

Drug Class Update: Fluoroquinolones, oral

Date of Review: April 2022

Date of Last Review: May 2018

Dates of Literature Search: 12/30/2017 – 12/07/2021

Current Status of PDL Class:

See **Appendix 1**.

Purpose for Class Update:

The purpose of this class update is to review new comparative evidence for efficacy and safety of oral fluoroquinolone (FQ) antibiotics.

Research Questions:

1. Is there new comparative evidence that oral FQs differ in efficacy/effectiveness in the clinical cure of acute bacterial infections?
2. Is there new comparative evidence that oral FQs differ in serious adverse events or tolerability when used to manage acute bacterial infections?
3. Are there subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender), other medications, or co-morbidities for which one oral FQ is more effective or associated with fewer adverse events?

Conclusions:

- Since the last class review, the Canadian Agency for Drugs and Technologies and Health (CADTH) published 5 systematic reviews focused on the efficacy of FQs for specific infections.¹⁻⁵ One systematic review focused on safety of FQs was published,⁶ and 4 high-quality guidelines⁷⁻¹⁰ were updated.

Systematic Reviews Focused on Efficacy

- No evidence was identified in 2019 by CADTH on the clinical effectiveness of FQs to treat otitis media in patients unable to take beta-lactam antibiotics.¹ Furthermore, no guidelines were found for the use of FQs for treatment of otitis media in patients unable to take beta-lactam antibiotics.¹
- A 2019 CADTH report reviewed evidence for the use of FQs in intra-abdominal infections. The evidence suggests FQs do not differ from comparators (e.g. beta-lactams, ertapenem, ceftriaxone with metronidazole) with respect to effectiveness and safety for the treatment of adults with intra-abdominal infections.² The 2017 United States (U.S.) Surgical Infection Society (SIS) guideline recommends intravenous (IV) moxifloxacin or ciprofloxacin plus metronidazole for the empiric treatment of adults with lower-risk infection, with caution advised for those in regions with a high incidence of FQ-resistant *E. coli* (strong recommendation; high-quality evidence).¹¹ For pediatric patients, the SIS does not recommend moxifloxacin for empiric treatment unless other options are not available (strong recommendation; low-quality evidence).¹¹

- A May 2019 CADTH report examined evidence for FQ use in patients with pneumonia.³ Among patients with severe community acquired pneumonia (CAP), beta-lactam/macrolide combination therapy may be more effective than beta-lactam/FQ combination therapy in reducing overall mortality and length of hospital stay.³ The 2014 National Institute for Health and Care Excellence (NICE) and 2016 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidance recommend that FQs not be routinely offered for low-severity CAP,¹² and for ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP),¹³ levofloxacin should be considered as an approach to cover methicillin-susceptible *S. aureus* (MSSA).
- A 2019 CADTH report evaluated FQs for the treatment of other respiratory infections.⁴ Moxifloxacin showed an efficacy (defined as clinical cure rates at test-of-cure visit) close to or above 90% in patients with rhinosinusitis.⁴ Levofloxacin showed an efficacy (clinical success, resolution of 3 or more acute rhinosinusitis symptoms) over 86%, although one study reported an efficacy of only 23.4% in patients with rhinosinusitis.⁴ No significant differences in total pathogen eradication were noted between FQs, macrolides, or beta-lactams in a meta-analysis of patients with bronchitis.⁴ In addition, 3 high-quality guidelines were identified; one informing the treatment of acute exacerbations of bronchiectasis (non-cystic fibrosis) from NICE,¹⁴ one informing the treatment of bronchiectasis in adults from the British Thoracic Society (BTS),¹⁵ and one informing the treatment of chronic suppurative lung disease (CSLD) and bronchiectasis from the Thoracic Society of Australia and New Zealand.¹⁶ The NICE guidance recommends levofloxacin for adults and ciprofloxacin (on specialist advice) for children as second-line oral treatments for patients at high risk of treatment failure or as first-line IV treatment.¹⁴
- An April 2019 CADTH report focused on the effectiveness of FQs for the treatment of urinary tract infections (UTI).⁵ Three separate systematic reviews included patients with acute pyelonephritis, women with cystitis, and patients who experienced antibiotic-associated psychosis during treatment of a UTI.⁵ In patients with pyelonephritis, the clinical success rates were not statistically different between cefaclor, ciprofloxacin, and norfloxacin at weeks 4 to 6.⁵ Fluoroquinolones were effective for clinical and microbiological outcomes in patients with cystitis, but it was advised that they should be reserved for more invasive infections in order to avoid inducing bacterial resistance.⁵ In terms of adverse events, there were cases of acute psychosis reported among patients treated with FQs, penicillins, or TMP-SMX for UTI.⁵ 2018 NICE guidance recommends ciprofloxacin for pyelonephritis for non-pregnant women and men aged 16 years and over.¹⁷ Fluoroquinolones are not recommended as first- or second-line therapy for catheter-associated UTI or lower UTI by NICE.^{18,19} In the European Association of Urology (EAU) guideline, FQs are not recommended for uncomplicated cystitis.²⁰ For recurrent UTIs, there are conflicting recommendations between guidelines. NICE does not recommend FQs for recurrent UTIs.²¹ However, the Society of Obstetricians and Gynecologists of Canada recommend daily prophylaxis with an FQ for women with 2 recurrent UTIs in 6 months or 3 recurrent UTIs in 12 months.²²

Systematic Review Focused on Safety

- A 2021 systematic review investigated the association of FQ treatment and the risks of aortic aneurysm (AA) and aortic dissection (AD).⁶ The pooled results of 9 studies showed that the use of FQs increased the risk of AA/AD by 69% (risk ratio [RR] 1.69; 95% CI, 1.08 to 2.64).⁶ Stratified by the comparators, the use of FQs was associated with a higher risk of AA/AD compared to azithromycin (pooled RR 2.31; 95% CI 1.54 to 1.47) and amoxicillin (pooled RR 1.57; 95% CI 1.39 to 1.78).⁶ In contrast, FQs were not associated with a higher risk of AA/AD, when compared with amoxicillin-clavulanate or ampicillin-sulbactam (pooled RR 1.18; 95% CI 0.81 to 1.73), and TMP-SMX (pooled RR 0.89; 95% CI 0.65 to 1.22).⁶ Since FQs had a similar risk of AA/AD compared to some other broad-spectrum antibiotics, it is possible the risk of AA/AD could be related to the underlying severity of disease but not the antibiotics themselves.⁶ Further prospective studies are warranted to clarify the role of FQs in the development of AA/AD after adjustment for underlying infection and its severity.⁶

Clinical Practice Guidelines

- In 2019, the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) updated clinical practice guidance on the management of adults patients with CAP.⁸ Respiratory FQs (levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily) are recommended for outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia (strong recommendation, moderate quality of evidence).⁸
- In 2019 the ATS, Centers for Disease Control and Prevention (CDC), European Respiratory Society (ERS), and IDSA jointly sponsored a new practice guideline on the treatment of multidrug-resistant tuberculosis (MDR-TB).⁷ One of the specific questions selected by the guideline writing committee addressed if

outcomes are safely improved in patients with MDR-TB when regimens include FQs compared with regimens that do not include FQs.⁷ The guideline recommends including moxifloxacin or levofloxacin in a regimen for treatment of patients with MDR-TB (strong recommendation, low certainty in the evidence).⁷

