Therapeutic Class Overview
Fluoroquinolones

INTRODUCTION

- The fluoroquinolones are broad-spectrum antibiotics grouped into generations based on their spectrum of activity *(Bolon 2011).*
  - First generation agents, which are structurally quinolones rather than fluoroquinolones, possess activity against aerobic gram-negative bacteria but are not effective against aerobic gram-positive bacteria or anaerobes.
    - The first generation agents (eg, nalidixic acid, cinoxacin) are no longer on the market.
  - Second generation agents, the original fluoroquinolones, contain a fluorine atom at position C-6. These agents offer improved coverage against gram-negative bacteria and moderately improved gram-positive coverage.
    - The available second generation fluoroquinolones include ciprofloxacin, levofloxacin, and ofloxacin. Lomefloxacin and norfloxacin are second generation agents which are no longer on the market.
  - Third generation agents achieve greater potency against gram-positive bacteria, particularly pneumococci, and also possess good activity against anaerobes.
    - All 3 of the third generation agents, gatifloxacin, grepafloxacin, and sparfloxacin, were removed from the market due to toxicities.
  - Fourth generation fluoroquinolones have superior coverage against pneumococci and anaerobes.
    - The available agent is moxifloxacin.
    - Trovafloxacin, was removed from the market due to toxicities, and there is a drug shortage of gemifloxacin.
  - The most recently approved fluoroquinolone, delafloxacin, has an even broader spectrum of antibiotic activity and is commonly referred to as a "next generation" fluoroquinolone.
- The fluoroquinolones have been used to treat a variety of infections including urinary tract infections, sinusitis, lower respiratory tract infections, intra-abdominal infections, infectious diarrhea, skin and skin structure infections, sexually transmitted diseases, and bacterial prostatitis. A few of the agents also have Food and Drug Administration (FDA) approval for inhalational anthrax and plague. There is also considerable off-label data for use in neutropenic patients and for treatment of tuberculosis and mycobacterial infections in patients with human immunodeficiency virus (HIV). Due to the boxed warning for disabling and potentially irreversible serious adverse reactions involving the tendons, muscles, joints, nerves, and central nervous system, fluoroquinolones should be reserved for patients with no other treatment options when used to treat acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections *(FDA press release 2016).*
- As with all antibiotics, local resistance patterns should be considered when prescribing these agents.
- Ciprofloxacin, delafloxacin, levofloxacin, and moxifloxacin are available as intravenous and oral formulations. Ciprofloxacin, levofloxacin, moxifloxacin, and ofloxacin are available in otic and/or ophthalmic formulations. Only the oral formulations and indications will be included in this review.
- Medispan class: Fluoroquinolones

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Avelox (moxifloxacin)	✔
Baxdela (delafloxacin)	-
Cipro (ciprofloxacin)	✔
ciprofloxacin extended release*	✔
Factive (gemifloxacin)π	-
Levaquin (levofloxacin)	✔
ofloxacin†	✔

* The branded product, Cipro XR, is no longer marketed.
† The branded product, Floxin, is no longer marketed.

ᵀᵀThis product is currently unavailable due to a drug shortage.

(Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018, Lexicomp 2018, FDA Drug Shortages 2018)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Avelox (moxifloxacin)	Baxdela (delafloxacin)	Cipro (ciprofloxacin)	ciprofloxacin extended release	Factive (gemifloxacin)	Levaquin (levofloxacin)	ofloxacin
Acute bacterial sinusitis caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.	✔ ∞		✔ ∞			✔ ∞	
Acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae* or *H. influenzae.*							✔ ∞
Acute bacterial exacerbation of chronic bronchitis caused by *S. pneumoniae*, *H. influenzae*, *Haemophilus parainfluenzae, Klebsiella pneumoniae,* methicillin-susceptible *Staphylococcus aureus, or M. catarrhalis.*	✔ ∞				✔ ‡ ∞	✔ ǂ ∞	
Community acquired pneumonia caused by *S. pneumoniae* or *H. influenzae.*							✔
Community acquired pneumonia caused by *S. pneumoniae**, *H. influenzae*, *M. catarrhalis,* methicillin-susceptible *S. aureus, K. pneumoniae, Mycoplasma pneumoniae, or Chlamydia pneumoniae.*	✔				✔ ǂǂ	✔ ∫	
Lower respiratory tract infections caused *by Escherichia coli, K. pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, H. influenzae, H. parainfluenzae*, or penicillin-susceptible *S. pneumoniae*.** Also, *M. catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.			✔				
Uncomplicated skin and skin structure infections caused by methicillin-susceptible *S. aureus* or *Streptococcus pyogenes.*	✔					✔	
Uncomplicated skin and skin structure infections caused by methicillin-susceptible *S. aureus*, *S. pyogenes,* or *P. mirabilis.*							✔
Complicated skin and skin structure infections caused by methicillin-susceptible *S. aureus, E. coli, K. pneumoniae, or E. cloacae.*	✔						
Complicated skin and skin structure infections caused by methicillin-susceptible *S. aureus, S. pyogenes, Enterococcus faecalis,* or *P. mirabilis.*						✔	
Skin and skin structure infections caused by *E. coli*, *K. pneumoniae*, *E. cloacae*, *P. aeruginosa*, methicillin-resistant and methicillin-susceptible *S. aureus*, *S. haemolyticus*, *S. lugdunensis*, *S. agalactiae*, *S. anginosus* Group, *S. pyogenes*, and *E. faecalis*		✔					
Skin and skin structure infections caused by *E. coli, K. pneumoniae, E. cloacae, P. mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, P. aeruginosa*, methicillin-susceptible *S. aureus*, methicillin-susceptible *Staphylococcus epidermidis,* or *S. pyogenes.*			✔				

Indication	Avelox (moxifloxacin)	Baxdela (delafloxacin)	Cipro (ciprofloxacin)	ciprofloxacin extended release	Factive (gemifloxacin)	Levaquin (levofloxacin)	ofloxacin
Bone and joint infections caused by *E. cloacae, Serratia marcescens*, or *P. aeruginosa*.			✔				
Complicated intra-abdominal infections caused by *E. coli, Bacteroides fragilis, Streptococcus anginosus, Streptococcus constellatus, E. faecalis, P. mirabilis, Clostridium perfringens, Bacteroides thetaiotaomicron,* or *Peptostreptococcus* species.	✔						
Complicated intra-abdominal infections (used in combination with metronidazole) caused by *E. coli, P. aeruginosa, P. mirabilis, K. pneumoniae*, or *B. fragilis*.			✔				
Uncomplicated urinary tract infection (acute cystitis) caused by *E. coli, P. mirabilis, E. faecalis,* or *Staphylococcus saprophyticus.*				✔ ∞			
Uncomplicated urinary tract infection caused by *E. coli, K. pneumoniae,* or *S. saprophyticus.*						✔ ∞	
Complicated urinary tract infection caused by *E. coli, P. mirabilis, K. pneumoniae, E. faecalis,* or *P. aeruginosa.*				✔		✔ ǂǂ	
Complicated urinary tract infection caused by *E. coli, P. mirabilis, K. pneumoniae, P. aeruginosa, or Citrobacter diversus.*							✔
Acute uncomplicated pyelonephritis caused by *E. coli.*				✔		✔	
Urinary tract infection caused by *E. coli, K. pneumoniae, E. cloacae, Serratia marcescens, P. mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter koseri* (*diversus*), *Citrobacter freundii, P. aeruginosa,* methicillin-susceptible *S. epidermidis, S. saprophyticus,* or vancomycin-susceptible *E. faecalis*.			✔ †				
Acute uncomplicated cystitis in females caused by *E. coli* or *S. saprophyticus*.			✔ ∞				
Acute uncomplicated cystitis caused by *C.diversus, Enterobacter aerogenes, E. coli, K. pneumoniae, P. mirabilis,* or *P. aeruginosa.*							✔ ∞
Chronic bacterial prostatitis caused *by E. coli* or *P. mirabilis.*			✔				
Chronic bacterial prostatitis caused *by E. coli, E. faecalis* or methicillin-susceptible *S. epidermidis.*						✔	
Prostatitis caused by *E. coli.*							✔
Infectious diarrhea caused by *E. coli* (enterotoxigenic isolates), *Campylobacter jejuni, Shigella boydii, Shigella dysenteriae, Shigella flexneri* or *Shigella sonnei*.			✔				
Typhoid fever (enteric fever) caused by *Salmonella typhi*.			✔				
Uncomplicated cervical and urethral gonorrhea caused by *Neisseria gonorrhoeae*.			✔				✔
Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.			✔ ††			✔	
Plague caused by *Yersinia pestis* (treatment and prophylaxis).	✔		✔ ††			✔	

