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Past, Present, and Future Perspectives of Levofloxacin

Levofloxacin—still going strong after more than 2 decades of continuous use

This special 2015 edition of Penetration celebrates more than 2 decades of continuous use of the extremely effective and globally useful antimicrobial, levofloxacin. Bringing together highlights published since its inception in 1992, the annual journal Penetration first reported on ofloxacin, a racemic fluoroquinolone, before focusing on its purified levo-isomer, levofloxacin. Over the subsequent years, Penetration has provided in-depth coverage of all aspects relating to this important antimicrobial—preclinical research, clinical trial data, epidemiological and public health issues, as well as sensitivity and resistance profiles. The following report provides a summary of the reviews and interviews published in all issues of Penetration, plus information from the Infection Update website (http://www.infectweb.com) as well as ongoing developments and latest information including studies published through 2015.

Fluoroquinolones—the development of a major new class of antimicrobials

Fluoroquinolones remain a major part of the pharmaceutical arsenal, providing clinicians with broad-spectrum coverage that is effective in treating infections of all major body systems. While many fluoroquinolones have been introduced into the market, levofloxacin, with more than 2 decades of continuous use, remains at the forefront as one of the leading examples of this class.

The history of these agents is based on the development of nalidixic acid in the early 1960s. The fluoroquinolones were formed by adding a fluorine atom to this compound, and since then continuous structural developments have seen many new agents being introduced. Ofloxacin, a racemic compound composed of 2 stereo-isomers, became available in 1985, and quickly gained a reputation as an excellent agent for urinary tract infections (UTIs) and lower respiratory tract infections (LRTIs). Ofloxacin exhibited extremely high oral absorption, and, coupled with its activity against most major Gram-negative pathogens, provided clinicians with an effective antibacterial that could safely be prescribed on an outpatient basis.

An expanding clinical role for levofloxacin

Since the advent of ofloxacin, the role of fluoroquinolones has continued to expand, as recognition of their utility in a range of diseases has become apparent. Their first use was in treating Gram-negative bacilli, especially those causing UTIs. They were also recommended for enteric infections, selective decontamination in patients with neutropenia, sexually transmitted infections including *Chlamydia* spp., and skin and soft tissue infections (SSTIs) including osteomyelitis. While they were also seen as useful in respiratory tract infections (RTIs), this was not the main therapeutic focus of the early fluoroquinolones. This completely changed with the introduction of levofloxacin, one of the first of the so-called respiratory fluoroquinolones. Developed in 1986 and introduced into the Japanese market in 1993, levofloxacin has approximately twice the potency of ofloxacin while maintaining an excellent safety profile. Mar-

keted throughout Asia, including China in 1995 and Taiwan in 2000, levofloxacin also gained global recognition with entry to the US market in 1996 where it was licensed by the US Food and Drug Administration (FDA) for the treatment of community-acquired pneumonia (CAP), acute exacerbations of chronic bronchitis (AECB), acute maxillary sinusitis, uncomplicated SSTIs, acute pyelonephritis, and complicated UTIs (cUTIs).

Levofloxacin—leading the fluoroquinolone field while others fail

While levofloxacin went from strength to strength, increasingly seen as the first-line choice for many infections, other fluoroquinolones were not so well received. Structural modification of the fluoroquinolone nucleus saw the development of many other fluoroquinolones throughout the 1980s and 1990s, but many of these had to be withdrawn from the market due to unacceptable safety profiles. In 1992, temafloxacin was withdrawn due to its association with hemolytic-uremic syndrome then, in 1999, trovafloxacin was withdrawn or its use was limited due to the development of serious hepatic events. Grepafloxacin was withdrawn in 1999 due to unacceptable cardiovascular toxicity, clinafloxacin was withdrawn due to phototoxicity and hypoglycemic effects, and sparfloxacin required labeling changes due to cardiotoxicity. In 2006, gatifloxacin was withdrawn due to dysglycemia. Standing removed from all of this has been levofloxacin, which throughout the past 2 decades has developed an enviable safety profile, based on extensive post-marketing data.

Levofloxacin—effective, safe, and avoiding resistance

Although introduced as a respiratory agent due to its activity against Gram-positive, Gram-negative, and atypical pathogens, levofloxacin also has proven efficacy in many other infections. When first administered, it was generally given as a 500 mg once-daily regimen, but a high-dose 750 mg strategy has been developed allowing shorter durations of treatment, with equal efficacy and tolerability. This regimen improves compliance, increases cost-effectiveness, and reduces the incidence of resistance. The 750 mg dose provides an effective once-daily outpatient therapy for severe infections that would have previously required hospital admission.

The threat of resistance has been a major concern hanging over many antimicrobials, and has been a major impetus for developing consensus guidelines for optimizing treatment. Fluoroquinolones are not all the same in regard to their potential to develop resistance, with levofloxacin being better positioned in this area compared with many of its comparators. In order for pathogens to become fully resistant to levofloxacin, they need to undergo 2 mutations, thereby drastically reducing the likelihood of this occurring.

Levofloxacin has been proven throughout its history to be an agent of great worth. It is extremely effective in all of the most debilitating infections, but also well tolerated and very cost-effective. Research relating to this agent continues to be published in peer-reviewed journals, pointing to the continuing utility of this exceptional antimicrobial.

The history of antimicrobials culminating in the development of levofloxacin

The world's first synthetic chemotherapeutic agent, salvarsan, was developed in 1910 aimed at treating syphilis. This was followed by the isolation of penicillin in 1929, which completely transformed the treatment of bacterial infections. Progress rapidly ensued with synthesis of the first sulfa drug, followed by streptomycin for its antituberculous properties, tetracycline, and other antibiotics with excellent antimicrobial efficacy. However, while these all advanced the treatment of infectious diseases significantly, resistant bacteria began to surface as early as the middle of the 20th century.

At that time, it was found that a chloroquinoline derivative, produced during the manufacturing of the antimalarial agent chloroquine, had antimicrobial activity. Investigation of this compound led to the discovery in 1962 of nalidixic acid, the first quinolone, which predominantly had antimicrobial activity against Gram-negative bacteria. Since then, almost every 2 decades has seen an expansion in the clinical significance of the quinolones. The first-generation quinolones were used for the treatment of intestinal infections and UTIs because of their antimicrobial spectrum and then the 1980s saw the emergence of broad-spectrum "new quinolones." During the 2000s, respiratory fluoroquinolones were developed with expanded activity that was effective in a wide range of infectious diseases. Daiichi Pharmaceutical Co., Ltd. (currently Daiichi Sankyo Co., Ltd.) has been involved in the discovery, research and development of quinolones for more than 40 years, with the release of 4 globally recognized agents that continue to be used to treat bacterial infections worldwide. The drug discovery research of Daiichi Pharmaceutical's 3 original quinolones, i.e., ofloxacin, levofloxacin, and sitafloxacin, began with the introduction of nalidixic acid into Japan in 1964. This was launched for the treatment

of enteric infections and UTIs.

The launch of ofloxacin

Using nalidixic acid as the prototype, Daiichi Pharmaceutical began to develop its own acidic quinolones with higher antimicrobial activities and broader antimicrobial spectra. During a 15-year period, over 1,000 acidic compounds were synthesized, however, they were often only effective against Gram-negative bacteria, were metabolically unstable or unsuitable for oral administration.

Pipemidic acid, discovered in 1972, and norfloxacin, in 1978, contained an amino substituent with excellent tissue penetration and urinary excretion. In particular, the fluorine-containing norfloxacin, exhibited good antimicrobial activity against Gram-positive bacteria. Daiichi Pharmaceutical had seen that research into the acidic quinolones was becoming limited and, using knowledge based on the importance of physicochemical characteristics, changed its targets from acidic agents to zwitterions or fluoroquinolones. From a group of potential candidates, Daiichi Pharmaceutical selected ofloxacin, which was shown to exceed norfloxacin in all microbiologically significant respects, and exhibited a high blood concentration, extensive urinary excretion, good tissue penetration, and a broad antimicrobial spectrum covering not only Gram-negative but also Gram-positive bacteria.

Levofloxacin purified—concentrating the efficacy of ofloxacin while maintaining safety

Ofloxacin was released in Japan under the trade name of Tarivid® in 1985, and was then launched in the US and Europe. Continuing research into the physicochemical and structural properties of ofloxacin, a racemic stereoisometric compound, resulted in separation into 2 enantiomers DR-3354 and DR-3355, the second of which was called levofloxacin. Evaluation of the antimicrobial activities of ofloxacin, DR-3354, and DR-3355 (levofloxacin) revealed that DR-3355 exhibited antimicrobial activity twice that of ofloxacin in most strains used, while the antimicrobial activity of DR-3354 was 1/10 to 1/100 that of DR-3355. In terms of safety, results from an acute toxicity study in mice demonstrated the median lethal dose (LD_{50}) of DR-3354 was lower than that of DR-3355, suggesting that DR-3354 was a major cause of adverse drug reactions (ADRs) to ofloxacin. These positive findings prompted the initiation of clinical research in 1987 and in December 1993, levofloxacin was launched in Japan under the trade name of Cravit®. As the world's first optically active fluoroquinolone, Daiichi Pharmaceutical launched levofloxacin throughout Asia from 1994 and licensed it out in the US and European countries during 1997 to 1998. As of 2015, levofloxacin is available in 124 countries.

When first introduced in Japan, levofloxacin was approved at a dose of 100–200 mg thrice daily. In contrast, the US started levofloxacin at a daily dose of 500 mg, according to pharmacokinetic/pharmacodynamic (PK/PD) modeling, which was new at that time (1). The once-daily 500 mg regimen was based on the exceptionally rapid absorption, and high concentrations achieved, coupled with a long half-life and this has become the world standard for levofloxacin therapy. Based on the exceptional safety profile of levofloxacin, it has been further developed as a once-daily, high-dose (750 mg) therapy, and even 1,000 mg daily, in order to treat more serious infections worldwide.

Unsurpassed safety record

Several reviews have been published on the safety of fluoroquinolones, reporting class effects found with all agents as well as ADRs that are specific to individual agents (2–4). Fluoroquinolones may induce various clinically significant ADRs such as prolongation of the QT interval, disturbances of blood glucose, liver toxicity, and skin rash. Many fluoroquinolones have been withdrawn during development as well as from the market after they were found to cause serious ADRs. In stark contrast, the risk of serious ADRs is not high with ofloxacin and levofloxacin, with the safety profile of levofloxacin well established internationally. In fact, levofloxacin has one of the most extensive post-marketing surveillance databases of all fluoroquinolones and, with more than 851 million prescriptions worldwide as of March 2013. It has a safety profile unsurpassed by other fluoroquinolones. This allows clinicians the world over to prescribe levofloxacin with the greatest confidence, knowing that not only does it possess excellent clinical efficacy, but also with the knowledge that this is coupled with an exceptional safety profile.

References

1. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998; 26: 1–10.
2. Rouveix B. Antibiotic safety assessment. Int J Antimicrob Agents 2003; 21: 215–21.
3. Owens RC Jr., Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. Clin Infect Dis 2005; 41 Suppl 2: S144–57.
4. Liu HH. Safety profile of the fluoroquinolones: focus on levofloxacin. Drug Saf 2010; 33: 353–69.

Chronological Table of Ofloxacin and Levofloxacin

Looking Back—How the Fluoroquinolones Developed into a Major Class of Antibiotics

1939	Chloroquine developed
1958	Chloroquinoline developed
1962	Development of nalidixic acid
1972	Development of pipemidic acid
1978	Development of the first fluoroquinolone norfloxacin
1982	Development of ofloxacin (*S*- and *R*-isomers)
1983	Development of ciprofloxacin
Mid 1980s	Introduction of the first-generation fluoroquinolones into clinical practice
	Improved Gram-negative activity

Levofloxacin—Leading the Fluoroquinolone Field

1986	Development of levofloxacin
	Twice as active as ofloxacin
Late 1980s/early 90s	Second-generation fluoroquinolones developed (temafloxacin, sparfloxacin, grepafloxacin, gatifloxacin)
	Improved Gram-positive activity
Early 90s–	Third-generation fluoroquinolones developed (trovafloxacin, moxifloxacin, clinafloxacin, gemifloxacin)
	Gram-positive/negative and anaerobe activity
90s–	Fourth-generation fluoroquinolones developed (clinafloxacin, sitafloxacin)
	Extended half-lives

How Safety Issues Thinned the Ranks of the Fluoroquinolones

1992	Temafloxacin withdrawn because of hemolytic uremic anemia (June)
1993	Levofloxacin launched in Japan
1996	Levofloxacin approved by US FDA (CAP, AECB, acute maxillary sinusitis, uncomplicated SSTIs, acute pyelonephritis, cUTIs) (December)
1999	Trovafloxacin withdrawn or its use limited because of hepatic events (June)
	Grepafloxacin withdrawn because of cardiovascular events (October)
	Clinafloxacin discontinued because of phototoxicity and hypoglycemic effects
	Sparfloxacin labeling safety changes because of QTc prolongation
2000	Levofloxacin approved by US FDA for CAP due to penicillin-resistant *Streptococcus pneumoniae* (PRSP)
2008	Gatifloxacin withdrawn because of hypoglycemia and hyperglycemia (October)

Surveillance Studies Summarized from Around the World and the Impact on Clinical Use

1999	Surveillance studies reported*
2000	PK/PD data supporting levofloxacin*
2001	Safety data positive for levofloxacin*
2002	Emphasis on UTIs and RTIs*
2003	RTIs and higher dosing strategies*
2004–06	Focus on RTIs and safety*
2009–11	Review of *Helicobacter pylori* infections*

* To learn more, please visit http://www.infectweb.com/

Levofloxacin—Still Going Strong After All These Years

1996 Levofloxacin approved by US FDA for CAP, AECB, acute maxillary sinusitis, uncomplicated SSTIs, acute pyelonephritis, cUTIs (December)

1997– Levofloxacin initially approved in UK, followed by 11 other European countries (Austria, Belgium, Denmark, Finland, Germany, Ireland, Italy, Luxembourg, the Netherlands, Portugal, Spain), and then, also approved in 13 other countries in Europe (Bulgaria, Cyprus, Czech Republic, Estonia, France, Greece, Hungary, Lithuania, Malta, Poland, Slovakia, Slovenia, Sweden)

2000 Levofloxacin approved by US FDA for CAP due to PRSP

2002 Levofloxacin approved by US FDA for hospital-acquired pneumonia (HAP)

2003 Levofloxacin approved by US FDA for chronic bacterial prostatitis

2004 Levofloxacin approved by US FDA for CAP due to multidrug-resistant *S. pneumoniae* (MDRSP)
Levofloxacin approved by US FDA for postexposure treatment of anthrax

2012 Levofloxacin approved by US FDA for plague

Launching in Asia for Oral Use

1994 Korea

1995 China

1998 Indonesia
Philippines
Pakistan

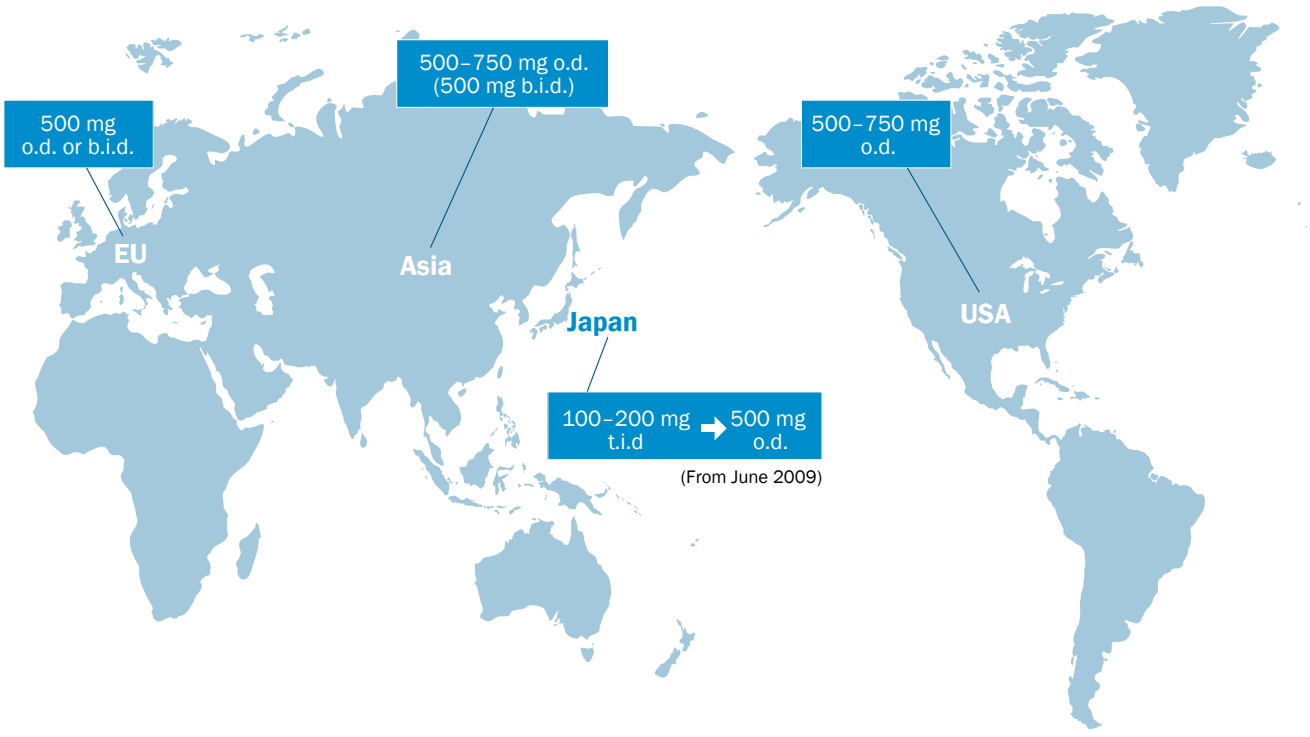
2000 Taiwan

2001 Singapore

2002 Thailand

2004 Hong Kong
Vietnam

Global development of levofloxacin



As of 2015, levofloxacin has been marketed in 124 countries around the world.
Abbreviations: o.d. = once daily; b.i.d. = twice daily; t.i.d. = thrice daily.

