Special Feature Article to look back on 15 years

A DRUG FOR ALL SEASONS

Reviewing the Last 15 Years of Continuous Levofloxacin Use

Looking Back – How the Fluoroquinolones developed into a Major Class of Antibiotics

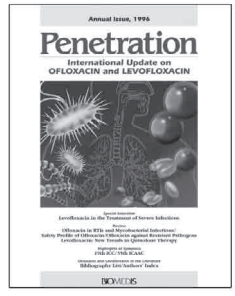
Fluoroquinolones have become one of the mainstays of antibacterial therapy, regarded as a major antimicrobial class, with efficacy against a wide range of important pathogens. And among the fluoroquinolones, levofloxacin continues to stand out as one, if not the, most important fluoroquinolone. While the history of these agents first started in 1962 with the development of nalidixic acid, it was not until the late 1970s that the first fluoroquinolone, norfloxacin, was produced. Ofloxacin, a racemic compound composed of two stereo isomers, was then introduced to the market in 1985, rapidly carving out a role for itself, particularly in the treatment of urinary tract disease and lower respiratory tract infections. The excellent oral absorption of ofloxacin with its broad spectrum of activity provided clinicians with an effective antibacterial that could safely be prescribed on an outpatient basis.

When first introduced fluoroquinolones were primarily recommended for Gram-negative bacilli, especially those causing urinary tract infections. They were also recommended for enteric infections, selective decontamination in patients with neutropenia, sexually transmitted diseases including *Chlamydia* spp., skin and soft tissue infections (SSSI) including osteomyelitis. While they were also seen as useful in respiratory tract infections (RTI) this was not the main therapeutic focus of the early fluoroquinolones.

First Issue

Levofloxacin – Leading the Fluoroquinolone Field

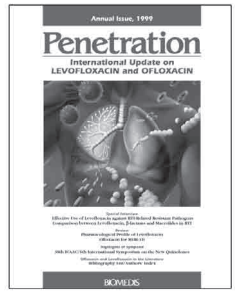
However this changed with the introduction of newer fluoroquinolones that had enhanced activity. This was seen immediately with the development of levofloxacin in 1986 and its introduction onto the Japanese market in 1993. Levofloxacin was prepared by purifying and isolating the racemic ofloxacin to produce the *levo* isomeric form. With twice the potency of its parent compound, coupled with great safety, levofloxacin proved to be a major antibacterial agent, and was subsequently approved by the FDA in 1996 for the treatment of community-acquired pneumonia (CAP), acute bacterial exacerbations of chronic bronchitis (ABECB), acute maxillary sinusitis, uncomplicated SSSI, acute pyelonephritis and complicated urinary tract infections (UTI).



1996

How Safety Issues Thinned the Ranks of the Fluoroquinolones

While in depth post-marketing surveillance data has continued to support the safety of levofloxacin, this has not been the case for many other fluoroquinolones. In the late 1980s there was an influx of other second and third generation agents, which due to chemical engineering developed increased activity against selected pathogens. However not all of these were successful with temafloxacin withdrawn in June 1992 due to patient's developing hemolytic uremic syndrome. This was followed by a spate of withdrawals in 1999 due to unacceptable adverse events: In June 1999 trovafloxacin was withdrawn or limited in its use due to the development of serious hepatic events; grepafloxacin was withdrawn in October 1999 following reports of cardiovascular effects, clinafloxacin was withdrawn due to phototoxicity and hypoglycaemic effects and sparfloxacin required labelling changes due to cardiovascular effects. Recently there have also been concerns over the glycemic effects associated with gatifloxacin. In contrast, throughout the past 15 years levofloxacin has been used continuously with its safety confirmed in over 300 million prescriptions.



1999

2006

Where to from Here?

One of the major issues concerning fluoroquinolones since the later 1990s was the need to maintain their efficacy by judicious prescribing in order to reduce the development of resistance. The potential to develop resistance is not the same for all fluoroquinolones, and in this regard levofloxacin has an advantage over other agents. In order for pathogens to become fully resistant to levofloxacin they need to undergo two mutations, thereby drastically reducing the likelihood of this occurring. The low rate of levofloxacin resistance has been confirmed in a number of ongoing global surveillance studies which continue to monitor the sensitivity of major pathogens. Resistance rates to levofloxacin have been stable over the past five years, averaging at less than 1% of high level resistance.

Since the introduction of levofloxacin it has carved out a significant niche for itself as a "respiratory" fluoroquinolone, effective in both upper and lower respiratory tract infections. In addition to its use in a wide range of infections, levofloxacin therapeutic regimens have changed in recent times with the advent of a high dose strategy that has been shown to be safe and effective, allowing shorter durations of therapy to be administered. This reduces cost as well as helping in the fight against development of resistance. The 750 mg dosing strategy is particularly advocated in US and European patients, providing an effective once daily outpatient therapy for severe infections that would have previously required hospital admission.

During the past 15 years Penetration has provided an in-depth exploration of the best scientific literature regarding this important agent. The following reviews summarise the most important scientific articles that have been published regarding levofloxacin over its history confirming it to be an agent of inestimable value. Based upon this in-depth scientific data it is possible to look to the future with confidence, assured that levofloxacin will remain a potent and safe antibiotic, used around the world to treat many infections.

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
1978	Development of first fluoroquinolone norfloxacin
1982	Ofloxacin (S & R isomers)
1983	Ciprofloxacin
Mid 1980s	Introduction of 1st 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 of Fluoroquinolones developed (Temafloxacin, Sparfloxacin, Grepafloxacin, Gatifloxacin) Improved Gram–positive activity Gatifloxacin–antianaerobe activity
Early 90s ~	Third generation fluoroquinolones developed (Trovafloxacin, Moxifloxacin, Clinafloxacin, Gemifloxacin) Gram–positive/ negative and anaerobe activity

How Safety Issues Thinned the Ranks of the Fluoroquinolones

1992	Temafloxacin syndrome (hemolytic uremic anemia) withdrawn (June)
1993	Levofloxacin launched in Japan
1996	Levofloxacin approved by US FDA (CAP, ACECB, acute maxillary sinusitis, uncomplicated SSSI, acute pyelonephritis, complicated UTI) (December)
1999	Trovafloxacin syndrome – serious hepatic events (withdrawn or limited June)
1999	Grepafloxacin withdrawn cardiovascular effects (October)
1999	Clinafloxacin withdrawn phototoxicity and hypoglycemic effects
1999	Sparfloxacin Labeling safety changes (QTc prolongation)
2000	Levofloxacin approved by US FDA for CAP due to PRSP

A Question of Resistance – Surveillance Studies Summarized from Around the World and the Impact on Clinical Use

1999	Surveillance studies reported – *see Special Interview, Penetration 1999*
2000	PK/PD data supporting Levofloxacin – *see Special Roundtable Discussion, Penetration 2000*
2001	Safety Data Positive for Levofloxacin – *see Special Roundtable Discussion, Penetration 2001*
2002	Emphasis on UTI and RTI – *see Penetration 2002*

Levofloxacin – Still Going Strong After All These Years

2002	Levofloxacin approved by US FDA for Hospital-acquired pneumonia
2003	RTI and Higher dosing strategy – *see Penetration 2003*
2004	Levofloxacin approved by US FDA for CAP due to MDRSP
2004–06	Focus on RTI and Safety-*see Penetration 2004–6*

Chronological Summary of interviews

1992

Newer Quinolones' Benefits: Cost Saving, Activity against Gram-negative Bacilli and Chlamydia
Michael Barza, MD
Professor of Medicine, Tufts University School of Medicine, and 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, Texas on the role of ofloxacin in the U.S.