Indication	Avelox (moxifloxacin)	Baxdela (delafloxacin)	Cipro (ciprofloxacin)	ciprofloxacin extended release	Factive (gemifloxacin)	Levaquin (levofloxacin)	ofloxacin
Urethritis and cervicitis caused by *Chlamydia trachomatis*							✔
Mixed infections of the urethra and cervix or pelvic inflammatory disease due to *N. gonorrhoeae and C. trachomatis.*							✔

* Multi-drug resistant isolates
∫ Also indicated for *H. parainfluenzae* and *Legionella pneumophilia*. Also indicated for nosocomial pneumonia caused by methicillin-susceptible *S. aureus*, *P. aeruginosa*, *S. marcescens, E. coli, K. pneumoniae, H. influenzae*, or *S. pneumoniae*. Adjunctive therapy should be used as clinically indicated. Where *P. aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended.
‡ Not indicated for *K. pneumoniae* or methicillin-susceptible *S. aureus.*
‡‡ Not indicated for methicillin-susceptible *S. aureus.*
ǂ Not indicated for *K. pneumoniae*.
ǂǂ Also indicated for *E. cloacae.*
** Ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *S. pneumoniae.*
† Complicated urinary tract infections and pyelonephritis due to *E. coli* for children one to 17 years but not drug of first choice.
†† For adults and children
∞ Reserve for use in patients who have no alternative treatment options.

(Prescribing information: Avelox 2017, Baxdela 2017, Cipro 2017, ciprofloxacin extended release tablet 2016, Factive 2016, Levaquin 2017, ofloxacin 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The efficacy of the fluoroquinolones has been well documented in the treatment of genitourinary, respiratory, dermatological, and other miscellaneous infections, including typhoid fever and complicated intra-abdominal infections.
- A meta-analysis demonstrated no significant differences in clinical or microbiological efficacy between the quinolones for the treatment of acute cystitis *(Rafalsky et al 2006)*. Another meta-analysis found no difference between fluoroquinolones and other classes of antibiotics for uncomplicated cystitis with regard to symptomatic cure (*Zalmanovici-Trestioreanu et al 2010*). For the treatment of urinary tract infections, 2 randomized clinical trials were conducted that directly compared the once-daily, extended-release formulation of ciprofloxacin with the equivalent dose of the twice-daily immediate release formulation (*Fourcroy et al 2005, Talan et al 2004*). Overall, the extended-release formulation was found to provide comparable bacteriological eradication rates and/or clinical cure rates as the immediate-release formulation with comparable rates of adverse reactions.
- Several head-to-head trials have demonstrated no significant differences between fluoroquinolone agents for the treatment of urinary tract infections (*Arredondo-Garcia et al 2004, Auquer et al 2002, Peterson et al 2008, Raz et al 2000, Richard et al 2008, Schaeffer et al 1992*). In one study, cefpodoxime did not demonstrate non-inferiority vs ciprofloxacin in the treatment of acute cystitis (*Hooten et al 2012*).
- Both levofloxacin and ciprofloxacin have demonstrated efficacy in the treatment of bacterial prostatitis (*Bundrick et al 2003, Naber et al 2008*). In a meta-analysis, no fluoroquinolone demonstrated consistent superiority over another for the treatment of chronic bacterial prostatitis (*Perletti et al 2013*).
- Four meta-analyses have been conducted comparing quinolones to other antibiotics for the treatment of acute sinusitis and community-acquired pneumonia (*Karageorgopoulos et al 2008, Salkind et al 2002, Varadakas et al 2008, Raz-*

