

Fluoroquinolones Hybrid Molecules as Promising Antibacterial Agents in the Fight against Antibacterial Resistance

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Table S1. Antimicrobial spectrum and indications for the antibacterial (F)QNs for human use; the generation is mentioned in parentheses (Ref. = references).

| Antibacterial (F)QNs | Antimicrobial spectrum, indications | Ref. |
|-----------------------------------|---|-------|
| Nalidixic acid (1 st) | Urinary tract infections caused by Gram-negative bacteria (<i>Escherichia coli</i> , <i>Klebsiella</i> , <i>Enterobacter</i> , <i>Citrobacter</i> , and <i>Proteus</i> spp., <i>Shigella</i> , <i>Salmonella</i> , and <i>Providencia</i>). Resistant pathogens: Strains of <i>Pseudomonas aeruginosa</i> , <i>Neisseria gonorrhoeae</i> , <i>Haemophilus influenzae</i> , Gram-positive cocci and anaerobes. | [1] |
| Pefloxacin (2 nd) | Gram-negative organisms and staphylococci; respiratory tract, urogenital tract, bone and joint infections, septicemia and surgical infections. | [2] |
| Norfloxacin (2 nd) | Gram-negative and Gram-positive aerobic bacteria. Urinary tract infections caused by <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Enterobacter cloacae</i> , <i>Proteus mirabilis</i> , indole-positive <i>Proteus</i> spp., including <i>Proteus vulgaris</i> , <i>Providencia rettgeri</i> , <i>Morganella morganii</i> , <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , and <i>Staphylococcus epidermidis</i> , and group-D streptococci. Generally not effective against anaerobic bacteria. The fluorine atom facilitates the activity against Gram-positive organisms, while the piperazine moiety improves antipseudomonal activity. | [1] |
| Ciprofloxacin (2 nd) | Bacterial gastroenteritis caused by Gram-negative bacilli (enteropathogenic <i>Escherichia coli</i> , <i>Salmonella</i> spp. (including <i>Salmonella typhi</i>), <i>Shigella</i> spp., <i>Vibrio</i> spp., and <i>Aeromonas hydrophilia</i>); respiratory tract infections (especially bronchitis and pneumonia caused by Gram-negative bacteria); infections of the skin, soft tissues, bones, and joints; uncomplicated and complicated urinary tract infections caused by Gram-negative bacteria; chronic infections characterised by renal tissue involvement; venereal diseases; postexposure treatment of inhalational anthrax. | [1] |
| Ofloxacin (2 nd) | Similar to ciprofloxacin. | [1] |
| Nadifloxacin (2 nd) | Gram-positive (e.g., <i>Staphylococcus aureus</i> , methicillin-resistant <i>Staphylococcus aureus</i> (MRSA), and <i>Staphylococcus epidermidis</i>) and Gram-negative (e.g., <i>Pseudomonas aeruginosa</i>) bacteria, including anaerobes (<i>Propionibacterium acnes</i>); topical use. | [3,4] |

| Antibacterial (F)QNs | Antimicrobial spectrum, indications | Ref. |
|---------------------------------|--|-------------|
| Levofloxacin (3 rd) | Antibacterial spectrum and indications similar to the racemate (ofloxacin). | [1,5–7] |
| Moxifloxacin (4 th) | Community-acquired respiratory tract infections caused by typical and atypical respiratory pathogens, intracellular respiratory pathogens; skin and skin structure infections, intra-abdominal infections; Gram-negative pathogens and anaerobes; <i>Mycobacteria</i> spp., <i>Legionella</i> . | [7–11] |
| Gemifloxacin (4 th) | Acute exacerbations of chronic bronchitis, community-acquired pneumonia; <i>Streptococcus pneumoniae</i> , <i>Klebsiella pneumoniae</i> , <i>Moraxella catarrhalis</i> , <i>Mycoplasma pneumoniae</i> , <i>Chlamydia pneumoniae</i> , <i>Haemophilus influenzae</i> ; withdrawn by the EMA in 2009 due to concern for genotoxic side effects. | [3,7,12–14] |
| Besifloxacin (4 th) | Topical use (ophthalmic); bacterial conjunctivitis. | [15,16] |
| Finafloxacin (4 th) | Acute otitis externa caused by susceptible strains of <i>Pseudomonas aeruginosa</i> and <i>Staphylococcus aureus</i> . | [17,18] |
| Delafloxacin (4 th) | Acute bacterial skin and skin structure infections caused by <i>Staphylococcus aureus</i> (including MRSA), <i>Staphylococcus haemolyticus</i> , <i>Staphylococcus lugdunensis</i> , <i>Streptococcus pyogenes</i> , <i>Streptococcus agalactiae</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Enterobacter cloacae</i> , <i>Pseudomonas aeruginosa</i> ; Community-acquired bacterial pneumonia caused by <i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i> (methicillin-susceptible (MSSA) isolates only), <i>Klebsiella pneumoniae</i> , <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Haemophilus influenzae</i> , <i>Haemophilus parainfluenzae</i> , <i>Chlamydia pneumoniae</i> , <i>Legionella pneumophila</i> , <i>Mycoplasma pneumoniae</i> . | [19,20] |

Table S2. Side effects/adverse reactions of the antibacterial (F)QNs ¹.