- In September 2019, NICE updated guidance focused on antibiotic prescribing to treat CAP in adults and children.⁹ Levofloxacin is only recommended as an alternative antibiotic for adults with high-severity CAP and a penicillin allergy.⁹ For children under 18 years of age, FQs are not recommended for treatment of any forms of CAP.⁹
- The NICE guidance focused on antimicrobial stewardship was updated in 2019.¹⁰ A section on FQ safety was added due to the numerous safety issues associated with FQ administration. Fluoroquinolones should not be used: 1) to treat self-limiting infections, or infections that are not severe; 2) to treat non-bacterial conditions or 3) to treat some mild to moderate infections (such as acute exacerbation of chronic bronchitis and chronic obstructive pulmonary disease), unless other antibiotics that are commonly recommended for these infections are not appropriate.¹⁰

Specific Subgroup Analysis

- No evidence was identified for subgroups of patients based on demographics (e.g., age, racial or ethnic groups, gender), other medications, or co-morbidities to demonstrate one oral FQ is more effective or associated with fewer adverse events over other FQs.

Expanded Indication

- Delafloxacin (BAXDELA) received expanded FDA-approval to treat adults with CAP.²³ When delafloxacin was initially approved in 2018, it was indicated for treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria. For the expanded indication, delafloxacin was evaluated in a single, noninferiority, multicenter, multinational, randomized, double-blind trial in adults with CAP (n = 859).²⁴ The primary end point was early clinical response, defined as improvement at 96 (± 24) hours after the first dose of study drug.²⁴ In the intent-to-treat (ITT) analysis population, ECR rates were 88.9% in the delafloxacin group and 89.0% in the moxifloxacin group (difference -0.2%; 95% CI -4.4% to 4.1%).²⁴ In this RCT, noninferiority of delafloxacin was demonstrated compared with moxifloxacin for treatment of CAP.²⁴

Recommendations:

- Based on the review of recently published evidence, recommend adding moxifloxacin as a preferred agent to the Preferred Drug List (PDL).
- After review of drug costs in Executive Session, no additional PDL changes were recommended.

Summary of Prior Reviews and Current Policy

Evidence for the comparative effectiveness of FQs was last reviewed by the Oregon Pharmacy and Therapeutic (P&T) Committee in May 2018. The efficacy and safety of delafloxacin, which received Food and Drug Administration (FDA) approval in 2017 for treatment of adults with ABSSSI, was also reviewed at this meeting. The oral FQs included on the Oregon PDL are presented in **Appendix 1**. Ciprofloxacin and levofloxacin are preferred agents on the PDL in order to maintain at least one FQ with broad coverage of gram-negative bacteria and at least one “respiratory” FQ as preferred options. In the third quarter of 2021, all of the Fee-For-Service oral FQ utilization was for ciprofloxacin and levofloxacin.

Background:

Discovery of quinolone antibiotic prototype, nalidixic acid, occurred during the synthesis of the antimalarial agent, chloroquine in the early 1960s.²⁵ Nalidixic acid never became a useful agent to treat systemic infections because of its narrow antibacterial spectrum, poor tissue penetrability, rapid emergence of bacterial resistance, and frequent adverse central nervous system (CNS) effects.²⁵ However, nalidixic acid did provide the chemical foundation upon which to build the modifications that would subsequently improve therapeutic properties and limit adverse effects of the quinolone antibiotics.²⁵ In rapid succession, norfloxacin,

ciprofloxacin, and levofloxacin were discovered, developed, and licensed for use.²⁶ The FQs are strong inhibitors of topoisomerase II (DNA gyrase) and topoisomerase IV, which interfere with bacterial DNA synthesis.²⁷ Fluoroquinolones are bactericidal and exhibit post-antibiotic effects of inhibition of bacterial growth even after the plasma concentration falls below the minimum inhibitory concentration (MIC).²⁷

Fluoroquinolones have good oral bioavailability and penetrate most body tissues. Other than moxifloxacin, the FQs are eliminated through the kidneys via active tubular secretion.²⁸ Fluoroquinolones have a broad spectrum of activity against gram-negative and gram-positive bacteria. They are used in the treatment of genitourinary infections, prostatitis, respiratory diseases, sexually transmitted diseases, gastroenteritis, and skin/soft tissue infections. The Food and Drug Administration (FDA)-approved indications for oral FQs are presented in **Table 1** for adults and **Table 2** for children. Due to the broad-spectrum activity of FQs, there is widespread incentive to preserve the efficacy of these drugs by reserving them as second-line when narrow-spectrum antibiotics can be utilized first. Resistance to FQs is also increasing rapidly and is considered a major concern in the clinical setting.²⁹ Because resistance to FQs is common, knowledge of local epidemiology is important when selecting an antibiotic.²⁹

Table 1. FDA-Approved Indications for Oral Fluoroquinolones in Adults with Normal Renal Function (CrCl > 50 mL/min)

Infection	Ciprofloxacin ³⁰	Ofloxacin ³¹	Levofloxacin ³²	Moxifloxacin ³³	Delafloxacin ²³
Skin and Skin Structure	X	X	X	X	X
Bone and Joint	X				
Complicated Intra-abdominal	X			X	
Infectious Diarrhea	X				
Typhoid Fever	X				
Uncomplicated Urethral and Cervical Gonorrhea	X	X			
Inhalational Anthrax (post-exposure)	X		X		
Plague	X		X	X	
Nosocomial Pneumonia			X		
Community Acquired Pneumonia	X	X	X	X	X
Acute Exacerbation of Chronic Bronchitis	X	X	X	X	
Chronic Bacterial Prostatitis	X	X	X		
Uncomplicated Urinary Tract	X	X	X		
Complicated Urinary Tract or Acute Pyelonephritis	X		X		
Uncomplicated Cystitis	X	X			
Acute Pelvic Inflammatory Disease		X			
Acute Bacterial Sinusitis	X		X	X	

Abbreviations: CrCl=creatinine clearance FDA=Food and Drug Administration; mL=milliliters; min=minute

Table 2. FDA-Approved Uses and Dosing Of Oral Fluoroquinolones in Pediatric Patients with Normal Renal Function (CrCl > 50mL/min)

Infection	Ciprofloxacin ³⁰	Levofloxacin ³²
Inhalational Anthrax (post-exposure)	X*	X
Plague	X*	X
Complicated Urinary Tract or Acute Pyelonephritis	X**	

**approved in patients from birth to 17 years of age*
***approved in patients from 1 to 17 years of age*
Abbreviations: CrCl=creatinine clearance FDA=Food and Drug Administration; mL=milliliters; min=minute