Chronological Summary of Interview Articles in Penetration

1992

Newer Quinolones' Benefits: Cost Saving, Activity against Gram-Negative Bacilli and *Chlamydia*

Michael Barza, MD

Professor of Medicine, Tufts University School of Medicine; Associate Chief, Division of Geographic Medicine and Infectious Diseases, New England Medical Center, Boston, MA, USA

1993

Ofloxacin in the USA—A Major Role against *Chlamydia* and Respiratory Infections

Layne O. Gentry, MD, FACP

Chief, Infectious Disease Section, St. Luke's Episcopal Hospital, Houston, TX, USA

Ofloxacin—A European Perspective

Jean-P. Thys, MD

Associate Professor of Infectious Diseases, Head of Infectious Diseases Clinic, Erasme University Hospital, Free University of Brussels, Brussels, Belgium

1994

Ofloxacin—An Expanding Role in the Field of Otorhinolaryngology

Pierre Gehanno, MD

Professor, Head of the Otorhinolaryngology Department, Hospital Bichat-Claude Bernard, Paris, France

1995

The Use of Ofloxacin in the Chronic Ambulatory Patients: The Benefits of Once-Daily Therapy

Helen Giamarellou, MD

Chief of the Department of Infectious Diseases and Associate Professor of Internal Medicine at the First Department of Propaedeutic Medicine, Athens University School of Medicine, Athens, Greece

1996

Levofloxacin: Therapeutic Advances in the Treatment of Severe Infections

S. Ragnar Norrby, MD, PhD

Visiting Professor, Department of Microbiology, Prince of Wales Hospital, Hong Kong

1997

Levofloxacin in the Treatment of Community-Acquired Pneumonia

Charles M. Fogarty, MD

Medical Director, Respiratory Therapy, Spartanburg Regional Medical Center, Spartanburg, SC, USA

Levofloxacin—An Extremely Useful Drug in the Treatment of Sinusitis

Thomas A. Sydnor, MD

President of the Virginia Medical Studies Group, Charlottesville, VA, USA

1998

Levofloxacin—The "Respiratory Fluoroquinolone"

Carl A. DeAbate, MD

Medical Director, Medical Research Center, New Orleans, LA, USA

Clinical Efficacy of Ofloxacin in Multidrug-Resistant Tuberculosis

Lee B. Reichman, MD, MPH, FACP, FCCP

Professor of Medicine, Preventive Medicine and Community Health; Director, New Jersey Medical School National Tuberculosis Center, Newark, NJ, USA

1999

Levofloxacin and Its Effective Use against RTI-Related Resistant Pathogens

Clyde Thornsberry, PhD

Chief Scientific Advisor, MRL Pharmaceutical Services, Brentwood, TN, USA

A Comparison of Clinical Outcomes Using Levofloxacin versus β-lactams and Macrolides in Respiratory Tract Infections

Raymond P. Smith, MD

Infectious Disease Section, Stratton VA Medical Center, Albany, NY, USA

2000

A Special Roundtable Discussion

The Role of Levofloxacin for the Treatment of Respiratory Tract Infections

Pharmacokinetics and Pharmacodynamics of Levofloxacin

George L. Drusano, MD

Professor and Director of the Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Albany Medical College, Albany, NY, USA

Antimicrobial Resistance in Respiratory Tract Pathogens: Results of an International Surveillance Study

Clyde Thornsberry, PhD

Chief Scientific Advisor, MRL Pharmaceutical Services, Brentwood, TN, USA

Clinical Efficacy of Levofloxacin in Respiratory Tract Infections

Thomas M. File, Jr., MD, FACP

Chief, Infectious Disease Service, Summa Health System, Akron, OH; Professor of Internal Medicine, Northeastern Ohio Universities College of Medicine, Rootstown, OH, USA

2001

A Special Roundtable Discussion 1

Quinolones Are Not All the Same: Different Safety Profiles for Specific Compounds

History of Quinolones and Their Side Effects

Ethan Rubinstein, MD

Department of Internal Medicine and Unit of Infectious Diseases, Tel Aviv University School of Medicine, Tel Aviv, Israel

Comparison of Side Effects of Levofloxacin versus Other Fluoroquinolones

Claude Carbon, MD

Internal Medicine Unit, Bichat-Claude Bernard Hospital, Paris, France

A Comparison of Side Effects of Levofloxacin to Other Agents in Regard to the Ecological and Microbiological Effects on Normal Human Flora

Jacques F. Acar, MD

Laboratoire de Microbiologie Médical, Fondation Hôpital Saint-Joseph, Paris, France

Evidence of Different Profiles of Side Effects and Drug-Drug Interactions among the Quinolones: The Pharmacokinetic Standpoint

Hartmut Lode, MD

Department of Chest and Infectious Diseases, City Hospital Berlin-H-Heckshorn, Berlin, Germany

Latest Industry Information on the Safety Profile of Levofloxacin in the US

James B. Kahn, MD, FIDSA

Infectious Disease Research, Ortho-McNeil Pharmaceutical Inc., Raritan, NJ, USA

Latest Industry Information on the Safety Profile of Levofloxacin in Japan

Katsuro Yagawa, MD

Drug Safety Administration Department, Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan

A Special Roundtable Discussion 2

Defining the Appropriate Critical Pathway for the Treatment of Infectious Diseases: Challenging Drug-Resistant Pathogens

Results of the Surveillance of Resistance for Gram-Positive and Gram-Negative Organisms

Clyde Thornsberry, PhD

Chief Scientific Advisor, MRL Pharmaceutical Services, Brentwood, TN, USA

Clinical Relevance of *In Vitro* Resistance: Respiratory Pathogens and Uropathogens

Antone A. Medeiros, MD

Division of Infectious Diseases, Brown University School of Medicine, Providence, RI, USA

Community-Acquired Pneumonia: Recent Treatment Strategies

Thomas M. File, Jr., MD, FACP

Chief, Infectious Disease Service, Summa Health System, Akron, OH; Professor of Internal Medicine, Northeastern Ohio Universities College of Medicine, Rootstown, OH, USA

Rhinosinusitis: Recent Treatment Strategies

Michael D. Poole, MD, PhD

Departments of Otolaryngology and Pediatrics, University of Texas Medical School, Houston, TX, USA

2002

The Role of Levofloxacin in Treating Urinary Tract Infections

George A. Richard, MD

Department of Pediatrics, Nephrology Division, University of Florida, Gainesville, FL, USA

New Era for the Treatment of Respiratory Tract Infections

Regional Resistance Situation in the World

Reuben Grüneberg, MD, FRCPath

Director, GR Micro Ltd., London, UK

Role of Levofloxacin in the Treatment of Community-Acquired Pneumonia

Lionel A. Mandell, MD, FRCPC

Professor of Medicine, Chief of Division of Infectious Diseases, McMaster University, Hamilton, ON, Canada

2003

Pharmacokinetic/Pharmacodynamic Breakpoints: Time to Consider New Parameters of Antimicrobial Efficacy

George L. Drusano, MD

Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Albany Medical College, Albany, NY, USA

Role of Levofloxacin in the Treatment of Rhinosinusitis

Michael D. Poole, MD, PhD

Professor of Otolaryngology and Pediatrics, Department of Otolaryngology, University of Texas Health Science Center at Houston, Houston, TX, USA

Role of Levofloxacin in the Treatment of Lower Respiratory Tract Infections

Peter Ball, FRCP (Ed)

Late Senior Lecturer, University of St. Andrews, Fife, Scotland, UK

2004

A Special Roundtable Discussion

Levofloxacin Stands Above the Rest: A Fluoroquinolone with Both Efficacy and Safety

Antimicrobial Resistance among *Streptococcus pneumoniae*: Implications for Therapy

Joseph P. Lynch, III, MD

Associate Chief, Division of Pulmonary and Critical Care Medicine, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, CA, USA

Rational-Dose Levofloxacin Therapy: Providing a Safe and Effective Treatment in Difficult Cases

Thomas M. File, Jr., MD

Chief, Infectious Disease Service, Summa Health System, Akron, OH; Professor of Internal Medicine, Northeastern Ohio Universities College of Medicine, Rootstown, OH, USA

Diagnosis and Management of Nosocomial Pneumonia: Levofloxacin vs. Imipenem

John Segreti, MD

Professor, Department of Internal Medicine, Section of Infectious Diseases, Rush Medical College, Chicago, IL, USA

Levofloxacin in the Medical Management of Community-Acquired Pneumonia

Andy I.M. Hoepelman, MD, PhD

Department of Acute Medicine and Infectious Diseases, Eijkman-Winkler Laboratory for Medical Microbiology, University Medical Center, Utrecht, the Netherlands

2005

The Use of Levofloxacin for the Treatment of Acute Exacerbation of Chronic Bronchitis

Hartmut Lode, MD, PhD

Department of Chest and Infectious Diseases, Helios Klinilum Emil von Behring, Academic Teaching Hospital of Charite, Berlin, Germany

2006

Levofloxacin for the Management of Hospital-Acquired, Ventilator-Associated and Healthcare-Associated Pneumonia

Marin H. Kollef, MD

Professor of Medicine, Washington University School of Medicine; Director, Medical Intensive Care Unit; Director, Respiratory Care Services, Barnes-Jewish Hospital, St. Louis, MO, USA

2007

The Efficacy, Tolerability, and Benefits of 750 mg Once-Daily Levofloxacin in the Treatment of Community-Acquired Pneumonia

Thomas M. File, Jr., MD, MS

Chief, Infectious Disease Service, Summa Health System, Akron, OH; Professor of Internal Medicine, Northeastern Ohio Universities College of Medicine, Rootstown, OH, USA

2008

The Role of 750 mg Once-Daily Levofloxacin in the Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Diseases

Ronald F. Grossman, MD, FRCPC, FCCP, FACP

Respirologist, Department of Medicine, The Credit Valley Hospital, Professor of Medicine, University of Toronto, Mississauga, ON, Canada

2009

The Way Forward: High-Dose, Short-Course Levofloxacin Leads the Field

Lala M. Dunbar, MD, PhD

Medicine/Emergency Medicine, Louisiana State University Health Sciences Center, New Orleans, LA, USA

2010

Tracking Susceptibility and Reducing Resistance—Fluoroquinolones at the Forefront in the Fight against Bacterial Pathogens

Rafael Cantón, PhD

Servicio de Microbiología, Hospital Universitario Ramón y Cajal and CIBER en Epidemiología y Salud Pública (CIBER-ESP), Madrid, Spain

2011

Optimal Management of RTI—Intriguing New Results in ABECOPD in Asia

Hans H. Liu, MD, FACP

Bryn Mawr Medical Specialists, Bryn Mawr, PA; Professor of Medicine, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA, USA

Institutional affiliations and titles are as of the date of publication.
You can learn more about these interviews on the following website.
http://www.infectweb.com

A Scientific History of Levofloxacin

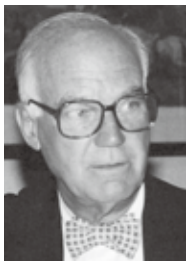
Respiratory Tract Infections

Levofloxacin, a leading "respiratory" fluoroquinolone, has cemented a place for itself as a first-line agent in treating both upper and lower RTIs.

Sinusitis

In the 1994 issue of Penetration, Pierre Gehanno, MD, described the role of ofloxacin in chronic otitis with purulent otorrhea and chronic sinusitis as a "breakthrough" (1). Ofloxacin penetrated into the inflammatory and non-inflammatory tissues that were not reached by other antimicrobials, resulting in levels at the site of infection significantly higher than the MICs of the principal respiratory pathogens. This feature, coupled with an excellent safety profile, allowed ofloxacin to be administered as long-term therapy, a necessary feature for successfully treating these chronic conditions.

Pierre Gehanno, MD
Professor, Head of the Otorhinolaryngology Department, Hospital Bichat-Claude Bernard, Paris, France



Thomas A. Sydnor, MD
President of the Virginia Medical Studies Group, Charlottesville, VA, USA

The development of levofloxacin, the levo-isomer of the racemic ofloxacin, then provided physicians with an even more effective agent than its parent compound. In 1997, Penetration interviewed Thomas A. Sydnor, MD, who reported national multicenter results confirming that levofloxacin was an excellent choice for treating community-acquired sinusitis (2). Dr. Sydnor emphasized the lack of significant drug-drug interactions associated with levofloxacin, in particular, its safety when administered with theophylline or steroids, agents used concomitantly by many RTI patients. Levofloxacin was reported to have better Gram-positive coverage than previous fluoroquinolones, and to be 2–4 fold more active against staphylococci and streptococci than ciprofloxacin. This review was supported by results from a clinical trial involving 329 patients who received levofloxacin 500 mg once daily (o.d.) for 10–14 days. Levofloxacin achieved a 92% bacterial eradication rate, an 88% clinical success rate (cure/improvement) at the post-therapy assessment, with 92% remaining well at 4–6 weeks after therapy (3).

Adding further evidence to levofloxacin's expanding role in ear, nose, and throat infections was a 2000 review by Jeffrey Adelglass, MD (4), who drew attention to the size of this problem, citing an estimated 20 million cases of acute bacterial sinusitis each year in the US alone. Dr. Adelglass noted the deteriorating efficacy associated with previously used agents such as β-lactams, tetracyclines, macrolides, and sulfonamides, and the poor tolerability of agents that were effective against PRSP. In contrast, levofloxacin possessed excellent activity against the causative pathogens becoming the first fluoroquinolone to be indicated for treatment of acute sinusitis.

Jeffrey Adelglass, MD
Dallas Clinical Research Institute, Inc., Dallas, TX, USA

While levofloxacin has been used continuously since then for treating many infections, it is important to note that the major pathogens responsible for sinusitis have remained susceptible. A 2011 Chinese study evaluating 51 patients with chronic rhinosinusitis treated with sinus surgery confirmed levofloxacin to be active against the causative pathogens (5). The antibiotic susceptibility rate for levofloxacin was 92.31%, contrasted with 81.58% for ciprofloxacin, 67.65% for trimethoprim–sulfamethoxazole (TMP–SMX), 45.0% for clarithromycin, 35.90% for ampicillin sodium and sulbactam sodium, 30.43% for cefuroxime sodium to a low of 8.33% for penicillin. The authors concluded that fluoroquinolones such as levofloxacin should be the agents of choice for preventing infections in sinus surgery.

These results supported data from a 2010 trial investigating the clinical efficacy and cost-effectiveness of oral antimicrobial prophylaxis with levofloxacin in patients undergoing endoscopic sinus surgery (ESS) (6). A prospective study of oral (PO) levofloxacin versus intravenous (IV) flomoxef to prevent postoperative infections after ESS was carried out in 93 patients who received either levofloxacin 200 mg PO 2 hours before and 6 hours after surgery, followed by 200 mg every 12 hours for 2 days or who received flomoxef 1 g IV at the start of surgery and 6 hours after surgery, followed by infusion twice daily (b.i.d.) for 2 days. No patients in the study developed post-surgical infections and the authors noted that, although not statistically significant, levofloxacin appeared to be associated with a lower rate of resistance development compared with flomoxef. Consequently, oral levofloxacin was

Institutional affiliations and titles are as of date of publication.

deemed to be a simple, cost-effective, and safe alternative to IV prophylaxis in ESS.