| Affected system | Symptom | Higher risk | Lower risk |
|---|---|--|--|
| Musculoskeletal and connective tissues | Arthralgia | Ciprofloxacin | Norfloxacin, Ofloxacin (1-3%), Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%), Gemifloxacin ($\leq 0.1\%$) |
| | Back pain | | Moxifloxacin (0.1-1%), Gemifloxacin ($\leq 0.1\%$) |
| | Joint stiffness | | Ciprofloxacin |
| | Leg cramps | | Gemifloxacin ($\leq 0.1\%$) |
| | Muscle injuries (including rupture) | | Levofloxacin (postmarketing) |
| | Muscle spasms | | Norfloxacin, Moxifloxacin (0.1-1%) |
| | Muscle weakness | | Ciprofloxacin, Moxifloxacin (postmarketing) |
| | Myalgia | Ciprofloxacin, Delafloxacin ($<2\%$) | Norfloxacin, Ofloxacin (1-3%), Levofloxacin (0.1-1%) |
| | Myasthenia | | Ciprofloxacin |
| | <i>Myasthenia Gravis</i> (exacerbation) | | Ciprofloxacin, Norfloxacin, Moxifloxacin (postmarketing) |
| | Pain in extremity | | Moxifloxacin (0.1-1%) |
| | Rhabdomyolysis | | Levofloxacin (postmarketing) |
| | Skeletal (and/or Musculoskeletal) pain | | Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%) |
| | Tendinitis | Ciprofloxacin, Norfloxacin | Nalidixic acid, Levofloxacin (0.1-1%) |
| | Tendon ruptures (including Achilles tendon) | Ciprofloxacin, Norfloxacin | Nalidixic acid, Levofloxacin (postmarketing), Moxifloxacin (postmarketing) |
| Central nervous system and psychiatric disorders | 6th cranial nerve palsy | | Nalidixic acid |
| | Abnormal EEG (electroencephalogram) | | Levofloxacin (postmarketing) |
| | Abnormal gait | | Ciprofloxacin, Moxifloxacin (postmarketing) |
| | Agitation | Ciprofloxacin | Pefloxacin, Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%) |
| | Altered coordination | | Moxifloxacin (postmarketing) |
| | Anorexia | | Ciprofloxacin, Norfloxacin (0.3-1.0%), Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%), Gemifloxacin (0.1-1%) |
| | Anxiety | Ciprofloxacin, Delafloxacin ($<2\%$) | Pefloxacin, Ofloxacin (1-3%), Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%) |

| Affected system | Symptom | Higher risk | Lower risk |
|-----------------|---|--|--|
| | Asthenia | | Norfloxacin (0.3-1.0%), Ofloxacin (<1%), Moxifloxacin (0.1-1%), Gemifloxacin (≤0.1%) |
| | Ataxia | | Ciprofloxacin, Norfloxacin |
| | Brief convulsions/ Seizures (eg. <i>Status Epilepticus</i>) | Ciprofloxacin | Nalidixic acid, Norfloxacin, Ofloxacin (1-3%), Levofloxacin (0.1-1%) |
| | Cognitive change | | Ofloxacin (1-3%) |
| | Confusional state | Ciprofloxacin | Norfloxacin, Ofloxacin (1-3%), Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%) |
| | Delirium | | Ciprofloxacin, |
| | Depersonalisation | | Ciprofloxacin |
| | Depression | Ciprofloxacin | Ofloxacin (1-3%), Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%) |
| | Disorientation | | Moxifloxacin (0.1-1%) |
| | Dizziness | Nalidixic acid, Ciprofloxacin, Norfloxacin (2.6%), Levofloxacin (≥1), Moxifloxacin (≥1%), Gemifloxacin (1.7%), Delafloxacin (<2%) | |
| | Dream abnormality | Delafloxacin (<2%) | Ofloxacin (1-3%), Levofloxacin (0.1-1%) |
| | Drowsiness | Nalidixic acid | |
| | Encephalopathy | | Levofloxacin (postmarketing) |
| | Euphoria | | Ofloxacin (1-3%) |
| | Guillain-Barré | | Norfloxacin |
| | Headache | Nalidixic acid, Ciprofloxacin, Norfloxacin (2.0%), Ofloxacin (9%), Levofloxacin (≥1), Moxifloxacin (≥1%), Gemifloxacin (4.2%), Besifloxacin (1-2%), Delafloxacin (3%), Finafloxacin (1.8%) | |
| | Hallucinations | Ciprofloxacin | Norfloxacin, Ofloxacin (1-3%), Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%) |
| | Hyperkinesias | | Levofloxacin (0.1-1%) |
| | Hypertonia | | Ciprofloxacin, Levofloxacin (0.1-1%) |
| | Increased intracranial pressure | Ciprofloxacin | Nalidixic acid, Norfloxacin |
| | Insomnia | Ciprofloxacin, Ofloxacin (7%), Levofloxacin (≥1), Moxifloxacin (≥1%), Delafloxacin (<2%) | Gemifloxacin (0.1-1%) |
| | Irritability | | Ciprofloxacin |
| | Lethargy | | Moxifloxacin (0.1-1%) |
| | Malaise | | Ciprofloxacin, Ofloxacin (<1%), Moxifloxacin (0.1-1.%) |