Fluoroquinolones are associated with serious AEs affecting the CNS, musculoskeletal, and peripheral nervous systems,³⁴ with more recent evidence of aortic aneurysm and aortic dissection.³⁵ Fluoroquinolones have also been associated with both hypoglycemia and hyperglycemia in diabetic and nondiabetic patients.^{36,37} The incidence of *C. difficile* infection also appears to be higher with FQ use when compared with some other antibiotics.³⁸ Fluoroquinolones should generally be avoided during pregnancy and lactation unless a safer alternative is not available.³⁹ In animal models, FQ use during pregnancy has been associated with cartilage and bone toxicity in developing fetuses.³⁹ Routine use of FQs in children should be limited to the treatment of infections for which no safe and effective alternative exists due to the potential risk of musculoskeletal toxicity.^{40,41} All FQs marketed in the United States (U.S.) contain a black boxed warning regarding the risk of serious AEs including tendinitis, tendon rupture, peripheral neuropathy, CNS effects, and exacerbation of myasthenia gravis.^{23,30-33} With these warnings, the FDA stated the benefit for use of FQs for acute sinusitis, acute bronchitis, and uncomplicated UTIs, does not outweigh risks of serious AEs and use in these indications should be reserved for those patients who lack any alternative treatment options.⁴² Notably, several FQs have been withdrawn from the market due to AEs; for instance, grepafloxacin was withdrawn from the worldwide market in 1999 due to seven fatal cardiovascular events; trovafloxacin was withdrawn from European and U.S. markets in 1999 due to reports of liver failure; gatifloxacin was removed from the market in 2006 following a study published on dysglycemia side effects; temafloxacin was withdrawn from the American and some European markets shortly following its approval in 1992 due to severe adverse reactions, including hemolytic anemia, acute renal failure, hepatotoxicity and 3 deaths; sparfloxacin was withdrawn from American markets in 2001 due to QT prolongation and phototoxicity; and alatrofloxacin was withdrawn worldwide in 2006 due to associations with liver toxicity and death.³

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

In 2019 the Canadian Agency for Drugs and Technologies and Health (CADTH) published 5 reports focused on the safety and efficacy of FQs for different infections including otitis media, intra-abdominal infections, pneumonia, other respiratory infections, and UTIs. No evidence regarding the clinical effectiveness of FQs to treat otitis media in patients unable to take beta-lactam antibiotics was identified by the CADTH reviewers.¹ Furthermore, no guidelines regarding the use of FQs for the treatment of otitis media in patients unable to take beta-lactam antibiotics were found.¹ CADTH reports for the use of FQs in the treatment of intra-abdominal, respiratory, and urinary tract infections supported by moderate- to high-quality evidence are summarized below.

Fluoroquinolones for Intra-Abdominal Infections

An April 2019 CADTH report evaluated the evidence for the use of FQs in the treatment of intra-abdominal infections.² Due to the development of resistance over time in some locations and the potential for severe adverse effects, decisions around the prescription of FQs for the treatment of intra-abdominal infections and the choice of a FQ regimen should consider local and regional susceptibility information, whether infections are hospital-, intensive care unit-, or community-associated, and the benefits and harms associated with their use.² One systematic review with meta-analysis, one meta-analysis without systematic review, 2 RCTs, and one evidence-based guideline met inclusion criteria for the CADTH report.² Intervention and comparator treatments were initiated intravenously, with the possibility to switch to oral treatment once the patient became stable.²

In the moderate-quality 2019 systematic review (n = 4,125), FQ-based regimens did not differ in efficacy from beta-lactam-based regimens for the treatment of complicated intra-abdominal infections in adults (RR 0.97; 95% CI 0.94 to 1.01).² In the moderate-quality, 2014 meta-analysis (n = 1,229), the authors concluded moxifloxacin had similar efficacy compared to 4 antibiotic regimens (piperacillin-tazobactam followed by amoxicillin-clavulanate; ceftriaxone plus metronidazole, followed by amoxicillin-clavulanate; ceftriaxone plus metronidazole; or ertapenem) for the treatment of complicated intra-abdominal infections in adults (pooled difference in success rates -3.96; 95% CI -7.06 to -1.05; P = 0.25).² A 2018 low-quality RCT of pediatric patients (n = 451) treated for complicated intra-abdominal infection, showed the moxifloxacin group experienced greater treatment success and clinical cure compared with ertapenem followed by amoxicillin-clavulanate, although statistical significance was not assessed.² In a 2017 low-quality RCT of adult patients with peritoneal dialysis related peritonitis (n = 80), there were no statistically significant differences in complete cure, primary treatment failure, secondary treatment failure, peritonitis-related death, successive episodes of peritonitis up to 3 months follow-up, successive episodes of peritonitis, transfer to hemodialysis, or maintenance of peritoneal dialysis between oral moxifloxacin and intraperitoneal ceftazidime.²

In a systematic review of patients with complicated intra-abdominal infection, FQ-based regimens did not differ from beta-lactam-based regimens with regard to all-cause mortality (RR 1.04; 95% CI 0.75 to 1.43), overall treatment-related AEs (RR 0.97; 95% CI 0.70 to 1.33), or early study withdrawal due to AEs (RR 1.07; 95% CI 0.86 to 1.33).² In the meta-analysis without systematic review that examined moxifloxacin for the treatment of complicated intra-abdominal infections, the rates of AEs were similar to the 4 comparator groups for overall AEs (67.3% vs 59.8%), drug-related AEs occurring in more than 5 patients in either group (20.9% vs. 20%), serious AEs (18.1% vs. 14.2%), premature discontinuations due to AEs (5.1% vs. 4.0%), and deaths (4.3% vs. 3.4%).² In the pediatric RCT, the investigators determined the rates of FQ AEs were similar to the ertapenem followed by amoxicillin-clavulanate group for all AEs, with the exception of QT prolongation.² In the adult RCT, there were greater occurrences of QT prolongation assessed by electrocardiogram (ECG) in the moxifloxacin group versus ceftazidime.² However, statistical significance was not examined for AE outcomes in either RCT.²

The 2017 SIS guideline provides recommendations on the use of FQs in the treatment of community-acquired intra-abdominal infections for adults and pediatric patients.¹¹ This high-quality guideline used rigorous methodology and provided support for implementation of recommendations.² For adults, IV moxifloxacin or the combination of ciprofloxacin plus metronidazole are recommended for the empiric treatment of those with lower-risk infection, with caution advised for

those in regions with a high incidence of FQ-resistant *E. coli* (strong recommendation; high-quality evidence).¹¹ Levofloxacin plus metronidazole is recommended where other FQs are unavailable (weak recommendation, low-quality evidence).¹¹ Fluoroquinolone-based regimens in general are recommended for initial empiric antimicrobial therapy in lower risk patients who have had major reactions to beta-lactams (weak recommendation; moderate-quality evidence).¹¹ For pediatric patients, the SIS does not recommend moxifloxacin for empiric treatment unless other options are not available (strong recommendation; low-quality evidence).¹¹ Ciprofloxacin plus metronidazole (weak recommendation, moderate-quality evidence) or levofloxacin (weak recommendation, low-quality evidence) are recommended for empiric treatment of children older than 1 month if other options are not suitable, particularly for children who have had life-threatening reactions to beta-lactam (weak recommendation, moderate-quality evidence).¹¹ The SIS recommends against empiric use of most FQ-based regimens in residents of geographic areas where a high prevalence of extended spectrum beta-lactamase-producing *Enterobacteriaceae* exists in the community (strong recommendation; moderate-quality evidence).¹¹