Acute exacerbations of chronic bronchitis

Another upper RTI (URTI) that places a substantial burden on healthcare systems is AECB. It has been estimated that 50–70% of AECB cases are caused by bacterial infections, and selecting the best antimicrobial is associated with improved outcomes and reduced healthcare costs (7). Respiratory fluoroquinolones such as levofloxacin exhibit a broad spectrum of activity against most AECB-causing pathogens and are used as first-line treatment in patients with comorbidities, severe airway obstruction, or recurrent exacerbations. The use of levofloxacin in these patients is based on a strong foundation of clinical research, starting with results using ofloxacin in chronic bronchitis reported by Peter Ball, MB, FRCP in the 1996 issue of Penetration (8). Ofloxacin was demonstrated to have high penetration into sputum, bronchial mucosa, and lung tissue, achieving levels over 20-fold higher than the MICs of all important pathogens. This was reflected in the clinical efficacy with overall response rates of 82–97%.

Peter Ball, MB, FRCP
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Although ofloxacin was documented as an effective agent in URTIs, the advent of levofloxacin ushered in a new era of respiratory fluoroquinolones. Levofloxacin was confirmed to have an excellent bronchopulmonary profile, with the high dose (750 mg) achieving even higher concentrations in respiratory cells and tissues, with concentrations in alveolar macrophages (AM) and epithelial lining fluid (ELF) well in excess of the MICs of community-acquired intracellular pathogens likely to cause AECB **(Table 1)** (9).

The clinical efficacy of levofloxacin in AECB was first confirmed in results from a 1998 multicenter, randomized study comparing the efficacy and safety of oral levofloxacin versus cefaclor. This study involved 373 patients who received either levofloxacin 500 mg o.d. for 5–7 days or cefaclor 250 mg thrice daily (t.i.d.) for 7–10 days (10). Results confirmed a shorter duration of treatment with levofloxacin (6.6 days for levofloxacin vs. 8.7 days for cefaclor) while achieving a higher bacterial eradication rate (94.0% vs. 87.0%) and a clinical success rate (cure/improvement) of 92% for both. However, a greater percentage of the levofloxacin group were cured (72.1% vs. 64.5%). The researchers concluded that not only was levofloxacin as effective as cefaclor, as a once-daily therapy, but it had the potential to be associated with greater compliance and to be more cost-effective.

Table 1 Steady-state levofloxacin concentrations in plasma, ELF, and AM

Sample collection time after 3rd dose (hr)	Mean (± SD) levofloxacin concentration (µg/mL)					
	Plasma (*n*)	Plasma	ELF (*n*)	ELF	AM (*n*)	AM
4	6	7.97 ± 2.51	6	7.52 ± 3.05	6	38.51 ± 43.72
12	6	5.76 ± 1.16	6	8.35 ± 6.00	5[a]	13.35 ± 14.41
24	6	2.24 ± 1.16	6	1.24 ± 0.87	6	9.03 ± 7.50

[a] One patient was removed from the analysis because a cell count was not obtained.
Abbreviations: ELF = epithelial lining fluid; AM = alveolar macrophages; SD = standard deviation.
Adapted from reference (9).

A review by Pramod M. Shah, MD, in the 2000 issue of Penetration reported results of clinical studies with levofloxacin and comparators in AECB **(Table 2)** (10–13). Results from a randomized, comparative trial investigating the efficacy and safety of levofloxacin (250 or 500 mg o.d.) with cefuroxime axetil (250 mg b.i.d.) both given for 7–10 days reported a cure rate of 78–79% for levofloxacin in the per protocol (PP) group compared with 66% for cefuroxime axetil. Subgroup analyses revealed that the efficacy of levofloxacin was even higher than comparators in patients who were hospitalized, or taking concomitant steroids or theophylline. Dr. Shah recommended assessing the disease severity by using the percentage deterioration in FEV_1 and advocated the use of levofloxacin in

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Table 2 Clinical studies with levofloxacin and comparators in AECB

Reference	Treatment	Dose	Treatment duration (days)	Clinical success rate *n* (%)	Bacteriologic eradication rate *n* (%)
DeAbate et al (11)	Levofloxacin	500 mg o.d.	5–7	222 (94.6)	190 (97.0)
	Cefuroxime axetil	250 mg b.i.d.	10	229 (92.6)	222 (95.0)
Habib et al (12)	Levofloxacin	500 mg o.d.	5–7	154 (92.0)	103 (94.0)
	Cefaclor	250 mg t.i.d.	7–10	155 (92.0)	89 (87.0)
Shah et al (13)	Levofloxacin	250 mg o.d.	7–10	156 (78.0)	144 (77.0)
	Levofloxacin	500 mg o.d.	7–10	137 (79.0)	127 (77.0)
	Cefuroxime axetil	250 mg b.i.d.	7–10	134 (66.0)	84 (68.0)

Abbreviations: AECB = acute exacerbations of chronic bronchitis; o.d. = once daily; b.i.d. = twice daily; t.i.d. = thrice daily.
Adapted from references (11–13).

(Penetration 2000; 25: Table 5)

patients with more severe disease.

The utility of respiratory fluoroquinolones continued to be recognized, with a review in the 2006 issue of Penetration by Hartmut M. Lode, MD, PhD, et al reporting that most guidelines recommended fluoroquinolones for antimicrobial management of exacerbations of chronic obstructive pulmonary disease (COPD) (14). Levofloxacin was deemed to be as effective and well tolerated as cefuroxime axetil, azithromycin, gemifloxacin, and clarithromycin, with the added advantage of requiring a shorter duration of treatment. In fact, when high-dose levofloxacin (750 mg) o.d. was given for 3 days compared with azithromycin o.d. for 5 days in uncomplicated disease, it achieved a higher success rate (93.0% vs. 90.1%) and, when compared with amoxicillin 875 mg/clavulanate 125 mg b.i.d. for 10 days in complicated patients, levofloxacin achieved a 79.2% cure rate compared with 81.7% for the comparator regimen (15).

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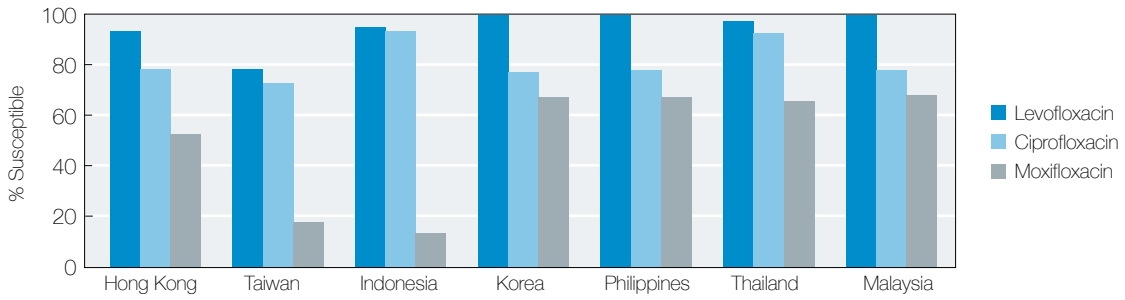
New results in acute bacterial exacerbations of COPD (ABECOPD) in Asia were reported in the 2011 issue of Penetration by Hans H. Liu, MD, FACP, who drew attention to the greater susceptibility rates for levofloxacin compared with moxifloxacin and ciprofloxacin. **(Figure 1)** (16, 17). He stressed the importance of knowing regional susceptibility patterns, and monitoring these for changes. This is of great importance in Asia where the etiology of ABECOPD can change dramatically between regions. He concluded that, unlike most other antimicrobials, levofloxacin has maintained excellent efficacy against all major RTI pathogens.

Clinical results supporting the use of levofloxacin in AECB have continued to accumulate with data from a 2013 study again confirming the continued efficacy of levofloxacin in AECB (18). This multicenter, parallel, double-blind, randomized clinical trial evaluated the efficacy of levofloxacin versus prulifloxacin in severe COPD with AECB. AECB patients were enrolled if they met the following criteria: aged 40 years or older, smokers/ex-smokers with severe COPD confirmed by spirometry ($FEV_1 \leq 50\%$ predicted and FEV_1/FVC ratio < 0.7). Patients were randomized to receive prulifloxacin 600 mg o.d. or levofloxacin 500 mg o.d. for 7 days. Three hundred and forty-six patients out of 351 were included in the intention-to-treat (ITT) analysis (174 prulifloxacin and 172 levofloxacin) with levofloxacin achieving a 96.5% cure rate compared with 92.5% for the prulifloxacin group. At the 6-month follow-up, more than 95% of patients had no relapse of AECB in both groups, confirming that levofloxacin continued to exhibit exceptional efficacy **(Table 3).**

Role of levofloxacin in AECB supported by evidence-based guidelines

As the clinical evidence grew for using fluoroquinolones in AECB, they came to be a feature of many evidence-based treatment guidelines. The oldest of these, the Lille consensus set, only recommended fluoroquinolones for patients with severe bronchitis. However, this was expanded to include use in patients in risk group II (those requiring hospitalization), or for severe AECB patients with 1 or more risk factors (aged 65 years or older, $FEV_1 < 50\%$ predicted, 4 or more exacerbations in 12 months, or comorbidities) (19). Guidelines stressed that *S. pneumoniae* resistance to penicillin, azithromycin, other macrolides, TMP–SMX, and cefuroxime continued to be a problem. In contrast, resistance to amoxicillin–clavulanate, ceftriaxone, levofloxacin, and vancomycin remained relatively low. The role of fluoroquinolones continued to expand, with a 2004 report from the Latin-American Thoracic Society recommending respiratory fluoroquinolones be used for mild infectious exacerbations of COPD and risk factors, as well as in those with moderate/severe disease. This was supported by the 2005 German evidence-based recommendations stating that fluoroquinolones should be used

Figure 1 Total ABECOPD pathogen susceptibility rate for 3 fluoroquinolones according to the country of origin



Abbreviation: ABECOPD = acute bacterial exacerbations of chronic obstructive pulmonary disease.
Adapted from references (17).

(Penetration 2011; 12: Figure 2)

Institutional affiliations and titles are as of date of publication.

Table 3 Clinical efficacy at the follow-up visit (next AECB episode or after 6 months from the end of treatment)

	Prulifloxacin		Levofloxacin	
	ITT	PP	ITT	PP
n	141 [c]	135 [c]	142 [b]	137 [b]
Relapse (%)	6 (4.3)	6 (4.4)	2 (1.4)	2 (1.5)
Mild relapse (%)	24 (17.0)	21 (15.6)	22 (15.5)	19 (13.9)
Persistent resolution (%)	111 (78.7)	108 (80.0)	118 (83.1)	116 (84.7)
Success (%) [a]	135 (95.7)	129 (95.6)	140 (98.6)	135 (98.5)
95% CI	92.4–99.1	92.1–99.0	96.6–100	96.5–100
Failure (%)	6 (4.3)	6 (4.4)	2 (1.4)	2 (1.5)
95% CI	0.9–7.6	1.0–7.9	-0.5–3.3	-0.5–3.5

[a] Mild relapse + persistent resolution.
[b] Including one patient withdrawn from the study due to exacerbations of chronic bronchitis, who did not have an ETV or follow-up visit.
[c] Excluding one not evaluable patient.
Abbreviations: AECB = acute exacerbations of chronic bronchitis; ITT = intention-to-treat; PP = per protocol; CI = confidence interval; ETV = early termination visit.
Adapted from reference (18).

in AECB patients with an FEV_1 less than 50% predicted and no risk factors for *Pseudomonas aeruginosa*.

In the last decade, evidence has continued to accumulate supporting the use of levofloxacin and respiratory fluoroquinolones in AECB. A 2010 review comparing the clinical efficacy and speed of recovery for short-course (≤ 5 days) fluoroquinolone therapy with standard therapy (≥ 7 days) evaluated 23 studies using short-course fluoroquinolones (7). This confirmed that the shorter duration of therapy was at least as effective as standard therapy of 7 or more days duration. In addition, short-course therapy appeared to be associated with a faster resolution of symptoms, a faster rate of recovery, fewer relapses, fewer and shorter hospitalizations, and a longer time between recurrences.

Community-acquired pneumonia

LRTIs are the third leading cause of death worldwide, imposing a huge impact on healthcare systems. This becomes even more of an issue in developing countries where they have been cited as the number one cause of death (20). CAP remains one of the most common and devastating of the LRTIs, especially among the elderly where it has gained the title "old man's friend." With an increasingly aging population, coupled with a reduction in activity of many agents due to the spread of resistance, the impact of CAP is set to become even more serious. In this setting, it is of the utmost importance that the respiratory fluoroquinolones, as exemplified by levofloxacin, are used in clearly planned strategies that maintain their efficacy.

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The history of fluoroquinolones in CAP has not been a straightforward one, with the first quinolones not seen as respiratory agents. In the 1996 issue of Penetration, S. Ragnar Norrby, MD, PhD, reported that fluoroquinolones should be used for HAP and AECB (21). At that stage, CAP was not an indication, unless caused by PRSP or β-lactam-resistant pathogens.

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However, the situation changed rapidly and, only a year later, Charles M. Fogarty, MD, commented on the increasingly recognized respiratory role for fluoroquinolones. He noted that along with an increased efficacy among new fluoroquinolones, this was also driven by an increasing recognition of the increasing resistance to other agents and the increasing role of atypical pathogens (22).

The launch of levofloxacin introduced to the market a potent agent with high activity against Gram-positive and Gram-negative pathogens (including penicillin-resistant strains of *S. pneumoniae*), as well as atypical pathogens, all of which are commonly implicated in causing not only CAP but also HAP. Not only did levofloxacin possess broad-spectrum activity, it was also found to be less likely to be associated with resistance, as the frequency of one-step mutations to resistant organisms appears to be lower with levofloxacin than for other fluoroquinolones. Levofloxacin inhibits DNA gyrase but, unlike many other fluoroquinolones, the agent uses 2 separate mechanisms. Dr. Fogarty performed a study assessing the efficacy and safety of levofloxacin 500 mg o.d. as empiric therapy for CAP, with 60 patients stratified into mild/moderate or severe disease. Ninety-five percent of patients were assessed as cured and the other 5% as improved. Once-daily therapy was very effective and, based on these results, Dr. Fogarty recommended levofloxacin as initial therapy in moderate/severe CAP patients (22).

Thomas M. File, Jr., MD, FACP, expanded on this in the 1998 issue of Penetration with an excellent review of the benefits of levofloxacin in CAP (23). Commenting on the difficulty in adequately covering resistant pathogens, Dr. File reported that levofloxacin has excellent activity against all key CAP pathogens, particularly *S. pneumoniae*, including those that are resistant to penicillin and other agents. It is also very active against *Haemophilus influenzae*, *Moraxella catarrhalis*, and methicillin-susceptible *Staphylococcus aureus* (MSSA) and has been shown to be more active against *Legionella pneumoniae* than the combination of erythromycin and rifampicin. This preclinical data was supported by clinical results confirming the efficacy and safety of levofloxacin 500 mg o.d. compared with parenteral ceftriaxone 1–2 g o.d. and/or cefuroxime axetil 500 mg PO b.i.d. (plus erythromycin or doxycycline if an atypical pathogen was suspected). Levofloxacin achieved a

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96% clinical success rate at 5–7 days post-therapy compared with 90% for ceftriaxone and/or cefuroxime, suggesting the superiority of levofloxacin. There was only a 3.5% clinical failure rate for levofloxacin compared with 9.6% for the comparator regimen. Levofloxacin was also safer with a 5.8% ADR rate compared with 8.5% for ceftriaxone. Dr. File noted that increasing resistance had made empiric therapy with β-lactams, macrolides, TMP–SMX, and tetracyclines problematic.

In the 2002 issue of Penetration, the topic of CAP was revisited by Pierre Veyssier, MD, who reported important results from a study investigating levofloxacin 500 mg IV to PO o.d. versus ceftriaxone 1–2 g IV every 24 hours plus erythromycin 500–1,000 mg IV every 6 hours in CAP patients at high risk of mortality (24). Levofloxacin was chosen due to its efficacy in high risk patients, and the fact that it had maintained this efficacy despite being widely used for other infections, with little development of resistance. In this trial, 132 patients received levofloxacin and 137 were randomized to the comparator arm. The clinical success rate for levofloxacin was 89.5% and only 83.1% for the comparator regimen. Levofloxacin was well tolerated with a 2.3% discontinuation compared with 8.8% for the comparators. In addition, the ability of levofloxacin to successfully treat atypical pathogens was emphasized, covering *Chlamydia* and *Legionella* spp. A randomized trial of patients with severe CAP investigated a subgroup of almost 10% of patients with *Chlamydophila pneumoniae*, and 83% of these patients were successfully treated with levofloxacin compared with only 67% in the comparator regimen (ceftriaxone plus erythromycin switching to clarithromycin plus amoxicillin–clavulanate). This study also looked at a subgroup of *Legionella* spp. infected patients and demonstrated a greater than 90% clinical and microbiological success rate with levofloxacin.