Pasteur et al 2015). Results from these analyses established the efficacy of the quinolones in respiratory infections. When compared to other antibiotics (β-lactams, macrolides, β-lactams/macrolide combination therapy, doxycycline, or a ketolide), treatment with quinolones was generally clinically comparable or superior. However, the majority of trials assessed in the meta-analysis by *Salkind et al* included sparfloxacin, trovafloxacin, and grepafloxacin, which are not currently available in the United States. In another meta-analysis, gemifloxacin was shown to have a higher treatment success rate than other fluoroquinolones and similar rates to β-lactams and macrolides in the treatment of community-acquired pneumonia and acute exacerbations of chronic bronchitis (*Zhang et al 2012*). Eradication rates were similar between gemifloxacin and other fluoroquinolones, β-lactams, and macrolides.

- A meta-analysis in patients with acute chronic obstructive pulmonary disease (COPD) exacerbations did not find a consistent significant benefit of antibiotics across outcomes with the exception of patients admitted to the intensive care unit (*Vollenweider et al 2012*). Additionally, a network meta-analysis in patients with acute COPD exacerbations showed that ofloxacin and ciprofloxacin had high clinical cure rates with median rates of adverse effects (*Zhang et al 2017*).
- For patients with skin and skin structure infections, 2 trials demonstrated similar clinical success and eradication rates with levofloxacin and ciprofloxacin (*Nichols et al 1997, Nicodemo et al 1998*). Additionally, results from clinical trials have revealed similar cure rates for delafloxacin compared to tigecycline, linezolid, and the combination of vancomycin/aztreonam in the treatment of acute bacterial skin and skin structure infections (*O'Riordan et al 2015, Kingsley et al 2016, O'Riordan et al 2016, Pullman et al 2017*).
- A meta-analysis of 4 randomized, controlled trials evaluated moxifloxacin vs other combination antibiotic regimens for the treatment of intra-abdominal infections (*Mu et al 2012*). This analysis showed that moxifloxacin had similar clinical cure rates, bacteriological success rates, and mortality compared with those of the control group.

CLINICAL GUIDELINES

- Treatment guidelines for the treatment of community-acquired pneumonia, urinary tract infections, skin and soft tissue infections, and vertebral osteomyelitis recommend fluoroquinolones as alternative agents (*Berbari et al 2015, Chow et al 2012, Gupta et al 2011, Mandell et al 2007, Stevens et al 2014*). An update of the Infectious Diseases Society of America (IDSA) community-acquired pneumonia in adults guideline is currently in progress.
- Fluoroquinolones may be considered first-line therapy for bacterial prostatitis, inhalational anthrax, and some types of infectious diarrhea *(Shane et al 2017, Stern et al 2008, Khan 2017*).
- The Centers for Disease Control and Prevention has determined that fluoroquinolones should no longer be used for the treatment of gonorrhea due to resistant organisms. They are not recommended for routine use in pelvic inflammatory disease unless antimicrobial susceptibility testing is performed and the fluoroquinolone will be administered in combination with metronidazole (*CDC 2015*).

SAFETY SUMMARY

- All fluoroquinolones carry a boxed warning for disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly observed adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (ie, hallucinations, anxiety, depression, insomnia, severe headaches, confusion).
  - The risk for fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart, or lung transplants.
- Due to the potentially permanent serious adverse events involving the tendons, muscles, joints, nerves, and central nervous system, the FDA published a safety communication, which recommends reserving the use of fluoroquinolones in acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections for patients with no alternative treatment options (*FDA press release 2016*). A subsequent safety alert released by the FDA stated that after review, it did not find that use of fluoroquinolones resulted in detached retina, aortic aneurysm, or aortic dissection (*FDA press release 2017*).
- Fluoroquinolones may cause QT interval prolongation, anaphylactic reactions, phototoxicity, *Clostridium difficile* diarrhea, and blood glucose disturbances. Additionally, fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis and should therefore be avoided.
- In a recent systematic review and meta-analysis, the use of fluoroquinolones was found to potentially increase the risk of serious arrhythmias and cardiovascular death. Moxifloxacin and levofloxacin showed a higher risk of serious arrhythmias (*Liu et al 2017*).