In summary, evidence from 2 moderate-quality systematic reviews, and 2 low-quality RCTs suggests FQs do not differ from comparators with respect to effectiveness and safety for the treatment of adults with intra-abdominal infections.² The 2017 SIS guideline provides recommendations for use of specific FQs in adults and children with community acquired intra-abdominal infections.² Key limitations were identified by authors of the CADTH report. There was limited or no evidence available on the effectiveness and safety of FQs for some populations of interest.² Pediatric patients were only examined in one small, pilot study and statistical significance was not calculated.² Complicated intra-abdominal infections and secondary peritonitis were examined but other uncomplicated types of intra-abdominal infection were not examined in clinical studies.² Finally, given that susceptibility to antibiotic resistance differs across regions, it is unclear if the included studies would be generalizable to specific geographic regions.²

Fluoroquinolones for the Treatment of Pneumonia

A May 2019 CADTH report identified 9 moderate-quality systematic reviews and 2 high-quality guidelines which examined evidence for FQ use in patients with pneumonia.³ The 9 systematic reviews describing patients with pneumonia identified various antibiotic regimens including: FQ versus either a macrolide or doxycycline, in combination with a beta-lactam; beta-lactam plus macrolide combination versus beta-lactam plus FQ combination; FQ monotherapy versus macrolide monotherapy; or ceftriaxone plus macrolide combination therapy versus FQ monotherapy.³ The CADTH authors noted potential limitations in findings due to a high risk of bias among the studies included in the systematic reviews.³ The generalizability of the findings is limited by variability of included study design, interventions, and comparators.³ Findings from 3 systematic reviews suggested that alternative antibiotic regimens may be more effective in reducing mortality compared to FQ-containing regimens.³ Among patients with severe community acquired pneumonia (CAP), beta-lactam plus macrolide combination therapy may be more effective than beta-lactam plus FQ combination therapy in reducing overall mortality (overall mortality rates were 19.4% versus 26.8%, respectively; OR 0.68; 95% CI 0.49 to 0.94; P = 0.02) and length of hospital stay (MD -3.05 days; 95% CI -6.01 to -0.09; P = 0.04).³ The remaining systematic reviews describing patients with pneumonia examined the efficacy of antibiotics using clinical cure or clinical failure as the primary outcome.³ One study reported that treatment with FQ monotherapy resulted in lower clinical failure than treatment with beta-lactam monotherapy (RR 0.72; 95% CI 0.57 to 0.91).³ A meta-analysis showed no statistically significant difference in treatment success between ceftriaxone combination therapy and respiratory FQ monotherapy (pooled RR 0.96; 95% CI 0.92 to 1.01).³ Drug-related adverse events were found to be significantly lower with ceftriaxone combination therapy than respiratory FQ monotherapy (pooled RR 1.27; 95% CI 1.04 to 1.55).³

The two guidelines cited low quality evidence as a consideration when implementing their recommendations.³ The 2014 NICE guidance is intended to be relevant to the management of most patients with CAP or HAP.¹² The 2016 clinical practice guidelines by the IDSA/ATS is intended for use by the healthcare professionals who care for patients at risk for HAP and VAP.¹³ It is recommended that for low-severity CAP, FQs should not routinely be offered,¹² and for VAP and HAP,¹³ levofloxacin should be considered as an approach to cover MSSA.

Fluoroquinolones for the Treatment of Other Respiratory Tract Infections

Five publications met the eligibility criteria and were included in a 2019 CADTH report which evaluated FQs in the treatment of other respiratory infections.⁴ Two of the included publications were moderate-quality systematic reviews; one systematic review which examined antibiotic use in patients with acute rhinosinusitis, and one systematic review with a meta-analysis and a network meta-analysis which examined anti-bacterial agents for patients with bronchitis.⁴ In addition, 3 high-quality guidelines were identified; one informing the treatment of acute exacerbations of bronchiectasis (non-cystic fibrosis) from NICE,¹⁴ one informing the treatment of bronchiectasis in adults from the BTS,¹⁵ and one informing the treatment of CSLD and bronchiectasis from the Thoracic Society of Australia and New Zealand.¹⁶

In the systematic review of the treatment of acute rhinosinusitis, 6 studies assessed the efficacy of levofloxacin and 5 studies evaluated moxifloxacin; however, the route of administration (e.g. oral, inhaled, IV) was not reported.⁴ The primary outcome was clinical cure rate (based on symptoms, and signs detected in physical and/or endoscopic exam) at 5 or 10 days.⁴ Six RCTs of levofloxacin reported efficacy (clinical success, resolution of 3 or more acute rhinosinusitis symptoms) over 86% (median efficacy 91.4%, range: 23.4 to 93.9%), although one study reported an efficacy of only 23.4%.⁴ Four of the RCTs of levofloxacin showed occurrence of minor AE to be less than 22.5%, although two RCTs showed it to be around 40%; no major AEs were reported.⁴ For moxifloxacin, the majority of the included RCTs demonstrated efficacy (defined as clinical cure rates at test-of-cure visit) close to or above 90% (median efficacy 86%, range: not reported).⁴ The minor AE profile of moxifloxacin ranged from 24.3% to 38.2% and no major AEs were observed.⁴ The authors noted that with the exception of one RCT, levofloxacin was shown to be the most effective FQ for treatment of acute rhinosinusitis.⁴

The systematic review focused on treatment of bronchitis based on evidence from 27 RCTs.⁴ The FQs and comparators in the RCTs included: levofloxacin versus amoxicillin-clavulanate; moxifloxacin versus amoxicillin-clavulanate; gemifloxacin versus amoxicillin-clavulanate; gatifloxacin versus amoxicillin-clavulanate; levofloxacin versus azithromycin; moxifloxacin versus azithromycin; gemifloxacin versus clarithromycin; moxifloxacin versus clarithromycin; gatifloxacin versus clarithromycin; and levofloxacin versus gemifloxacin.⁴ Of note, gatifloxacin and gemifloxacin are no longer marketed in the U.S. The route of treatment (e.g. oral or IV) and the length of follow-up was not reported for any RCTs.⁴ The main outcomes were total pathogen eradications and the total incidence of adverse events.⁴ No significant differences across the included medications in treatment efficacy for total pathogen eradication were noted in the meta-analysis.⁴ However, the results showed that patients treated with gemifloxacin had a lower risk of adverse events when compared to patients treated with amoxicillin-clavulanate (OR = 0.58, 95% CI 0.36 to 0.91).⁴ Furthermore, patients treated with FQs compared to amoxicillin-clavulanate had a reduced risk of diarrhea, including moxifloxacin (OR 0.39, 95% CI 0.18 to 0.82), gemifloxacin (OR 0.22, 95% CI 0.09 to 0.50) and gatifloxacin (OR 0.31, 95% CI 0.13 to 0.85). This reduction was also observed among patients treated with levofloxacin compared to those treated with azithromycin (OR 0.41, 95% CI 0.17 to 0.96).⁴ For the FQs, the authors reported that gemifloxacin and levofloxacin had a relatively high ranking in total pathogen eradication efficacy.⁴ Though moxifloxacin revealed good performance in total pathogen eradication and pathogen eradication of *H. influenzae*, it was accompanied with a poor performance in pathogen eradication of *S. pneumoniae*.⁴

