommendations Development and Evaluation | Guideline Validation |
|---|---|---|---|---|---|---|
| Patients with UTI | non-antibiotic treatment considered | including mortality, infection, and complications | the first version in 2001<br><br>Search terms and databases not reported | | Evidence | |

AGREE = Appraisal of Guidelines for Research and Evaluation; AWMF = Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften; CDSR = Cochrane database of systematic reviews; CENTRAL = Cochrane Central Register of Controlled Trials; DARE = Database of abstracts of effectiveness; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HTA = Health Technology Assessment; UK = United Kingdom; UTI = urinary tract infection.

# Appendix 3: Critical Appraisal of Included Publications

## Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR 2 checklist[15]

| Strengths | Limitations |
|---|---|
| Cattrall et al., 2018[19] | |
| - Research questions, inclusion criteria, and the PICO components clearly described<br>- Comprehensive literature searches<br>- Study selection in duplicate<br>- Included studies described in detail<br>- Risk of bias assessment with the Cochrane Risk of Bias tool<br>- Risk of bias of primary studies considered while interpreting the results<br>- Heterogeneity between studies discussed | - Review protocol not published *a priori*<br>- The rationales to select the types of study design not explained<br>- Data extraction not in duplicate<br>- List of excluded studies not provided<br>- Sources of funding of the primary studies not reported<br>- Funding sources not provided |
| Grigoryan et al., 2014[14] | |
| - Research questions, inclusion criteria, and the PICO components clearly described<br>- Comprehensive literature searches in PubMed and the Cochrane Database<br>- Included studies described in detail<br>- Risk of bias assessment with the American Heart Association rating grades<br>- Risk of bias of primary studies considered while interpreting the results<br>- Funding sources provided | - Review protocol not published *a priori*<br>- The rationales to select the types of study design not explained<br>- Data extraction not in duplicate<br>- List of excluded studies not provided<br>- Sources of funding of the primary studies not reported<br>- Study selection not in duplicate<br>- Heterogeneity between studies not discussed |
| Mostafa et al., 2014[13] | |
| - Research questions, inclusion criteria, and the PICO components clearly described<br>- Comprehensive literature searches in multiple databases<br>- Study selection in duplicate<br>**- Included studies described in detail**<br>**- The rationales to select the types of study design explained**<br>- Funding sources provided | - Review protocol not published *a priori*<br>- Data extraction not in duplicate<br>- List of excluded studies not provided<br>- Sources of funding of the primary studies not reported<br>- Risk of bias assessment not described<br>- Risk of bias of primary studies not considered while interpreting the results<br>- Heterogeneity between studies not discussed |

PICO = population, intervention, comparator, and outcome.

## Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black checklist[16]

| Strengths | Limitations |
|---|---|
| **RCTs** | |
| Lojanapiwat et al., 2019[9] | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described<br>- Random variability of the outcomes provided<br>- All important adverse events reported<br>- The characteristics of the patients lost to follow-up described<br>- Actual probability values reported<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Statistical tests for the main outcomes appropriate<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population<br>- Different groups recruited from the same period of time<br>- Patients randomized to different groups<br>- Patients lost to follow-up considered<br>- Sample size estimated before study | - Patients not blinded<br>- Outcome assessors not blinded<br>- Allocation concealment not described<br>- Confounding not adjusted in the analysis |
| Connolly et al., 2018[20] | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described<br>- Random variability of the outcomes provided<br>- All important adverse events reported<br>- The characteristics of the patients lost to follow-up described<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Statistical tests for the main outcomes appropriate<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population<br>- Different groups recruited from the same period of time<br>- Patients randomized to different groups<br>- Patients blinded<br>- Outcome assessors blinded<br>- Allocation concealment described<br>- Patients lost to follow-up considered | - Confounding not adjusted in the analysis<br>- Actual probability values not reported |

## Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black checklist[16]

| Strengths | Limitations |
|---|---|
| - Sample size estimated before study | |
| Vente et al., 2018[21] | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described<br>**- All important adverse events reported**<br>**- Treatment received probably representative of the treatment the majority of patients received**<br>**- Data dredging not likely**<br>**- Similar lengths of follow-up**<br>**- Statistical tests for the main outcomes appropriate**<br>**- Compliance with the interventions reliable**<br>**- Main outcome measures accurate**<br>**- Different groups recruited from the same population**<br>**- Different groups recruited from the same period of time**<br>**- Patients** randomized to different groups<br>- **Patients** blinded<br>- Outcome assessors blinded<br>- Allocation concealment described | - Confounding not adjusted in the analysis<br>- Patients lost to follow-up not considered<br>- Sample size not estimated before study<br>- Random variability of the outcomes unavailable<br>- The characteristics of the patients lost to follow-up unavailable or not described<br>- Actual probability values not reported |
| Dinh et al., 2017[22] | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described<br>- Random variability of the outcomes provided<br>- All important adverse events reported<br>- Actual probability values reported<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Statistical tests for the main outcomes appropriate<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population<br>- Different groups recruited from the same period of time<br>- Patients randomized to different groups<br>- Patients lost to follow-up considered | - Patients not blinded<br>- Outcome assessors not blinded<br>- Allocation concealment not described<br>- Confounding not adjusted in the analysis<br>- The characteristics of the patients lost to follow-up not described<br>- Sample size not estimated before study |
| Malaisri et al., 2017[10] | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described | - Patients not blinded<br>- Outcome assessors not blinded<br>- Allocation concealment not described<br>- Confounding not adjusted in the analysis |

## Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black checklist[16]

| Strengths | Limitations |
|---|---|
| - Distributions of principal confounders described<br>- Main findings described<br>- Random variability of the outcomes provided<br>- All important adverse events reported<br>- Actual probability values reported<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Statistical tests for the main outcomes appropriate<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population<br>- Different groups recruited from the same period of time<br>- Patients randomized to different groups<br>- Patients lost to follow-up considered<br>- Sample size estimated before study | - The characteristics of the patients lost to follow-up not described |
| Ren et al., 2017[23] | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described<br>- Random variability of the outcomes provided<br>- All important adverse events reported<br>- Actual probability values reported<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Statistical tests for the main outcomes appropriate<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population<br>- Different groups recruited from the same period of time<br>- Patients randomized to different groups<br>- Patients lost to follow-up considered<br>- Sample size estimated before study | - Patients not blinded<br>- Outcome assessors not blinded<br>- Allocation concealment not described<br>- Confounding not adjusted in the analysis<br>- The characteristics of the patients lost to follow-up not described |
| Mospan et al., 2016[24] | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described<br>- Random variability of the outcomes provided<br>- Actual probability values reported<br>- Treatment received probably representative of the treatment the | - Allocation concealment not described<br>- Important adverse events not reported<br>- The characteristics of the patients lost to follow-up not described<br>- Sample size not estimated before study |

## Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black checklist[16]

| Strengths | Limitations |
|---|---|
| majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Statistical tests for the main outcomes appropriate<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population<br>- Different groups recruited from the same period of time<br>- Patients randomized to different groups<br>- Patients lost to follow-up considered<br>- Patients blinded<br>- Outcome assessors blinded<br>- Confounding adjusted in the analysis | |
| Pasiechnikov et al., 2015[25] | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described<br>- All important adverse events reported<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Statistical tests for the main outcomes appropriate<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population<br>- Different groups recruited from the same period of time<br>- Patients randomized to different groups<br>- Patients lost to follow-up considered | - Patients not blinded<br>- Outcome assessors not blinded<br>- Allocation concealment not described<br>- Patient characteristics not described<br>- Random variability of the outcomes not provided<br>- The characteristics of the patients lost to follow-up not described<br>- Actual probability values not reported<br>- Sample size not estimated before study |
| Vachhani et al., 2015[27] | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described<br>- Random variability of the outcomes provided<br>- All important adverse events reported<br>- Actual probability values reported<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Statistical tests for the main outcomes appropriate<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population | - Patients not blinded<br>- Outcome assessors not blinded<br>- Allocation concealment not described<br>- Confounding not adjusted in the analysis<br>- The characteristics of the patients lost to follow-up not described<br>- Sample size not estimated before study |

## Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black checklist[16]

| Strengths | Limitations |
|---|---|
| - Different groups recruited from the same period of time<br>- Patients randomized to different groups<br>- Patients lost to follow-up considered | |
| Wagenlehner et al., 2015[26] | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described<br>- Random variability of the outcomes provided<br>- All important adverse events reported<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Statistical tests for the main outcomes appropriate<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population<br>- Different groups recruited from the same period of time<br>- Patients randomized to different groups<br>- Patients lost to follow-up considered<br>- Sample size estimated before study<br>- Patients blinded<br>- Outcome assessors blinded | - Allocation concealment not described<br>- Confounding not adjusted in the analysis<br>- The characteristics of the patients lost to follow-up not described<br>- Actual probability values not reported |
| **Non-randomized studies** | |
| Ahmed et al., 2019[28] | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described<br>- Random variability of the outcomes provided<br>- All important adverse events reported<br>- Actual probability values reported<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Statistical tests for the main outcomes appropriate<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population<br>- Different groups recruited from the same period of time | - Patients not blinded<br>- Outcome assessors not blinded<br>- Allocation concealment not described<br>- Confounding adjusted in the analysis with propensity score matching<br>- The characteristics of the patients lost to follow-up not described<br>- Patients not randomized to different groups<br>- Patients lost to follow-up not considered<br>- Sample size not estimated before study |

## Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black checklist[16]

| Strengths | Limitations |
|---|---|
| **Bischoff et al., 2018[29]** | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Main findings described<br>- Random variability of the outcomes provided<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Statistical tests for the main outcomes appropriate<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population<br>- Different groups recruited from the same period of time<br>- Confounding adjusted in the analysis | - Patients not blinded<br>- Outcome assessors not blinded<br>- Allocation concealment not described<br>- Distributions of principal confounders not described<br>- Important adverse events not reported<br>- The characteristics of the patients lost to follow-up not described<br>- Actual probability values not reported<br>- Patients not randomized to different groups<br>- Patients lost to follow-up not considered<br>- Sample size not estimated before study |
| **Fox et al., 2017[30]** | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described<br>- Random variability of the outcomes provided<br>- Actual probability values reported<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Statistical tests for the main outcomes appropriate<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population<br>- Different groups recruited from the same period of time<br>- Confounding adjusted in the analysis | - Patients not blinded<br>- Outcome assessors not blinded<br>- Allocation concealment not described<br>- Important adverse events not reported<br>- The characteristics of the patients lost to follow-up not described<br>- Patients not randomized to different groups<br>- Patients lost to follow-up not considered<br>- Sample size not estimated before study |
| **Lin et al., 2016[31]** | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described<br>- Random variability of the outcomes provided<br>- Actual probability values reported<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely | - Patients not blinded<br>- Outcome assessors not blinded<br>- Allocation concealment not described<br>- Confounding not adjusted in the analysis<br>- Important adverse events not reported<br>- The characteristics of the patients lost to follow-up not described<br>- Patients not randomized to different groups<br>- Sample size not estimated before study |

## Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black checklist[16]

| Strengths | Limitations |
|---|---|
| - Similar lengths of follow-up<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population<br>- Different groups recruited from the same period of time<br>- Patients lost to follow-up considered | |
| Saum et al., 2016[32] | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described<br>- Random variability of the outcomes provided<br>- Actual probability values reported<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population<br>- Different groups recruited from the same period of time<br>- Patients lost to follow-up considered | - Patients not blinded<br>- Outcome assessors not blinded<br>- Allocation concealment not described<br>- Confounding not adjusted in the analysis<br>- Important adverse events not reported<br>- The characteristics of the patients lost to follow-up described<br>- Patients not randomized to different groups<br>- Sample size not estimated before study |
| Stewardson et al., 2015[33] | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described<br>- Random variability of the outcomes provided<br>- Actual probability values reported<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Statistical tests for the main outcomes appropriate<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same period of time | - Patients not blinded<br>- Outcome assessors not blinded<br>- Allocation concealment not described<br>- Confounding not adjusted in the analysis<br>- Important adverse events not reported<br>- The characteristics of the patients lost to follow-up not described<br>- Patients enrolled probably not representative of the population from which they were recruited<br>- Different groups probably not recruited from the same population<br>- Patients not randomized to different groups<br>- Patients lost to follow-up not considered<br>- Sample size not estimated before study |
| Lee et al., 2014[34] | |
| - Study hypothesis and objectives described<br>- Main outcomes described in the Methods<br>- Patient characteristics described<br>- Interventions of interest described<br>- Distributions of principal confounders described<br>- Main findings described | - Patients not blinded<br>- Outcome assessors not blinded<br>- Allocation concealment not described<br>- Important adverse events not reported<br>- The characteristics of the patients lost to follow-up not described |

## Table 6: Strengths and Limitations of Clinical Studies using the Downs and Black checklist[16]

| Strengths | Limitations |
|---|---|
| - Random variability of the outcomes provided<br>- Treatment received probably representative of the treatment the majority of patients received<br>- Data dredging not likely<br>- Similar lengths of follow-up<br>- Statistical tests for the main outcomes appropriate<br>- Compliance with the interventions reliable<br>- Main outcome measures accurate<br>- Different groups recruited from the same population<br>- Different groups recruited from the same period of time<br>- Confounding adjusted in the analysis | - Actual probability values not reported<br>- Patients not randomized to different groups<br>- Patients lost to follow-up not considered<br>- Sample size not estimated before study |

## Table 7: Strengths and Limitations of Guidelines using AGREE II[17]

| Item | Guideline | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Kranz et al., 2018[36] | NICE, 2018[37] Pyelonephritis (acute): antimicrobial prescribing | NICE 2018,[4] Urinary tract infection (catheter-associated): antimicrobial prescribing | NICE 2018,[38] Urinary tract infection (lower): antimicrobial prescribing | NICE 2018,[39] Urinary tract infection (recurrent): antimicrobial prescribing | Society of Obstetricians and Gynaecologists of Canada, 2017[40] | Kranz et al., 2017[41] | European Association of Urology, 2015[3] [a] |
| Domain 1: Scope and Purpose | | | | | | | | |
| 1. The overall objective(s) of the guideline is (are) specifically described. | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed |
| 2. The health question(s) covered by the guideline is (are) specifically described. | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed |
| 3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described. | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed |
| Domain 2: Stakeholder Involvement | | | | | | | | |
| 4. The guideline development group includes individuals from all relevant professional groups. | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Agreed | Strongly agreed |
| 5. The views and preferences of the target population (patients, public, etc.) have been sought. | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly disagreed | Agreed | Strongly disagreed |

## Table 7: Strengths and Limitations of Guidelines using AGREE II[17]

| Item | Guideline | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 6. The target users of the guideline are clearly defined. | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed |
| Domain 3: Rigour of Development | | | | | | | | |
| 7. Systematic methods were used to search for evidence. | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed |
| 8. The criteria for selecting the evidence are clearly described. | Strongly disagreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Agreed | Strongly disagreed |
| 9. The strengths and limitations of the body of evidence are clearly described. | Strongly disagreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed |
| 10. The methods for formulating the recommendations are clearly described. | Strongly disagreed | Agreed | Agreed | Agreed | Agreed | Strongly agreed | Disagreed | Strongly disagreed |
| 11. The health benefits, side effects, and risks have been considered in formulating the recommendations. | Partly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Partly agreed | Partly agreed | Partly agreed |
| 12. There is an explicit link between the recommendations and the supporting evidence. | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed |
| 13. The guideline has been externally reviewed by experts prior to its publication. | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Partly agreed |
| 14. A procedure for updating the guideline is provided. | Strongly disagreed | Strongly disagreed | Strongly disagreed | Strongly disagreed | Strongly disagreed | Strongly disagreed | Strongly agreed | Strongly disagreed |