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The role of levofloxacin in different subgroups of CAP patients has been evaluated with a report by Po-Ren Hsueh, MD, describing the use of levofloxacin in Asian patients. Introduced into Taiwan in 2000, levofloxacin was included in the Taiwanese guidelines for treating CAP. Managing and preventing resistance has been a prime motivator of treatment strategies in Taiwan which in 2001–2003 reported a 60–80% overall prevalence of intermediate PRSP and a 10–20% rate of high-level PRSP. Over 90% of isolates during this period were highly resistant to macrolides and over 80% were resistant to TMP–SMX. Also, β-lactamase production was found in 50–60% of *H. influenzae* and greater than 95% of *M. catarrhalis* isolates. Data from the Surveillance from Multicenter Antimicrobial Resistance in Taiwan (SMART) program revealed that the level of resistance to levofloxacin remained low compared with that in Hong Kong, with no signs of clonal spread. In a clinical trial of 38 patients with pathogen-confirmed CAP, 16 received levofloxacin and 22 amoxicillin–clarithromycin. Results demonstrated a higher bacterial eradication rate for levofloxacin (81.3% vs. 72.7%). Dr. Hsueh concluded that levofloxacin is an excellent choice for LRTIs in this setting (25).

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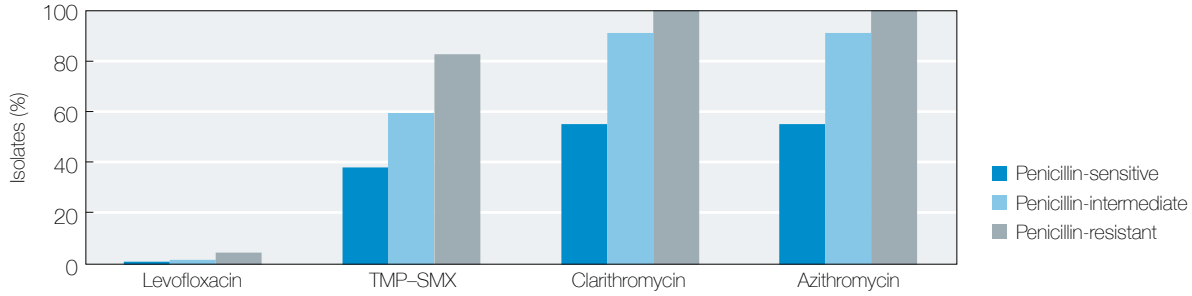
In order to ensure maximum efficacy when treating CAP, it is important to have information about regional susceptibility profiles. In this regard, latest trends in pneumococcal resistance in Asia have shown that, among nonmeningeal isolates of *S. pneumoniae*, penicillin resistance is 0.7%, while 72.7% are resistant to erythromycin and 59.3% are multidrug-resistant (26). The continued activity of levofloxacin against CAP pathogens in Asia has been confirmed in the Global Landscape On the Bactericidal Activity of Levofloxacin (GLOBAL) surveillance study **(Figure 2)** (27). This confirms that resistance to levofloxacin among *S. pneumoniae* is much lower than that reported for TMP–SMX, clarithromycin, and azithromycin, making it an important agent for CAP.

Clinical evidence supporting the continued antimicrobial activity of levofloxacin against RTI pathogens given in Asia was provided by a trial comparing the efficacy and safety of levofloxacin

Figure 2 Percentage of *S. pneumoniae* isolates in Asia resistant to selected antibiotics (*n* = 815)



Abbreviation: TMP–SMX = trimethoprim–sulfamethoxazole.
Adapted from reference (27).

(Penetration 2007; 18: Figure 1)

Institutional affiliations and titles are as of date of publication.

750 mg IV for 5 days versus 500 mg IV for 7–14 days in CAP (28). A total of 241 patients were enrolled, with 121 randomized to receive a 750 mg dose and 120 a 500 mg dose. The high-dose group was treated for a median duration of 5.0 days (median total dose 3,750 mg) compared with 9.0 days for the 500-mg group (median total dose 4,500 mg). The bacterial eradication rate was 100% in both groups. The high-dose group achieved an overall efficacy rate of 86.2% compared with 84.7% in the 500-mg group [95% confidence interval: 1.6 (-7.8–10.9)]. The most common clinical ADRs were injection site adverse reactions in both groups followed by insomnia, nausea, and skin rashes. The most commonly reported possible drug-related laboratory changes included a decrease in neutrophils, white blood cells, alanine aminotransferase, and an increase in aspartate aminotransferase. This was the same for both dosage groups. Most ADRs were mild. The researchers concluded that levofloxacin 750 mg IV for 5 days was as effective and well tolerated as 500 mg IV for 7–14 days for the treatment of CAP.

Another subgroup of CAP patients treated with levofloxacin involves those with reduced immune function. A retrospective analysis showed that the patients with CAP treated with a fluoroquinolone had a lower mortality (7% vs. 17%, $p < 0.05$) and a shorter median length of stay (LOS) in hospital (29%) (24). In addition, monotherapy with a fluoroquinolone was also associated with lower mortality rates and shortened hospital stay.

Levofloxacin and CAP evidence-based guidelines

Over the last 20 years, guidelines outlining the optimal management of CAP have been developed by a range of professional societies. In the 2000 issue of Penetration, Claude Carbon, MD, summarized many of these and reported that the Infectious Diseases Society of America (IDSA) guidelines recommended macrolides, fluoroquinolones, and doxycycline for outpatients while hospitalized patients in a general ward should be treated with a β-lactam, with or without a macrolide, or a fluoroquinolone alone. For patients in an intensive care unit (ICU), a macrolide or fluoroquinolone plus a third-generation parenteral cephalosporin were recommended. Dr. Carbon concluded that newer fluoroquinolones, including levofloxacin, could be considered as first-line monotherapy for CAP because of their wider spectrum of activity and clinical efficacy (29).

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This topic was further addressed by John G. Bartlett, MD (30) in the 2005 issue of Penetration with a summary of the latest CAP treatment guidelines and the role of levofloxacin. He noted that the efficacy and safety of levofloxacin have been assessed in a large number of clinical trials, involving both ambulatory patients and hospitalized patients. While *S. pneumoniae* remains the principal pathogen, concern remains regarding resistance. Therefore, it is a great advantage that levofloxacin continues to exhibit the lowest rate of *S. pneumoniae* resistance based on susceptibility to penicillin. With 2 mutations required for high-level quinolone resistance, overall resistance trends have shown that the fluoroquinolone resistance rates, including levofloxacin, are less than 2%. Dr. Bartlett reported on the antimicrobials recommended for each specific pathogen **(Table 4)** (31).

The IDSA guidelines recommend that ambulatory outpatients with CAP be treated with doxycycline or a macrolide,

Table 4 Pathogen-specific therapy

Causative agent	Preferred treatment	Role of levofloxacin
S. pneumoniae	Cefotaxime Ceftriaxone Amoxicillin	Empiric therapy: β-lactam + macrolide or fluoroquinolone[a] (alone)
Atypicals		
Legionella spp.	Fluoroquinolone[a] Azithromycin	Preferred agent
C. pneumoniae	Macrolide Fluoroquinolone	Alternative to macrolides and doxycycline
M. pneumoniae	Macrolide Fluoroquinolone	Alternative to macrolides and doxycycline
Aspiration pneumonia	Clindamycin β-lactam, β-lactamase inhibitor	Fluoroquinolones not recommended
H. influenzae	Cephalosporin Azithromycin Doxycycline TMP–SMX	Fluoroquinolones[a] are alternatives

[a] Includes levofloxacin as a respiratory quinolone (levofloxacin, gatifloxacin, moxifloxacin).
Abbreviation: TMP–SMX = trimethoprim–sulfamethoxazole.
Adapted from reference (31).

(Penetration 2005; 16: Table 1)

and fluoroquinolones are advocated for those patients with comorbidities or recent antibiotic exposure. In hospitalized patients, a pathogen should be identified, although the majority of patients continue to be treated empirically. Using cephalosporins as the reference standard, the combination of a macrolide and cephalosporin reduced mortality by 24% while monotherapy with a fluoroquinolone reduced mortality by 36%. This led to the recommendation for empiric use of fluoroquinolones or a macrolide plus cephalosporin in patients with CAP requiring hospitalization. The IDSA recommendations for treating CAP in an ICU patient is to combine a β-lactam with a respiratory fluoroquinolone or macrolide, although there are no data showing that this combination therapy is better than a fluoroquinolone alone. In addition, levofloxacin has been approved by the US FDA for treating CAP caused by MDRSP defined as an isolate resistant to 2 or more of the following antibiotics: penicillin, second-generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines, and TMP–SMX. Dr. Bartlett concluded that levofloxacin continues to play a prominent role in the IDSA guidelines for the treatment of CAP based on evidence from randomized trials, PK data and lengthy post-marketing surveillance (31).

The continued use of levofloxacin in RTIs has resulted in the publication of more reviews. One of these in 2012 reported that levofloxacin provided optimal monotherapy for AECB and CAP and was valuable as a high-dose component of combination therapy for HAP. It was also associated with improved bioavailability and a favorable safety profile allowing the possibility of shorter stays in hospital (32).

The latest reports continue to support the IDSA/American Thoracic Society (ATS) guidelines, noting an important role for fluoroquinolones in CAP. The most recent of these is a 2014 Cochrane review, which is an update of their 2009 publication on antibiotic therapies for CAP in an outpatient setting (20). The review included a further 11 randomized controlled trials in the update, assessing clinical, bacteriological, and adverse events (AEs). While there was no significant difference in the efficacy of the antibiotics, there were some differences in AEs. Nemonoxacin produced higher gastrointestinal and nervous system AEs when compared with levofloxacin, and high-dose amoxicillin (1 g t.i.d.) was associated with a higher incidence of gastritis and diarrhea compared with clarithromycin, azithromycin, and levofloxacin. The authors concluded that while the study data was limited due to the very low number of studies assessing the same antibiotic pairs, with insufficient data to make changes to earlier evidence-based recommendations for antibiotics in ambulatory CAP, they did find 2 studies reporting significantly more AEs with cethromycin, when compared with levofloxacin. They concluded that multidrug comparisons using similar administration schedules are needed to provide clearer evidence for practice recommendations.

Treatment of CAP caused by atypical pathogens

In the 2000 issue of Penetration, the problem of Legionnaires' disease was addressed by Burke A. Cunha, MD, who described levofloxacin as the most cost-effective of the available fluoroquinolones for treating *Legionella* infections (33). Laboratory data and animal studies have indicated that fluoroquinolones and newer macrolides exhibit high anti-*Legionella* activity, resulting in newer fluoroquinolones, including levofloxacin, becoming first-line agents for treating these infections. The IDSA recommends doxycycline, azithromycin, and various fluoroquinolones for *Legionella* infections due to AEs associated with erythromycin and the ability of agents such as levofloxacin to be effective in a once-daily dosing schedule.

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Resistance to levofloxacin among *Legionella* infections has not been a clinical problem and in the 2006 issue of Penetration, Rosa M[a] Blázquez Garrido, MD, reported results from a prospective, non-randomized study of 292 patients hospitalized with *L.* pneumonia that demonstrated levofloxacin to be clinically effective in these patients (34). Patients received either clarithromycin or levofloxacin and were stratified according to severity of disease. Two hundred and twenty-four of the 292 had mild/moderate disease and 68 had a more severe form. After admission, 35 patients received azithromycin, 32 clarithromycin, and 187 levofloxacin. The clinical response was 99.3% for levofloxacin and 100% for the macrolides. Patients with severe disease treated with macrolides were more likely to develop complications and had a significantly longer LOS in hospital **(Table 5)**. These results indicate the excellent efficacy of levofloxacin and the use of IV-to-PO switch therapy with levofloxacin is very beneficial. Levofloxacin also possesses the advantage of an extremely low rate of drug-drug interactions. Patients can be stabilized in hospital and then sent home on oral therapy allowing for a much more cost-effective treatment regimen. Levofloxacin was shown to be well tolerated in this study providing a safe, efficacious, and cost-effective treatment for Legionnaires' disease.

In addition to *Legionella,* levofloxacin has been shown to have a role to play in treating other atypical pathogens, including *Mycoplasma pneumoniae* and *C. pneumoniae*. In a 2003 review in Penetration, Francesco Blasi, MD, PhD, et al (35) reported on the growing importance of these pathogens in RTIs and the expanding role for levofloxacin. *C. pneumoniae* is

Institutional affiliations and titles are as of date of publication.

Table 5 Clinical outcome of patients treated with levofloxacin vs. macrolides

	Fine ≤ 3 (*n* = 168)			Fine ≥ 4 (*n* = 40)			Total (*n* = 208)		
	Macrolide (*n* = 54)	Levofloxacin (*n* = 114)	*p* value IR (CI 95%)	Macrolide [a] (*n* = 11)	Levofloxacin (*n* = 29)	*p* value IR (CI 95%)	Macrolide (*n* = 65)	Levofloxacin (*n* = 143)	*p* value IR (CI 95%)
Duration of fever (mean days ± CI 95%)	4.7 ± 0.6	4.5 ± 0.4	0.5	4.2 ± 2.2	4.2 ± 1	0.9	4.6 ± 0.6	4.4 ± 0.4	0.5
Complications	0	0	—	3 (27.2%)	1 (3.4%)	0.02 9 (0.8–79.3)	3 (4.6%)	1 (0.6%)	0.08 7.6 (0.6–55.9)
Outcome (cured)	54 (100%)	114 (100%)	—	11 (100%)	28 (96.5%)	0.5 1.0 (0.5–2.0)	65 (100%)	142 (99.3%)	0.4 1.0 (0.7–1.3)
Side effects	8 (14.8%)	12 (10.5%)	0.4 1.4 (0.5–3.1)	2 (18%)	3 (10.3%)	0.6 1.7 (0.2–7.5)	10 (15.3%)	15 (10.4%)	0.3 1.4 (0.6–2.8)
Hospital stay (mean days ± CI 95%)	4.3 ± 1.3	4 ± 0.3	0.6	11.3 ± 5.4	5.5 ± 1.0	0.04	7.2 ± 2.6	4.4 ± 0.3	0.03

[a] All patients were treated with clarithromycin.
Abbreviations: IR = incidence ratio; CI = confidence interval.

(Penetration 2006; 31: Table 1)

considered the most common non-viral intracellular RTI pathogen responsible for pharyngitis, sinusitis, otitis as well as bronchitis, AECB, asthma, and CAP. *M. pneumoniae* is also an important atypical pathogen and, due to its lack of a cell wall, is resistant to antimicrobials such as β-lactams, sulfonamides, rifampicin, and glycopeptides. In contrast, agents such as fluoroquinolones are active against both *Mycoplasma* and *Chlamydia* spp.

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Hospital-acquired pneumonia

In the 2006 issue of Penetration, Marin H. Kollef, MD, stressed the high healthcare costs incurred in treating patients with HAP, which is the second most common nosocomial infection in the US associated with a crude mortality rate as high as 30–70% (36). These costs are even higher in patients requiring mechanical ventilation who develop a ventilator-associated pneumonia. Initial treatment of HAP is usually empiric, involving a broad-spectrum regimen providing coverage of all likely pathogens. A meta-analysis of 5 trials comparing fluoroquinolones with other treatments in HAP revealed a pooled odds ratio (OR) suggesting a survival advantage for fluoroquinolones, and the pooled microbiological eradication rate was 66.4% for fluoroquinolones versus 57.3% for comparators. The pooled OR favored fluoroquinolones, at a level that approached statistical significance. Generally, the emergence of resistance was also lower with fluoroquinolones compared with imipenem/cilastatin. Levofloxacin, an anti-pseudomonal fluoroquinolone, is useful in this setting and has been used in a dose of 750 mg o.d., taking advantage of its concentration-dependent kill and long post-antibiotic effect. While first given IV, levofloxacin can be safely and effectively used in an early step-down regimen.

The profile of pathogens responsible for HAP has remained stable, with a 2013 study assessing the bacterial profile of patients hospitalized with LRTIs showing that the predominant isolates are *S. pneumoniae* (36%), *C. pneumoniae* (18%), and *M. pneumoniae* (12%), all of which were highly sensitive to levofloxacin, moxifloxacin, macrolides, and cefepime (37). Among those diagnosed with HAP, the predominant isolates were methicillin-resistant *S. aureus* (MRSA) (23%), *Klebsiella pneumoniae* (14%), and polymicrobial in 12% with very high resistance to β-lactam/β-lactamase inhibitors and cephalosporins. For acute exacerbations of COPD (AECOPD), *H. influenzae* was the commonest organism. The authors concluded that respiratory fluoroquinolones, macrolides, and cefepime were the most efficient antibiotics for the treatment of LRTIs in this region.