The BTS guideline was developed for healthcare practitioners who are involved in the care of adult patients with bronchiectasis (e.g. primary care clinicians, hospital teams in infectious disease, respiratory medicine, microbiologists, and radiologists).⁴ The NICE guideline is intended for health professionals as well as people with bronchiectasis, their families and caregivers.⁴ The Thoracic Society of Australia and New Zealand guideline is intended for the management of children and adults in Australia and New Zealand with CSLD and bronchiectasis, including urban and rural-remote indigenous people.⁴ The BTS and the Thoracic Society of Australia and New Zealand guideline recommend ciprofloxacin as a first-line treatment for patients with *P. aeruginosa*.^{15,16} The NICE guidance recommends levofloxacin for adults and ciprofloxacin (on specialist advice) for children as second-line oral treatments for patients at high risk of treatment failure or as first-line IV treatment.¹⁴ While the 3 guidelines provide similar recommendations for the use of FQs in the treatment of bronchiectasis, the variable

findings and methodological limitations in the body of evidence identified for other conditions, including bronchitis and acute rhinosinusitis, limit generalizability and warrant caution in its interpretation for the clinical effectiveness and cost-effectiveness of FQs for the treatment of respiratory tract infections other than pneumonia.⁴

Fluoroquinolones for the Treatment of Urinary Tract Infection

An April 2019 CADTH report focused on the effectiveness of FQs for the treatment of UTIs.⁵ Evidence was identified for the following FQs: ciprofloxacin, gatifloxacin, levofloxacin, norfloxacin, and ofloxacin.⁵ Three low-quality systematic reviews, 9 high-quality RCTs, 1 moderate-quality RCT, 6 moderate-quality, non-randomized studies, and 6 high-quality guidelines met inclusion criteria.⁵ The outcomes considered in the systematic reviews were clinical success in the treatment of acute pyelonephritis, symptom cure, symptom resolution, recurrence of cystitis, treatment duration, and AEs.⁵ In the RCTs, the outcomes were clinical success rates, microbiological eradication, microbiological recurrence, clinical relapse, early response, susceptibilities of pathogens, cure rates, symptom-free cure, clinical effectiveness rates, treatment failure, composite cure, and AEs.⁵

The 3 systematic reviews included patients with acute pyelonephritis, women with cystitis, and patients with antibiotic-associated psychosis.⁵ Fluoroquinolones were compared with other antibiotics (trimethoprim-sulfamethoxazole [TMP-SMX], loracarbef, nitrofurantoin, fosfomycin, beta-lactams, and metronidazole) or with another FQ in the review focused on pyelonephritis.⁵ The clinical success rates were not statistically different between cefaclor, ciprofloxacin, and norfloxacin at weeks 4 to 6.⁵ Relatively high rates of AEs were observed in one trial of ciprofloxacin (24%) and TMP-SMX (33%) compared to the incidence of AEs in other RCTs.⁵ In another systematic review focused on adult women with uncomplicated cystitis, FQs were compared to TMP-SMX, nitrofurantoin, or fosfomycin.⁵ Fluoroquinolones were effective for clinical and microbiological outcomes, but it was advised that they should be reserved for more invasive infections in order to avoid inducing bacterial resistance.⁵ The authors concluded that options of antibiotics for women with diabetes without voiding abnormalities were similar to those for women without diabetes.⁵ In the third systematic review, a systematic search was conducted for cases of acute psychosis that occurred during UTI treatment.⁵ Acute psychosis was considered a potential AE of antibiotic treatment of UTIs, although the mechanism remained unknown. Three classes of antibiotics were implicated: FQs, penicillins, and TMP-SMX.⁵

The RCTs revealed different FQ efficacy rates depending upon the active comparator and severity of the UTI.⁵ Patients with acute pyelonephritis, complicated UTIs, uncomplicated UTIs, or acute obstructive pyelonephritis were recruited for the 10 RCTs.⁵ In the RCTs, the FQs included: levofloxacin, ciprofloxacin, and norfloxacin. The FQs were compared with ceftriaxone, ertapenem, ceftazidime, TMP-SMX, or ceftolozane-tazobactam. 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.⁵ Compared to TMP-SMX, levofloxacin and norfloxacin did not statistically differ for the treatment of uncomplicated UTIs based on bacterial cure rates.⁵ Compared to levofloxacin, the combination of ceftolozane and tazobactam was associated with statistically significantly better responses in a composite of microbiological eradication and clinical cure in patients with complicated lower UTIs or pyelonephritis.⁵

There were 2 RCTs in which different routes or treatment durations of FQs were compared. The first compared a short-course (5-day) of IV levofloxacin to the conventional combination of IV and oral levofloxacin regimen (i.e. total of 7 to 14 days of IV and oral treatment), which were similarly effective in clinical and microbiological efficacy, tolerance, and safety among patients with complicated UTIs or acute pyelonephritis.⁵ From a clinician perspective, the short-course regimen was a more convenient alternative.⁵ The need for antimicrobial treatment was not significantly different between patients treated with a 10-day IV ciprofloxacin regimen or a 5-day IV levofloxacin regimen among male patients with complicated UTIs.⁵ In patients with acute uncomplicated pyelonephritis, clinical and microbiological cure were not statistically different between those treated with 5- or 10-days of ofloxacin or levofloxacin.⁵

In the non-randomized studies, elderly patients with suspected UTIs, UTIs and a positive urine culture, *E. coli* pyelonephritis, community-acquired complicated UTIs, or a diagnosis of UTI were studied.⁵ Treatment with FQs (i.e., ciprofloxacin, levofloxacin, norfloxacin, or ofloxacin) was compared to treatment with the following antibiotics: cephalexin, amoxicillin-clavulanate, nitrofurantoin, piperacillin-tazobactam, gentamicin, cefuroxime, cefpodoxime, ceftazidime, TMP-SMX, ceftriaxone, ertapenem, first-generation cephalosporins (including cefazolin or cephalexin), penicillins (ampicillin-sulbactam, amoxicillin-clavulanate, or piperacillin-tazobactam), nitrofurantoin, or fosfomycin.⁵ Compared with nitrofurantoin, the use of ciprofloxacin, cephalexin, or amoxicillin-clavulanate was associated with lower rates of treatment failure, defined by re-consultation and re-prescription, in older people with UTIs.⁵ The risks of UTI-related hospitalization or death did not statistically differ between patients treated with nitrofurantoin and those treated with ciprofloxacin, cephalexin, or amoxicillin-clavulanate.⁵ When ciprofloxacin, piperacillin-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 risk factors.⁵ Compared to ciprofloxacin, 7-day TMP-SMX treatment was similarly effective for pyelonephritis based on the occurrence of subsequent symptomatic UTIs.⁵ 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 drug-drug interactions with warfarin compared to ceftriaxone, which was associated with significantly higher peak international normalized ratio (INR) readings, significantly greater change in INR, and significantly greater percentage change in INR.⁵ Patients with UTIs treated with norfloxacin or ofloxacin there were statistically significantly lower composite treatment failure rates compared to patients treated with ciprofloxacin or TMP-SMX.⁵