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, 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 Propedeutic 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; Repiratory 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
Medical Director, Medical Research Center, New Orleans, LA, 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 VA Medical Center Albany, NY, USA

2000

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, MD
Chairman of the RTD, Professor of Internal Medicine, Northeastern Ohio Universities College of Medicine, Rootstown, OH, and Infectious Disease Service, Summa Health System, Akron, OH, USA

2001

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, Foundation 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 on Levofloxacin in Japan
Katsuro Yagawa, MD
Drug Safety Administration Department, Daiichi Pharmaceutical Co., Ltd, Japan

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
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-Aquired Pneumonia: Recent Treatment Strategies
Thomas M. File, Jr., MD, FACP
Northeastern Ohio Universities College of Medicine, Rootstown, OH, and Infectious Disease Service, Summa Health System, Akron, OH, USA

Rhinosinusitis: Recent Treatment Strategies
Michael D. Poole, MD, PhD
Department of Otolaryngology and Pediatrics, University of Texas Medical School, Houston, TX, USA

2002

The Role of Levofloxacinin Treating Urinary Tract Infections
George A. Richard, MD
Department of Pediatrics, Nephrology Division, University of Florida, Gainesville, FL, USA

2003

Pharmacokinetic/Pharmaco-dynamic 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

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

Antimicrobial Resistantce 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 UCLA, Los Angeles, CA, USA

Rational-dose Levofloxacin Therapy: Providing a Safe and Effective-Treatment in Difficult Cases
Thomas M. File, Jr., MD
Professor of Internal Medicine, Northeastern Ohio Universities College of Medicine, Rootstown, OH, Chief, Infectious Disease Service, Summa Health System, Akron, 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
Martin 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

You can learn more about these interviews on the following website.
www.infectweb.com

A 15 Year Scientific History of Ofloxacin and Levofloxacin

Upper Respiratory Tract Infections

SINUSITIS

Institutional affiliations and titles are as of date of publication.

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, USA

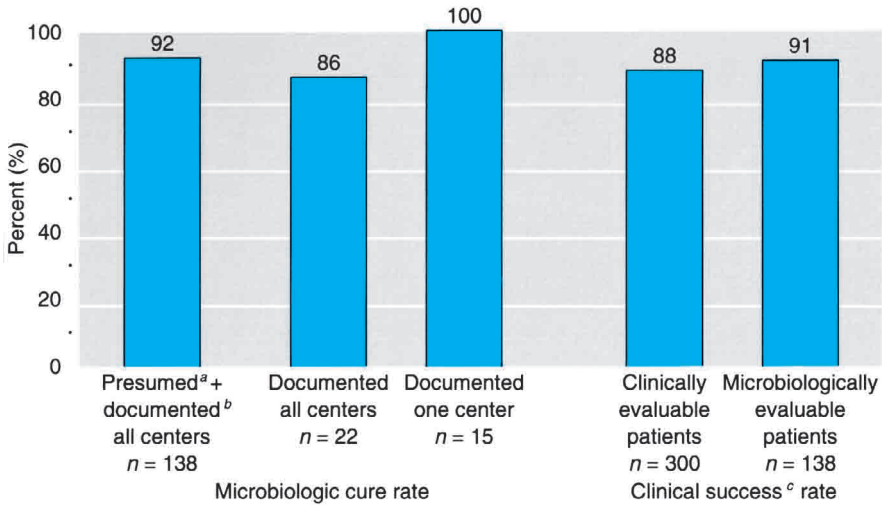
Jeffrey Adelglass, MD
Dallas Clinical Research Institute, Dallas, TX, USA

Introducing ofloxacin in its role as an upper respiratory agent was Pierre Gehanno, MD. In 1994 Dr. Gehanno was interviewed by Penetration and began by saying that fluoroquinolones have two major roles in URTI- chronic otitis with purulent otorrhea and chronic sinusitis. Use of ofloxacin for the former indication was seen as a breakthrough as it allowed a medical treatment for a condition that had previously required surgical intervention and significantly reduced the risk of complications such as meningitis and abscess formation. The advent of the fluoroquinolones also provided a much improved therapy for chronic sinusitis, allowing penetration into the non-inflammatory surrounding tissue that other classes of antimicrobials had not penetrated. Ofloxacin provided two major advantages to the ENT clinician - an antibacterial spectrum that covered all the major pathogens causing chronic infection, in particular *P. aeruginosa*, *P. mirabilis* and *S. aureus*. The second advantage was the excellent penetration of ofloxacin into the tissues, achieving antimicrobial levels at the site of infection significantly higher than the minimum inhibitory concentrations (MIC) of the principal pathogens. He commented that due to ofloxacin's excellent tolerability it could also be administered for several months in chronic infections involving bone. When compared to other fluoroquinolones, ofloxacin had greater bioavailability achieving higher tissue levels and its long half life resulted in levels remaining high for long periods. At this time treatment was given using a 200 mg twice daily schedule (increased to 800 mg daily if needed) for 10–15 days. Dr. Gehanno described the advent of fluoroquinolones as "a revolution for ENT treatment".

Highlighting the rapid movement of knowledge in this area, it was only three years later that the role of levofloxacin, ofloxacin's purified *levo* isomer, was investigated in the field of ENT. Penetration interviewed Thomas A. Sydnor, MD who summarized the clinical results achieved with levofloxacin in chronic sinusitis. Results from a nationwide multicenter study confirmed that levofloxacin was an excellent choice for treating community-acquired sinusitis. Dr. Sydnor emphasized the lack of significant drug-drug interactions associated with levofloxacin; in particular its safety when administered with theophylline or steroids, agents that many patients with RTI use. The principal pathogens causing maxillary sinusitis remain *S. pneumoniae*, responsible for 31%, with another 20% due to unencapsulated *H. influenzae*. Levofloxacin was reported by Dr. Sydnor to have better Gram-positive coverage than previous fluoroquinolones, and to be 2–4 fold more active against staphylococci and streptococci than ciprofloxacin. Emergence of resistance seen with β-lactams and macrolides was not an issue with levofloxacin. At the time of this report approximately 50% of *S. pneumoniae* cultured from hospitalized patients with sinus infections were of intermediate resistance to penicillin. In addition resistance to β-lactams had emerged and increased rapidly from its first inception and was likely to worsen. Dr. Sydnor reported results from a clinical trial which enrolled 329 patients throughout the US. Eligible adults had symptoms less than 4 weeks in duration, with typical signs and symptoms and a positive sinus X-ray. After enrolment patients had an antral sinus fluid aspiration and were treated with 500 mg levofloxacin once daily for 10 days. Patients were asked not to use antacids within 2 hours of taking the levofloxacin. Assessment included pre-and post-therapy cultures, symptomatic evaluation and radiographic changes at day 3–7 post-therapy. Levofloxacin was associated with a 100% bacterial eradication rate. Clinical response at 3–5 days post-therapy revealed a 74% cure rate, while 18% improved and only 8% failed. At the late post-therapy check 92% were judged to be cured (Figure 1) (1). Side effects were minimal, with a discontinuation rate of only 1.8%. Compliance with this schedule was excellent and Dr. Sydnor concluded that levofloxacin was an exceedingly useful agent for acute sinusitis and acute otitis media in adults.