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A prospective clinical trial assessing the efficacy and safety of levofloxacin 500 mg IV in patients with nursing and healthcare-associated pneumonia (NHCAP) categories B and C (other antibacterial agents were allowed to be used with levofloxacin) was published in 2014 (38). A total of 62 patients were registered with 54 enrolled for clinical evaluation. Levofloxacin was effective in 85.2% of NHCAP cases (81.8% of category B and 90.5% of category C). In addition, when assessed according to severity, levofloxacin achieved a 100% success rate in patients with mild disease, 86.7% in those with moderate disease, and 77.8% in those with severe/very severe disease. Nine patients had ADRs possibly related to levofloxacin leading the researchers to

conclude that levofloxacin was effective and relatively safe for categories B and C in patients with NHCAP.

This has been confirmed in a 2012 review of levofloxacin in RTIs, including HAP. The authors concluded that the high-dose (750 mg), short-course (5 days) levofloxacin regimen also provides the potential benefit, especially in HAP, of achieving higher drug concentrations, increased adherence and the potential to reduce the development of resistance (32).

Tuberculosis

Tuberculosis (TB) continues to pose a huge problem globally, in particular multidrug-resistant TB (MDR-TB) forms. The importance of this issue has long been recognized by Penetration, with an interview with Lee B. Reichman, MD, MPH, FACP, FCCP, in 1998 calling the advent of MDR-TB a "disaster." Since then the problem has only intensified, spreading around the world, becoming what the World Health Organization (WHO) terms a "major public health problem." Drug resistance arises not only because of the use of inappropriate antibiotics in ineffective regimens, but also through failure to ensure complete compliance with treatment. Dr. Reichman noted that in Western countries resources are available to deal with this issue, with directly observed therapy reducing the incidence of MDR-TB in New York from almost 20% down to 5%. In addition, China and Singapore were noted as having effective programs aimed at dealing with this public health problem, but the majority of affected countries do not have the resources or political will to deal with it. Dr. Reichman recommended an 800 mg o.d. dose of ofloxacin, which he thought would provide additional benefits, since levofloxacin was not available at that time (39).

The issue of optimizing TB treatment was assessed in 2 reviews in the 2011 issue of Penetration with Wing Wai Yew, MBBS, FRCP, noting the efficacy of levofloxacin in this disease, and a potential role as a component of MDR-TB regimens (40). The issue of the safety of levofloxacin in these patients requiring multiple antimicrobials for long periods was considered by Chao-Chi Ho, MD, PhD, et al who concluded that it was safe to use levofloxacin in these patients **(Table 6)** (41–45).

Since then, data has become available confirming his view that levofloxacin would be useful in this setting. A report in 2008 described the population PK parameters of levofloxacin, gatifloxacin, and moxifloxacin following multiple PO doses (46). Twenty-nine patients with

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Table 6 Overview of selected studies published in English

Population	Study design	No. of subjects	Treatment	Comparator	Endpoints	Results	Reference
MDR-TB	Retrospective analysis	99	Levofloxacin + anti-TB drugs (40 patients)	Ofloxacin + anti-TB drugs (59 patients)	Comparison of levofloxacin and ofloxacin in the treatment of MDR-TB	Levofloxacin was more efficacious than ofloxacin when incorporated into multidrug regimens used for MDR-TB	(42)
Pulmonary TB and HIV (+)	Multicenter RCT	101	Levofloxacin + 4 combined anti-TB drugs (53 patients)	Four combined anti-TB drugs (48 patients)	Eight week culture response and effectiveness of 9 months vs. 6 months of intermittent therapy for HIV-related pansusceptible pulmonary TB	Levofloxacin added no benefit to a 4-drug induction regimen. Both 9 and 6 months of intermittent therapy were associated with low treatment failure rates	(43)
Active TB confirmed by culture	Case-control study	460	Levofloxacin + anti-TB drugs (without INH or RIF) (102 patients)	Anti-TB drugs (with INH and RIF) (358 patients)	Overall rate of major adverse events associated with levofloxacin-containing regimen	Similar rate of adverse events compared with conventional first-line regimens despite a history of adverse events	(44)
Clinical diagnosis of TB with first-line anti-TB drug-induced hepatotoxicity	Prospective observational study	134	Re-challenge with levofloxacin + EMB ± SM (52 patients)	Re-challenge with EMB ± SM (27 patients)	Safety of using levofloxacin in an endemic area with a high incidence of drug-induced liver injury	Levofloxacin produced no additional hepatotoxicity when used in patients with hepatitis induced by first-line anti-TB drugs	(45)

Abbreviations: MDR = multidrug-resistant; TB = tuberculosis; HIV = human immunodeficiency virus; RCT = randomized controlled trial; INH = isoniazid; RIF = rifampin; EMB = ethambutol; SM = streptomycin.
Adapted from references (42–45).

(Penetration 2011; 27: Table 1)

Institutional affiliations and titles are as of date of publication.

TB received 7 days of either levofloxacin 1,000 mg o.d., or gatifloxacin or moxifloxacin 400 mg o.d. The 3 drugs were well tolerated. Levofloxacin produced the highest maximum plasma concentrations (median: 15.55 µg/mL, gatifloxacin 4.75 µg/mL, moxifloxacin 6.13 µg/mL), the largest volume of distribution (median: 81 L, gatifloxacin 79 L, moxifloxacin 63 L), and the longest elimination half-life (median: 7.4 hr, gatifloxacin 5.0 hr, moxifloxacin 6.5 hr). The researchers concluded that levofloxacin had the most favorable PK/PD profile in these TB patients.

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Further data on the PK/PD features of levofloxacin were reported in a study of 12 patients with pulmonary MDR-TB undergoing surgery to remove cavitary lesions (47). Serum was obtained pre- and post-surgery to measure the levofloxacin concentrations and the levofloxacin concentrations were also measured in dialysate fluid post-surgery. Levofloxacin was prescribed for a median of 373 days before surgery at a median dose 11.8 mg/kg. The median serum levofloxacin C_{max} was 6.5 µg/mL and in 11 evaluable patients the median cavitary concentration was 4.36 µg/mL (range 0.46–8.82) with a median cavitary-serum levofloxacin ratio of 1.33 (range 0.63–2.36). These results confirmed that levofloxacin had excellent penetration into chronic cavitary TB lesions with a good correlation between serum and cavitary concentrations. Optimizing serum concentrations will help ensure optimal cavitary concentrations of levofloxacin, which may improve treatment outcomes.

A review published in 2014 described the development of new drugs and TB regimens and reported that levofloxacin and moxifloxacin have equally good efficacy and safety in the early phase of treatment of MDR-TB (48). In addition, the authors confirmed that late-generation fluoroquinolones in combination with first- and second-line anti-TB drugs have been used to shorten the treatment duration in drug-susceptible and MDR-TB.

The role of levofloxacin in treating TB has been recognized by its inclusion in the 2013 WHO guidelines that recommend the use of at least 4 second-line drugs (a fluoroquinolone such as levofloxacin, an injectable agent, prothionamide, and cycloserine or para-aminosalicylic acid) in addition to pyrazinamide (49). For extensively drug-resistant TB, other agents such as linezolid, clofazimine, and amoxicillin–clavulanate need to be included.

A 2014 review evaluating respiratory fluoroquinolones (e.g., moxifloxacin, gemifloxacin, and high-dose levofloxacin) in CAP upheld their recommendation as empirical antimicrobial therapy. However, the review delved deeper into the issue of whether fluoroquinolones should be used for CAP in areas with a high prevalence of TB due to the perception that they contribute both to delays in the diagnosis of pulmonary TB and to the emergence of fluoroquinolone-resistant strains of *Mycobacterium tuberculosis* (50). The authors concluded that the evidence suggests that the use of fluoroquinolones as recommended for 5–10 days as empirical treatment for CAP, according to current clinical management guidelines, is appropriate even in TB-endemic regions. They also noted that it is critical to quickly exclude *M. tuberculosis* as a cause of CAP using the most rapid relevant diagnostic investigations in the management of all patients with CAP.

Pediatric use of fluoroquinolones

Increasing resistance to commonly used antibiotics in a pediatric setting has stimulated a reevaluation of the potential role of fluoroquinolones in treating these infections. While PK data is limited in children, especially those aged less than 5 years, the available evidence demonstrates that there are substantially lower serum concentrations in children compared with adults at currently recommended doses, probably due to faster elimination. However, due to concerns over side effects in children, notably arthropathy and severe musculoskeletal problems, fluoroquinolones have not been used. However, this situation is changing, with recent short- and long-term assessments indicating that this risk is marginal for levofloxacin and this could lead to more frequent use in children. Even when given for longer periods, there is no evidence suggesting reduced tolerability associated with long-term fluoroquinolone regimens in children (51, 52). This is important as fluoroquinolones are now being considered in a pediatric setting for treating MDR-TB. At present, the use of fluoroquinolones in children should be limited to selected respiratory infections, exacerbations of lung disease in cystic fibrosis, central nervous system (CNS) infections, enteric infections, febrile neutropenia, as well as serious infections attributable to fluoroquinolone-susceptible pathogen(s) in children with life-threatening allergies to alternative agents.

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Urinary Tract Infections

Levofloxacin, with its high bioavailability, renal excretion, exceptional PK/PD features, and broad-spectrum antibacterial activity is an excellent therapy for genitourinary infections.

Prostatitis

Ofloxacin was first introduced predominantly for urological infections, where it was quickly recognized as producing excellent clinical results for both acute and chronic conditions. In 1993, Penetration provided a clear clinical summary of the role of ofloxacin in prostatitis, a previously difficult-to-manage disease. Kurt G. Naber, MD, PhD, drew on both preclinical and clinical studies to confirm ofloxacin's efficacy, noting that it achieved a much higher concentration in urological tissues than β-lactams (1). The role of ofloxacin in this field was further supported by David R.P. Guay, PharmD, FCP, FCCP, in the 1997 issue of Penetration, who demonstrated that ofloxacin was able to achieve concentrations exceeding the MICs of the majority of urinary pathogens (2).

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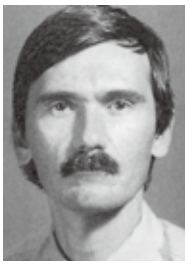

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The development of levofloxacin added to the urological efficacy of its parent compound, and in the 2009 Penetration review, Dr. Naber demonstrated that levofloxacin was effective in the management of bacterial prostatitis, a disease he described as "an often overlooked global healthcare issue." With an estimated 50% of all men set to suffer symptoms of prostatitis at some stage in their life, there is a great need for an effective and safe agent. He described fluoroquinolones, in particular levofloxacin, as the drug of choice for chronic prostatitis, as effective as ciprofloxacin but with the added advantages of better prostatic and seminal fluid penetration coupled with more acceptable administration regimens (3).

This view has been supported by results from a 2012 study comparing the efficacy and safety of levofloxacin versus ciprofloxacin for chronic bacterial prostatitis (CBP) in Chinese patients (4). A total of 471 patients with symptoms were enrolled, with 408 having microbiologically confirmed disease. Patients were randomized to receive either levofloxacin 500 mg PO o.d. or ciprofloxacin 500 mg b.i.d. for 4 weeks. One to 4 weeks after the end of therapy, the clinical cure rate and bacterial clearance rate were 93.30% and 86.06%, respectively, for levofloxacin, vs. 71.86% and 60.03%, respectively, for ciprofloxacin **(Table 1)**. In addition, the rates of AEs were slightly lower in the levofloxacin group.

The management of CBP requires a long duration of treatment. To investigate whether the standard 28-day therapy could be shortened, a trial was performed evaluating high-dose levofloxacin 750 mg o.d. for 2 or 3 weeks versus the standard levofloxacin 500 mg o.d. for 4 weeks (5). A total of 241 subjects were enrolled with a post-therapy clinical success rate for the high-dose 2-week treatment of 63.0%, and 64.9% for the high-dose 3-week schedule, both of which were non-inferior to the 69.3% success rate achieved by 500 mg for 4 weeks. However, at 3 and 6 months post-therapy, clinical success rates were higher for the 500-mg, 4-week treatment group, although the difference was not statistically significant. AE rates were similar for the 3 treatment groups, but discontinuation of therapy due to AEs was higher with the 750-mg regimen for both 2 and 3 weeks versus 500 mg for 4 weeks. The authors concluded that while high doses for shorter durations were no worse than standard 4-week therapy immediately after treatment, at the 6-month follow-up, there was evidence that the 4-week treatment schedule was better, possibly helping to extend the relapse-free interval in patients with CBP.

A study investigating the efficacy and safety of levofloxacin in CBP in daily clinical practice evaluated results in 62 patients with a confirmed diagnosis based on expressed prostatic secretion, treated with a median of 29 days levofloxacin 500 mg o.d. (6). The clinical symptoms, including dysuria, painful ejaculation, and perineal pain, as well as CRP and leukocyte counts significantly improved following levofloxacin therapy. At the end of treatment, 93.5% of the patients were cured or improved and 93.5% were able to resume their regular activities after 10 days (median). This study confirmed the efficacy and safety of levofloxacin in the treatment of CBP in daily clinical practice.

The result was supported by an observational study that assessed the efficacy and safety of levofloxacin 500 mg o.d. for 28 days in CBP (7). All symptoms decreased by Day 28, with the rate of

Table 1 Clinical efficacy of levofloxacin and ciprofloxacin in patients with confirmed bacterial infections at baseline

Index	Levofloxacin (*n* = 209)	Ciprofloxacin (*n* = 199)
Clinical efficacy, *n* (%)	195 (93.30)	143 (71.86)
Clinical cure, *n* (%)	115 (55.02)	68 (34.17)
Clinically improvement, *n* (%)	80 (38.28)	75 (37.69)
Failure, *n* (%)	13 (6.22)	56 (28.14)
Non-evaluable, *n* (%)	0	0

CMH statistic: including non-evaluable patients, 35.08 ($p = 0.0000$); excluding non-evaluable patients, 35.45 ($p = 0.0000$). The CMH test was conducted twice by including and excluding the non-evaluable patients in both groups. Clinical efficacy, which included clinical cure and clinical improvement, was determined at visit 5 (1–4 weeks after the end of therapy).
Abbreviation: CMH = Cochran–Mantel–Haenszel.
Adapted from reference (4).

dysuria falling from 86.1% to 10.6%, painful ejaculation from 71% to 2.6%, and perineal discomfort from 60.3% to 7.3% **(Figure)**.

Another retrospective trial assessed the clinical outcomes of patients with type III inflammatory chronic prostatitis treated with fluoroquinolones, with and without an α-blocker (8). Patients were classified into 6 groups (ciprofloxacin, ofloxacin, levofloxacin, ciprofloxacin + tamsulosin, ofloxacin + tamsulosin, and levofloxacin + tamsulosin). The median National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) scores decreased significantly in all groups ($p < 0.05$) with levofloxacin reducing the median total NIH-CPSI scores more than ciprofloxacin and ofloxacin monotherapies. The combination therapies were better than antibiotic therapies alone with the best result provided by the levofloxacin + tamsulosin combination.

Pyelonephritis

Levofloxacin offers the clinician a very cost-effective therapeutic option, a huge advantage in an area that is well known to inflict a substantial healthcare burden. In 2002, Penetration interviewed George A. Richard, MD, who drew attention to levofloxacin's extremely high bioavailability, achieving a peak:MIC ratio many times greater than 12.2, which is indicative of a potentially excellent outcome (9). Levofloxacin also demonstrated a significant post-antibiotic effect, continuing to suppress bacterial growth between doses, and covered the majority of UTI pathogens, achieving an overall microbiological eradication rate of 95.5% for all uropathogens. With resistance to other agents increasing (e.g., TMP–SMX, ampicillin, and amoxicillin), the continued efficacy of levofloxacin was seen as extremely beneficial. The administration of levofloxacin was also easier, requiring once-daily dosing for 3 days, resulting in greater patient acceptance and compliance. When levofloxacin was given for longer periods in patients with comorbidities, it remained well tolerated. Dr. Richard stressed that β-lactams are not recommended for acute cystitis, and that severe acute pyelonephritis requires 14 days of treatment, again with fluoroquinolones being the drug of choice. He also drew attention to the need to consider the patient's comorbidities and other drugs being used concomitantly. Levofloxacin is very safe in this regard and does not react with theophylline, digoxin, and other drugs metabolized by cytochrome P450. In contrast, other antimicrobials, including other fluoroquinolones with significant hepatic metabolism, have the potential to undergo such interactions. Dr. Richard drew on extensive clinical data to confirm the efficacy of levofloxacin in UTIs, uncomplicated cystitis, and pyelonephritis. He concluded that once-daily levofloxacin is as effective as any currently available agent, but with the added advantage of having a low rate of adverse effects. Levofloxacin achieves higher urine concentrations than gatifloxacin and is supported by much more extensive safety data. It has also been used in a patient-initiated treatment protocol where women with acute cystitis self-medicated. This administration regimen was found to be safe, effective, and convenient.