## Table 7: Strengths and Limitations of Guidelines using AGREE II[17]

| Item | Guideline | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Domain 4: Clarity of Presentation | | | | | | | | |
| 15. The recommendations are specific and unambiguous. | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed |
| 16. The different options for management of the condition or health issue are clearly presented. | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed |
| 17. Key recommendations are easily identifiable. | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed |
| Domain 5: Applicability | | | | | | | | |
| 18. The guideline describes facilitators and barriers to its application. | Strongly disagreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly disagreed | Strongly disagreed | Strongly disagreed |
| 19. The guideline provides advice and/or tools on how the recommendations can be put into practice. | Strongly disagreed | Agreed | Agreed | Agreed | Agreed | Strongly disagreed | Strongly disagreed | Strongly disagreed |
| 20. The potential resource implications of applying the recommendations have been considered. | Strongly disagreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly disagreed | Strongly disagreed | Strongly disagreed |
| 21. The guideline presents monitoring and/or auditing criteria. | Strongly disagreed | Strongly disagreed | Strongly disagreed | Strongly disagreed | Strongly disagreed | Strongly disagreed | Strongly disagreed | Strongly disagreed |
| Domain 6: Editorial Independence | | | | | | | | |
| 22. The views of the funding body have not influenced the content of the guideline. | Partly agreed | Strongly disagreed | Strongly disagreed | Strongly disagreed | Strongly disagreed | Strongly disagreed | Agreed | Strongly agreed |

## Table 7: Strengths and Limitations of Guidelines using AGREE II[17]

| Item | Guideline | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 23. Competing interests of guideline development group members have been recorded and addressed. | Strongly disagreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly agreed | Strongly disagreed | Strongly agreed | Strongly agreed |

[a] The guideline by the European Association of Urology, 2015,[3] was updated in 2019,[35] however only the 2015 version was critically appraised for this report.

# Appendix 4: Main Study Findings and Authors' Conclusions

## Table 8: Summary of Findings Included Systematic Reviews and Meta-Analyses

| Main Study Findings | Authors' Conclusion |
|---|---|
| **Cattrall et al., 2018[19]** | |
| **Clinical success of the outpatient treatment of pyelonephritis**<br>- comparable among cefaclor, ciprofloxacin and norfloxacin at 4 to 6 weeks, 83 to 95%<br><br>Adverse effects<br>- Relatively high rates in a trial of ciprofloxacin (24%) and trimethoprim-sulfamethoxazole (33%)<br><br>Heterogeneity<br>- "*Significant heterogeneity between all aspects of the trial designs*" (p. 2285)<br>- "*all studies having a potential for bias*" (p. 2285) | - "*a need for high-quality clinical trials into the oral antibiotic treatment of pyelonephritis, with more consistent designs and reporting of outcomes*" (p. 2285)<br>- "*data to support further research into oral norfloxacin and cefaclor for the outpatient treatment of pyelonephritis in adults*" (p. 2285) |
| **Grigoryan et al., 2014[14]** | |
| **Uncomplicated cystitis**<br>- Trimethoprim-sulfamethoxazole (160/800mg twice daily for 3 days), nitrofurantoin monohydrate/ macrocrystals (100mg twice daily for 5-7 days), and fosfomycin trometamol (3 g in a single dose) all appropriate first-line therapies<br><br>Fluoroquinolones<br>- "***Nine trials included ciprofloxacin, and 3 trials included norfloxacin. Overall, both clinical and microbiological efficacy of fluoroquinolones are comparable with that of other first-line agents (Table 1 and eTable 4 in the Supplement)***" (p. 1681)<br>- "*effective for clinical outcomes but should be reserved for more invasive infections*" (p. 1677)<br><br>Immediate antimicrobial therapy<br>- "*recommended rather than delayed treatment or symptom management with ibuprofen alone*" (p. 1677)<br><br>Acute urinary tract infection in men<br>- "*Limited observational studies support 7 to 14 days of therapy*" (p. 1677)<br><br>Women with diabetes without voiding abnormalities presenting with acute cystitis<br>- treated similarly to women without diabetes based on 1 observational study and review authors' expert opinion | - "*Immediate antimicrobial therapy with trimethoprim-sulfamethoxazole, nitrofurantoin, or fosfomycin is indicated for acute cystitis in adult women*" (p. 1677)<br>- "*Increasing resistance rates among uropathogens have complicated treatment of acute cystitis*" (p. 1677)<br>- "*Individualized assessment of risk factors for resistance and regimen tolerability is needed to choose the optimum empirical regimen*" (p. 1677) |
| **Mostafa et al., 2014[13]** | |
| **Antibiotic treatment and psychosis**<br>- "*a majority (60%) of reported cases were "highly suggestive" of a potential causal relationship between antibiotic treatment and psychosis, including 3 cases with a recurrence of psychosis after rechallenge with the same antibiotic*" (p. 483) | - "*acute psychosis is a potential adverse effect of antibiotic treatment of UTI, although the mechanism(s) underlying this association remains unclear*" (p. 483) |

## Table 8: Summary of Findings Included Systematic Reviews and Meta-Analyses

| Main Study Findings | Authors' Conclusion |
|---|---|
| - "*3 different classes of antibiotics were implicated in this association, including fluoroquinolones, penicillins, and trimethoprim-sulfamethoxazole*" (p. 483)<br>- "*for most of the reported cases, both the onset and resolution of psychosis occurred within 1 week of initiation and discontinuation of the antibiotic, respectively*" (p. 483)<br>- "*approximately half of the cases did not require treatment with antipsychotics*" (p. 483)<br>- "*affected men were significantly more likely to have a psychiatric history*" (p. 483) | |

UTI = urinary tract infection.

## Table 9: Summary of Findings of Included Primary Clinical Studies

| Main Study Findings | Authors' Conclusion |
|---|---|
| **Randomized Controlled Trials** | |
| Lojanapiwat et al., 2019[9] | |
| **Sitafloxacin versus ceftriaxone**<br>- "*The causative pathogen in most patients with APN or cUTI was Escherichia coli*" (p. 173)<br><br>Clinical success rates at the end of treatment<br>- STFX regimen noninferior to the CTRX/CFDN regimen (86.6% vs 83.8% for ITT analysis and 97.2% vs 99.0% for PP analysis, respectively)<br><br>Adverse events with mild-to-moderate severity<br>- Similar between groups | - "*Oral STFX is noninferior to intravenous CTRX followed by oral CFDN in adult patients with APN and cUTI*" (p. 173)<br>- "*Lower rates of resistance compared to CTRX and/or CFDN and oral administration suggest STFX as a more attractive treatment option in this patient population*" (p. 173) |
| Connolly et al., 2018[20] | |
| **Levofloxacin versus plazomicin 10 mg/kg versus plazomicin 15 mg/kg**<br><br>**Microbiological eradication rates**<br>- 58.6% (17 patients with microbiological eradication at test of cure /29 patients treated [95% CI, 38.9 to 76.5%]) versus 50.0% (6 /12 [95% confidence interval (CI), 21.1 to 78.9%]), 60.8% (31/51 [95% CI, 46.1 to 74.2%]) in the MITT population<br>- 81.0% (17/21 [95% CI, 58.1 to 94.6%]) versus 85.7% (6/7 [95% CI, 42.1 to 99.6%]), 88.6% (31/35 [95% CI, 73.3 to 96.8%]) in the ME population<br><br>**Clinical cure rate at the TOC**<br>- 65.5% (95% CI, 45.7 to 82.1%) versus 66.7% (95% CI, 34.9 to 90.1%), 70.6% (95% CI, 56.2 to 82.5%) in the MITT population<br><br>Adverse events<br>- 47.7% versus 31.8%, 35.1%<br><br>Serum creatinine values<br>- Generally stable over the course of the study.<br><br>Plazomicin toxicity<br>- "*No plazomicin-treated patients with evaluable audiometry data had postbaseline sensorineural, conductive, or mixed hearing loss*" (p. 1) | - "*plazomicin demonstrated microbiological and clinical success and an overall safety profile supportive of further clinical development*" (p. 1) |
| Vente et al., 2018[21] | |
| **Finafloxacin versus ciprofloxacin**<br><br>**Resistance**<br>- ciprofloxacin resistant : total of 21% of the isolates<br>- primed pathogens carrying a mutation(s) potentially fostering fluoroquinolone resistance development: 13.7%<br>- extended-spectrum -lactamases (ESBLs): 7.1%<br>**Finafloxacin** | - "*Finafloxacin demonstrated early and rapid activity against uropathogens, including fluoroquinoloneresistant and/or multiresistant pathogens or ESBL producers*" (p. 1)<br>- "*ciprofloxacin was less active against this subset of resistant pathogens*" (p. 1) |