Adding further evidence to the efficacy in this setting, and the continued and expanding role of levofloxacin in ENT was a review article in 2000 by Jeffrey Adelglass, MD. Dr. Adelglass emphasized the extent of the problem with an estimated 20 million cases of acute bacterial sinusitis each year in the US alone, requiring a huge input of medical man-hours. He noted that previously used agents such as β-lactams, tetracyclines, macrolides and sulfa drugs were becom-

Figure 1. Summary of efficacy results: microbiologic and clinical response at two to five days post-therapy



[a] Presumed eradication based on clinical response of cured or improved (microbiologically evaluable patients).
[b] Documented eradication based on post-therapy culture results (microbiologically evaluable patients).
[c] Clinical success = clinical outcome of cured or improved.
Adapted from reference (1)

(Penetration 1997; 19: Figure)

ing less effective, and that other agents that retained efficacy against penicillin-resistant *S. pneumoniae* (PRSP) were often poorly tolerated. In contrast levofloxacin possessed excellent activity against pathogens responsible for sinusitis, with only 0.6% strains of *S. pneumoniae* resistant to levofloxacin in 2000. Levofloxacin was the first fluoroquinolone indicated for treatment of acute sinusitis, and since that time had built up an increasing body of evidence supporting its use, with clinical success rates of over 88–96% reported.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS (AECB)

Peter Ball, MB, FRCP wrote a review article on the use of ofloxacin in chronic bronchitis in 1996. Noting that there was still controversy over the use of fluoroquinolones in respiratory disease due to some wellknown pneumococcal failures of ciprofloxacin, he went on to state that further analyses had shown the fluoroquinolones to be as effective as other classes of antibiotics and the predominant pathogens, *H. influenzae* and *M. catarrhalis*, were exquisitely sensitive. Ofloxacin penetrated exceedingly well into sputum, bronchial mucosa and lung tissue, achieving levels over 20-fold higher than the MIC's of all important pathogens. This was confirmed in clinical efficacy with overall response rates of 82–97%. The usual dose of ofloxacin was 400 mg, either once daily or as a 200 mg b.i.d. schedule. However a study by Gentry et al. used a higher dose of 400 mg bid achieving a 97% clinical response rate. Dr. Ball noted that some patients with AECB developed a secondary pneumonia and therefore agents such as ofloxacin that are effective in combating this complication provided the clinician with additional benefit. Comparative studies assessing ofloxacin with other agents including amoxicillin, amoxicillin-clavulanate, doxycycline, co-trimoxazole confirmed ofloxacin's efficacy. In addition sequential, historically controlled studies in patients with significant co-morbidity showed ofloxacin produced consistently better results than ciprofloxacin when clinical and bacteriological results were combined. Ofloxacin also resulted in a considerable symptom-free interval after treatment of AECB. Dr. Ball concluded that ofloxacin with its clinically proven, once daily regimen, lack of theophylline interaction, moderate activity against *P. aeruginosa* and safety provided an excellent choice for AECB.

Results from a multicenter, randomized study comparing the efficacy and safety of oral levofloxacin vs. cefaclor in AECB were reported in 1998. A trial by Habib, Gentry and colleagues used 500 mg levofloxacin once daily for 5–7 days compared to cefaclor 250 mg t.i.d. for 7–10

Peter Ball, MB,FRCP
Infectious Diseases Unit,Victoria Hospital, Kirkcaldy, Scotland

Table 1. 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. (2)	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. (3)	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. (4)	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)

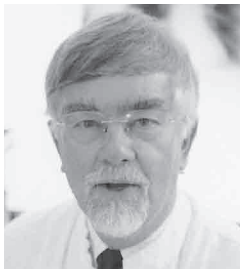
Abbreviations: AECB = acute exacerbation of chronic bronchitis, o.d. = once a day, b.i.d. = twice a day, t.i.d. = thrice a day.
Adapted from references (2–4).

(Penetration 2000; 25: Table 5)

days. 373 patients were enrolled with the levofloxacin group treated for a mean of 6.6 days compared to 8.7 days for cefaclor. The overall bacteriological eradication rate for levofloxacin was 95% compared to 86.5% for cefaclor. Levofloxacin achieved clinical cure in 92% (72% cured, 19.5% improved) compared to 64.4% cured for the cefaclor group and 27.1% improved. Thus the researchers confirmed that oral levofloxacin was comparable to and as effective as cefaclor in regard top both microbiological and clinical response in AECB. It was also associated with a potential lower cost of a once daily therapy and shorter duration, coupled with greater compliance.

Pramod M. Shah, MD
Klinikum der Johann Wolfgang Goethe-Universität, Zentrum der Inneren Medizin, Medizinische Klinik III , Schwerpunkt Infektiologie, Frankfurt, Germany

Further data was reported in 2000 by Pramod M. Shah, MD, who reported results of clinical studies with levofloxacin and comparators in AECB (Table 1) (2–4). Results from a randomized, double-blind, double-dummy, three arm parallel, multicenter study compared the safety and efficacy of levofloxacin (250 mg or 500 mg once daily) with cefuroxime axetil (250 mg twice daily) both given for 7–10 days. The cure rates in the intention-to-treat (ITT) population were 70% for levofloxacin 250 mg and 500 mg, and 61% for cefuroxime axetil. In the per protocol (PP) group the results were 78% and 79% for the two levofloxacin arms, respectively, and 66% for cefuroxime axetil. The issue of pneumococcal resistance was highlighted by Dr. Shah who noted that results from the Alexander Project, started in 1992 to investigate global susceptibility data on community-acquired LRTI's, reported that in 1996 penicillin-resistance rates for strains of *S. pneumoniae* were 16% in the US and as high as 50% in Hong Kong. Macrolide resistance rates were even higher than for penicillin and β-lactamase production was increasing worldwide seriously compromising the efficacy of previously first-line LRTI agents. Sub-group analyses of several randomized controlled trials comparing levofloxacin to either cefuroxime axetil or cefaclor revealed that the efficacy of levofloxacin was even higher than comparator agents in patients who were hospitalized, or taking concomitant steroids or theophylline. Dr. Shah recommended assessing the severity of disease by using percentage deterioration in FEV_1 and advocated the use of levofloxacin in patients with more severe disease.

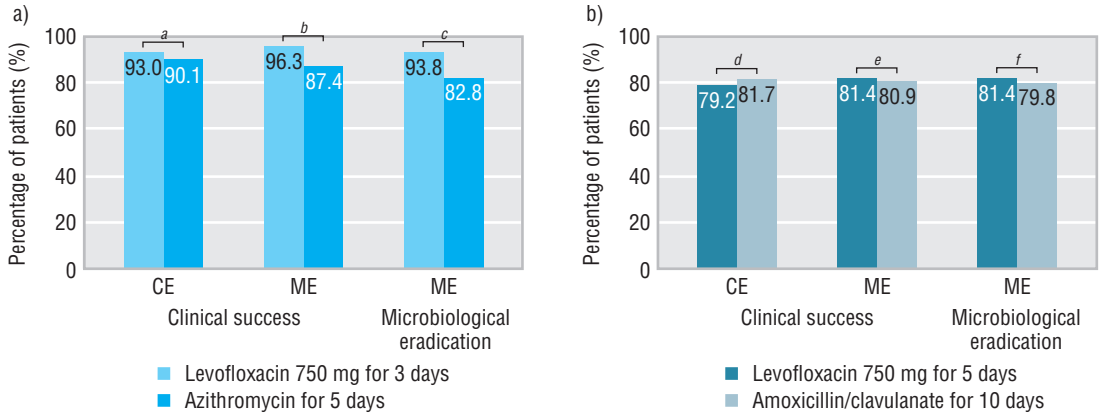


Hartmut M. Lode, MD, PhD
Department of Chest and Infectious Diseases, Helios Klinikum Emil von Behring, Academic Teaching Hospital of Charite, Berlin, Germany