| Affected system | Symptom | Higher risk | Lower risk |
|------------------------------|--|--|---|
| | Manic reaction | | Ciprofloxacin |
| | Migraine | | Ciprofloxacin |
| | Myoclonus | | Ciprofloxacin, Norfloxacin |
| | Nervousness | Ciprofloxacin, Ofloxacin (1-3%) | Pefloxacin, Moxifloxacin (0.1-1%) |
| | Nightmares | Ciprofloxacin | Levofloxacin (0.1-1%) |
| | Paranoia | Ciprofloxacin | Levofloxacin (postmarketing) |
| | Phobia | | Ciprofloxacin |
| | | | Norfloxacin, Levofloxacin |
| | Psychotic reactions | | (postmarketing), Moxifloxacin |
| | | | (postmarketing) |
| | Restlessness | | Ciprofloxacin, Norfloxacin, |
| | | | Moxifloxacin (0.1-1%) |
| | Sleep disorders | Ofloxacin (1-3%) | Levofloxacin (0.1-1%) |
| | Somnolence | Ofloxacin (1-3%) | Levofloxacin (0.1-1%), Moxifloxacin |
| | | | (0.1-1%), Gemifloxacin (0.1-1%) |
| | Suicide attempt and Suicidal ideation | | Levofloxacin (postmarketing), Moxifloxacin (postmarketing) |
| | (Pre)Syncope | Ofloxacin (1-3%), Delafloxacin (<2%) | Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%), Gemifloxacin (postmarketing) |
| | Toxic psychosis | Ciprofloxacin | Nalidixic acid, Norfloxacin |
| | Transient ischemic attack | | Gemifloxacin (postmarketing) |
| | | | Norfloxacin, Ofloxacin (1-3%), Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%), Gemifloxacin (≤0.1%) |
| | Tremor | Ciprofloxacin | Ciprofloxacin |
| | Twitching | | Ofloxacin (1-3%), Levofloxacin (0.1-1%), Gemifloxacin (≤0.1%) |
| | Vertigo | Nalidixic acid | |
| | Weakness | Nalidixic acid, Ciprofloxacin | Norfloxacin |
| Peripheral nervous system | Dysesthesia | Ciprofloxacin | Nalidixic acid, Norfloxacin |
| | Hypoesthesia | Ciprofloxacin, Delafloxacin (<2%) | Nalidixic acid, Norfloxacin, Moxifloxacin (0.1-1%) |
| | Paresthesia | Ciprofloxacin, Delafloxacin (<2%) | Nalidixic acid, Norfloxacin (0.3-1.0%), Ofloxacin (1-3%), Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%) |
| | Peripheral neuropathy | Ciprofloxacin | Nalidixic acid, Pefloxacin, Norfloxacin, Levofloxacin (postmarketing), Moxifloxacin (postmarketing) |
| | Polyneuropathy | | Ciprofloxacin, Moxifloxacin (postmarketing) |
| Eyes/ Ears/ Nose/ Mouth | Ageusia | | Ciprofloxacin, Levofloxacin (postmarketing) |
| | Anosmia | | Ciprofloxacin, Levofloxacin (postmarketing) |
| | Blurred vision | Besifloxacin (1-2%), Delafloxacin (<2%) | Ciprofloxacin, Levofloxacin (postmarketing), Moxifloxacin (0.1-1%) |

| Affected system | Symptom | Higher risk | Lower risk |
|-----------------------|---|--------------------------------------|---|
| | Conjunctival redness | Besifloxacin (2%) | |
| | Decreased visual acuity | | Ciprofloxacin, Levofloxacin (postmarketing) |
| | Diplopia | | Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing) |
| | Disturbed vision (eg. chromatopsia and photopsia) | Ofloxacin (1-3%) | Ciprofloxacin, Levofloxacin (postmarketing), Gemifloxacin ($\leq 0.1\%$) |
| | Dry mouth | Ofloxacin (1-3%) | Moxifloxacin (0.1-1%), Gemifloxacin (0.1-1%) |
| | Dysgeusia | Delafloxacin (<2%), Ofloxacin (1-3%) | Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing), Moxifloxacin (0.1-1%), Gemifloxacin (0.1-1%) |
| | Dysphonia | | Levofloxacin (postmarketing) |
| | Ear discomfort | | Finaxofloxacin (0.3%) |
| | Ear pain | | Finaxofloxacin (0.5%) |
| | Ear pruritus | Finaxofloxacin (1.3%) | |
| | Epistaxis | | Levofloxacin (0.1-1%), Ofloxacin (<1%) |
| | Eye irritation | Besifloxacin (1-2%) | |
| | Eye pain | Besifloxacin (1-2%) | |
| | Eye pruritus | Besifloxacin (1-2%) | |
| | Glossitis | | Levofloxacin (0.1-1%), Ciprofloxacin, Norfloxacin, Ofloxacin (1-3%), Levofloxacin (postmarketing), Moxifloxacin (postmarketing) |
| | Hearing loss | | Ciprofloxacin, Norfloxacin, Ciprofloxacin |
| | Nystagmus | | |
| | Oral candidiasis | Delafloxacin (<2%) | |
| | Otitis externa | Finaxofloxacin (1.8%) | |
| | Otitis media | Finaxofloxacin (1.3%) | |
| | Papilledema | | Nalidixic acid |
| | Parosmia | | Levofloxacin (postmarketing) |
| | Photophobia | | Ofloxacin (1-3%) |
| | Retinal hemorrhage | | Gemifloxacin (postmarketing) |
| | Scotoma | | Levofloxacin (postmarketing) |
| | Stomatitis | | Norfloxacin, Levofloxacin (0.1-1%), Ciprofloxacin, Norfloxacin, Ofloxacin (1-3%), Levofloxacin (postmarketing), Moxifloxacin (0.1-1%) |
| | Tinnitus | Delafloxacin (<2%) | |
| | Vertigo | Delafloxacin (<2%) | Moxifloxacin (0.1-1%) |
| | Vision loss | | Moxifloxacin (postmarketing) |
| | Uveitis | | Norfloxacin |
| Cardiovascular system | Angina Pectoris | | Ciprofloxacin, Moxifloxacin (0.1-1%) |
| | Arrhythmia | | Ciprofloxacin, Norfloxacin |
| | Atrial fibrillation | | Moxifloxacin (0.1-1%) |
| | Bradycardia | Delafloxacin (<2%) | Moxifloxacin (0.1-1%) |