## Table 9: Summary of Findings of Included Primary Clinical Studies

| Main Study Findings | Authors' Conclusion |
|---|---|
| - very good early clinical activity<br><br>**Microbiological eradication rates**<br>- "88.6% (n = 132), compared to 78.7% (n = 61) for ciprofloxacin" (p. 1)<br>- "*69.6% (n = 23), compared to 35.7% (n = 14) for ciprofloxacin, in patients with ciprofloxacin-resistant uropathogens*" (p. 1)<br>- "*94.1% (n = 17), compared to 80.0% (n = 10) for ciprofloxacin, in patients infected with uropathogens primed for fluoroquinolone resistance uropathogens*" (p. 1)<br>- "*91.7% (n = 11), compared to 0% for ciprofloxacin, in patients infected with ESBL producers*" (p. 1) | |
| Dinh et al., 2017[22] | |
| **Ofloxacin or levofloxacin 5 versus 10 days**<br><br>**Main bacterium**<br>- Escherichia coli (n = 86; 97.7%)<br>- 3 (3.4%) patients with a positive blood culture<br><br>**Post-hoc analysis**<br>**Clinical cure 10 days after the end of the treatment**<br>- 28/30 (93.3%) in the 5-day arm versus 36/38 (94.7%) in the 10-day arm (p = 1.00)<br>**Clinical cure at day 30**<br>- 23/23 (100%) in the 5-day arm versus 20/ 20 (100%) in the 10-day arm (p = 1.00)<br>**Microbiological cure rate**<br>- 20/23 (87.0%) in the 5-day arm versus 16/20 (80.0%) in the 10-day arm (p = 1.00) | - "*The efficacy of 5 days of fluoroquinolone treatment does not seem different from 10 days of treatment for AUP*" (p. 1444) |
| Malaisri et al., 2017[10] | |
| **Sitafloxacin versus ertapenem after initial treatment**<br>- "*a lower proportion of previous urinary catheter insertion in the sitafloxacin group (15.8% vs. 52.9%, p = 0.018)*" (p. 556)<br><br>**Signs and symptoms at presentation**<br>- not significantly different<br>- "*except a higher proportion of patients with chills in the sitafloxacin group (68.4% vs. 29.4%, p = 0.019)*" (p. 556)<br><br>**Clinical cure at day 10**<br>- "*all but one patient in the ertapenem group had clinical cure*" (p. 556)<br><br>**Microbiological eradication**<br>- comparable (84.2% vs. 75%, ***P*** = 0.677)<br><br>**Adverse effects**<br>- No significant adverse effects | - "*Treatment of non-bacteremic acute pyelonephritis caused by ESBL-EC with carbapenem followed by oral sitafloxacin is effective and well-tolerated*" (p. 556)<br>- "*Sitafloxacin may be considered as an alternative choice of switch therapy in this clinical setting*" (p. 556) |
| Ren et al., 2017[23] | |

## Table 9: Summary of Findings of Included Primary Clinical Studies

| Main Study Findings | Authors' Conclusion |
|---|---|
| **Intravenous levofloxacin (short course) versus intravenous and then oral levofloxacin (conventional)**<br><br>**Median dose**<br>- 3555.4 mg versus 4874.2 mg<br><br>**Clinical effectiveness**<br>- short-course therapy (89.87%, 142/158) non-inferior to conventional therapy (89.31%, 142/159) in the intention-to-treat analysis<br><br>**Microbiological effectiveness rates**<br>- Similar<br>- 89.55%, 60/67 versus 86.30%, 63/73; p > 0.05<br>Other parameters, including clinical and microbiological recurrence rates<br>- No significant differences<br><br>**Incidence of adverse effects and drug-related adverse effects**<br>- Similar<br>- 21.95%, 36/164; 18.90%, 31/164 versus23.03%, 38/165; 15.76%, 26/165 | - "*Patients with cUTIs and APN who were given short-course LVFX therapy and conventional LVFX therapy had similar outcomes in clinical and microbiological efficacy, tolerance, and safety*" (p. 500)<br>- "*The short-course therapy described here is a more convenient alternative to the conventional regimen with potential implication in anti-resistance and cost saving*" (p. 500) |
| Mospan et al., 2016[24] | |
| **5-day levofloxacin versus 10-day ciprofloxacin**<br><br>**Clinical success rates between males and females**<br>- Not statistically different between antibiotic groups in either the mITT or ME populations at the end of therapy or post-therapy | "*males with UTI may be treated with a shorter course of antimicrobial therapy for UTI than previously recommended*" (p. 654) |
| Pasiechnikov et al., 2015[25] | |
| **Ciprofloxacin versus ceftazidime**<br><br>**Cure rate**<br>- Higher for ceftazidime<br><br>**Clinical cure rate by group**<br>- percutaneous nephrostomy group: 83.6% versus 95.2%<br>- ureteral stenting group: 74.1% versus 86.4%<br><br>**Microbiological cure rates by group**<br>- percutaneous nephrostomy group: 80.0% versus 92.9% (***P***<0.05)<br>- ureteral stenting group: 69.4% versus 82.4% (***P***<0.05) | - "*percutaneous nephrostomy ensures a better clinical cure than ureteral stenting at early and late follow-ups regardless of the drug regimens which were chosen*" (p. 163)<br>- "*percutaneous nephrostomy combined with ceftazidime treatment can be considered as the most effective option in patients with acute obstructive pyelonephritis*" (p. 163) |
| Vachhani et al., 2015[27] | |
| **Levofloxacin versus norfloxacin versus co-trimoxazole**<br>- "*a total of 175 patients, Escherichia coli (74.29%) was the most common organism isolated followed by Klebsiella (11.43%), Streptococcus (6.29%), Staphylococcus saphrophyticus (5.14%), and Pseudomonas (2.86%)*" (p. 159) | "*short-course treatment with co-trimoxazole 960 mg twice a day, norfloxacin 400 mg twice a day and levofloxacin 250 mg once a day are almost equally effective for treatment of uncomplicated UTI*" (p. 159) |

## Table 9: Summary of Findings of Included Primary Clinical Studies

| Main Study Findings | Authors' Conclusion |
|---|---|
| **Bacteriological cure rates**<br>- 83.3%, 87.7% and 86.2% (***P***>0.05) | |
| Wagenlehner et al., 2015[26] | |
| **Levofloxacin versus ceftolozane/ tazobactam**<br><br>**Composite cure**<br>- Ceftolozane-tazobactam non-inferior to levofloxacin (306 [76·9%] of 398 vs 275 [68·4%] of 402, 95% CI 2·3–14·6)<br>- Moreover, ceftolozane-tazobactam superiority indicated<br><br>Adverse event profiles<br>- Similar<br>- Mainly non-serious | "*Treatment with ceftolozane-tazobactam led to better responses than high-dose levofloxacin in patients with complicated lower-urinary-tract infections or pyelonephritis*" (p. 1949) |
| **Non-randomized studies** | |
| Ahmed et al., 2019[28] | |
| **Ciprofloxacin, cephalexin, and co-amoxiclav compared with nitrofurantoin**<br><br>**Re-consultation and re-prescription**<br>- lower odds for cefalexin, ciprofloxacin, or co-amoxiclav (OR = 0.85, 95% CI = 0.75–0.98; OR = 0.48, 95% CI = 0.38–0.61, OR = 0.77, 95% CI = 0.64–0.93 respectively)<br><br>**Hospitalization for sepsis**<br>- greater odds for cefalexin or ciprofloxacin (OR = 1.89, 95% CI = 1.03–3.47; OR = 3.21, 95% CI = 1.59–6.50 respectively)<br><br>**Death**<br>- greater odds of death for cefalexin (OR = 1.44, 95% CI = 1.12–1.85) | "*Compared with nitrofurantoin, prescribing of alternative antibiotics for UTI in older people may be associated with lower rates of treatment failure but was not associated with reduced risk of UTI-related hospitalization or death*" (p. 1) |
| Bischoff et al., 2018[29] | |
| **Ciprofloxacin, piperacillin with tazobactam (Pip/taz), gentamicin, cefuroxime, cefpodoxime, and ceftazidime, compared to each other**<br>- 137 of 469 patients with UTI had a positive urine culture<br>- MDR pathogen found in 36.5% of 137 patients<br><br>**Overall susceptibility**<br>- less than 85% for standard antimicrobial agents<br><br>**Risk factors for MDR or any of these resistances**<br>- residence in nursing homes, male gender, hospitalization within the last 30 days, renal transplantation, antibiotic treatment within the last 30 days, indwelling urinary catheter and recurrent<br><br>**Logistic regression**<br>**Susceptibility in patients with no risk factors** | - Risk factors for resistances and MDR in UTI identified<br>- "*With no risk factor cephalosporins seem to be the best choice for empiric therapy*" (p. 1)<br>- "*in patients with risk factors the beta-lactam penicillin Piperacillin with Tazobactam is an equal or better choice compared to fluoroquinolones, cephalosporins or gentamicin*" (p. 1)<br>- "*importance of monitoring local resistance rates and its risk factors in order to improve empiric therapy in a local environment*" (p. 1) |