This topic was recently revisited in the 2006 publication of Penetration with a review article by Hartmut M, Lode, MD, PhD. and M Schmidt-Ioanas, MD, PhD. who noted that while antimicrobial management of exacerbations of chronic obstructive pulmonary disease (COPD) remains controversial, most guidelines now include fluoroquinolones. Dr. Lode summarized data from randomized trials using levofloxacin and the current treatment guidelines available. Levofloxacin was as effective and well tolerated as cefuroxime axetil, azithromycin, gemifloxacin, and clarithromycin. It had added advantages of being able to be given in shorter administration schedules with a 5-day course achieving clinical and bacteriological results equivalent to that achieved following the more usual 7 day course. Further evaluation of a higher dose 750 mg therapy for three days was compared with azithromycin once daily for 5 days in patients with uncomplicated disease or amoxicillin/clavulanate 125 mg twice daily for 10 days in complicated patients. Levofloxacin-treated patients achieved a 93.0% success rates compared to 90.1% for azithromycin and in the patients with more complicated disease levofloxacin achieved a 79.2% cure compared to 81.7% for the comparator regime (Figure 2) (5). Microbiological evaluation revealed better results for the 3 day course of levofloxacin compared to the 5 day azithromycin, and equivalent results for the 5 day course of levofloxacin compared to the 10 day course of amoxicillin/clavulanate.

Dr. Lode noted that five sets of guidelines for AECB are available. The oldest of these the Lille consensus set only recommend the use of fluoroquinolones for patients with severe bronchi-

Figure 2. Clinical success rates and microbiological eradication rates at post-therapy visits, by a) uncomplicated and b) complicated treatment.



Note: The 95% confidence intervals around the difference between treatment groups, comparator minus levofloxacin, are indicated ([a] -9.6–3.8; [b] -17.6– -0.1; [c] -21.2– -0.8; [d] -7.8–12.9; [e] -12.7–11.7; [f] -13.9–10.7).
Abbreviations: CE = clinically evaluable, ME = microbiologically evaluable.
Adapted from reference (5).

(Penetration 2006; 24: Figure 3)

tis. However since then there have been 4 more updated guidelines - the recommendations of which are summarized as follows. Canadian guidelines recommend fluoroquinolones in AECB mostly for patients in risk group II (those requiring hospitalization) (Table 2) (6). Another set of guidelines, this time from the US consensus conference, recommends using risk stratification and the use of fluoroquinolones for more severe AECB patients and those with one or more risk factors. This consensus group stressed that *S. pneumoniae* resistance to penicillin, azithromycin and other macrolides, trimethoprim-sulfamethoxazole (TMP-SMX) and cefuroxime continues to be a problem in the US. In contrast resistance to amoxicillin/clavulanate, ceftriaxone, levofloxacin and vancomycin remains relatively low. They recommended using a risk stratification approach algorithm, with the respiratory fluoroquinolones kept for the more severe AECB patients and for those having one or more risk factors (age greater than 65 years, FEV_1 less than 50% predicted value, four or more exacerbations in 12 months or co-morbidities. The 2004 Latin-American Thoracic Society recommends that for infectious exacerbations of COPD respiratory fluoroquinolones be used in those patients with mild disease and risk factors, as well as in those with moderate-severe disease. A 2005 German set of evidence-based recommendations state that the fluoroquinolones should be used in patients with AECB with a FEV_1 less than 50% of predicted values and no risk factors for *P. aeruginosa*. Dr. Lode emphasizes the size of the problem with over €10.3 billion in health care costs annually in the European Union alone.

COMMUNITY-ACQUIRED PNEUMONIA (CAP)

Since the introduction of the respiratory fluoroquinolones consensus on their use has changed dramatically, and this is particularly evident in their role in treating CAP. In 1996 S. Ragnar Norrby, MD, PhD reported that such fluoroquinolones should be used for hospital acquired pneumonia and AECB. At that stage CAP was not an indication, unless it was due to PRSP or β-lactam resistant pathogen. The following year in 1997 Charles M. Fogarty, MD was able to use data from the well-known File study to describe how the role of respiratory fluoroquinolones was increasing. Dr. Fogarty noted that the use of fluoroquinolones in CAP had been an area of debate, but with changes in resistance profiles and the recognition of the role of atypical pathogens, the role of the fluoroquinolones was expanding. Levofloxacin has broad spectrum activity, excellent penetration and is well tolerated. In addition it is 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 fluoroquinolone uses two separate mechanisms. Dr. Fogarty performed a study assessing the efficacy and safety of 500 mg levofloxacin once daily as empiric therapy for CAP, with patients stratified into mild-moderate or severe disease using APACHE scoring. Sixty patients were fully evaluable and

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Table 2. Empiric therapy in patients with acute exacerbations of chronic bronchitis (AECB)

Risk group	Basic clinical state	Symptoms and risk factors	Probable pathogens	First choice	Alternatives for treatment failure
0	Acute tracheobronchitis	Cough and sputum without previous pulmonary disease	Usually viral	None unless symptoms persist for > 10–14 days	Macrolide or tetracycline
I	Chronic bronchitis without risk factors (simple)	Increased cough and sputum, sputum purulence, and increased dyspnea	*Haemophilus influenzae*, *Haemophilus* species, *Moraxella catarrhalis*, *Streptococcus pneumoniae*	2nd generation macrolide, 2nd or 3rd generation cephalosporin, amoxicillin, doxycycline, TMP–SMX	Fluoroquinolone, β-lactam/β-lactamase inhibitor
II	Chronic bronchitis with risk factors (complicated)	As in group I plus ≥ 1 of the following: • FEV_1 < 50% predicted • ≥ 4 exacerbations/year • Cardiac disease • Use of home oxygen • Chronic oral steroid use • Antibiotic use in the past 3 months	As in group I plus *Klebsiella* species plus other Gram-negative pathogens Increased probability of β-lactam resistance	Fluoroquinolone or β-lactam/β-lactamase inhibitor	May require parenteral therapy Consider referral to a specialist or hospital
III	Chronic suppurative bronchitis	As in group II with constant purulent sputum • Some have bronchiectasis • FEV_1 < 35% predicted • Multiple risk factors (e.g. frequent exacerbations and FEV_1 < 50% predicted)	As in group II plus *Pseudomonas aeruginosa* and multi-resistant *Enterobacteriaceae*	Ambulatory patients: tailor treatment to airway pathogen, *P. aeruginosa* common (ciprofloxacin) Hospitalized patients: parenteral therapy usually required	—

Abbreviations: FEV_1 = forced expiratory volume in 1 second, TMP–SMX = trimethoprim–sulfamethoxazole.
Adapted from reference (6).

(Penetration 2006; 25: Table 1)

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95% were assessed as cured and the other 5% as improved. Once-daily therapy (with an intravenous option in severely ill patients) was a great benefit and based on these results Dr. Fogarty recommended levofloxacin as initial therapy in moderately to severely ill CAP patients.