| Affected system | Symptom | Higher risk | Lower risk |
|-------------------|------------------------------|---|---|
| | Cardiac failure | | Moxifloxacin (0.1-1%) |
| | Cardiopulmonary arrest | | Ciprofloxacin, Ofloxacin (<1%), Levofloxacin (0.1-1%), , Moxifloxacin (0.1-1%), Moxifloxacin (postmarketing) |
| | Cardiovascular collapse | | Norfloxacin |
| | Edema | Levofloxacin ($\geq 1\%$), Delafloxacin (<2%) | Ofloxacin (<1%), Moxifloxacin (0.1-1%), Gemifloxacin (postmarketing) |
| | Hypertension | Delafloxacin (<2%) | Ofloxacin (<1%), Moxifloxacin (0.1-1%) |
| | Hypotension | Delafloxacin (<2%) | Ciprofloxacin, Norfloxacin, Ofloxacin (<1%), Moxifloxacin (0.1-1%) |
| | Myocardial infarction | | Ciprofloxacin |
| | Palpitations | Delafloxacin (<2%) | Ofloxacin (<1%), Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%) |
| | Supraventricular tachycardia | | Gemifloxacin (postmarketing) |
| | Syncope | | Ciprofloxacin, Norfloxacin, Ciprofloxacin, Levofloxacin |
| | Sinus tachycardia | Delafloxacin (<2%) | (postmarketing), Moxifloxacin (0.1-1%) |
| | <i>Torsade de pointes</i> | | Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing), Moxifloxacin (postmarketing) |
| | Vasodilation | | Ofloxacin (<1%), Levofloxacin (postmarketing) |
| | Ventricular arrhythmia | | Ciprofloxacin, Levofloxacin (0.1-1%), |
| | Ventricular tachyarrhythmias | | Moxifloxacin (postmarketing) |
| | Ventricular tachycardia | | Levofloxacin (0.1-1%), Nalidixic acid, Ciprofloxacin, Norfloxacin, Levofloxacin |
| | QTc interval prolongation | | (postmarketing), Moxifloxacin (0.1-1%), Gemifloxacin (postmarketing) |
| Respiratory tract | Asthma | | Moxifloxacin (0.1-1%) |
| | Bronchospasm | | Ciprofloxacin, Moxifloxacin (0.1-1%) |
| | Cough | | Ofloxacin (1-3%) Ciprofloxacin, Norfloxacin, |
| | Dyspnea | Levofloxacin ($\geq 1\%$) | Moxifloxacin (0.1-1%), Gemifloxacin ($\leq 0.1\%$) |
| | Hemoptysis | | Ciprofloxacin |
| | Laryngeal edema | | Ciprofloxacin |
| | Pharyngeal edema | | Ciprofloxacin, Norfloxacin |

| Affected system | Symptom | Higher risk | Lower risk |
|------------------------|---------------------------------|--|---|
| | Pharyngitis | Ofloxacin (1-3%) | Gemifloxacin ($\leq 0.1\%$) |
| | Pneumonia | | Gemifloxacin ($\leq 0.1\%$) |
| | Respiratory arrest | | Ofloxacin (1-3%) |
| | Rhinorrhea | | Ofloxacin (1-3%) |
| | Wheezing | | Moxifloxacin (0.1-1%) |
| Gastrointestinal tract | | Nalidixic acid, Norfloxacin (1.6%), Ofloxacin (1-3%), Levofloxacin ($\geq 1\%$), Moxifloxacin ($\geq 1\%$), Gemifloxacin (2.2%), Delafloxacin ($< 2\%$) | Ciprofloxacin |
| | Abdominal discomfort/pain | | |
| | Abdominal distension | | Moxifloxacin (0.1-1%) |
| | Constipation | Ofloxacin (1-3%), Levofloxacin ($\geq 1\%$), Moxifloxacin ($\geq 1\%$) | Norfloxacin (0.3-1.0%), Gemifloxacin (0.1-1%) |
| | | Nalidixic acid, Ciprofloxacin (1.6%), Ofloxacin (4%), | |
| | Diarrhea | Levofloxacin ($\geq 1\%$), Moxifloxacin ($\geq 1\%$), Gemifloxacin (5.0%), Delafloxacin (8%) | Norfloxacin (0.3-1.0%) |
| | | | |
| | Dyspepsia | Levofloxacin ($\geq 1\%$), Moxifloxacin ($\geq 1\%$), Delafloxacin ($< 2\%$) | Norfloxacin (0.3-1.0%), Ofloxacin ($< 1\%$), Gemifloxacin (0.1-1%) |
| | Dysphagia | | Norfloxacin |
| | Esophagitis | | Levofloxacin (0.1-1%), Norfloxacin (0.3-1.0%), Moxifloxacin (0.1-1%), Gemifloxacin (0.1-1%) |
| | Flatulence | Ofloxacin (1-3%) | |
| | | | |
| | Gastritis | | Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%), Gemifloxacin (0.1-1%) |
| | Gastroenteritis | | Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%), Gemifloxacin ($\leq 0.1\%$) |
| | Gastrointestinal bleeding | | Ciprofloxacin |
| | Gastrointestinal candidiasis | | Ciprofloxacin |
| | Gastrointestinal distress | Ofloxacin (1-3%) | |
| | | | |
| | Gastroesophageal reflux disease | | Moxifloxacin (0.1-1%) |
| | Intestinal perforation | | Ciprofloxacin |
| | | | |
| | Nausea | Nalidixic acid, Ciprofloxacin (2.5%), Norfloxacin (2.6%), Ofloxacin (10%), Levofloxacin ($\geq 1\%$), Moxifloxacin ($\geq 1\%$), Gemifloxacin (3.7%), Delafloxacin (8%), Finafloxacin (1%) | |