The 2018 SOGC,²² 2019 EAU,²⁰ and 2018 NICE guidelines provide recommendations for the use of FQs for different UTI categories. Guidance from NICE is published in 4 separate documents focused on: 1) catheter-associated UTIs,¹⁸ 2) pyelonephritis,¹⁷ 3) lower urinary tract infections,¹⁹ and 4) recurrent UTIs.²¹ The NICE guidance for pyelonephritis recommends ciprofloxacin for non-pregnant women and men aged 16 years and over.¹⁷ In NICE guidance, FQs are not recommended as first- or second-line therapy for catheter-associated UTIs¹⁸ or lower UTIs.¹⁹ For recurrent UTIs, FQs are not recommended.²¹ In the EAU guidance, ciprofloxacin, levofloxacin, and ofloxacin are not recommended in uncomplicated cystitis (strong evidence).²⁰ Ciprofloxacin and levofloxacin are recommended for initial empirical oral therapy in uncomplicated pyelonephritis (no evidence level).²⁰ 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.²⁰ The EAU advises not to use FQs empirically in patients from urology departments or those exposed to FQs in the last 6 months.²⁰ In contrast, in the SOGC guidance, FQs are recommended as one of the antibiotics used for daily prophylaxis for women with two recurrent UTIs in 6 months or 3 recurrent UTIs in 12 months.²²

Association between the Risk of Aortic Aneurysm/Aortic Dissection and the Use of Fluoroquinolones

A 2021 systematic review investigated the association of FQ treatment and the risks of aortic aneurysm and aortic dissection.⁶ The literature search was conducted through February 2021. Nine case series and cohort studies met inclusion criteria.⁶ Three studies each were conducted in Taiwan and the U.S., and one each in Canada, France and Sweden.⁶ No RCTs were identified. All 9 observational studies had a low risk of bias according to study design, data collection and analyses.⁶ The quality of the evidence for the outcome of aortic aneurysm/aortic dissection using grading of recommendations assessment, development and evaluation (GRADE) methodology was rated as moderate.⁶

The pooled results of 9 studies showed that the use of FQs increased the risk of aortic aneurysm/aortic dissection by 69% (RR 1.69; 95% CI 1.08 to 2.64; $I^2 = 99.8\%$).⁶ Similar results were found for aortic aneurysm (pooled RR 1.58; 95% CI 1.21 to 2.07; $I^2 = 95.6\%$) but no significant association was observed for aortic dissection (pooled RR 1.23; 95% CI 0.93 to 1.62).⁶ Stratified by the comparators, the use of FQs was associated with a higher risk of aortic aneurysm/aortic dissection compared to azithromycin (pooled RR 2.31; 95% CI 1.54 to 1.47) and amoxicillin (pooled RR 1.57; 95% CI 1.39 to 1.78).⁶ In contrast, FQs were not associated with a higher risk of aortic aneurysm/aortic dissection when compared with amoxicillin-clavulanate or ampicillin-sulbactam (pooled RR 1.18; 95% CI

0.81 to 1.73), TMP-SMX (pooled RR 0.89; 95% CI 0.65 to 1.22) or other antibiotics (pooled RR 1.14; 95% CI 0.90 to 1.46).⁶ Clinically, amoxicillin and azithromycin would be only prescribed for patients with mild infections, and FQs and other broad-spectrum antibiotics would be prescribed for patients with moderate or severe infections.⁶ Although most of the findings in this meta-analysis suggest a possible association between the use of FQs and the development of aortic aneurysm/aortic dissection, there is still concern about the results because the included studies had high heterogeneity (most I² 50% or greater) and the findings of the asymmetric funnel plot indicated possible publication bias.⁶ Fluoroquinolones were associated with an increased risk of aortic aneurysm or aortic dissection, although the level of evidence was not robust.⁶ However, compared with other broad-spectrum antibiotics (i.e. some beta-lactams, TMP-SMX), FQs had a similar risk of aortic aneurysm/aortic dissection, suggesting that the risk of aortic aneurysm/aortic dissection could be related to the underlying severity of disease but not antibiotics themselves.⁶ Further prospective studies are warranted to clarify the role of FQs in the development of aortic aneurysm/aortic dissection after adjustment for underlying infection and its severity.⁶

After review, 5 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria),⁴³⁻⁴⁷ wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

High Quality Guidelines:

American Thoracic Society/Infectious Diseases Society of America: Management of Adults with Community-Acquired Pneumonia

In 2019, the ATS and IDSA updated clinical practice guidance on the management of adult patients with CAP.⁸ A multidisciplinary panel conducted pragmatic systematic reviews of the relevant research and applied GRADE methodology for clinical recommendations.⁸ Antibiotic recommendations for the empiric treatment of CAP were based on selecting agents effective against the major treatable bacterial causes of CAP.⁸ Traditionally, these bacterial pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, *Legionella* species, *Chlamydia pneumoniae*, and *Moraxella catarrhalis*.⁸ The microbial etiology of CAP is changing, particularly with the widespread introduction of the pneumococcal conjugate vaccine, and there is increased recognition of the role of viral pathogens.⁸ Recommendations focused on antibiotic selection and duration of therapy are summarized below.

- *In the Outpatient Setting, Which Antibiotics Are Recommended for Empiric Treatment of CAP in Adults?*
 1. For outpatient adults with comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancy; or asplenia the following antibiotics are recommended (in no particular order of preference):
 - amoxicillin/clavulanate 500 mg/125 mg three times daily, or amoxicillin/clavulanate 875 mg/125 mg twice daily, or 2,000 mg/125 mg twice daily, or a cephalosporin (cefepodoxime 200 mg twice daily or cefuroxime 500 mg twice daily); AND
 - macrolide (azithromycin 500 mg on first day then 250 mg daily, clarithromycin [500 mg twice daily or extended release 1,000 mg once daily]) (strong recommendation, moderate quality of evidence for combination therapy), or doxycycline 100 mg twice daily (conditional recommendation, low quality of evidence for combination therapy); OR
 - respiratory FQ (levofloxacin 750 mg daily, moxifloxacin 400 mg daily, or gemifloxacin 320 mg daily) (strong recommendation, moderate quality of evidence).⁸
- *In Outpatient and Inpatient Adults with CAP Who Are Improving, What Is the Appropriate Duration of Antibiotic Treatment?*
 - The duration of antibiotic therapy should be guided by a validated measure of clinical stability (resolution of vital sign abnormalities [heart rate, respiratory rate, blood pressure, oxygen saturation, and temperature], ability to eat, and normal mentation), and antibiotic therapy should be continued until the patient achieves stability and for no less than a total of 5 days (strong recommendation, moderate quality of evidence).⁹

American Thoracic Society, Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America: Treatment of Multidrug-Resistant Tuberculosis