This was followed by an excellent review by Thomas M. File, MD, in the 1998 issue which added further data to the growing knowledge of levofloxacin in CAP. Commenting on the difficulty in adequately covering resistant pathogens Dr. File summarized the *in vitro* activity, pharmacokinetics and clinical studies of levofloxacin in CAP. Levofloxacin has excellent activity against all key CAP pathogens, particularly *S. pneumoniae* including those that are resistant to penicillin and other agents, which represented a significant advantage over older fluoroquinolones. During the 1991–94 period no increase in resistance to levofloxacin was seen. It was also very active against other important respiratory pathogens including *H. influenzae* and *M. catarrhalis*, methicillin-susceptible *S. aureus* (MSSA) and was shown to be more active against *Legionella pneumoniae* than the combination of erythromycin and rifampin. To prove the value of levofloxacin Dr. File reported results from Japanese trials, US non-comparative trials and comparative multicenter studies. In the latter the safety and efficacy of levofloxacin 500 mg once daily was compared to parenteral ceftriaxone 1–2 g/day and/or oral cefuroxime axetil 500 mg bid (plus erythromycin or doxycycline if an atypical pathogen was suspected). Levofloxacin therapy was evaluated in 226 patients while 230 patients receiving the comparator regimen were evaluable. Levofloxacin achieved a 96% clinical success rate at 5–7 days post-therapy compared to 90% for ceftriaxone and/or cefuroxime, results suggesting the superiority of levofloxacin (Table 3) (7). There was only a 3.5% clinical failure rate for levofloxacin compared to 9.6% for the comparator regime. Further sub-group analysis revealed that the clinical success rate for patients with a pneumococcal bacteremia was 100% for levofloxacin and 99% for the three atypical pathogen infected patients, compared to 94% for the comparator group, many of whom also required erythromycin. Drug related adverse events were reduced in the levofloxacin arm, 5.8% compared

to 8.5% for ceftriaxone. Dr. File stressed the need for empiric therapy in CAP and in the past this was usually β-lactams, macrolides TMP-SMX and tetracyclines. However increasing resistance has made many of these agents less effective and levofloxacin fulfils an important role in this regard. He also drew attention to the increasing issue of cost-reduction and that by using oral levofloxacin therapy the cost of alternative intravenous therapy is significantly reduced.

Claude Carbon, MD continued this theme with a 2000 Review on new strategies in CAP. Noting that early identification of the causative pathogen is often problematic, effective empiric therapies need to be available which can treat this serious and common disease. Therefore there is a need for agents that possess an antibacterial spectrum covering the full range of potential pathogens, and fluoroquinolones are such agents. In addition effective antimicrobials need to penetrate not only into respiratory tissues and secretions but also i into intracellular pathogens and alveolar macrophages. Again fluoroquinolones rise to this challenge, achieving intracellular concentrations within the therapeutic range of the majority of intracellular pathogens. In contrast to this, most β-lactams do not exceed 50% of their serum level within bronchial secretions, and some agents, such as aminoglycosides, only reach 30–40% of their serum level in the lung and even less in the inter- and intracellular milieu. Dr. Carbon also commented on the trend to reduce the duration of therapy in order to reduce the possibility of developing resistance and noted that an important trend is the use of step-down or sequential switch therapy, with treatment started intravenously and then changed to oral as soon as possible. He then presented the guidelines for management of CAP that were available at that time, including those of the 1993 British Thoracic Society, 1993 Canadian CAP Consensus Conference Group, 1992 French Language Society of Infectious Diseases, 1998 Infectious Diseases Society of America (IDSA). The IDSA guidelines categorized treatment into recommendations for hospitalized patients and for outpatients. Macrolides, fluoroquinolones and doxycycline were recommended for the latter category while hospitalized patients in a general ward should be treated with a β-lactam with or without a macrolide or a fluoroquinolone alone. Alternatives included cefuroxime axetil with or without a macrolides. For patients in 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. He recommended more studies into cost-efficacy of treatment regimes and finished by sounding a warning about any potential extension of indications into the pediatric setting as this could jeopardize the continued efficacy of these agents.

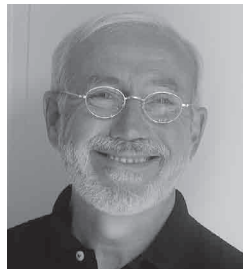
In the 2002 issue of Penetration the topic of CAP was revisited with Pierre Veyssier, MD looking specifically at the treatment of severe infections in patients with risk factors for complications. Dr. Veyssier used guidelines from IDSA to stratify patients into five risk groups based upon the Pneumonia Severity Scoring index (PSSI) which was associated with changes in mortality, with classes III–V requiring hospitalization. A different approach was presented from the American Thoracic Society (ATS) which stratified patients into four groups depending on the need for hospitalization, severity of illness, presence of two key risk factors (cardiopulmonary disease and smoking) and risk of infection with *P. aeruginosa* or drug-resistant *S. pneumoniae* (DRSP). Once high-risk patients are identified a clear treatment regimen needs to be initiated with results from a study by File et al providing extra information on at-risk subgroups of CAP patients, showing that 100% of those with pneumococcal bacteremia were successfully

Table 3. Levofloxacin (IV/PO) vs. ceftriaxone (IV)/cefuroxime (PO) for community-acquired pneumonia clinical response

	Levofloxacin	Ceftriaxone/cefuroxime
Total patients		
Number	226	230
% response (cure/improved)	96%	90% (95% CI –10.7, –1.3)
By pathogen (No. with response/total treated)		
Streptococcus pneumoniae	30/30 (100%)	31/33 (94%)
Haemophilus influenzae	30/30 (100%)	19/24 (79%)
Staphylococcus aureus	10/10 (100%)	8/9 (89%)
Haemophilus parainfluenzae	7/8 (88%)	16/22 (73%)
Moraxella catarrhalis	7/7 (100%)	4/4 (100%)
Klebsiella pneumoniae	3/3 (100%)	6/8 (75%)
Chlamydia pneumoniae	46/47 (98%)	40/44 (91%)
Mycoplasma pneumoniae	19/19 (100%)	22/22 (100%)
Legionella pneumophila	5/5 (100%)	2/3 (67%)

Abbreviations: CI = confidence interval, IV = intravenous, PO = oral.
Adapted from reference (7).

(Penetration 1998; 28: Table 3)



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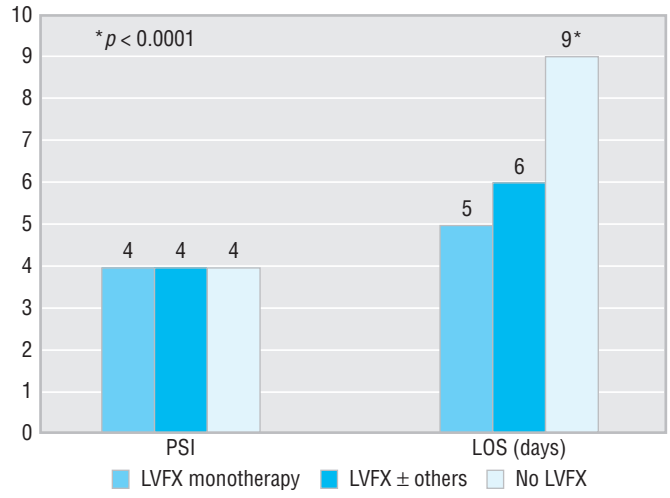
Pierre Veyssier, MD
Médecine Interne, Centre Hospitalier de Compiègne, Compiègne, France

Figure 3. Shorter duration of hospital stay associated with levofloxacin as empiric therapy.