| Affected system | Symptom | Higher risk | Lower risk |
|------------------------------------|--|--|--|
| | Non-specified gastrointestinal disorder | | Gemifloxacin ($\leq 0.1\%$) |
| | Pancreatitis | | Ciprofloxacin, Norfloxacin, Levofloxacin (0.1-1%), Ciprofloxacin, Norfloxacin, Levofloxacin (0.1-1%), Gemifloxacin (postmarketing - antibiotic-associated colitis) |
| | Pseudomembranous colitis (eg. <i>Clostridium difficile</i>) | Delafloxacin ($< 2\%$) | |
| | Vomiting | Nalidixic acid, Ciprofloxacin (1%), Ofloxacin (4%), Levofloxacin ($\geq 1\%$), Moxifloxacin ($\geq 1\%$), Gemifloxacin (1.6%), Delafloxacin (2%) | Norfloxacin (0.3-1.0%), Gemifloxacin (0.1-1%) |
| Hepatobiliary Disorders | Abnormal hepatic function | Ciprofloxacin (1.3%) | Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%) |
| | Acute hepatic failure | | Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing), Moxifloxacin (postmarketing) |
| | Acute hepatic necrosis | | Ciprofloxacin, Norfloxacin, Moxifloxacin (postmarketing) |
| | Cholestasis/Cholestatic jaundice | | Nalidixic acid, Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing), Moxifloxacin (postmarketing) |
| | Hepatitis | | Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing), Moxifloxacin (postmarketing) |
| Renal and Urinary Disorders | Abnormal renal function | Delafloxacin ($< 2\%$) | Levofloxacin (0.1-1%) |
| | Abnormal urine | | Gemifloxacin ($\leq 0.1\%$) |
| | Acute renal insufficiency or failure | Delafloxacin ($< 2\%$) | Ciprofloxacin, Norfloxacin, Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%), Gemifloxacin (postmarketing) |
| | Dysuria | | Ofloxacin (1-3%) Moxifloxacin (0.1-1%) |
| | Interstitial nephritis | | Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing), Moxifloxacin (postmarketing) |
| | Urinary retention | | Ofloxacin (1-3%) |
| | Crystalluria | | Ciprofloxacin, Norfloxacin |
| | Albuminuria | | Norfloxacin |
| | Candiduria | | Norfloxacin |
| | Cylindruria | | Ciprofloxacin, Norfloxacin |
| | Hematuria | | Ciprofloxacin, Norfloxacin |
| | Agranulocytosis | | Ciprofloxacin, Norfloxacin, Moxifloxacin (postmarketing) |

| Affected system | Symptom | Higher risk | Lower risk |
|---|--|-----------------------------|--|
| Blood/ Lymphatic system | Anaemia (eg. hemolytic, aplastic) | Moxifloxacin ($\geq 1\%$) | Nalidixic acid, Ciprofloxacin, Norfloxacin, Levofloxacin (0.1-1%), Gemifloxacin ($\leq 0.1\%$) |
| | Granulocytopenia | | Levofloxacin (0.1-1%), Gemifloxacin ($\leq 0.1\%$) |
| | Leukocytosis | | Ciprofloxacin, Moxifloxacin (0.1-1%) |
| | Leukopenia | | Nalidixic acid, Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing), Moxifloxacin (0.1-1%), Gemifloxacin (0.1-1%) |
| | Monocytosis | | Ciprofloxacin |
| | Neutropenia | | Norfloxacin, Moxifloxacin (0.1-1%), Gemifloxacin (0.5%) |
| | Neutrophilia | | Gemifloxacin (0.5%) |
| | Pancytopenia | | Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing), Moxifloxacin (postmarketing) |
| | Petechia | | Ciprofloxacin |
| | Thrombocythemia | | Ciprofloxacin, Moxifloxacin (0.1-1%), Gemifloxacin (0.1-1%) |
| | Thrombocytopenia | | Nalidixic acid, Ciprofloxacin, Norfloxacin, Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%), Gemifloxacin ($\leq 0.1\%$) |
| | Thrombotic thrombocytopenic purpura | | Ciprofloxacin, Norfloxacin |
| Metabolism and Nutrition Disorders | Cholesterol elevation | Ofloxacin (1-3%) | |
| | Decreased appetite | | Moxifloxacin (0.1-1%) |
| | Dehydration | | Moxifloxacin (0.1-1%) |
| | Hyperglycemia | Delafloxacin ($< 2\%$) | Ciprofloxacin, Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%), Gemifloxacin (0.1-1%) |
| | Hyperlipidemia | | Moxifloxacin (0.1-1%) |
| | Hypoglycemia | | Ciprofloxacin, Norfloxacin, Levofloxacin (0.1-1%) |
| | Thirst | | Ofloxacin (1-3%) |
| Skin and Allergic Reactions | Weight Loss | | Ofloxacin (1-3%) |
| | Acute generalised exanthematous pustulosis | | Ciprofloxacin |
| | Allergic dermatitis | | Moxifloxacin (0.1-1%), Gemifloxacin (0.1-1%) |
| | Allergic pneumonitis | | Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing), Moxifloxacin (postmarketing) |
| | Allergic reaction | | Levofloxacin (0.1-1%) |