In 2019 the ATS, CDC, ERS, and IDSA jointly sponsored a new practice guideline on the treatment of MDR-TB.⁷ A carefully selected panel of experts, screened for conflicts of interest, including specialists in pulmonary medicine, infectious diseases, pediatrics, primary care, public health, epidemiology, economics, pharmacokinetics, microbiology, systematic review methodology, and patient advocacy, was assembled to assess the evidence supporting each recommendation.⁷ One of the specific questions selected by the guideline writing committee addressed if outcomes are safely improved in patients with MDR-TB when regimens include FQs compared with regimens that do not include FQs.⁷ Ofloxacin, followed by levofloxacin, followed by moxifloxacin sequentially improved the earlier generation's spectrum of activity, including mycobacteria, and their antimycobacterial action increased as evidenced by lower minimum inhibitory concentrations (MICs) and increasing success in clinical use.⁷ Physicians began using these drugs to treat MDR-TB on the basis of *in vitro* data, with subsequent case series and observational studies showing efficacy although none of the FQs are currently indicated by the FDA for the treatment of TB.⁷ Among patients with susceptible isolates, levofloxacin-containing regimens compared with no FQ were associated with greater treatment success (adjusted OR 4.2; 95% CI 3.3 to 5.4) and fewer patient deaths (adjusted OR 0.6; 95% CI 0.5 to 0.7). Moxifloxacin, compared with a regimen that did not include a FQ, was also associated with greater treatment success (adjusted OR 3.8; 95% CI 2.8 to 5.2) and fewer patient deaths (adjusted OR 0.5; 95% CI 0.4 to 0.6).⁷ In pairwise comparisons, both levofloxacin and moxifloxacin were associated with statistically significantly better treatment outcomes than ofloxacin.⁷ The adjusted ORs of death were lower for the two later-generation FQs when compared with ofloxacin (levofloxacin: adjusted OR 0.8; 95% CI 0.6 to 0.9; moxifloxacin: adjusted OR 0.8; 95% CI 0.6 to 1.0).⁷ Ofloxacin and ciprofloxacin are considered inferior FQs against *M. tuberculosis*.⁷ Levofloxacin and moxifloxacin did not statistically differ from each other.⁷

The guideline recommends including moxifloxacin or levofloxacin in a regimen for treatment of patients with MDR-TB (strong recommendation, low certainty in the evidence).⁷ The recommendation for the use of moxifloxacin or levofloxacin is strong despite very low certainty in the evidence because the panel viewed the statistically significant reduction in mortality, improved treatment success, and relatively AEs associated with MDR-TB treatment with FQ regimens.⁷

National Institute for Health and Care Excellence: Community-Acquired Pneumonia: Antimicrobial Prescribing

In September 2019, NICE updated guidance focused on antibiotic prescribing to treat CAP in adults and children.⁹ For adults aged 18 years and over, a 5-day course of amoxicillin, doxycycline, or clarithromycin are recommended to treat mild, moderate, or severe CAP.⁹ Erythromycin is recommended in pregnancy.⁹ Levofloxacin is only recommended as an alternative antibiotic for adults with high-severity CAP and a penicillin allergy.⁹ For children under 18 years of age, FQs are not recommended for treatment of any forms of CAP.⁹ First choice oral antibiotic recommendations for treatment of CAP in children include amoxicillin or clarithromycin dosed according to age or weight.⁹

National Institute for Health and Care Excellence: Antimicrobial Stewardship

The NICE guidance focused on antimicrobial stewardship was updated in 2019.¹⁰ A section on FQ safety was added due to the numerous safety issues associated with FQs. For example, in the November 2018 edition of the Drug Safety Update, the Medicines and Healthcare products Regulatory Agency (MHRA) highlighted a small increased risk of aortic aneurysm and dissection with systemic and inhaled FQs, and recommended caution and advice for prescribing in people with a high risk.¹⁰ In the March 2019 edition of the Drug Safety Update, the MHRA highlighted new restrictions and precautions for use with the FQs following an European-Union-wide review into the safety of these antibiotics.¹⁰ The review found that very rarely, people having treatment with these antibiotics by mouth, injection or inhalation reported long-lasting and disabling side effects, mainly involving muscles, tendons, joints and the nervous system.¹⁰ The marketing authorizations of ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin were restricted in the UK. They should not be used: 1) to treat self-limiting infections, or infections that are not severe; 2) to treat non-bacterial conditions or 3) to treat some mild to moderate infections (such as acute exacerbation of chronic

bronchitis and chronic obstructive pulmonary disease), unless other antibiotics that are commonly recommended for these infections are not appropriate.¹⁰ Ciprofloxacin or levofloxacin should not be prescribed for uncomplicated cystitis unless other antibiotics that are commonly recommended are not appropriate.¹⁰

Fluoroquinolones should be avoided when treating infections in people who have previously experienced serious adverse events with FQs.¹⁰ They should be used with caution especially in people who are at higher risk of tendon injury, such as people older than 60 years, or people with kidney problems or who have had an organ transplant.¹⁰ Using a FQ together with a corticosteroid should be avoided because the risk of FQ-induced tendinitis and tendon rupture may be exacerbated.¹⁰ The MHRA recommends that people should be advised to stop treatment with FQs at the first signs of a serious adverse reaction, such as tendinitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy, and central nervous system effects, and to contact their doctor immediately for further advice.¹⁰

After review, 2 guidelines were excluded due to poor quality.^{48,49}

New Indications:

On 10/24/2019 delafloxacin (BAXDELA) received expanded FDA-approval to treat adults with CAP.²³ When delafloxacin was initially approved in 2018, it was only indicated for treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria. Delafloxacin is indicated in adults for the treatment of CAP caused by the following susceptible microorganisms: *Streptococcus pneumoniae*, *Staphylococcus aureus* (MSSA isolates only), *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Chlamydia pneumoniae*, *Legionella pneumophila*, and *Mycoplasma pneumoniae*.²³ Use in patients under 18 years of age is not recommended.²³

For the expanded indication, delafloxacin was evaluated in a single noninferiority, multicenter, multinational, randomized, double-blind trial in adults with CAP (n = 859).²⁴ In this trial, delafloxacin every 12 hours was compared to moxifloxacin administered every 24 hours for 5 to 10 days. In the moxifloxacin arm, the investigator could switch patients to linezolid 600 mg every 12 hours if MRSA was confirmed (0.4% of participants).²⁴ Subjects with a history of QT prolongation or arrhythmias were excluded due to moxifloxacin being the comparator.²⁴ The primary end point was early clinical response (ECR), defined as improvement at 96 (\pm 24) hours after the first dose of study drug.²⁴ In the ITT population analysis, ECR rates were 88.9% in the delafloxacin group and 89.0% in the moxifloxacin group (difference -0.2%; 95% CI -4.4% to 4.1%).²⁴ Noninferiority of delafloxacin compared with moxifloxacin was demonstrated in patients with CAP. Treatment-emergent AEs that were considered at least possibly related to the study drug occurred in 65 subjects (15.2%) in the delafloxacin group and 54 (12.6%) in the moxifloxacin group.²⁴ In this trial, the most frequently reported AEs reported with delafloxacin administration were diarrhea and elevated liver function tests.²⁴

New FDA Safety Alerts:

Table 1. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Ciprofloxacin Delafloxacin Gemifloxacin Levofloxacin Moxifloxacin Ofloxacin	CIPRO BAXDELA FACTIVE LEVAQUIN AVELOX OFLOXACIN	12/20/2018	FDA Safety Announcement ⁵⁰	The use of fluoroquinolone antibiotics has been associated with the rupture or dissection of aortic aneurysms. People at risk for aortic aneurysms include those with a history of peripheral atherosclerotic vascular diseases, hypertension, and certain genetic disorders that involve blood vessel changes such as Marfan syndrome and Ehlers-Danlos syndrome, and the elderly. Prescribe fluoroquinolones to these patients only when no other treatment options are available. FDA is requiring that a new warning about the rare but serious risk of aortic aneurysm be added to the prescribing information and patient Medication Guide of all fluoroquinolone antibiotics. In patients with a history of aneurysms, routine checkups and treatment for an aortic aneurysm can help prevent growth and rupture. ⁵⁰
Ciprofloxacin Delafloxacin Gemifloxacin Levofloxacin Moxifloxacin Ofloxacin	CIPRO BAXDELA FACTIVE LEVAQUIN AVELOX OFLOXACIN	7/10/2018	FDA Safety Announcement ⁵¹	Fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects. Health care professionals should be aware of the potential risk of hypoglycemia sometimes resulting in coma, occurring more frequently in the elderly and those with diabetes taking an oral hypoglycemic medicine or insulin. Alert patients of the symptoms of hypoglycemia and carefully monitor blood glucose levels in these patients, and discuss with them how to treat themselves if they have symptoms of hypoglycemia. Inform patients about the risk of psychiatric adverse reactions that can occur after just one dose. Stop fluoroquinolone treatment immediately if a patient reports any central nervous system side effects, including psychiatric adverse reactions, or blood glucose disturbances and switch to a non-fluoroquinolone antibiotic if possible. ⁵¹