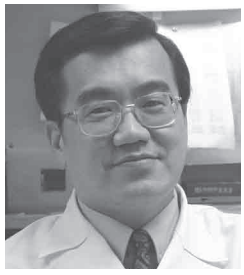
Abbreviations: PSI = Pneumonia severity-of-illness index class, LOS = length of hospital stay, LVFX monotherapy = levofloxacin monotherapy, LVFX ± others = levofloxacin plus or minus other antibiotics, such as a second-generation cephalosporin alone or a second-generation cephalosporin in combination with a macrolide, No LVXF = empiric antibiotic regimen not including levofloxacin, such as a second generation cephalosporin alone or a second-generation cephalosporin in combination with a macrolide.

Adapted from reference (8).

(Penetration 2002; 47: Figure 2)

treated by levofloxacin. Dr. Veyssier reported results from an important study by Kahn et al. which investigated levofloxacin 500 mg IV to PO once daily versus ceftriaxone 1–2g IV every 24 hours plus erythromycin 500–1000 mg IV every 6 hours in CAP patients at high risk of mortality. Stringent criteria to identify the patients were used. Levofloxacin was chosen due to earlier reports showing its efficacy in high risk patients. In addition, levofloxacin has maintained its efficacy despite being widely used for other infections, with the mean MICs of levofloxacin against PSSP and PRSP not changing significantly and maintaining an excellent AUC/MIC ratio even against *S. pneumoniae* resistant to other fluoroquinolones. 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 as well tolerated with a 2.3% discontinuation compared to 8.8% for the comparators. In addition the role of levofloxacin in managing atypical pathogens was emphasized by Dr. Veyssier, with agents needing to cover *Chlamydia* and *Legionella* spp. A randomized trial of patients with severe CAP investigated a subgroup of patients with *Chlamydia pneumoniae* (9.4% of study population) - 83% of these patients were successfully treated with levofloxacin compared to 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.

Results were also reported from assessing levofloxacin in immunocompromised patients with CAP. A retrospective analysis showed that the patients with CAP treated with a fluoroquinolone demonstrated a lower mortality (7% vs. 17%, $p < 0.05$) and a shorter median length of stay in hospital (Figure 3) (8). In addition monotherapy with a fluoroquinolone was also associated with lower mortality rates and shortened hospital stay.



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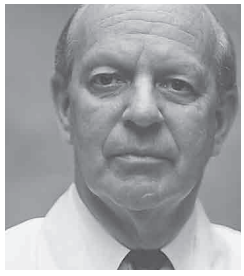
The role of levofloxacin in CAP in Asian patients was reported by Po-Ren Hsueh, MD who described pneumonia as the eighth leading cause of death in Taiwan. Introduced into Taiwan in 2000, levofloxacin was then included in the Taiwanese guidelines for treating CAP. Managing and preventing resistance has been a prime motivator of treatment strategies in Taiwan, which in 2001–2003 had a recorded 60–80% overall prevalence of intermediate PRSP and 10–20% rate of high-level PRSP Over 90% of isolates during this period were highly resistant to macrolides (including erythromycin, clarithromycin and azithromycin), and over 80% were resistant to TMP-SMX. β-lactamase production was found in 50–60% of *H. influenzae* and greater than 95% of *M. catarrhalis* isolates. Previous studies revealed that levofloxacin possessed excellent *in vitro* activity against *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* including resistant strains. Recent data from the SMART surveillance reveals that the level of resistance to levofloxacin remains low compared to that in Hong Kong, with no signs of clonally spread. In a clinical trail 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 LRTI.



John G. Bartlett, MD
Johns Hopkins University, School of Medicine, Baltimore, MD, USA.

This issue was further addressed in the 2005 issue with a summation of latest CAP treatment guidelines and the role of levofloxacin by John G. Bartlett, MD. He described LRTI as one of the fastest moving field of medicine in terms of "changes in treatment strategies, new discoveries and controversies." Reflecting this rapid change is the need for the practice guidelines put out by IDSA to be updated almost every two years. He noted that the efficacy and safety of levofloxacin has been assessed in a large number of clinical trials, involving both ambulatory patients and hospitalized patients. While *S. pneumoniae* remains the principal pathogen, concern continues to rise regarding resistance in this pathogen. Therefore it is a great advantage that levofloxacin

Table 4. Pathogen specific therapy

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

[a] Includes levofloxacin as a respiratory quinolone (levofloxacin, gatifloxacin, moxifloxacin).
Abbreviations: spp. = species, TMP–SMX = trimethoprim–sulfamethoxazole.
Adapted from reference (9).

(Penetration 2005; 16: Table 1)

continues to have the lowest rate of resistance among *S. pneumoniae* based on susceptibility to penicillin. With two mutations required for high level resistance Quinolone resistance, overall resistance trends have shown the fluoroquinolone resistance rates (including levofloxacin) to be less than 2%. Dr. Bartlett reported on the antimicrobials recommended for each specific pathogen (Table 4) (9).

IDSA guidelines recommend that ambulatory outpatients with CAP be treated with doxycycline or a macrolides, and fluoroquinolones are advocated for those patients with co-morbidities 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 macrolides plus cephalosporin in patients with CAP requiring hospitalization. The IDSA recommendation for treating CAP in an ICU patient is to combine a β-lactam with a respiratory fluoroquinolone or macrolide, although there is no data to support this combination therapy as better than a fluoroquinolone alone. In addition, levofloxacin has been approved by the FDA for treating CAP caused by multi-drug resistant strains (MDRSP) which are defined as isolates resistant to two or more of the following antibiotics; penicillin, 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprin/sulfamthoxazole. Dr. Bartlett concluded that levofloxacin continues to play a prominent role in IDSA guidelines for the treatment of CAP based on evidence from randomized trials, pharmacokinetic data and lengthy post-marketing surveillance. He noted the importance of retaining the excellent utility of this agent by judicious prescribing.

TREATMENT OF CAP CAUSED BY ATYPICAL PATHOGENS

In 2000, the problem of Legionnaires disease was addressed by Burke A. Cunha, MD. *In vitro* efficacy of levofloxacin against *Legionella* spp. is high, and this coupled with its intracellular and alveolar macrophage penetration makes it an ideal agent for treating these infections (Table 5) (10). Levofloxacin was described by Dr. Cunha as the most cost-effective of the available fluoroquinolones in treating *Legionella* infections and data from other review articles confirmed this, including the 2006 article by Rosa M Blazquez Garrido, MD. Dr. Blazquez Garrido noted that the urinary antigen test is particularly useful in severe cases of CAP to help provide a rapid diagnosis of *Legionella* pneumonia although in milder cases the incidence may be under reported.