- The most common adverse events with fluoroquinolones include gastrointestinal (eg, nausea, vomiting, diarrhea) and central nervous system (eg, dizziness, headache) toxicities. Rash is frequently observed with fluoroquinolones and is especially common with gemifloxacin.
- All fluoroquinolones bind to multivalent cations. Administration of a fluoroquinolone should be separated by at least two hours from products containing aluminum, magnesium, iron, or zinc.
- Additional drug interactions include Class IA and Class III antiarrhythmics, nonsteroidal anti-inflammatory drugs, phenytoin, probenecid, sulfonylureas, theophylline, tizanidine, and warfarin.
- Oral dosing of ciprofloxacin, gemifloxacin, levofloxacin, and ofloxacin should be adjusted in renal impairment. Delafloxacin is not recommended for use in patients with end stage renal disease. The daily dose of ofloxacin should not exceed 400 mg in patients with severe liver dysfunction.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Avelox (moxifloxacin)*,†	Tablet	Oral	Every 24 hours	
Baxdela (delafloxacin)*	Tablet	Oral	Every 12 hours	Not recommended in ESRD (eGFR < 15 including hemodialysis)
Cipro (ciprofloxacin)*,†	Tablet, suspension	Oral	Every 12 hours	Oral dose adjustments are recommended in renal impairment. Ofloxacin dose should not exceed 400 mg per day in patients with severe liver dysfunction disorders.
ciprofloxacin extended release	Tablet	Oral	Every 24 hours	
Factive (gemifloxacin)	Tablet	Oral	Every 24 hours	
Levaquin (levofloxacin)* ,†	Tablet, oral solution	Oral	Every 24 hours	
ofloxacin†	Tablet	Oral	Every 12 hours	

Abbreviations: eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease
* Also available as intravenous solution
† Also available as otic and/or ophthalmic formulations
See the current prescribing information for full details

CONCLUSION

- Fluoroquinolones have a broad spectrum of activity and may be used to treat a variety of infections. Current clinical evidence supports the efficacy of all products in this class for their FDA-approved indications, and efficacy appears comparable among agents. No fluoroquinolone has consistently demonstrated superiority over another.
- Fluoroquinolones should be considered first-line therapy for bacterial prostatitis, inhalational anthrax, and some types of infectious diarrhea (*Shane et al 2017, Stern et al 2008, Khan 2017*).
  - Treatment guidelines recommend fluoroquinolones as alternative agents for the treatment of community-acquired pneumonia, urinary tract infections, skin and soft tissue infections, and vertebral osteomyelitis (*Berberi et al 2015, Gupta et al 2011, Mandell et al 2007, Solomkin et al 2010, Stevens et al 2014*). They are not generally recommended for the treatment of bacterial sinusitis (*Chow et al 2012*). The Centers for Disease Control and Prevention has determined that fluoroquinolones should no longer be used for the treatment of gonorrhea due to resistant organisms (*CDC 2015*).
- All fluoroquinolones share a boxed warning for disabling and potentially irreversible serious adverse reactions such as tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (ie, hallucinations, anxiety, depression, insomnia, severe headaches, confusion). Due to the risk for permanent adverse effects, the FDA warns that fluoroquinolones should be reserved for patients with no other treatment options when used to treat acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections (*FDA press release 2016*).
- Additional warnings for the class include QT prolongation, blood glucose disturbances, *Clostridium difficile*-associated diarrhea, and phototoxicity. Fluoroquinolones should be avoided in patients with a history of myasthenia gravis.

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