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The efficacy of levofloxacin in UTIs has been confirmed in later reports from Dr. Naber et al published in the 2005 issue of Penetration. He reported a 98% clinical success rate when treating acute uncomplicated UTIs with 3 days of levofloxacin 250 mg. This dose was increased to 250–500 mg o.d. for 5–10 days for acute uncomplicated pyelonephritis and mild/moderate cUTIs, increasing further to 750 mg o.d. in patients requiring hospitalization for more severe disease (10).

The issue of increasing resistance to other commonly used agents, particularly ampicillin and TMP–SMX-resistance among *Escherichia coli*, has resulted in fluoroquinolones becoming a first-line treatment. However, it was stressed that appropriate dosage regimens need to be used to ensure the continued activity of this valuable agent. With this in mind, Dr.

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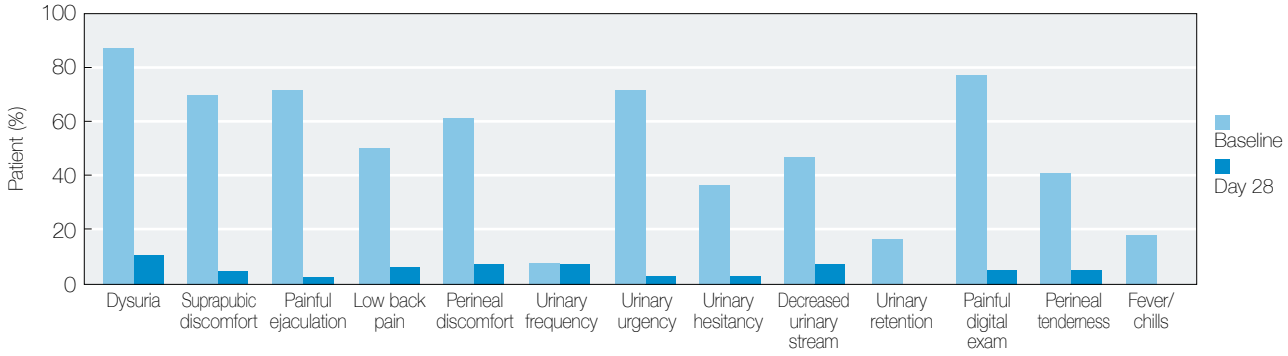
Figure A comparison of symptoms of CBP reported at baseline and at Day 28 after treatment with levofloxacin 500 mg o.d. (n = 151)



Abbreviations: CBP = chronic bacterial prostatitis; o.d. = once daily.
Adapted from reference (7).

Institutional affiliations and titles are as of date of publication.

Naber recommended using levofloxacin b.i.d. for *P. aeruginosa* in order to ensure that the minimum bactericidal concentration is maintained over a 24-hour period, blocking the growth of first step mutants (10).

With urosepsis accounting for 20–30% of all patients with septicemia, Ercole Concia, MD, et al in the 2008 Penetration review (11) stressed the need for antimicrobials with strong and reliable efficacy, active against uropathogens resistant to co-trimoxazole. Levofloxacin has double the renal excretion rate of ciprofloxacin, making it an ideal fluoroquinolone to use for UTIs. It can be started as IV therapy and then easily switched to PO treatment when appropriate. This role in urology was developed further in the 2009 review, with an in-depth look at high-dose, short-course levofloxacin in cUTIs and pyelonephritis. In the 2009 issue of Penetration, Seth R. Strote, MD, et al confirmed that the shorter duration of levofloxacin therapy is as effective as other longer standard regimens, and is likely to be associated with greater compliance and patient satisfaction **(Table 2)** (12, 13).

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These results were further supported by an extensive 2010 Penetration review written by Jessina C. McGregor, PhD, et al that summarized clinical results with levofloxacin in cUTIs and pyelonephritis, concluding that levofloxacin demonstrated high rates of microbiological and clinical success (14).

Urethritis

Levofloxacin has also been used in non-gonococcal urethritis (NGU) with a study evaluating levofloxacin 500 mg o.d. for 7 days (15). A total of 53 symptomatic and 5 asymptomatic NGU patients were evaluated with microbiological cure being achieved in 91% of the 32 symptomatic and 80% of the 5 asymptomatic NGU patients. Clinical cure was also obtained in 92% of the 53 symptomatic NGU patients. The microbiological eradication rate for *C. trachomatis* was 92% in 24 patients. The microbiological and clinical efficacy of levofloxacin 500 mg PO o.d. for 7 days for NGU patients was the same as for those treated with a single dose of azithromycin 1,000 mg.

Prophylactic therapy

A report has highlighted a new role for levofloxacin in a urological setting aimed at reducing catheter-related infections (16). This trial compared the preventive effects of levofloxacin-impregnated versus standard catheters in catheter-related *P. aeruginosa* infections. The catheters were immersed in *Pseudomonas*-containing media, incubated and then bacterial counts were measured. The catheters were implanted into individual mice, which were then challenged with *P. aeruginosa* isolates. Bacterial counts on catheters and surrounding tissues were determined at Day 1 and 5 post-challenge and scanning electron microscopy assessed the bacterial colonization and biofilm formation. Levofloxacin was rapidly released from the catheters, and these had significantly fewer bacteria compared with non-levofloxacin treated catheters, both on the catheter and in surrounding tissues. Scanning electron microscope images also confirmed significantly fewer bacteria on levofloxacin catheters compared with bacteria and microcolonies adhering to standard catheters. After Day 5, no bacteria were found on impregnated catheters, compared with clusters surrounding mucus-like substance and biofilms on standard catheters. The authors concluded that levofloxacin-impregnated catheters are a promising new strategy for prevention of catheter-related *P. aeruginosa* infections.

Asia-Pacific guidelines for complicated urinary tract infections

Treatment of UTIs, the most prevalent infectious diseases in the

Table 2 Microbiological eradication and clinical response rates at post-therapy

Population	Levofloxacin 750 mg o.d. for 5 days 10–17 days postactive therapy		Ciprofloxacin 400/500 mg b.i.d. for 10 days 5–12 days postactive therapy		Difference (95% CI)
	n/N	(%)	*n/N*	(%)	
Microbiological eradication rate[a]					
mITT	253/317	(79.8)	241/302	(79.8)	0 (-6.3–6.3)
ME	228/265	(86.0)	215/241	(89.2)	3.2 (-2.5–8.9)
Clinical success rate[a]					
mITT	257/317	(81.1)	242/302	(80.1)	-0.9 (-7.2–5.3)
ME	229/265	(86.4)	213/241	(88.4)	2.0 (-3.9–7.8)

[a] Subjects with an outcome of unknown in the mITT population are included in the denominator.
Abbreviations: o.d. = once daily; b.i.d. = twice daily; CI = confidence interval; mITT = modified intention-to-treat; ME = microbiologically evaluable.
Adapted from reference (13).

(Penetration 2009; 31: Table 3)

general population, is particularly challenging in the Asia-Pacific region due to large regional differences in resistance rates and healthcare systems. A consensus report (17) reviewing the epidemiology and appropriate antimicrobial therapy of cUTIs in the Asia-Pacific region has shown that ≥ 30% of *E. coli* are resistant to third-generation cephalosporins (cefotaxime, ceftriaxone, and ceftazidime) and cefepime, and resistance to fluoroquinolones is increasing. Prevalence of extended-spectrum β-lactamase (ESBL)-producing urinary *E. coli* is 60% in India, followed by 48% in Hong Kong, and 33% in Singapore. Therefore, it is important that clinicians ensure appropriate use of TMP–SMX, fluoroquinolones, and cephalosporins for the empirical treatment of UTIs, particularly cUTIs among moderate/severe patients. Fluoroquinolones (e.g., levofloxacin 750 mg o.d.) are listed among the primary drugs of choice for treating acute complicated pyelonephritis, emphysematous pyelonephritis, and renal and perinephric abscesses as well as nosocomial or catheter-related UTIs in regions where the fluoroquinolone-resistance rates for urinary *E. coli* are ≤ 20%. Empiric antimicrobial treatment for serious cUTIs in which risk factors for resistant organisms are present should include broad-spectrum antibiotics such as carbapenems and piperacillin–tazobactam. Aminoglycosides, tigecycline, and polymyxins can be used for the treatment of multidrug-resistant organisms or serious cUTIs when first-line options are deemed inappropriate or patients fail to respond to therapy.

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Other Clinical Indications

Levofloxacin has proven efficacy in treating infections affecting most body systems, including gastrointestinal disease and SSTIs as well as immunocompromised patients.

Typhoid fever

Typhoid fever remains a common problem with an estimated 21.5 million cases annually (1). More prevalent in developing countries, it is associated with significant morbidity and mortality, especially if untreated. The ability of fluoroquinolones to treat this infection has long been recognized, with the 1994 issue of Penetration publishing a report by Fu Wang, MD (2), on the use of ofloxacin in typhoid fever. At that time, chloramphenicol was the most commonly used agent, followed by TMP–SMX and ampicillin, although these were limited in efficacy due to a lack of full coverage and ADRs. Fluoroquinolones possess a broad antimicrobial spectrum, particularly against most Gram-negative pathogens and *Enterobacteriaceae*, including *Salmonella typhi* resistant to chloramphenicol, TMP–SMX, and ampicillin. The rapid oral absorption and penetration into relevant tissues make ofloxacin an effective agent, with clinical trials showing it to be consistently better than its comparators, including ciprofloxacin, norfloxacin, and chloramphenicol. Ofloxacin

Institutional affiliations and titles are as of date of publication.

also provides effective treatment of carriers, making it the agent of choice in treating typhoid fever caused by chloramphenicol-resistant strains.

R.H.H. Nelwan, MD, clarified the role of fluoroquinolones, including levofloxacin in typhoid in the 2005 issue of Penetration. Due to levofloxacin's intracellular penetration, it can target typhoid bacilli inside macrophages, resulting in increased bacterial clearance. Results from a trial of levofloxacin 500 mg o.d. for 7 days in 53 hospitalized adults found that all evaluable patients demonstrated an excellent response (3), with fever subsiding a mean of 2.43 days after treatment in cases of confirmed disease and in 2.22 days in cases judged probable. In contrast, the average time for fever to be reduced in cases treated with chloramphenicol was 4–5 days or 5–7 days for those receiving TMP–SMX or ampicillin.

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Levofloxacin was also well tolerated and the once-daily, shorter duration of treatment was seen as advantageous. However, Dr. Nelwan stressed the need to be vigilant to ensure resistance does not develop, and recommended that a longer duration of levofloxacin therapy should be used in areas with nalidixic acid-resistance.

Dr. Nelwan then updated this material in the 2008 issue of Penetration (4), where he used a case report to illustrate the continued efficacy and safety of levofloxacin in patients with typhoid fever who had been unsuccessfully treated with ciprofloxacin. He concluded that levofloxacin is very useful in these patients as the chance of it exacerbating the condition is minimal, with a lower rate of adverse reactions compared with other standard therapy.

Clinical results evaluating the efficacy of levofloxacin in uncomplicated enteric (typhoid) fever were reported by a group of researchers in 2011 (5). A total of 100 patients with blood cultures positive for *Salmonella* spp. who fulfilled the diagnostic criteria for typhoid were enrolled and randomized into 2 groups. Group A (50 patients) received levofloxacin 750 mg PO o.d. and Group B (50 patients) was treated with levofloxacin 500 mg IV o.d. for 7 days. Forty-six patients in Group A were cured compared with 48 patients in Group B. These results confirmed the efficacy of levofloxacin, both in IV and PO formulations, for treating uncomplicated typhoid fever.

A study comparing the PK of levofloxacin in healthy volunteers and in typhoid fever patients has also been reported (6). A total of 12 subjects were divided into Group A (healthy volunteers) and Group B (typhoid patients). A single dose of levofloxacin 500 mg PO was administered, blood was collected over 72 hours, and plasma levofloxacin concentrations were measured. The mean PK values in Group A versus Group B were as follows: C_{max} (6.79 μg/mL vs. 6.90 μg/mL), T_{max} (1.84 hr vs. 1.82 hr), $t_{1/2}$ (10.03 hr vs. 9.42 hr), Ka (2.23 hr^{-1} vs. 2.21 hr^{-1}), AUC (110.09 μg · hr/mL vs. 105.55 μg · hr/mL), Vd (85.84 L vs. 64.31 L), Cl (4.57 L/hr vs. 4.75 L/hr). Analysis revealed that there was no statistical difference in PK values between healthy volunteers and typhoid patients with the authors concluding there is no need to adjust the dose of levofloxacin in typhoid patients.

Helicobacter pylori

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The importance of *H. pylori* in causing gastritis, gastroduodenal ulcers, and gastric cancers is well known, with a 2009 review in Penetration by Javier P. Gisbert, MD, clearly summarizing the difficulties in eradicating this infection (7). He noted that, despite more than 20 years of treatment, an ideal regimen still remains to be found. With the most commonly used first-line treatments [proton pump inhibitors (PPIs), plus clarithromycin and either amoxicillin or metronidazole] failing in 20% of cases alternatives were needed and levofloxacin-based regimens provided an answer. Studies have highlighted the synergistic effect between fluoroquinolones such as levofloxacin and PPIs against *H. pylori* and *in vitro* studies confirmed the activity of levofloxacin against *H. pylori* strains resistant to clarithromycin and metronidazole. Dr. Gisbert stated that the levofloxacin–amoxicillin–PPI combination regimen provides an effective alternative to clarithromycin-based regimens and may be used as first-line therapy, especially in areas with high rates of clarithromycin resistance **(Table)** (8–13). In addition, levofloxacin has been proposed as part of "rescue" therapies as a second-line strategy, offering an alternative to quadruple therapy (PPI–bismuth–tetracycline–metronidazole) in patients with previous PPI–clarithromycin–amoxicillin failure. The levofloxacin-based therapy provides an encouraging third-line strategy after failure of other regimens, and can be administered with good results even after 3 previous eradication failures with several antibiotics, including rifabutin.

These results have been confirmed in a 2015 report evaluating the efficacy and tolerability of a second-line quadruple regimen containing levofloxacin and bismuth in patients whose previous *H. pylori* eradication treatment had failed (14). Failed therapies included standard triple therapy (PPI–clarithromycin–amoxicillin) or a non-bismuth quadruple therapy (PPI–clarithromycin–amoxicillin–metronidazole). A total of 200 consecutive patients received 14 days of therapy including esomeprazole 40 mg b.i.d., amoxicillin 1 g b.i.d., levofloxacin 500 mg o.d., and bismuth 240 mg b.i.d. According to PP and ITT analyses, the eradication rates were 91.1% and 90%, respectively. Cure rates were similar regard-

Table Studies evaluating a combination of levofloxacin, amoxicillin, and a PPI as first-line treatment for *H. pylori* infections

Author	Year of publication	No. of patients	Duration of treatment	Levofloxacin (dose)	Amoxicillin (dose)	PPI (type and dose)	ITT eradication rate (%)
Antos et al (8)	2006	30	7	500 mg b.i.d	1 g b.i.d	Esomeprazole 40 mg b.i.d	87
Cammarota et al (9)	2000	50	7	500 mg o.d.	1 g b.i.d	Rabeprazole 20 mg o.d.	92
Di Caro et al (10)	2002	40	7	500 mg o.d.	1 g b.i.d	Rabeprazole 20 mg o.d.	90
Gisbert et al (11)	2008	75	10	500 mg b.i.d	1 g b.i.d	Esomeprazole 20 mg b.i.d	83
Marzio et al (12)	2006	39	10	500 mg b.i.d	1 g b.i.d	Esomeprazole 20 mg b.i.d	92
Rispo et al (13)	2007	65	7	250 mg b.i.d	1 g b.i.d	Esomeprazole 20 mg b.i.d	91

Abbreviations: PPI = proton pump inhibitor; ITT = intention-to-treat; b.i.d. = twice daily, o.d. = once daily.
Adapted from references (8–13).

(Penetration 2009; 40: Table 1)

less of previous failed treatment. Adverse effects were reported in 46% of patients, with nausea (17%) and diarrhea (16%) being the most common. The authors concluded that 14-day bismuth- and levofloxacin-containing quadruple therapy is an effective treatment with a greater than 90% cure rate. It is a simple and safe second-line strategy in patients whose previous therapy has failed.

Another trial has compared levofloxacin-based triple therapy versus moxifloxacin-based triple therapy and standard treatment in the eradication of *H. pylori* as first-line therapy (15). A total of 102 patients were randomized to the levofloxacin group (levofloxacin 500 mg o.d., amoxicillin 1 g b.i.d., and lansoprazole 30 mg b.i.d. for 10 days), with 101 patients in the moxifloxacin group (moxifloxacin 400 mg o.d., amoxicillin 1 g b.i.d., and lansoprazole 30 mg b.i.d.), and 103 patients in the standard clarithromycin-based group (clarithromycin 500 mg b.i.d., amoxicillin 1 g b.i.d., and lansoprazole 30 mg b.i.d.). PP analysis revealed an eradication rate of 92% in the levofloxacin group, 91.8% in the moxifloxacin group, and 82.4% in the standard group. Levofloxacin and moxifloxacin were both significantly better at eradicating *H. pylori* than standard therapy ($p < 0.05$), but there was no difference between the levofloxacin- and moxifloxacin-based triple therapies.

