QUINOLONE ANTIMICROBIAL AGENTS 3rd Edition
QUINOLONE ANTIMICROBIAL AGENTS

3rd Edition

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The quinolone class of antimicrobial agents has emerged as one of the most widely used classes of antimicrobials in clinical medicine. For this reason, the first edition of *Quinolone Antimicrobial Agents* was organized to bring together in a single volume information about their chemistry, antimicrobial activity, pharmacology, and clinical uses. As their use and numbers increased, additional information was covered in the second edition. Now with the substantial amount of new information on these agents that has become available since the publication of the second edition of *Quinolone Antimicrobial Agents* in 1993, an expanded third edition has been organized in a single, convenient volume to include comprehensive coverage of current information on a larger number of compounds, their clinical applications, and the limitations to their use, including updates on the important and expanding data on bacterial resistance and profiles of adverse effects. Like the first and second editions, this edition is designed for use by clinicians, clinical microbiologists, pharmacologists, pharmacists, basic scientists, and others needing information about these drugs.

The third edition of *Quinolone Antimicrobial Agents* now includes 30 chapters organized into sections on mechanisms and spectrum of activity and resistance (5 chapters), pharmacology (3 chapters), clinical applications (16 chapters), and adverse and other effects (6 chapters). All chapters are either new or completely updated. The area of greatest expansion has been in the section on adverse and other effects because of the substantial body of new information in this area that has become available since the second edition.

We are grateful for all of the considerable efforts of the authors of the individual chapters and the assistance and patience of the editors at ofthe American Society for Microbiology ASM Press. Particular thanks are due to our families for their patience, support, and inspiration during this project.

David C. Hooper
Ethan Rubinstein
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INTRODUCTION

The quinolones (also called fluoroquinolones, 4-quinolones, and quinolone carboxylic acids) are analogs of the earlier developed agent nalidixic acid. Although nalidixic acid is a related naphthyridone, this chemical group is now generally included within the quinolone class. Nalidixic acid, the first member of the class, was originally isolated by Lesher and associates (1) from a distillate during chloroquine synthesis and thus was a by-product of antimalarial research (2). Additional older analogs include oxolinic acid, pipemidic acid, and cinoxacin. These older or first-generation analogs are not considered further in this book, except for purposes of comparison with the newer agents.

The second generation of quinolones, about which we have considerable information, includes norfloxacin, ciprofloxacin, ofloxacin, enoxacin, and pefloxacin. These agents are substantially more potent in vitro and have broader antibacterial spectra than nalidixic acid but maintain the favorable property of being absorbed after oral administration. Additional advantageous pharmacologic properties include relatively long half-lives due to slow of elimination that allow twice-daily dosing, excellent distribution into many tissues and body fluids, and penetration into human cells, resulting in antimicrobial activity in so called “sanctuaries” as well as against some intracellular pathogens. Although differences in spectra of activity exist, this generation of quinolones in general exhibits striking potency against enteric gram-negative bacilli; additional lesser activity against nonenteric, gram-negative bacilli and some staphylococci, and generally marginal activity against streptococci and anaerobes.

The third generation of quinolones that followed maintained many of the favorable properties of the second generation and added increases in potency against gram-positive bacteria and, in some cases, against anaerobes and mycobacteria and in many cases also added longer half-lives of elimination that supported once-daily dosing. A few compounds in the second generation (e.g., lomefloxacin and fleroxacin) also had long half-lives and once-daily dosing, and others (e.g., sparfloxacin, and tosufloxacin) had enhancements of activity against gram-positive and anaerobic bacteria, but none became widely used in the United States and in Europe. The earliest of the third generation compounds was tamafoxacin, and later in succession levofloxacin, trovafloxacin, gatifloxacin, and moxifloxacin became members of this group.

In general, the tolerability of many of the marketed quinolones has been good and comparable to that of other commonly used classes of antimicrobials, and with many of the second-generation agents and some of the third-generation agents have been given to millions of patients. Some adverse effects related to particular structural properties were recognized among second-generation agents, e.g., the photosensitivity caused by lomefloxacin and sparfloxacin due to a halide substituent at position 8, were recognized. Other adverse effects were unexpected and incompletely recognized until after drug release, e.g., a hemolytic uremic syndrome with tamafoxacin and severe hepatotoxicity with trovafloxacin, were unexpected and incompletely recognized until after drug release, resulting in part because of the rarity of their occurrence. The mechanisms of some of these rare reactions are still incompletely understood, and thus the tolerability of each member of the quinolone class must be considered individually.

The information provided in the third edition of Quinolone Antimicrobial Agents is organized into sections on mechanisms and spectrum of activity and resistance (5 chapters), pharmacology (3 chapters),
clinical applications (16 chapters), and adverse and other effects (6 chapters). All chapters are either new or completely updated. The area of greatest expansion has been in the section on adverse and other effects because of the substantial body of new information in this area that has become available since the second edition.

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