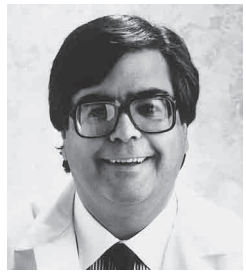


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Table 5. *In vitro* activities of antimicrobials against *Legionella*

Antibiotic	No. of strains tested with inoculum of 10^4[a]	MIC (µg/ml) at inoculum size shown (CFU/spot)					
		Range		MIC_{50}		MIC_{90}	
		10^4	10^5	10^4	10^5	10^4	10^5
Erythromycin	27	0.008–0.25	0.06–0.5	0.03	0.12	0.12	0.12
Clarithromycin	27	≤ 0.004	≤ 0.004–0.03	≤ 0.004	≤ 0.004	≤ 0.004	≤ 0.004
Roxithromycin	27	≤ 0.004–0.06	0.03–0.25	0.015	0.06	0.03	0.12
Rifampin	27	≤ 0.0005–0.015	≤ 0.0005–0.015	≤ 0.0005	≤ 0.0005	0.002	0.008
Dalfopristin–quinupristin	24	0.015–0.05	0.12–1	0.12	0.25	0.5	0.5
Doxycycline	24	0.5–2	1.0–8.0	1	4	2	8
Linezolid	24	1.0–4	4.0–8	2	4	4	8
Clindamycin	27	0.008–8	1.0–16	2	8	8	8
Levofloxacin	27	≤ 0.004–0.03	0.015–0.06	0.008	0.015	0.015	0.03

[a] *n* = 30 strains for the larger inoculum in all cases.
Abbreviations: MIC_{50}, MIC_{90} = minimum inhibitory concentration at which 50% and 90% of tested strains are inhibited, respectively, CFU = colony-forming unit.
Adapted from reference (10).

(Penetration 2000; 33: Table 1)

Table 6. 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)

Based on past practice erythromycin was the drug most commonly used to treat Legionnaire's disease, although latest laboratory data and animal studies indicated that fluoroquinolones and newer macrolides have greater anti-Legionella activity. This has resulted in the newer fluoroquinolones including levofloxacin being put forward as the drug of choice for this infection. IDSA recommends doxycycline, azithromycin and various fluoroquinolones for *Legionella* infections due to adverse events associated with erythromycin and the ability of agents such as levofloxacin to be effective in a once daily schedule. At present, resistance among *Legionella* to levofloxacin has not been a clinical problem and it has been shown to be clinically effective in an observational, prospective, non-randomized study of 292 patients hospitalized with *Legionella* pneumonia. Patients received either clarithromycin or levofloxacin and were stratified according to severity of disease using the Fine scale. 224 of the 292 had mild-moderate disease (Fine class I–III) and 68 had severe disease. After admission 35 received azithromycin, 32 clarithromycin, 187 levofloxacin. Patients who received additional rifampin were excluded from the analyses. The clinical response with levofloxacin was 99.3% and 100% for the macrolides (Table 6) (11). Patients with severe disease treated with macrolides were more likely to develop complications and had a significantly longer length of stay in hospital. These results indicate the excellent efficacy of levofloxacin and

the use of IV/PO switch therapy with levofloxacin is very advantageous. 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, effective 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 *Chlamydia pneumoniae*. In a review published in the 2003 issue of Penetration, Drs' Francesco Blasi, MD, PhD, Roberto Consentini, MD and Paolo Tarsia, MD reported on the growing importance of these pathogens in RTI and the expanding role for levofloxacin. *Chlamydia pneumoniae* is considered the most common non-viral intracellular RTI pathogen responsible for pharyngitis, sinusitis, otitis as well s bronchitis, AECB, asthma and CAP. *Mycoplasma pneumoniae* is also an important atypical pathogen, and due to its lack of a cell wall is resistant to antimicrobials such as β-lactams, sulphonamides, rifampicin and glycopeptides. In contrast agents such as fluoroquinolones are active against both *Mycoplasma* and *Chlamydia*. Macrolides are also reasonable first line treatment options. Surveillance studies will become increasingly important as the effect of these pathogens is recognized.

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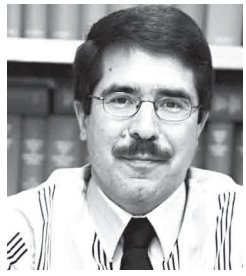
HOSPITAL-ACQUIRED PNEUMONIA (HAP)

In 2006, 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%. These costs are even higher in patients requiring mechanical ventilation who develop a ventilator-associated pneumonia (VAP). Initial treatment of HAP is usually empiric, utilising a broad spectrum regimen providing coverage of all likely pathogens. As culture results become available therapy can become more targeted, with antimicrobials generally given for 7–8 days. The time of onset is an important prognostic sign, with late onset HAP (> 5 days) more likely to be caused by multi-drug resistant (MDR) pathogens, and associated with higher mortality. However those with early onset HAP, but who had received prior antimicrobial treatment or had been hospitalised within the past 90 days are also at increased risk of MDR disease. A meta-analysis of five trials comparing fluoroquinolones to 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 favoured fluoroquinolones, at a level that approached statistical significance. Generally the emergence of resistance was also less with fluoroquinolones compared with imipenem/cilastin. Levofloxacin, as an anti-pseudomonal fluoroquinolone is useful in this setting, and has been used in a dose of 750 mg once daily, taking advantage of its concentration-dependent kill and long post-antibiotic effect. While first given intravenously, levofloxacin can be safely and effectively used in an early step-down regimen. Dr. Kollef stressed when treating HAP it is important to identify patients at risk of MDR disease, be aware of local susceptibilities and practice de-escalation therapy, prescribing antibiotics for the shortest time clinically indicated.



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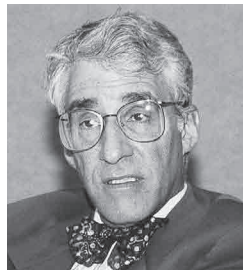
TUBERCULOSIS

One major RTI of worldwide importance is tuberculosis and the rise of multi-drug resistant (MDR-TB) forms has become problematic. In 1998 Lee B. Reichman, MD was interviewed for his views on the role of ofloxacin in treating what he termed a "disaster". Dr. Reichman noted that in Western countries resources are available to deal with this issue, with directly observed therapy (DOT) 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 programmes 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 commented that the first rule is to get drug susceptibilities done and therapy needs to be driven by objective susceptibility data. Dr. Reichman uses ofloxacin in preference to other fluoroquinolones, although at that time levofloxacin was not available and he believed that that would be even more useful. Due to the toxicity of some other fluoroquinolones he would not use them for long term therapy. Dr. Reichman recommended an 800 mg once daily dose of ofloxacin with greater compliance and using it in combination with other anti-tuberculosis agents to ensure resistance does not develop.



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Urinary Tract Infections

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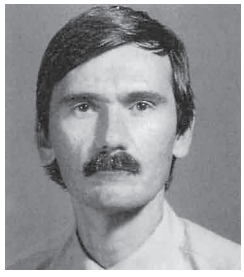

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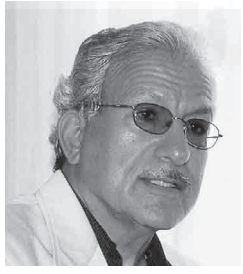

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PROSTATITIS

Since their introduction fluoroquinolones have been recognized as leading agents for the treatment of urinary tract infections (UTI). Of particular note in this field was ofloxacin, which due to its renal metabolism, pharmacokinetic (PK) and pharmacodynamic (PD) profile, and high oral bioavailability, was quickly recognized as an exceptional clinical agent for managing these common infections. Ofloxacin provided the clinician with excellent coverage of likely pathogens, penetrated into all urinary tissues and fluids and was well tolerated. With these features, ofloxacin rapidly gained a role in both general practice and hospital management of urological diseases. Until the advent of ofloxacin, one of the most difficult to treat UTI had been prostatitis, with few other agents able to penetrate into prostatic fluid. Reporting on the role of ofloxacin in the 1993 issue of Penetration was Kurt G. Naber, MD, PhD. Dr. Naber noted that preclinical studies confirmed that ofloxacin was able to maintain its efficacy in both acid and alkaline fluids. In comparison to β-lactams, ofloxacin achieved much higher concentrations in the relevant tissues; a median concentration in prostatic fluid about a third of plasma levels, twice that in seminal fluid and achieved plasma levels in prostatic tissue. Clinical trials were then reported using a daily dose of ofloxacin ranging from 300–600 mg. The duration of treatment varied greatly in the trials, ranging from one to eight weeks. Despite concerns over differences in diagnostic technique between the studies cited, Dr. Naber concluded that the high bacteriological cure rates ranging from 67–91% were promising, indicating a potential role for ofloxacin that required further investigation.