## Table 9: Summary of Findings of Included Primary Clinical Studies

| Main Study Findings | Authors' Conclusion |
|---|---|
| - Ciprofloxacin 90%, Pip/taz 88%, Gentamicin 95%, Cefuroxime 98%, Cefpodoxime 98% and Ceftazidime 100%. Susceptibility in patients with 1 risk factor<br>- Ciprofloxacin had 80%, Pip/taz 80%, Gentamicin 88%, Cefuroxime 78%, Cefpodoxime 78% and Ceftazidime 83% Susceptibility in patients with 2 or more risk factors<br>- Ciprofloxacin 52%, Cefuroxime to 54% and Cefpodoxime to 61%. Pip/taz, Gentamicin 75%, Ceftazidime remain 77% | |
| Fox et al., 2017[30] | |
| **TMP-SMX versus ciprofloxacin**<br>- "*Of 272 women meeting eligibility criteria, 81 (30%) and 191 (70%) received 7 days of TMP-SMX and 7 days of ciprofloxacin, respectively*" (p. 1)<br><br>**Likelihood of a recurrent UTI within 30 days**<br>- not significantly different (aOR: 2.30, 95% confidence interval: 0.72–7.42) in an adjusted model | - "*7 days of TMP-SMX therapy may result in similar clinical outcomes compared with 7 days of ciprofloxacin for the treatment of pyelonephritis*" (p. 1)<br>- "*Considering the frequency of pyelonephritis and risks of antibiotic resistance and associated toxicities, decreasing the duration of antibiotic therapy for pyelonephritis may impact a large number of women*" (p. 1) |
| Lin et al., 2016[31] | |
| **Ceftriaxone (CRO), levofloxacin (LVX), and ertapenem (ETP)**<br>- 358 eligible cases: 139 with CRO, 128 with ETP, and 91 with LVX<br><br>**Most common pathogen**<br>- *Escherichia coli*<br><br>**Susceptibilities**<br>- Higher and more superior than first-line antibiotics<br><br>**Time to defervescence since admission**<br>- ETP associated with a significantly shorter time (CRO: 39 hours, ETP: 30 hours, and LVX: 38 h; ***P*** = 0.031)<br><br>**Hospitalization stay**<br>- ETP associated with shorter hospitalization stay (CRO: 4 days, ETP: 3 days, and LVX: 4 days; ***P*** < 0.001)<br><br>**Average antibiotic costs**<br>- significantly lower for CRO than the other two groups [CRO: 62.4 United States dollars (USD), ETP: 185.33 USD, and LVX: 204.85 USD; ***P*** < 0.001] | - "*The resistance of cUTIs isolates to first-line antibiotic is high*" (p. 238)<br>- "*Using ETP, CRO, and LVX in the treatment of cUTIs for good clinical response should be suggested*" (p. 238)<br>- "*ETP had better susceptibility than CRO and LVX, reached defervescence sooner, and was associated with shorter hospital stays*" (p. 238)<br>- "*However, using CRO in cUTIs was less expensive than the other two agents*" (p. 238) |
| Saum et al., 2016[32] | |
| **Ceftriaxone, first-generation cephalosporins, penicillins, and ciprofloxacin compared with each other**<br><br>**Peak INR value**<br>- Ceftriaxone with a statistically significant higher value compared to all other antibiotics (ceftriaxone: 3.56, first-generation cephalosporins: 2.66, penicillins: 2.98, ciprofloxacin: 2.3; ***P*** = 0.004) | - "*Ceftriaxone interacts with warfarin to increase a patient's INR value more than other commonly administered antibiotics for UTI treatment*" (p. 121)<br>- "*Other antibiotics should be preferred for UTI treatment in patients on warfarin*" (p. 121) |

## Table 9: Summary of Findings of Included Primary Clinical Studies

| Main Study Findings | Authors' Conclusion |
|---|---|
| **Change in INR**<br>- Ceftriaxone with a statistically significant greater extent (+1.19, +0.66, +0.8, +0.275; ***P*** = 0.006)<br><br>**Percentage change in INR**<br>- Ceftriaxone with a statistically significant greater percentage change compared to ciprofloxacin (54.4% vs 12.7%; ***P*** = 0.037) | |
| Stewardson et al., 2015[33] | |
| **Ciprofloxacin versus nitrofurantoin versus Fosfomycin**<br><br>**Gut microbiota**<br>- "*Ciprofloxacin had a significant global impact on the gut microbiota whereas nitrofurantoin did not*" (p. 344.e1)<br><br>**Ciprofloxacin treatment**<br>- "*correlated with a reduced proportion of Bifidobacterium (Actinobacteria), Alistipes (Bacteroidetes) and four genera from the phylum Firmicutes (Faecalibacterium, Oscillospira, Ruminococcus and Dialister) and an increased relative abundance of Bacteroides (Bacteroidetes) and the Firmicutes genera Blautia, Eubacterium and Roseburia*" (p. 344.e1)<br>- "*Substantial recovery had occurred 4 weeks later*" (p. 344.e1)<br><br>**Nitrofurantoin**<br>- "*correlated with a reduced relative proportion of the genus Clostridium and an increased proportion of the genus Faecalibacterium*" (p. 344.e1) | "*This study supports use of nitrofurantoin over fluoroquinolones for treatment of uncomplicated UTIs to minimize perturbation of intestinal microbiota*" (p. 344.e1) |
| Lee et al., 2014[34] | |
| **Norfloxacin, ofloxacin, levofloxacin, ciprofloxacin, and trimethoprim–sulfamethoxazole compared to one another**<br>- 73,675 individuals with UTI<br>- 54,796 (74.4%) received trimethoprim–sulfamethoxazole (TMP-SMX), 4184 (5.7%) received ciprofloxacin, 3142 (4.3%) received levofloxacin, 5984 (8.1%) received ofloxacin, and 5569 (7.6%) received norfloxacin<br><br>**Composite treatment failure**<br>- Significantly lowered for norfloxacin in propensity score (PS) matching analyses (OR, 0.73; 95% CI, 0.54–0.99) , compared with TMP-SMX<br>- Significantly lowered for norfloxacin (PS-matched OR, 0.68; 95% CI, 0.47–0.98) and ofloxacin (PS-matched OR, 0.70; 95%CI, 0.49–0.99) compared with ciprofloxacin<br><br>Subgroup analysis<br>- Norfloxacin and ofloxacin more effective in female patients without complications (including indwelling catheters, bedridden status and spinal cord injury), compared with TMP-SMX or ciprofloxacin | - "*Among outpatients receiving oral fluoroquinolone therapy for UTIs, there was evidence of superiority of norfloxacin or ofloxacin over ciprofloxacin or TMP-SMX in terms of treatment failure*" (p. 1) |

aOR = adjusted odds ratio; APN = acute pyelonephritis; AUP = cute uncomplicated pyelonephritis; CFDN = cefdinir; CI = confidence interval; CRO = Ceftriaxone; CTRX = ceftriaxone, cUTI = complicated urinary tract infection; EC = *E. coli*; ESBL = extended-spectrum –lactamase; ETP = ertapenem; INR = international normalized ratio; LVFX or LVX = levofloxacin; MDR = multi-drug resistant; ME = microbiologically evaluable; MITT or mITT = modified intent-to-treat; OR = odds ratio; PS = propensity score; STFX = sitafloxacin; TMP-SMX = trimethoprim/sulfamethoxazole; UTI = urinary tract infection.