| Affected system | Symptom | Higher risk | Lower risk |
|-----------------|---|---|--|
| | Anaphylactoid reaction (including anaphylactic shock) | | Nalidixic acid, Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing), Moxifloxacin (postmarketing), Gemifloxacin (postmarketing) |
| | Angioedema (including laryngeal edema) | | Nalidixic acid, Ciprofloxacin, Norfloxacin, Ofloxacin (1-3%), Moxifloxacin (postmarketing) |
| | Angioneurotic edema | | Levofloxacin (postmarketing) |
| | Arthralgia with joint stiffness and swelling | | Nalidixic acid |
| | Atopic dermatitis | | Gemifloxacin ($\leq 0.1\%$) |
| | Contact dermatitis | | Nadifloxacin |
| | Dermatitis | Delafloxacin ($< 2\%$) | |
| | Diaphoresis | | Ofloxacin (1-3%) |
| | Dry skin | | Nadifloxacin |
| | Erythema | Delafloxacin ($< 2\%$) | Nadifloxacin, Moxifloxacin (0.1-1%) |
| | <i>Erythema Multiforme</i> | | Nalidixic acid, Ciprofloxacin, Levofloxacin (postmarketing), Gemifloxacin (postmarketing) |
| | <i>Erythema Nodosum</i> | | Ciprofloxacin |
| | Exfoliative dermatitis | | Ciprofloxacin |
| | Fever | Ofloxacin (1-3%), Moxifloxacin ($\geq 1\%$) | Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing) |
| | Fixed eruption | | Ciprofloxacin |
| | Flushing | Delafloxacin ($< 2\%$) | Ciprofloxacin, Gemifloxacin ($\leq 0.1\%$), Nadifloxacin |
| | Hypersensitivity | Delafloxacin ($< 2\%$) | Ciprofloxacin |
| | Hypopigmentation of the skin | | Nadifloxacin |
| | Leukocytoclastic vasculitis | | Levofloxacin (postmarketing) |
| | Papules | | Nadifloxacin |
| | Photosensitivity/Phototoxicity reactions | | Nalidixic acid, Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing), Moxifloxacin (postmarketing), Gemifloxacin (0.039%) |
| | Pruritus | Nalidixic acid, Ofloxacin (1-3%), Nadifloxacin ($> 1.8\%$), Levofloxacin ($\geq 1\%$), Delafloxacin ($< 2\%$) | Ciprofloxacin, Pefloxacin, Norfloxacin, Moxifloxacin (0.1-1%), Gemifloxacin (0.1-1%) |
| | Rash | Nalidixic acid, Ciprofloxacin (1%), Norfloxacin, Ofloxacin (1-3%), Levofloxacin ($\geq 1\%$), Gemifloxacin (3.5%), Delafloxacin ($< 2\%$) | Pefloxacin, Moxifloxacin (0.1-1%) |

| Affected system | Symptom | Higher risk | Lower risk |
|---|--|------------------------------------|---|
| | Serum sickness | | Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing) |
| | Skin exfoliation | | Gemifloxacin (postmarketing) |
| | Skin irritation | Delafloxacin (<2%) | Nadifloxacin |
| | Skin warmth | | Nadifloxacin |
| | Stevens-Johnson Syndrome | | Nalidixic acid, Ciprofloxacin, Norfloxacin, Levofloxacin (postmarketing), Moxifloxacin (postmarketing) |
| | Sweating | | Ciprofloxacin |
| | Toxic epidermal necrolysis | | Levofloxacin (postmarketing), Moxifloxacin (postmarketing) |
| | Urticaria | Nalidixic acid, Delafloxacin (<2%) | Ciprofloxacin, Pefloxacin, Norfloxacin, Ofloxacin (1-3%), Nadifloxacin, Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%), Gemifloxacin (0.1-1%) |
| Genital/ Reproductive System | Burning, pain and rash of the female genitalia | | Ofloxacin (<1%) |
| | Dysmenorrhea | | Ofloxacin (<1%) |
| | External genital pruritus (in women) | Ofloxacin (6%) | Gemifloxacin (0.1-1%) |
| | Genital moniliasis | | Levofloxacin (0.1-1%), Gemifloxacin (0.1-1%) |
| | Menorrhagia | | Ofloxacin (<1%) |
| | Metrorrhagia | | Ofloxacin (<1%) |
| | Vaginal and/ or Vulvovaginal candidiasis | Delafloxacin (<2%) | Ciprofloxacin, Norfloxacin, Moxifloxacin (0.1-1.%) |
| | Vaginal discharge | Ofloxacin (1-3%) | |
| | Vaginal infection | | Moxifloxacin (0.1-1.%) |
| | Vaginitis | Ofloxacin (5%), Levofloxacin (≥1%) | Gemifloxacin (0.1-1%) |
| Laboratory Abnormalities | Decreased CPK (Creatine Phosphokinase) | | Gemifloxacin (0.2%) |
| | Decreased Hematocrit and/or Hemoglobin | | Norfloxacin (0.6%), Moxifloxacin (0.1-1%), Gemifloxacin (0.3%) |
| | Decreased Platelet Count | Norfloxacin(1.0%) | Gemifloxacin (0.2%) |
| | Decreased PT (Prothrombin Time) | | Ciprofloxacin |
| | Decreased RBC (Red Blood Cells) | | Gemifloxacin (0.1%) |
| | Decreased Total Protein | | Gemifloxacin (0.2%) |