Randomized Controlled Trials:

A total of 40 citations were manually reviewed from the initial literature search. After further review, 39 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Drekonja DM, et al ⁵² DB, PC, NI 2 VA Medical Centers	1. Ciprofloxacin 500 mg po BID x 7 days, followed by placebo for 7 days or 2. TMP-SMX 160/800 mg po BID x 7 days followed by placebo for 7 days Vs. 3. Ciprofloxacin 500 mg po BID x 14 days or 4. TMP-SMX 160/800mg po BID x 14 days	-Afebrile males aged 18 yrs and older -Prescribed ciprofloxacin or TMP-SMX for UTI -New onset: dysuria, urinary frequency, urinary urgency, perineal, flank or suprapubic pain N=272	Resolution of the initial UTI symptoms by day 14 after completion of active antibiotic treatment	Symptom Resolution 1. 7-day treatment: 122/131 (93.4%) 2. 14-day treatment: 111/123 (90.2%) Difference: 2.9% 1 sided 97.5% CI: -5.2 to infinity NI threshold met In afebrile males with suspected UTI, ciprofloxacin or TMP-SMX for 7 days was noninferior to 14 days with regard to resolution of UTI symptoms 14 days after initiation of antibiotic therapy.	-Urine cultures not completed to confirm bacterial UTI, which could bias results to finding no statistically significant difference between 7 vs. 14 days. -Study population limited to US veterans only. -Target enrollment of 290 subjects was not met, which may have impacted power to detect differences between groups -NI margin was based on expert opinion, rather than evidence

Abbreviations: BID = twice a day; DB = double blind; NI = noninferiority; PC = placebo control; po = oral; RCT = randomized clinical trial; TMP-SMX = trimethoprim-sulfamethoxazole; UTI = urinary tract infection; VA = Veterans Affairs; yrs = years

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
ciprofloxacin	CIPRO	ORAL	SUS MC REC	Y
ciprofloxacin	CIPROFLOXACIN	ORAL	SUS MC REC	Y
ciprofloxacin HCl	CIPRO	ORAL	TABLET	Y
ciprofloxacin HCl	CIPROFLOXACIN HCL	ORAL	TABLET	Y
levofloxacin	LEVOFLOXACIN	ORAL	SOLUTION	Y
levofloxacin	LEVOFLOXACIN	ORAL	TABLET	Y
ciprofloxacin/ciprofloxacin HCl	CIPRO XR	ORAL	TBMP 24HR	N
delafloxacin meglumine	BAXDELA	ORAL	TABLET	N
lomefloxacin HCl	MAXAQUIN	ORAL	TABLET	N
moxifloxacin HCl	MOXIFLOXACIN HCL	ORAL	TABLET	N
ofloxacin	OFLOXACIN	ORAL	TABLET	N

Appendix 2: Abstracts of Comparative Clinical Trials

Drekonja DM, Trautner B, Amundson C, Kuskowski M, Johnson JR. Effect of 7 vs 14 Days of Antibiotic Therapy on Resolution of Symptoms Among Afebrile Men With Urinary Tract Infection: A Randomized Clinical Trial. *JAMA*. 2021; 326(4):324-331. doi:10.1001/jama.2021.9899⁵²

Objective To determine whether 7 days of treatment is noninferior to 14 days when using ciprofloxacin or trimethoprim/sulfamethoxazole to treat urinary tract infection (UTI) in afebrile men.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled noninferiority trial of afebrile men with presumed symptomatic UTI treated with ciprofloxacin or trimethoprim/sulfamethoxazole at 2 US Veterans Affairs medical centers (enrollment, April 2014 through December 2019; final follow-up, January 28, 2020). Of 1058 eligible men, 272 were randomized.

Interventions Participants continued the antibiotic prescribed by their treating clinician for 7 days of treatment and were randomized to receive continued antibiotic therapy (n = 136) or placebo (n = 136) for days 8 to 14 of treatment.

Main Outcomes and Measures the prespecified primary outcome was resolution of UTI symptoms by 14 days after completion of active antibiotic treatment. A noninferiority margin of 10% was selected. The as-treated population (participants who took ≥ 26 of 28 doses and missed no more than 2 consecutive doses) was used for the primary analysis, and a secondary analysis included all patients as randomized, regardless of treatment adherence. Secondary outcomes included recurrence of UTI symptoms and/or adverse events within 28 days of stopping study medication.

Results Among 272 patients (median [interquartile range] age, 69 [62-73] years) who were randomized, 100% completed the trial and 254 (93.4%) were included in the primary as-treated analysis. Symptom resolution occurred in 122/131 (93.1%) participants in the 7-day group vs 111/123 (90.2%) in the 14-day group (difference, 2.9% [1-sided 97.5% CI, -5.2% to ∞]), meeting the noninferiority criterion. In the secondary as-randomized analysis, symptom resolution occurred in 125/136 (91.9%) participants in the 7-day group vs 123/136 (90.4%) in the 14-day group (difference, 1.5% [1-sided 97.5% CI, -5.8% to ∞]) Recurrence of UTI symptoms occurred in 13/131 (9.9%) participants in the 7-day group vs 15/123 (12.9%) in the 14-day group (difference, -3.0% [95% CI, -10.8% to 6.2%]; $P = .70$). Adverse events occurred in 28/136 (20.6%) participants in the 7-day group vs 33/136 (24.3%) in the 14-day group.

Conclusions and Relevance Among afebrile men with suspected UTI, treatment with ciprofloxacin or trimethoprim/sulfamethoxazole for 7 days was noninferior to 14 days of treatment with regard to resolution of UTI symptoms by 14 days after antibiotic therapy. The findings support the use of a 7-day course of ciprofloxacin or trimethoprim/sulfamethoxazole as an alternative to a 14-day course for treatment of afebrile men with UTI.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November Week 4 2021, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 7, 2021

1 exp Fluoroquinolones/	27800
2 exp Ciprofloxacin/	10633
3 exp Levofloxacin/	3566
4 exp Ofloxacin/	5951
5 exp Moxifloxacin.mp.	2710
6 exp Gemifloxacin.mp.	279
7 delafloxacin.mp.	1326
8 lomefloxacin.mp	574
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	27945
10 limit 9 to (English language and humans and yr="2018-Current" and clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)	398
11 Administration, Oral/ or oral.mp.	126144
12 10 or 11	40