## Table 10: Summary of Recommendations in Included Guidelines

| Recommendations | Strength of Evidence and Recommendations |
|---|---|
| Kranz et al., 2018[36] | |
| **Acute Uncomplicated Cystitis: Standard Group (Otherwise Healthy Women in the Premenopause)**<br>- "*nonantibiotic, symptomatic treatment can be considered in cases of AUC with mild or moderate symptoms*" (p. 274) | Oxford criteria for the level of evidence (I-V) ratings and Recommendations grading (A: strong recommendation: should/should not B: weak recommendation: ought to/ought not to C: recommendation inconclusive: may be considered) |
| **Asymptomatic Bacteriuria**<br>- "*ASB should be actively sought, and if present, it should be treated*" (p. 274) | - IA-B<br>- Ia-A |
| **General Comment on Antibiotic Treatment of AUC (acute uncomplicated cystitis)** | - No evidence levels |
| - "*the fluoroquinolones and cephalosporins are associated with the greatest risk of microbiological collateral damage by selection of multiple drug resistant pathogens or an elevated risk of Clostridium difficile-associated colitis*" (p. 276) | - V |
| - "*Since fluoroquinolones and cephalosporins have an important role in the treatment of complicated infections, the clinical consequences of increased resistance by their use in uncomplicated infections were rated as more severe than for other antibiotics recommended for the treatment of AUC*" (p. 276) | - V-A |
| - "*fluoroquinolones and cephalosporins should not be used in the treatment of AUC unless there is no alternative*" (p.276) | - V |
| **Acute Uncomplicated Pyelonephritis: Standard Group**<br>- "*In choosing the best antibiotic to use, the eradication rates, sensitivity, collateral damage, and special characteristics regarding adverse drug reactions should be taken into account*" (p. 275) | - No evidence levels |
| - Oral treatment in mild to moderate infection: ciprofloxacin, levofloxacin, cefpodoxim-proxetil, and ceftibuten in Table 3 (in the guideline) | |
| **Prevention of Recurrent Urinary Tract Infection: Standard Group**<br>- "*Before initiation of long-term prophylactic drug treatment, a woman with rUTI should be counseled in detail on avoidance of risks (e.g., not drinking enough, overcooling, excessive intimate hygiene*" (p. 276) | - Ib-A<br>- Ib-C |
| - "*Immunoprophylaxis by means of 3 parenteral injections of inactivated specified enterobacteria at 1-week intervals can be used*" (p. 276) | - Ib-C |
| - "*mannose can be recommended*" (p. 276) | - Ib-C |
| - "*various phytotherapeutic agents (bearberry leaves with dandelion root and horseradish root with nasturtium herb proven in studies) may be considered*" (p. 276) | - IV-B |
| - "*If the patient's level of suffering is high, failure of behavioral modification and non-antibiotic prophylaxis ought to be followed by continual long-term antibiotic prophylaxis for 3–6 months*" (p. 276) | - Ib-B |
| - "*In the presence of an association with sexual intercourse, postcoital prophylaxis with a single dose ought to be used instead of longterm administration of antibiotics*" (p. 277) | - No evidence levels |
| - Norfloxacin and ofloxacin recommended for long-term | |

## Table 10: Summary of Recommendations in Included Guidelines

| Recommendations | Strength of Evidence and Recommendations |
|---|---|
| continuous prophylaxis and postcoital single-dose prophylaxis | |
| NICE, 2018[37]<br>Pyelonephritis (acute): antimicrobial prescribing | |
| "*1.1.5 Offer an antibiotic (see the recommendations on choice of antibiotic) to people with acute pyelonephritis. Take account of:*<br>● *the severity of symptoms*<br>● *the risk of developing complications, which is higher in people with known or suspected structural or functional abnormality of the genitourinary tract or immunosuppression*<br>● *previous urine culture and susceptibility results*<br>● *previous antibiotic use, which may have led to resistant bacteria*" (p. 5)<br>"*1.3.1 When prescribing an antibiotic for acute pyelonephritis, take account of local antimicrobial resistance data and follow:*<br>● *table 1 for non-pregnant women and men aged 16 years and over*<br>● *table 2 for pregnant women aged 12 years and over*<br>● *table 3 for children and young people under 16 years. 1.3.2 Give oral antibiotics first line if the person can take oral medicines, and the severity of their condition does not require intravenous antibiotics.*<br>*1.3.3 Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible*" (p. 7)<br><br>Table 1, 2, 3 (in the guideline): fluoroquinolones not included as first or second-line therapy, except for Ciprofloxacin (consider safety issues 500 mg twice a day for 7 days listed as first-choice oral antibiotic and Ciprofloxacin (consider safety issues) 400 mg twice or three times a day as first-choice intravenous antibiotic for non-pregnant women and men aged 16 years and over in Table 1 (in the guideline).<br>Alternative second-line therapies not specified and requiring specialist consultation | No evidence levels reported |
| NICE 2018,[4] UK<br>Urinary tract infection (catheter-associated): antimicrobial prescribing | |
| "*1.1.3 Consider removing or, if this cannot be done, changing the catheter as soon as possible in people with a catheter-associated UTI if it has been in place for more than 7 days. Do not allow catheter removal or change to delay antibiotic treatment*" (p. 5)<br>"*1.1.6 Offer an antibiotic (see the recommendations on choice of antibiotic) to people with catheter-associated UTI. Take account of:*<br>● *the severity of symptoms*<br>● *the risk of developing complications, which is higher in people with known or suspected structural or functional abnormality of the genitourinary tract, or immunosuppression*<br>● *previous urine culture and susceptibility results*<br>● *previous antibiotic use, which may have led to resistant bacteria*" (p. 5) | No evidence levels reported |

## Table 10: Summary of Recommendations in Included Guidelines

| Recommendations | Strength of Evidence and Recommendations |
|---|---|
| "*1.3.1 When prescribing an antibiotic for catheter-associated UTI, take account of local antimicrobial resistance data and: follow*<br>● *table 1 for non-pregnant women and men aged 16 years and over follow*<br>● *table 2 for pregnant women aged 12 years and overfollow*<br>● *table 3 for children and young people under 16 years*" (p. 7)<br>"*1.3.2 Give oral antibiotics first line if the person can take oral medicines, and the severity of their condition does not require intravenous antibiotics*" (p. 8)<br>"*1.3.3 Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible*" (p. 8)<br><br>Table 1, 2, 3 (in the guideline): fluoroquinolones not included as first or second-line therapy, except for Ciprofloxacin (consider safety issues) 400 mg twice or three times a day listed as first-choice intravenous antibiotic in Table 1 (in the guideline)<br>Alternative second-line therapies not specified and requiring specialist consultation | |
| NICE 2018,[38]<br>Urinary tract infection (lower): antimicrobial prescribing | |
| "*1.1.5 Offer an immediate antibiotic prescription (see the recommendations on choice of antibiotic) to pregnant women and men with lower UTI. Take account of: previous urine culture and susceptibility results previous antibiotic use, which may have led to resistant bacteria*" (p. 6)<br>"*1.4.1 When prescribing antibiotic treatment for lower UTI, take account of local antimicrobial resistance data and follow:*<br>● *table 1 for non-pregnant women aged 16 years and over*<br>● *table 2 for pregnant women aged 12 years and over*<br>● *table 3 for men aged 16 years and over*<br>● *table 4 for children and young people under 16 years*" (p. 9)<br><br>Table 1, 2, 3 (in the guideline): fluoroquinolones not included as first or second-line therapy; alternative second-line therapies may need specialist consultation<br>Alternative second-line therapies not specified and requiring specialist consultation | No evidence levels reported |
| NICE 2018,[39]<br>Urinary tract infection (recurrent): antimicrobial prescribing | |
| **Antibiotic prophylaxis**<br>"*1.1.7 For women with recurrent UTI who are not pregnant, consider a trial of antibiotic prophylaxis only if behavioural and personal hygiene measures, and vaginal oestrogen (in postmenopausal women) are not effective or not appropriate*" (p. 6)<br>"*1.1.8 For women with recurrent UTI who are not pregnant, ensure that any current UTI has been adequately treated then consider single-dose antibiotic prophylaxis for use when exposed to an identifiable trigger (see the recommendations on* | No evidence levels reported |