| Affected system | Symptom | Higher risk | Lower risk |
|-----------------|---|--|---|
| | Decreased WBC (White Blood Cells) | Norfloxacin (1.3%) | |
| | Eosinophilia | | Ciprofloxacin, Levofloxacin (postmarketing), Norfloxacin (0.6%), Moxifloxacin (0.1-1%), Naladixic acid |
| | Hypercalcemia | | Gemifloxacin (<0.1%) |
| | Hyperkalemia | | Ciprofloxacin, Levofloxacin (0.1- 1%), Gemifloxacin (0.3%) |
| | Hypernatremia | | Gemifloxacin (0.1%) |
| | Hypoalbuminemia | | Gemifloxacin (0.3%) |
| | Hypocalcemia | | Gemifloxacin (0.1%) |
| | Hypokalemia | Moxifloxacin ($\geq 1\%$) | Gemifloxacin (0.1%) |
| | Hyponatremia | | Gemifloxacin (0.1-1%) |
| | Increased ALP (Alkaline Phosphatase) | Delafloxacin (<2%) | Ciprofloxacin, Levofloxacin (0.1- 1%), Moxifloxacin (0.1-1%), Gemifloxacin (0.4%) |
| | Increased ALT (Alanine Transaminase) | Moxifloxacin ($\geq 1\%$) Gemifloxacin (1.7%) | Ciprofloxacin |
| | Increased AST (Aspartate Aminotransferase) (SGOT - Serum glutamic oxaloacetic transaminase) | Norfloxacin (1.6%), Gemifloxacin (0.13%) | Ciprofloxacin, Moxifloxacin (0.1- 1%) |
| | Increased blood amylase | | Moxifloxacin (0.1-1%) |
| | Increased blood CPK (Creatine Phosphokinase) | Delafloxacin (<2%) | Ciprofloxacin, Moxifloxacin (0.1- 1%), Gemifloxacin (0.7%) |
| | Increased blood uric acid | | Ciprofloxacin, Moxifloxacin (0.1- 1%) |
| | Increased BUN (Blood Urea Nitrogen) | | Ciprofloxacin, Moxifloxacin (0.1- 1%), Gemifloxacin (0.3%) |
| | Increased LDH (Lactate Dehydrogenase) | | Ciprofloxacin, Moxifloxacin (0.1- 1%), Gemifloxacin (<0.1%) |
| | Increased lipase | | Norfloxacin (0.6%) |
| | Increased GGT (gamma-Glutamyl Transferase) | | Moxifloxacin (0.1-1%), Gemifloxacin ($\leq 0.1\%$) |
| | Increased Hematocrit and/or Hemoglobin | | Ciprofloxacin, Gemifloxacin (0.1+ %) |
| | Increased hepatic enzymes | Delafloxacin (3%) | Levofloxacin (0.1-1%), |