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Levofloxacin has also been investigated as second-line therapy for eradicating *H. pylori* in a 2010 Penetration review by Simona Di Caro, MD, et al (16). They described levofloxacin as the most promising alternative as a rescue regimen, with broad-spectrum activity, wide distribution with high levels in excess of plasma concentrations in many tissues. They concluded that available data support the use of the 10-day levofloxacin 500 mg o.d./amoxicillin regimen as second-line treatment, although it is necessary to assess local resistance patterns to ensure activity is maintained.

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The review of the second Asia-Pacific guidelines for *H. pylori* infections reported in the 2011 issue of Penetration by Kwong Ming Fock, MBBS, MMed (Int Med), FRCP, FRACP, FACP, FAMS, et al noted an increasing resistance to clarithromycin and metronidazole in parts of Asia leading to reduced efficacy of triple therapies. When there is concern over resistance, the authors recommended standard triple therapy that has not been previously used, bismuth-based quadruple therapy, levofloxacin-based triple therapy, and rifabutin-based triple therapy. They concluded that levofloxacin-based salvage therapy achieved an overall *H. pylori* eradication rate of 80%, and was more effective than quadruple therapy with less adverse effects, and was better when given as a 10-day regimen compared with a 7-day regimen (17).

Skin and soft tissue infections

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Levofloxacin is well recognized as being a useful therapeutic agent for the management of bacterial SSTIs. A review article in the 1998 issue of Penetration by Antonio Nicodemo, MD, reported that most SSTIs are caused by Gram-positive pathogens, although Gram-negatives may be involved in more complicated cases, especially in patients with comorbidities such as diabetes (18). It is therefore important that antimicrobials possess a broad antimicrobial spectrum in order to cover all likely pathogens. Levofloxacin has a number of advantages including penetration into the relevant tissues achieving a high concentration at infected sites, a prolonged elimination half-life allowing once-daily dosing, and easy switching from IV to PO, that make it first-choice therapy for many infections.

Dr. Nicodemo evaluated the efficacy of levofloxacin in uncomplicated SSTIs, comparing levofloxacin 500 mg o.d. for 7 days with ciprofloxacin 500 mg b.i.d. for 10 days. A total of 253 patients were evaluated (129 levofloxacin and 124 ciprofloxacin) with levofloxacin achieving a clinical success rate of 96.1% compared with 93.5% for ciprofloxacin. The microbiological eradication rates were also higher for levofloxacin at 93% versus 90% for ciprofloxacin. He concluded that these results confirmed the efficacy of once-daily levofloxacin, and commented

Institutional affiliations and titles are as of date of publication.

that it provides the potential for a more cost-effective therapy by enabling an earlier switch to PO administration resulting in earlier patient discharge (18).

Neutropenia

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Febrile neutropenia is associated with an increased LOS in hospital and higher mortality and, thus, effective measures to prevent this problem are likely to result in significant benefits. A review by Hamayun Imran, MD, MSc, et al in the 2009 issue of Penetration reported a meta-analysis of randomized, blinded, placebo-controlled trials of fluoroquinolone prophylaxis in neutropenic patients. A total of 2,721 patients were included in the analysis, with results demonstrating a reduction in all-cause mortality following prophylaxis with fluoroquinolones. Fluoroquinolones also reduced the number of febrile episodes, particularly in patients with solid tumors treated as outpatients. Results also suggested a different effect with levofloxacin compared with trials using other fluoroquinolones resulting in the National Comprehensive Cancer Network suggesting levofloxacin as the preferred fluoroquinolone to be used in these patients (19).

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Additional evidence supporting the use of levofloxacin as prophylaxis in neutropenic patients was reported in a 2011 Penetration review by Brahm H. Segal, MD. He noted that fluoroquinolones are probably the most commonly used prophylactic agents in this setting but, due to concerns over selection of resistant bacteria, prophylaxis is generally reserved for those at high risk of infectious complications (20).

This issue of potential fluoroquinolone resistance was evaluated in a trial that examined the incidence of quinolone-resistant *E. coli* before and after levofloxacin prophylaxis in 68 neutropenic patients (21). Levofloxacin-resistant *E. coli* isolates were detected in 11 and 13 of all patients before and after the prophylaxis, respectively, which was not statistically significant ($p = 0.65$). The authors concluded that pre-prophylactic colonization with quinolone-resistant *E. coli* may reflect the spread of ESBL, and that levofloxacin prophylaxis for neutropenia did not result in a significant acquisition of quinolone-resistant *E. coli*.

The effect of levofloxacin 500 mg PO o.d. as prophylaxis in multiple myeloma has also been evaluated (22). The levofloxacin prophylactic group ($n = 80$) were associated with significantly reduced severe infections compared with a historical control group ($n = 139$) without levofloxacin prophylaxis. The study concluded that levofloxacin prophylaxis may be effective in the prevention of severe infections in multiple myeloma patients receiving bortezomib-based regimens. The prevention of these febrile episodes is likely to result in improved patient satisfaction as well as a reduction in healthcare costs.

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Pharmacology

Levofloxacin possesses excellent PK/PD features that make it a very effective agent with increased compliance and a reduced capacity to cause resistance.

Pharmacokinetics/pharmacodynamics

In the 2000 issue of Penetration, George L. Drusano, MD, outlined the pharmacological profile of fluoroquinolones and how these relate to clinical outcome. Fluoroquinolones work in a concentration-dependent manner, with the antibacterial killing rate related to the AUC–time curve relative to the MIC (AUC:MIC ratio). Dr. Drusano used a PK model to show that a once-daily fluoroquinolone dose that achieved a 10:1 peak:MIC ratio killed all isolates and prevented the emergence of resistance. However, if this ratio was not achieved, the AUC:MIC was linked to outcome. Dr. Drusano then performed a prospective study to identify the breakpoint that would be associated with a higher likelihood of a good clinical outcome (1). He demonstrated that optimal results were achieved if the peak:MIC ratio was greater than 12:1 or if the AUC:MIC was 50:1. These results provided the rationale for the development of a once-daily levofloxacin dosing schedule.

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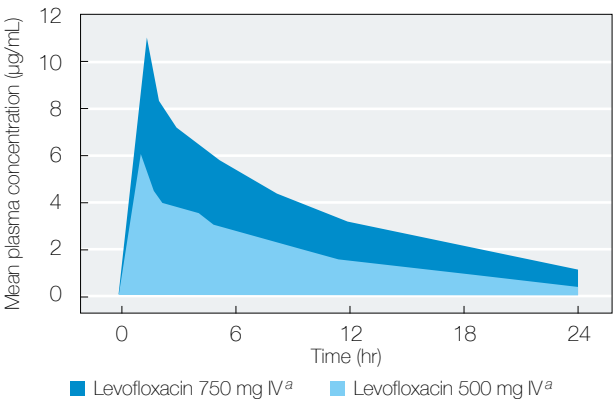
The specific PK/PD features of levofloxacin and relative potencies of fluoroquinolones were then assessed by Lala M. Dunbar, MD, PhD, in an interview reported in the 2009 issue of Penetration. She noted that levofloxacin is rapidly bactericidal, with exceptional oral bioavailability and linear PK. This remains a feature of the higher 750 mg dose of levofloxacin, which has the benefit of achieving and maintaining greater plasma concentrations throughout a 24-hour period **(Figure)** (2, 3).

Dr. Dunbar stressed that higher doses of levofloxacin achieve higher peak concentrations translating into more antibacterial agent being available at the site of infection and increased pathogen killing. She also reported that 2–4 hours after PO administration the concentrations achieved in tissues such as ELF or AM can be higher than that recorded in plasma—a feature she described as an important advantage where levofloxacin is able to achieve high intracellular concentrations making it an effective agent for treating intracellular atypical pathogens.

In terms of PK/PD features, it has also been shown that, following PO administration, levofloxacin is rapidly absorbed resulting in the IV and PO formulations being bioequivalent, providing physicians with the well recognized benefit of an easy switch between these formulations, resulting in faster transfer from an inpatient to an outpatient setting.

Figure Peak plasma levels of levofloxacin



[a] In healthy volunteers who received a single dose.
Abbreviation: IV = intravenous.
Adapted from reference (3).

(Penetration 2009; 6: Figure 1)

Dr. Dunbar reported that the plasma protein binding of levofloxacin is lower than that of many other fluoroquinolones, with a subsequent higher percentage of free drug being available for action. Using PD data, Dr. Dunbar then clarified the relative potencies of fluoroquinolones. The AUC:MIC ratio for the levofloxacin 750 mg dose was 71, the highest of the fluoroquinolone dose combinations evaluated and much higher than that achieved by moxifloxacin, gatifloxacin, or ciprofloxacin **(Table)** (3–7).

New data has been published confirming the PK/PD features of levofloxacin among different patients groups. Noting that most PK/PD data is obtained from healthy volunteers, a group of researchers investigated the intrapulmonary profile of

Table Pharmacodynamic activity of fluoroquinolones against *S. pneumoniae*

Antimicrobial	*S. pneumoniae* MIC_{90}	AUC (24hr) Total/free	AUC (24hr)/ MIC_{90}
Levofloxacin 500 mg o.d.	1	48.0/33.6	34
Levofloxacin 750 mg o.d.	1	101.0/70.7	71
Moxifloxacin 400 mg o.d.	0.25	33.8/17.6	70
Gatifloxacin 400 mg o.d.	0.5	33.8/27.0	54
Ciprofloxacin 500 mg b.i.d.	2	20.2/14.1	7

Abbreviations: o.d. = once daily; b.i.d. = twice daily.
Adapted from references (3–7).

(Penetration 2009; 7: Table 1)

Institutional affiliations and titles are as of date of publication.

high-dose levofloxacin in patients with AECB (8). Data was collected from 18 AECB patients who had received levofloxacin 750 mg o.d. for 5 days. The mean plasma concentrations at 4, 12, and 24 hours were 8.0, 5.8, and 2.2 µg/mL, respectively, while the mean ELF values at 4, 12, and 24 hours were 7.5, 8.3, and 1.2 µg/mL, respectively, and the mean AM concentrations at 4, 12, and 24 hours were 38.5, 13.4, and 9.0 µg/mL, respectively. The ELF:plasma ratio at the infection site was 113%, demonstrating that levofloxacin 750 mg o.d. achieved levels sufficient for the successful treatment of the most common AECB pathogens.

The intrapulmonary concentration of levofloxacin has also been measured in patients with idiopathic pulmonary fibrosis (IPF), a group of patients with significantly impaired pulmonary diffusion (9). The ELF levofloxacin concentration in the control group was 27.81 µg/mL, compared with 10.17 µg/mL in the IPF group. The intrapulmonary concentration of levofloxacin in IPF patients was lower than in those with normal lung function. However, it was shown that the ELF levofloxacin concentration following 500 mg once-daily administration was higher than the MIC values of common respiratory pathogens leading the authors to conclude that levofloxacin is expected to exhibit excellent antibacterial efficacy when treating IPF patients.

Resistance

Concern has continued to grow over the increase in antibacterial resistance worldwide. When the fluoroquinolones were introduced to the market, they were seen as excellent agents able to be used effectively against many resistant bacteria. Unfortunately, indiscriminate use has blunted the efficacy of some of these agents in particular regions. However, it is possible to improve this situation by using clear-cut, evidence-based guidelines that maximize the efficacy of treatment while reducing the likelihood of developing resistance. Thus, it is important to be aware of regional susceptibility profiles and use this knowledge to tailor treatment for individual patients.

Surveillance studies have provided excellent data on antimicrobial susceptibility patterns, monitoring changes as they occur. The need for making clinicians aware of this surveillance data has long been recognized by Penetration, with a report in the 1995 issue summarizing the prevalence of fluoroquinolone resistance in Europe, using ciprofloxacin as the benchmark. Results from 1983, 1986, 1989, and 1990 have been reported showing that resistance rates varied from 0% for *Proteus vulgaris* to 26% for *Providencia stuartii*, with a low resistance to *Enterobacteriaceae* spp. below 1%, while resistance to *Pseudomonas* spp. ranged from 0.7% to 7% and for *S. aureus* from 1% to 6.8%. Striking regional differences were noted with southern areas such as Greece and Spain having much higher resistance rates.

In the 1999 issue of Penetration, an interview with Clyde Thornsberry, PhD, drew attention to the problem of PRSP, as well as resistance to β-lactams and macrolides (10). He noted that levofloxacin was very active against penicillin-resistant, β-lactam- and macrolide-resistant organisms, as well as many atypical respiratory pathogens. In the US, PRSP rates increased dramatically to 20% in the 1990s, and then continued to increase. This situation became worse with many PRSP isolates also being resistant to other agents such as macrolides. However, Dr. Thornsberry stressed that the association between PRSP and resistance to macrolides, β-lactams, and other agents does not extend to fluoroquinolones. The other major concern raised by Dr. Thornsberry was the increasing β-lactamase production by *H. influenzae* and *M. catarrhalis*. Results from the Tracking Resistance in the United States Today (TRUST) study reported that approximately 20% of *S. pneumoniae* were of intermediate sensitivity to penicillin and 14% had high-level resistance, which was described as "alarming." Extrapolating from this data, Dr. Thornsberry commented that the rate of high-level PRSP in the US could reach 40% within a few years. In regard to *H. influenzae*, 33.4% produced β-lactamase, and nearly all *M. catarrhalis* were resistant to ampicillin. However, 100% of these isolates retained sensitivity to levofloxacin.

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The *in vitro* efficacy of levofloxacin against PRSP was further confirmed by a report from Taiwan in the same issue of Penetration by Bor-Shen Hu, MD. Results confirmed that the levofloxacin MIC_{90} against *S. pneumoniae* was 1 µg/mL, making it 2-fold more potent than ofloxacin and 4-fold more active than ciprofloxacin, with all isolates susceptible to levofloxacin (11).

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In 2003, Penetration published an update of surveillance results, presented by Mark E. Jones, PhD, et al (12). The authors showed that PRSP rates varied dramatically, with rates greater than 60% in Spain and France. Resistance was also high in Japan (44% intermediate and 10.1% high), but was strikingly lower in Germany and the UK which both had rates less than 11%. Macrolide resistance was higher than penicillin resistance in all countries evaluated, with over 70% of Chinese isolates and almost 60% of French isolates resistant to both azithromycin and clarithromycin. Pneumococcal resistance to TMP–SMX varied, with high levels of resistance in China but not in Japan.

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The surveillance results confirmed that, despite the widespread

use of ciprofloxacin, there were only a few reports of reduced fluoroquinolone susceptibility. An international surveillance study demonstrated that resistance to levofloxacin was uncommon with no levofloxacin resistance documented in the UK, Brazil, South Africa, or Italy. The highest level of resistance was seen in Hong Kong (8%) and China (3.3%), with lower levels in Spain (1.6%) and Mexico (1.5%) (13–15). Levofloxacin was highly active against *L. pneumophila,* with activity superior to the macrolides and far greater than doxycycline. It was also active against *H. influenzae* and *M. catarrhalis.*

The continued activity of levofloxacin was supported by a report in the 2005 issue of Penetration by Dr. Cunha who noted that even after years of extensive use worldwide, it is exceedingly rare to find strains of *S. pneumoniae* highly resistant to levofloxacin. When increasing fluoroquinolone resistance is noted, it usually relates to ciprofloxacin. In treating MDRSP, Dr. Cunha recommended a 7–10 day course of levofloxacin 500 mg or a shorter 5-day course of the higher-dose 750 mg schedule (16).

In 2010, Penetration interviewed Rafael Cantón, PhD, on susceptibility tracking and how to reduce the development of resistance (17). At that time, he commented that European results confirmed that, for all major RTI pathogens, fluoroquinolones achieved the highest overall susceptibility rate (92.8%) compared with 60.5% for clarithromycin, 85.7% for amoxicillin–clavulanate, and 89.6% for cefuroxime. A total of 99.3% of *S. pneumoniae* strains were susceptible to levofloxacin and moxifloxacin. He thought that the fact that fluoroquinolone resistance among *S. pneumoniae* had remained relatively low was due to using the PK/PD features of these agents to develop optimal regimens. He also noted that more mutation steps were required for levofloxacin and moxifloxacin to select resistant pneumococcal strains compared with ciprofloxacin, gemifloxacin, trovafloxacin, and clinafloxacin. Results from a mutagenic study have also confirmed that levofloxacin and moxifloxacin have less mutagenic potency than other fluoroquinolones (18).