## Table 10: Summary of Recommendations in Included Guidelines

| Recommendations | Strength of Evidence and Recommendations |
|---|---|
| *choice of antibiotic prophylaxis). Take account of:*<br>● *the severity and frequency of previous symptoms*<br>● *the risk of developing complications*<br>● *previous urine culture and susceptibility results*<br>● *previous antibiotic use, which may have led to resistant bacteria*<br>● *the woman's preferences for antibiotic use*" (p. 6)<br>"*1.3.1 When prescribing antibiotic prophylaxis for recurrent UTI, take account of local antimicrobial resistance data and: follow the recommendations in*<br>● *table 1 for people aged 16 years and over follow the recommendations in*<br>● *table 2 for children and young people under 16 years*" (p. 10)<br><br>Fluoroquinolones not listed in Table 1 or 2 (in the guideline) | |
| Society of Obstetricians and Gynaecologists of Canada, 2017[40] | |
| "*4. Prophylaxis for recurrent urinary tract infection should not be undertaken until a negative culture 1 to 2 weeks after treatment has confirmed eradication of the urinary tract infection*" (p. e422)<br>"*5. Continuous daily antibiotic prophylaxis using cotrimoxazole, nitrofurantoin, cephalexin, trimethoprim, trimethoprim-sulfamethoxazole, or a quinolone during a 6- to 12-month period should be offered to women with 2: 2 urinary tract infections in 6 months or 2: 3 urinary tract infections in 12 months*" (p. e423)<br>"*12. Pregnant women at risk of recurrent urinary tract infection should be offered continuous or post-coital prophylaxis with nitrofurantoin or cephalexin, except during the last 4 weeks of pregnancy*" (p. e423) | - III-L (Canadian Task Force on Preventive Health Care evidence quality and recommendation rating)<br><br>- I-A<br><br>- II-1B |
| Kranz et al., 2017[41] | |
| "*Treatment The following criteria should be taken into account when deciding which antibiotic to use (evidence level Ia-A):*<br>• *The patient's individual risk*<br>• *The spectrum of pathogens and antibiotic sensitivity*<br>• *The efficacy of the antimicrobial substance*<br>• *The adverse drug reactions*<br>• *The effects on the resistance situation in the individual patient (collateral damage) and/or the general population (epidemiological effects)*" (p. 869)<br><br>**Acute uncomplicated cystitis: standard group**<br>"*nonantibiotic, symptomatic treatment may be considered in cases of AUC with mild or moderate symptoms*" (p. 870)<br><br>Asymptomatic bacteriuria<br>"*ASB should be actively sought in such cases, and if found it should be treated*" (p. 870)<br><br>**General comment on antibiotic treatment of acute uncomplicated cystitis**<br>"*Since fluoroquinolones and cephalosporins have an important* | - no evidence levels reported<br><br>- IA-B (2009 criteria of the Oxford Centre for Evidence-based Medicine)<br><br>- IA-A |

## Table 10: Summary of Recommendations in Included Guidelines

| Recommendations | Strength of Evidence and Recommendations |
|---|---|
| *role in complicated infections, the clinical consequences of increased resistance by using them in uncomplicated infections was rated as more severe than for other antibiotics recommended for the treatment of AUC"*<br>"*It is thus strongly recommended that the fluoroquinolones and cephalosporins are not used in the treatment of AUC unless there is a contraindication for alternative substances*" (p. 871) | - V<br>- V-A |
| **Acute uncomplicated pyelonephritis: standard group**<br>"*Patients with AUP should receive efficacious antibiotic treatment as soon as possible, because kidney damage (30), though not frequent, is more likely with increasing duration, severity, and frequency of such infections. In choosing the best antibiotic, the eradication rates, sensitivity, collateral damage, and special characteristics with regard to adverse drug reactions should be taken into account*" (p. 871) | - V |
| **Prevention of recurring urinary tract infection: standard group**<br>- "*Before initiation of long-term prophylactic drug treatment, a woman with rUTI should be counseled in detail on avoidance of risks (e.g., not drinking enough, overcooling, excessive intimate hygiene)*" (p. 872)<br>- "*If appropriate preventive measures have been taken but rUTI persists, long-term antibiotic prophylaxis ought to be preceded by oral administration of an E. coli lysate (OM-89) for 3 months*" (p. 872)<br>- "*Immunoprophylaxis by means of three parenteral injections of inactivated specified enterobacteria at 1-week intervals may be considered*" (p. 872)<br>- "*If the patient's level of suffering is high, failure of behavioral modification and nonantibiotic prophylaxis ough to be followed by continual long-term antibiotic prophylaxis for 3 to 6 months*" (p. 872)<br>- "*In the presence of an association with sexual intercourse, postcoital prophylaxis with a single dose ought to be used instead of long-term administration of antibiotics*" (p. 872) | - Ib-A<br>- Ia-B<br>- Ib-C<br>- IV-B<br>- Ib-B |
| TABLE 1 (in the guideline) Recommended empirical short-term antibiotic treatment of uncomplicated cystitis in women in the premenopause (standard group): fluoroquinolones not first-choice antibiotics, including ciprofloxacin, levofloxacin, norfloxacin, and ofloxacin | - No evidence levels |
| TABLE 2 (in the guideline) Recommended empirical short-term antibiotic treatment of uncomplicated pyelonephritis in women in the premenopause (standard group): ciprofloxacin and levofloxacin are two of the recommended oral antibiotics for mild to moderate disease and the first-choice antibiotics in severe disease | - No evidence levels |
| TABLE 3 (in the guideline) Long-term antibiotic prophylaxis of recurring urinary tract infection: ciprofloxacin and norfloxacin | - No evidence levels |