| Affected system | Symptom | Higher risk | Lower risk |
|-----------------|--|---|--|
| | Increased muscle enzymes | | Levofloxacin (postmarketing) |
| | Increased non-proteins Nitrogen | | Gemifloxacin ($\leq 0.1\%$) |
| | Increased triglycerides | | Moxifloxacin (0.1-1%) |
| | Methemoglobinemia | | Ciprofloxacin |
| | Prolonged aPTT (activated Partial Thromboplastin Time) | | Moxifloxacin (0.1-1%) |
| | Prolonged INR (International Normalized Ratio) | | Ciprofloxacin, Gemifloxacin (postmarketing) |
| | Prolonged PT (Prothrombin Time) | | Ciprofloxacin, Levofloxacin (postmarketing), Moxifloxacin (0.1-1%) |
| Other | Anal/ Rectal pain | | Norfloxacin (0.3-1.0%) |
| | Bleeding diathesis | | Ciprofloxacin |
| | Chest discomfort/pain | Ofloxacin (1-3%), Levofloxacin ($\geq 1\%$) | Moxifloxacin (0.1-1%), Moxifloxacin (0.1-1%) |
| | Chills | | Ofloxacin ($< 1\%$), Moxifloxacin (0.1-1%) |
| | Discomfort | Delafloxacin ($< 2\%$) | |
| | Extremity pain | | Ofloxacin ($< 1\%$) |
| | Facial edema | | Ciprofloxacin, Gemifloxacin ($\leq 0.1\%$) |
| | Facial pain | | Moxifloxacin (0.1-1%) |
| | Fatigue | Ofloxacin (1-3%) | Moxifloxacin (0.1-1%), Gemifloxacin (0.1-1%) |
| | Fungal infections | Delafloxacin ($< 2\%$) | Moxifloxacin (0.1-1%), Gemifloxacin (0.1-1%) |
| | Hemorrhage | | Gemifloxacin (postmarketing) |
| | Hot flashes | | Gemifloxacin ($\leq 0.1\%$) |
| | Hyperhidrosis | | Norfloxacin (0.3-1.0%), Moxifloxacin (0.1-1%) |
| | Infusion site bruise | Delafloxacin ($< 2\%$) | |
| | Injection site reactions | Levofloxacin ($\geq 1\%$), Delafloxacin ($< 2\%$) | Moxifloxacin (0.1-1%) |
| | Metabolic acidosis | | Nalidixic acid, Ciprofloxacin, Norfloxacin |
| | Monoliasis | Levofloxacin ($\geq 1\%$) | |
| | Multiple organ dysfunction syndrome | | Levofloxacin (postmarketing) |
| | Night Sweats | | Moxifloxacin (0.1-1%) |

| Affected system | Symptom | Higher risk | Lower risk |
|-----------------|------------|---|---|
| | Pain | | Ciprofloxacin, Ofloxacin (<1%), Moxifloxacin (0.1-1%), Gemifloxacin (≤0.1%) |
| | Phlebitis | Delafloxacin (<2%) | Levofloxacin (0.1-1%), Moxifloxacin (0.1-1%) |
| | Swelling | Delafloxacin (<2%) | |
| | Thrombosis | Delafloxacin (<2%) | |
| | Trunk pain | Ofloxacin (1-3%), Delafloxacin (<2%) | |
| | Vasculitis | | Ciprofloxacin, Norfloxacin, Ofloxacin (1-3%) |

¹ References: Besifloxacin [21], Ciprofloxacin [22], Delafloxacin [23], Finafloxacin [18,24], Gemifloxacin [25], Levofloxacin [26], Moxifloxacin [27], Nadifloxacin [28], Nalidixic acid [29], Norfloxacin [30], Ofloxacin [31], Pefloxacin [32].

Table S3. Pathogens classified by WHO according to the urgency of antibiotic discovery need [33].

| Critical priority | High priority | Medium priority |
|---|--|---|
| <i>Acinetobacter baumannii</i> , carbapenem – R ¹ | <i>Enterococcus faecium</i> , vancomycin – R | <i>Streptococcus pneumoniae</i> , penicillin-non-susceptible |
| <i>Pseudomonas aeruginosa</i> , carbapenem – R | <i>Staphylococcus aureus</i> , methicillin – R vancomycin – I ¹ , R | <i>Haemophilus influenzae</i> , ampicillin – R |
| Enterobacteriaceae, carbapenem – R ESBL ¹ -producing | <i>Helicobacter pylori</i> , clarithromycin – R | <i>Shigella</i> spp., fluoroquinolone – R |
| | <i>Campylobacter</i> spp., fluoroquinolone – R | |
| | <i>Salmonellae</i> , fluoroquinolone – R | |
| | <i>Neisseria gonorrhoeae</i> , cephalosporin – R fluoroquinolone – R | |

¹ R = resistant; ESBL = extended spectrum β -lactamase; I = intermediate

Table S4. The emergence of resistance to newer antibiotics (Ref. = references).

| Antibiotic | Resistant bacteria | Resistance rate | Ref. |
|--|--------------------------------|--|------------|
| Tigecycline (initial US Approval: 2005) [34] | <i>Acinetobacter baumannii</i> | – | [35] |
| Ceftolozane/tazobactam (initial US Approval: 2014) [36] | <i>Pseudomonas aeruginosa</i> | 0 – 8.3% | [37] |
| | Enterobacteriaceae | <0.6% (overall) | [39–43] |
| | | <2.3 % (MDR ¹ and XDR ¹ strains) | [40,44,45] |
| | | 24.7% (CR ¹ strains) | [41,46,47] |
| | | 90.8 – 98.6% (most MBL ¹ -positive strains) | [41,42,48] |
| Ceftazidime/avibactam (initial US Approval: 2015) [38] | <i>Klebsiella pneumoniae</i> | <5.2% (overall) | [48–50] |
| | | 16.7% or up to 21% (CR ¹ strains) | [50,51] |
| | <i>Pseudomonas aeruginosa</i> | 2.9% | [44] |
| | | 18% | [52] |
| | | >95% (MBL ¹ -positive strains) | [48,53] |
| | <i>Acinetobacter baumannii</i> | >55% | [54,55] |
| | | 73.6% (strains from intensive care units) | [54] |
| Cefiderocol (initial US Approval: 2019) [56] | <i>Acinetobacter baumannii</i> | – | [57] |

¹ MDR = multidrug-resistant; XDR = extensively drug-resistant; CR = carbapenem-resistant; MBL = metallo- β -lactamase; ESBL = extended spectrum β -lactamase

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24. Cross-Discipline Team Leader Review XTORO (Finafloxacin Otic Suspension) 0.3%.
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