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Chris M. Pillar, PhD, et al, using the GLOBAL surveillance network, reported the susceptibility of *S. pneumoniae* and *H. influenzae* in Europe and Asia to levofloxacin and other agents in the 2010 issue of Penetration. They concluded that levofloxacin remained highly active against the pneumococcal isolates regardless of resistant phenotype, including multidrug resistance and maintained a consistent MIC_{50} and MIC_{90} of 1 μg/mL over time. They also reported that *H. influenzae* remained greater than 99.9% susceptible to levofloxacin regardless of the resistance phenotype (19).

Updated Chinese susceptibility results showed that 56.7% of *S. pneumoniae* isolates were penicillin non-susceptible *S. pneumoniae*, greater than 90% were resistant to macrolides and 39.9% were resistant to oral cephalosporins (20). In contrast, over 97.8% were susceptible to levofloxacin. A total of 21.9% of *H. influenzae* isolates were β-lactamase positive and the authors concluded that, while macrolides and oral cephalosporins have limited activity against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis,* levofloxacin exhibited good activity against these pathogens.

Susceptibility reports show that levofloxacin resistance in *H. influenzae* has increased significantly in Taiwan, from 2.0% in 2004 to 24.3% in 2010 ($p < 0.001$), with investigations revealing that the increase is mainly due to clonal spread in the elderly (21).

While it is well known that susceptibility profiles of antimicrobials need to be continuously updated to ensure an optimal choice of antibiotics, susceptibility testing of *M. catarrhalis* is often not performed. Therefore, a 2014 report outlining the susceptibility profile of this pathogen was an important addition to the respiratory database. A total of 117 clinical *M. catarrhalis* isolates were isolated and tested from 5 Canadian hospitals and 2 private laboratory centers in British Columbia from January to December 2012 (22). All isolates were sensitive to amoxicillin–clavulanate, doxycycline, clarithromycin, TMP–SMX, and levofloxacin supporting their continued therapeutic and empirical use.

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Safety

Levofloxacin has an excellent and extensive safety record, confirmed in multiple clinical trials and a substantial post-marketing surveillance database.

A 1999 Penetration review article by Andrew T. Chow, PhD, et al demonstrated that levofloxacin is only moderately protein-bound in plasma, has negligible hepatic metabolism, and is passively excreted by the kidney, all resulting in a lack of drug-drug interactions, apart from the one exhibited by all fluoroquinolones, namely, that involving metal-containing antacids (1).

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A comprehensive comparison of safety among the fluoroquinolones was prepared in a 2001 Penetration report, which emphasized levofloxacin's exceptional safety record, with a staggering 130 million prescriptions at that time (2). In stark contrast, comparators (temafloxacin, grepafloxacin, trovafloxacin, fleroxacin, and clinafloxacin) were withdrawn or their use restricted due to unacceptable ADRs.

Keith A. Rodvold, PharmD, FCP, FCCP, added further data outlining the safety of fluoroquinolones in the 2006 issue of Penetration (3). Phototoxicity has been shown to be more likely with a halogen at C-8 (lomefloxacin, sparfloxacin, fleroxacin, clinafloxacin, and sitafloxacin), while substitution at C-7 relates to CNS effects. Other agents with 2, 4-difluorophenyl moieties at C-1 are more likely to produce severe unexpected ADRs, as evidenced by trovafloxacin, temafloxacin, and tosufloxacin.

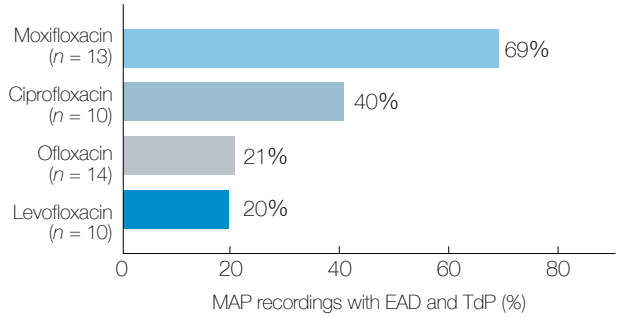
Gastrointestinal are the most common side effects reported to occur in 2–20% of patients treated with fluoroquinolones, followed by CNS and skin problems (4). Most ADRs are mild with anaphylactic reactions being rare, although the reporting of spontaneous anaphylactic ADRs in Germany showed that 54% of all 166 cases were caused by moxifloxacin, compared with a much lower rate of 15% for levofloxacin (5).

One concern associated with fluoroquinolones has been the development of musculoskeletal ADRs, especially in children and those taking steroids. There have also been reports of hypoglycemia and hyperglycemia leading to the need to take extra care in diabetic patients. These ADRs appear to be more commonly associated with gatifloxacin, with pharmacoepidemiological evidence clearly showing that gatifloxacin induces hypoglycemia, and that both hypoglycemia and hyperglycemia occur more frequently with gatifloxacin than with other commonly used fluoroquinolones (6).

Cardiac ADRs have also been reported for fluoroquinolones, particularly prolongation of the QTc interval. While a class effect, this is associated with some individual fluoroquinolones more than others, with sparfloxacin having the greatest rate of cardiac ADRs, followed by grepafloxacin, moxifloxacin, gatifloxacin, and is much less likely with levofloxacin and ciprofloxacin. In fact, levofloxacin has the lowest incidence of torsades de pointes and moxifloxacin has the highest in a proarrhythmia heart model **(Figure)** (7).

There has also been a trend to use higher-dose, shorter-course therapy and levofloxacin has been shown to be well

Figure Incidence of TdP in association with low potassium



Note: All fluoroquinolones (100–1,000 μM) were infused just above the heart.
Abbreviations: TdP = torsades de pointes; MAP = monophasic action potential; EAD = early after depolarization.
Adapted from reference (7).

tolerated at a 750 mg dose while, in contrast, the potential safety of gatifloxacin and moxifloxacin at higher doses is unclear. The safety of levofloxacin 750 mg was described by Ronald F. Grossman, MD, FRCPC, FCCP, FACP, in the 2008 issue of Penetration who stated that this high dose was well tolerated with approximately 9% of patients reporting ADRs, a similar percentage to that reported by patients treated with amoxicillin–clavulanate (8).

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Dr. Ho et al assessed the safety of levofloxacin in TB in the 2011 issue of Penetration. Due to the need for long-term treatment with multiple agents, it is important to use antimicrobials that are well tolerated and do not interact with other drugs. The authors performed a detailed literature review and concluded that ADRs did not increase even after adding levofloxacin to TB regimens and, even when used in patients with drug-induced hepatotoxicity, there was no worsening of the hepatotoxicity. They concluded that data support the safety of levofloxacin in TB (9).

One other ADR of concern with fluoroquinolones is that of *Clostridium difficile*-associated diarrhea (CDAD). Results have confirmed that levofloxacin is not independently associated with the development of CDAD, in strong contrast to gatifloxacin and moxifloxacin, both of which have been implicated. In fact, when a formulary change substituted levofloxacin with moxifloxacin or gatifloxacin, an outbreak of CDAD was reported, and case-control studies have identified moxifloxacin as a risk factor for CDAD (10).

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Dosage and Administration

Levofloxacin provides the physician with an antimicrobial that can be easily administered in regimens that allow individualized care, resulting in improvements in outcome and reduction in costs.

Sequential IV/PO therapy

One of the major advantages possessed by levofloxacin and its parent compound ofloxacin is its remarkable bioavailability when given IV and PO. This results in the ability to use oral levofloxacin when many other comparators need to be given IV. However, in certain circumstances, the IV formulation is required, such as serious infections, and when patients are unable to take drugs orally. The clinical question then arises of when to change a patient from IV to PO therapy and, in this regard, ofloxacin and levofloxacin are seen as leaders as far as fluoroquinolones are concerned.

Institutional affiliations and titles are as of date of publication.

The almost 100% oral bioavailability also means that, when switching from the IV formulation, no dose adjustment is required, which again makes switching administration very simple. Dr. Norrby reported the clinical advantage of such sequential therapy in the 2001 issue of Penetration, specifically looking at hospitalized patients with LRTIs (1). He emphasized the advantages of sequential levofloxacin therapy, noting that it allowed earlier discharge from hospital with a reduction in hospital costs as well as reducing costly intensive home care compared with ceftriaxone. Dr. Norrby cited supporting evidence from trials comparing levofloxacin IV and/or PO versus ceftriaxone followed by cefuroxime axetil. In one study (2), patients received levofloxacin 500 mg o.d. IV or PO, or parenteral ceftriaxone 1–2 g o.d. or b.i.d., and/or cefuroxime axetil 500 mg PO b.i.d. In the levofloxacin group, 2.2% received only parenteral therapy and 61% received only oral levofloxacin. In contrast, only 50% of the cephalosporin group received PO therapy alone. The levofloxacin-treated patients had a 96% clinical success rate and 98% microbiological eradication rate, compared with 90% and 85%, respectively, for the comparator.

The reduction in healthcare costs was supported by a study evaluating a critical pathway in pneumonia, comparing patients treated with levofloxacin versus standard treatment (3). Levofloxacin-treated patients achieved equivalent clinical outcomes, with a 1.7-day reduction in LOS in hospital as well as an 18% decrease in the admission of low-risk patients, resulting in a US $1,700 reduction in healthcare costs.

The 2004 issue of Penetration published a review by Hadiarto Manggunnegoro, MD, et al that provided further evidence supporting the usefulness of IV/PO levofloxacin therapy compared with cephalosporins in CAP (4). Patients treated with levofloxacin 500 mg IV or PO o.d. for 10 days had an 89% success rate compared with 79% for those treated with ceftriaxone 2 g IV o.d. followed by cefuroxime axetil 500 mg PO b.i.d. for 10 days. The mean duration of IV therapy for levofloxacin was 2.4 days compared with 3.05 days for the comparator. The levofloxacin-treated patients required less time in hospital and had an 81% clinical cure rate at 1–3 days post-therapy compared with the much lower 62% for ceftriaxone/cefuroxime axetil. These results confirmed that an early switch from IV to PO levofloxacin in hospitalized patients with moderate/severe CAP was successful in 89% and provided a better and cheaper alternative to ceftriaxone/cefuroxime axetil.

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These results were confirmed by a trial which investigated switching from IV to PO therapy and compared levofloxacin 750 mg with 500 mg (5). Results confirmed that high-dose levofloxacin is associated with faster switching to PO therapy, with an average of 2.85 doses of IV treatment compared with 3.52 doses for the 500-mg regimen. This was then reflected in a reduction in the time spent in hospital, and a subsequent reduction in total medical manpower required and the cost fell from US $150.65 per patient for the 500 mg dose to US $115.47 per patient for those switched earlier on the 750 mg dose.

High-dose, short-course regimen

As levofloxacin use increased, it became apparent that it was associated with even more positive PK/PD features when administered as a high-dose with Dr. Dunbar reporting in an interview in the 2009 issue of Penetration that the 750 mg, short-course levofloxacin regimen was "the way forward." The 750-mg levofloxacin dose was associated with higher AUC levels compared with moxifloxacin 400 mg, gatifloxacin 400 mg, and ciprofloxacin 500 mg and took advantage of the concentration-dependent antibacterial activity of levofloxacin. Dr. Dunbar noted that this levofloxacin regimen possessed the advantages of greater compliance, better cost-effectiveness and the potential to halt any increase in resistance (6).

The 2008 issue of Penetration further evaluated the role of high-dose, short-course therapy in AECOPD and CAP. Dr. Grossman focused on AECOPD and commented that an increased understanding of fluoroquinolone PD had suggested that the high-dose therapy would be associated with a more rapid and extensive bacterial eradication, which allows shorter duration of treatment without compromising efficacy. He used results from a clinical trial that stratified AECOPD patients according to the severity of their illness who were then randomized to receive either levofloxacin 750 mg PO for 3 days versus an initial dose of 500 mg azithromycin followed by 250 mg PO for 4 days. If the patients had complicated disease, levofloxacin 750 mg was given for 5 days or amoxicillin 875 mg/clavulanate 125 mg PO b.i.d. for 10 days. In these complicated patients, microbiological eradication was 81.4% for the levofloxacin arm compared with 79.8% for the amoxicillin–clavulanate arm and the clinical response was similar for both groups. The high-dose therapy was well tolerated with 9% ADRs being reported, a value similar to that in the amoxicillin–clavulanate group (7).

Andrew F. Shorr, MD, MPH, FCCP, evaluated high-dose levofloxacin therapy in CAP in the 2008 issue of Penetration and described a retrospective analysis to compare the 750-mg 5-day regimen with the 500-mg 10-day regimen (8). Results confirmed that the higher dose was as effective and well tolerated as the longer duration regimen and subgroup analysis revealed that the higher-dose therapy was also as

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effective and safe in patients with severe disease.

In order to ensure optimal therapy for individual patients, it is important that the regimen used is tailored to specific patient subgroups. With this in mind, an updated review has looked at the personalized therapeutics of levofloxacin and, using 20 years of literature reports, the PK data were summarized for selected patient subgroups, and an investigation was carried out to see how this should be reflected in dosage and administration regimens **(Table)** (9–16).

Table Pharmacokinetic concerns in personalized therapeutics for levofloxacin in specific patient populations

Specific patient population	Pharmacokinetic alterations	Medication therapy management
Obese vs. normal-weight	Marked variability in levofloxacin clearance was evident in the obese population. Obese individuals with normal renal function may clear levofloxacin more efficiently than normal-weight individuals (10).	Clinicians should be mindful of the potential variability in drug exposure in obese individuals and consider the potential impact of underdosing. Moxifloxacin may be an alternative to levofloxacin if clinically indicated.
Cystic fibrosis vs. noncystic fibrosis	Standard 2-hour spacing of calcium formulation and levofloxacin was insufficient to prevent a chelation interaction in patients with cystic fibrosis. Oral absorption of levofloxacin is slower among patients with cystic fibrosis compared with patients without cystic fibrosis (11).	Multivalent cations should be maximally separated from oral levofloxacin administration.
Male vs. female	Levofloxacin package insert does not have any mention of sex-specific differences in pharmacokinetics. Two studies reported no influence of sex on oral levofloxacin pharmacokinetics; however, one study found that V_{ss} remained significantly lower in women compared with men when pharmacokinetic parameters of intravenous levofloxacin were adjusted for body weight (12). Inconsistent conclusions might be associated with sample size and administration route.	It is necessary to address whether sex has an influence on the pharmacokinetics, efficacy, and toxicity of levofloxacin by conducting future studies with larger sample sizes.
Children vs. adults	Children younger than 5 years cleared levofloxacin nearly twice as fast as adults and, as a result, have a total systemic exposure (i.e., AUC) approximately one half that of adults (13).	Children ≥ 5 years need a daily dose of 10 mg/kg, whereas children 6 months to < 5 years should receive 10 mg/kg every 12 hours.
Elderly patients vs. younger patients	Levofloxacin 500 mg o.d. has a 95.7% probability of achieving an AUC_{0-24}/MIC of 30 for elderly patients (≥ 65 years) compared with 72.7% for younger patients (< 65 years). Levofloxacin pharmacokinetics in elderly patients with CAP are markedly different from those in younger patients (14).	Levofloxacin administered at a dose of 750 mg o.d. results in a high probability of target attainment and improved bacteriological outcome against *S. pneumoniae* in patients with CAP.
Intensive care patients	ICU patients on levofloxacin showed significant pharmacokinetic differences compared with healthy subjects. The mean steady-state total body exposure to levofloxacin in ICU patients treated for early-onset VAP during the 12-hour dosage interval was about 30–40% lower than that in healthy volunteers (15).	IV levofloxacin 500 mg b.i.d. is suitable for the treatment of early-onset VAP in ICU patients with normal renal function.
Patients with a CLCR less than 50 mL/min	CLCR explained most of the population variability in the plasma clearance of levofloxacin (16).	Levofloxacin dosage adjustment should be individualized on the basis of a CLCR, especially in those with CLCR less than 50 mL/min.

Abbreviations: CAP = community-acquired pneumonia; ICU = intensive care unit; VAP = ventilator-associated pneumonia; IV = intravenous; b.i.d. = twice daily; CLCR = creatinine clearance.
Adapted from reference (9).

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Summary

Levofloxacin has maintained unparalleled activity since being developed in 1986 and introduced to the Japanese market in 1993. It has gone on to become a leading antimicrobial worldwide and, arguably the leading fluoroquinolone, due to its high potency, excellent tolerability, and ability to treat a wide range of infections.

Data has continued to accumulate highlighting the PK/PD advantages possessed by this remarkable agent, advantages that are reflected in its excellent clinical activity. Over this time, other fluoroquinolones have come onto the market, but none has matched levofloxacin in terms of maintaining excellent activity balanced with exceptional patient satisfaction.