## Table 10: Summary of Recommendations in Included Guidelines

| Recommendations | Strength of Evidence and Recommendations |
|---|---|
| recommended for continuous long-term prophylaxis; norfloxacin and ofloxacin recommended for postcoital single-dose prophylaxis | |
| European Association of Urology, 2015[3]<br>Updated in 2019[35] | |
| **3C CYSTITIS AND PYELONEPHRITIS IN ADULTS**<br>**3C.3.2 Disease management** | |
| - "*Antibiotic therapy is recommended because clinical success is significantly more likely in women treated with antibiotics compared with placebo*" (p. 15) | Classification system modified from the Oxford Centre for Evidence-based Medicine Levels of Evidence- LE: 1a, GR: A (applicable to uncomplicated cystitis only in the 2019 update)[35] |
| - "*The choice of antibiotic therapy should be guided by [52]:*<br>*• spectrum and susceptibility patterns of the aetiological uropathogens;*<br>*• efficacy for the particular indication in clinical studies;*<br>*• tolerability and adverse reactions;*<br>*• adverse ecological effects;*<br>*• cost;*<br>*• availability*" (p. 15) | - No evidence levels (applicable to uncomplicated cystitis only in the 2019 update)[35] |
| - "*According to these principles and the available susceptibility patterns in Europe, fosfomycin trometamol 3 g single dose, pivmecillinam 400 mg tid for 3 days, and nitrofurantoin macrocrystal 100 mg bid for 5 days, are considered as drugs of first choice in many countries, when available*" (p. 15) | - LE: 1a, GR: A (applicable to uncomplicated cystitis only in the 2019 update)[35] |
| - "*Alternative antibiotics include trimethoprim alone or combined with a sulphonamide, and the fluoroquinolone class. Co-trimoxazole (160/800 mg bid for 3 days) or trimethoprim (200 mg for 5 days) should only be considered as drugs of first choice in areas with known resistance rates for E. coli of < 20%*" (p. 15) | - LE: 1b, GR: B (fluoroquinolones not recommended in the 2019 update because of the potential impact on pathogen resistance)[35] |
| - "*Short courses of antimicrobial therapy can also be considered for the treatment of cystitis in pregnancy*" (p. 15) | - LE: 1a, GR: A (applicable to uncomplicated cystitis only in the 2019 update)[35] |
| - "*In men a treatment duration of at least 7 days is recommended, preferably with TMP-SMX or a fluoroquinolone if in accordance with the susceptibility testing*" (p. 15) | - LE: 4; GR: B (applicable to uncomplicated cystitis only in the 2019 update)[35] |
| - "*Alternative antibiotics include trimethoprim alone or combined with a sulphonamide, and the fluoroquinolone class. Co-trimoxazole (160/800 mg bid for 3 days) or trimethoprim (200 mg for 5 days) should only be considered as drugs of first choice in areas with known resistance rates for E. coli of < 20%*" (p. 15) | - LE: 1b, GR: B (strong evidence to avoid fluoroquinolones as alternatives to first-line therapy; applicable to uncomplicated cystitis only in the 2019 update)[35])[35] |
| Ciprofloxacin, Levofloxacin, and Ofloxacin recommended as alternative antibiotics in "*Table 3: Recommended antimicrobial therapy in acute uncomplicated cystitis in otherwise healthy women*" (p. 16) | - No evidence levels (strong evidence to avoid fluoroquinolones as alternatives to first-line therapy for the treatment of uncomplicated cystitis in the 2019 update)[35] |
| - "*In mild and moderate cases of acute uncomplicated pyelonephritis (see Table 4), oral therapy of 10-14 days is usually sufficient*" (p. 17) | - LE: 1b, GR: B (this recommendation not available in the 2019 update) |
| - "*A fluoroquinolone for 7-10 days can be recommended as first-line therapy if the resistance rate of E. coli is still < 10%* | - LE: 1b, GR: A (this recommendation not available in the 2019 update) |
| - *"If the fluoroquinolone dose is increased, the treatment can* | - LE: 1b, GR: B (this recommendation not available in the 2019 |

## Table 10: Summary of Recommendations in Included Guidelines

| Recommendations | Strength of Evidence and Recommendations |
|---|---|
| *probably be reduced to 5 days*" (p. 17) | update) |
| - 2019 update: "***Fluoroquinolones and cephalosporines are the only microbial agents that can be recommended for oral empirical treatment of uncomplicated pyelonephritis***" (page number unavailable) | - 1b |
| - 2019 update: "***Intravenous antimicrobial regimens for uncomplicated pyelonephritis may include a fluoroquinolone, an aminoglycoside (with or without ampicillin), or an extended-spectrum cephalosporin or penicillin***" (page number unavailable) | - 1b |
| **- Ciprofloxacin and levofloxacin recommended as first-line treatment in "*Table 4: Suggested regimens for empirical parenteral antimicrobial therapy in uncomplicated pyelonephritis***" (page number unavailable) | - No evidence levels |
| **3C.4.2.1 Mild and moderate cases**<br>Ciprofloxacin and Levofloxacin recommended in "*Table 4: Recommended initial empiric oral antimicrobial therapy in mild and moderate acute uncomplicated pyelonephritis*" (p. 18) | - No evidence levels (this recommendation not available in the 2019 update) |
| **3C.4.2.2 Severe cases**<br>Ciprofloxacin and Levofloxacin recommended in "*Table 5: Recommended initial empirical parenteral antimicrobial therapy in severe acute uncomplicated pyelonephritis*" (p. 18) | - No evidence levels (this recommendation not available in the 2019 update) |
| - "*In men with febrile UTI, pyelonephritis, or recurrent infection, or whenever a complicating factor is suspected a minimum treatment duration of 2 weeks is recommended preferably with a fluoroquinolone since prostatic involvement is frequent*" (p. 19) | - LE: 2a, GR: B |
| **3D COMPLICATED UTIs WITH UROLOGICAL AND NEPHROLOGICAL RISK FACTORS IN ADULTS**<br>Fluoroquinolones, unspecified, listed in "*Antibiotics recommended for initial empirical treatment, if local resistance pattern is still < 20%*" and "*Antibiotics recommended for empirical treatment in case of initial failure, or for severe cases*" in "*Table 7: Antimicrobial treatment options for empirical therapy*" (p.25) | - No evidence levels |
| - 2019 update: "***If the prevalence of fluoroquinolone resistance is thought to be < 10% and the patient has contraindications for third generation cephalosporins or an aminoglycoside, ciprofloxacin can be prescribed as an empirical treatment in women with complicated pyelonephritis***" (page number unavailable) | - 2 |
| - 2019 update: "Only use ciprofloxacin provided that the local resistance percentages are < 10% when; the entire treatment is given orally; patients do not require hospitalisation; patient has an anaphylaxis for beta-lactam antimicrobials" (page number unavailable) | - Strong |
| - 2019 update: "***Do not use ciprofloxacin and other fluoroquinolones for the empirical treatment of complicated*** | - Strong |

## Table 10: Summary of Recommendations in Included Guidelines

| Recommendations | Strength of Evidence and Recommendations |
|---|---|
| ***UTI in patients from urology departments or when patients have used fluoroquinolones in the last six months***" (page number unavailable) | |
| **3E SEPSIS SYNDROME IN UROLOGY (UROSEPSIS)**<br>**3G UTIs IN CHILDREN**<br>Fluoroquinolones not listed in "*Table 12: Dosing of antimicrobial agents in children aged 3 months to 12 years*" (p. 40) | - No evidence levels |
| **3H URETHRITIS**<br>Fluoroquinolones not listed in "*Table 13: Recommendations of antimicrobials for the treatment of gonorrhea*" (p.41) | - No evidence levels |

ASB = asymptomatic bacteriuria; AUC = acute uncomplicated cystitis; GR = grade of recommendation; LE = level of evidence; NICE = National Institute for Health and Care Excellence; rUTI = recurrent urinary tract infection; UTI = urinary tract infection.

# Appendix 5: Additional References of Potential Interest

## Reviews without systematic literature searches

Antibiotic therapy for acute uncomplicated pyelonephritis in women. Take resistance into account. *Prescrire Int.* 2014;23(155):296-300.

Recurrent uncomplicated cystitis in women: allowing patients to self-initiate antibiotic therapy. *Prescrire Int.* 2014;23(146):47-49.

Wiedemann B, Heisig A, Heisig P. Uncomplicated urinary tract infections and antibiotic resistance-epidemiological and mechanistic aspects. *Antibiotics (Basel).* 2014;3(3):341-352

## Guidelines without systematic literature searches

Robinson JL, Finlay JC, Lang ME, et al. Urinary tract infection in infants and children: Diagnosis and management. Ottawa (ON): Canadian Paediatric Society; 2017: https://www.cps.ca/en/documents/position/urinary-tract-infections-in-children. Accessed 2019 Apr 25.

Robinson JL, Finlay JC, Lang ME, et al. Prophylactic antibiotics for children with recurrent urinary tract infections. Ottawa (ON): Canadian Paediatric Society; 2018: https://www.cps.ca/en/documents/position/prophylactic-antibiotics-recurrent-urinary-tract-infections. Accessed 2019 Apr 25.

Canadian Coordinating Office for Health Technology Assessment. Clinical and economic considerations in the use of fluoroquinolones. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA). Ottawa (ON); 1997: https://www.cadth.ca/sites/default/files/pdf/quinolones_ov_e.pdf. Accessed 2019 Apr 25.