Drawing further attention to the potential of ofloxacin in UTIs was a review article by David R. P. Guay, Pharm D, FCP, FCCP in the 1997 Issue of Penetration, which clarified the advantageous PK/PD features of ofloxacin for these common infections. With renal clearance ranging from 51–98% of total body clearance in the presence of normal renal function, and 10–65% in the presence of renal dysfunction, ofloxacin was able to achieve concentrations exceeding the MICs of the majority of urinary pathogens. Urinary bacteriostatic and bacteriocidal activity of ofloxacin was assessed, confirming it to have substantial activity. Dr. Guay concluded that apart from its interaction with cations, ofloxacin appeared to have few troublesome features that could potentially compromise its efficacy in UTI.

UTI/PYELONEHRITIS

The advent of levofloxacin was shown to provide even greater benefits than its parent compound in the management of infectious diseases, including those in the field of urology. Levofloxacin was seen as offering the clinician a very cost-effective therapeutic option, a huge advantage in an area that is well known to inflict a huge health care burden upon all countries, with UTI estimated to add $1 billion to the cost of community care in the US alone. In 2002, Penetration interviewed George A. Richard, MD on the role of levofloxacin in these conditions. Dr. Richard noted that levofloxacin has extremely high bioavailability, achieving a peak: MIC ratio many times greater than 12.2, indicative of potential excellent outcome (Table 7) (12). It also demonstrates a significant post-antibiotic effect, with suppression of the organisms between doses. It has a wide antibacterial spectrum, covering the majority of UTI pathogens, including *E. coli*, *S. saprophyticus*, *Proteus mirabilis*, *Klebsiella* spp., *Aerococcus* and *Enterobacter* spp., achieving an overall microbiological eradication rate of 95.5% for all uropathogens. With resistance increasing to agents such as TMP-SMX, ampicillin and amoxicillin the continued efficacy of levofloxacin makes it of even greater value. Dr. Richard noted that the FDA had approved levofloxacin for acute cystitis, pyelonephritis and chronic bacteriuria. For acute cystitis he preferred to use fluoroquinolones such as levofloxacin rather than TMP-SMX as it could be administered once-daily for three days and was especially useful in areas with high local resistance patterns. If the patient had co-morbidities such as diabetes then treatment should be continued for a longer period, such as 7 days. Dr. Richard stressed that β-lactams are not recommended for acute cystitis, although nitrofurantoin was acceptable. In regard to treating acute pyelonephritis, if the infection is severe, treatment should last for 14 days, again with fluoroquinolones being the drug of choice. Dr. Richard preferred levofloxacin due to its once-daily schedule and the availability of an intravenous formulation,

Table 7. Pharmacokinetic variables associated with levofloxacin therapy[a]

Regimen	C_{max} (μg/ml)	t_{max} (hr)	AUC (μg/hr/ml)	CL/F (ml/min)	$t_{1/2}$ (hr)	CL_R (ml/min)
Single dose						
250 mg PO	2.8 ± 0.4	1.6 ± 1.0	27.2 ± 3.9	156 ± 20	7.3 ± 0.9	142 ± 21
500 mg PO	5.1 ± 0.8	1.3 ± 0.6	47.9 ± 6.8	178 ± 28	6.3 ± 0.6	103 ± 20
750 mg PO	7.13 ± 1.44	1.9 ± 0.7	82 ± 14	157 ± 28	7.7 ± 1.3	118 ± 28
1,000 mg PO	8.85 ± 1.86	1.7 ± 0.4	111 ± 21	156 ± 34	7.9 ± 1.5	113 ± 26
500 mg IV	6.2 ± 1.0	1.0 ± 0.1	48.3 ± 5.4	175 ± 20	6.4 ± 0.7	112 ± 25
Multiple dose						
500 mg PO q.d. × 3 days	6.55 ± 1.84	1.17 ± 0.52	53.5 ± 10.3	116 ± 35	7.95 ± 1.35	NA
500 mg PO q.d. × 10 days	5.7 ± 1.4	1.1 ± 0.4	47.5 ± 6.7	175 ± 25	7.6 ± 1.6	116 ± 31
750 mg PO q.d. × 10 days	8.6 ± 1.86	1.9 ± 0.7	91 ± 18	143 ± 29	8.8 ± 1.3	116 ± 28
1,000 mg PO q.d. × 10 days	11.8 ± 2.52	1.7 ± 0.6	118 ± 19	146 ± 29	8.9 ± 2.5	116 ± 23
500 mg IV q.d. × 10 days	6.4 ± 0.8	NA	54.6 ± 11.1	158 ± 29	7.0 ± 0.8	99 ± 28

[a] Values are mean ± SD.

Abbreviations: C_{max} = maximum serum drug concentration, t_{max} = time to maximum serum drug concentration, AUC = area under the serum concentration versus time curve, CL/F = whole body clearance, $t_{1/2}$ = serum elimination half-life, CL_R = renal clearance, PO = oral, IV = intravenous, q.d. = once daily, NA = not applicable.

Adapted from reference (12).

(Penetration 2002; 6: Table 1)

allowing switch therapy to be initiated. In mild pyelonephritis, guidelines recommended 7 days of therapy with a fluoroquinolone or TMP-SMX but Dr. Richard preferred 5–7 days. Dr. Richard commented that when treating patients with complicated UTIs it is important to think of co-morbidities, as many urological patients often take a range of other medications. Therefore the potential for drug-drug interactions needs to be assessed. Levofloxacin is very safe in this regard with few clinically important interactions. It does not react with theophylline, digoxin and other drugs metabolized in the cytochrome P450 system. In contrast, other antimicrobials including other fluoroquinolones with significant hepatic metabolism, do have the potential for such interactions to occur. By using levofloxacin, particularly with the ease of switch therapy from IV/PO, Dr. Richard commented that patients can be discharged from hospital sooner and costs reduced.

Data from randomized comparative trials have been available for a number of UTI including uncomplicated cystitis and pyelonephritis that confirm the clinical efficacy of these agents (Table 8) (13–15). Summarizing these results Dr. Richard noted that the comparative trials of once-daily levofloxacin confirm it to be as effective as any current drug used. In addition levofloxacin had a low rate of adverse effects and was very well tolerated by all patients. When comparing levofloxacin to other fluoroquinolones Dr. Richard drew on data from a comparative trial with gatifloxacin. While both achieved excellent results he noted that the concentrations of gatifloxacin in the urine were less than that achieved by levofloxacin and that gatifloxacin does not have the extensive safety data that levofloxacin has. Dr. Richard also drew attention to the issue of uncomplicated UTIs and a study assessing levofloxacin in a patient-initiated treatment protocol. In this study levofloxacin was self-medicated by women with acute cystitis and proven to be a safe, effective and convenient treatment, removing the need for these women to be treated with long-term prophylactic antimicrobials. The role of levofloxacin in UTIs was therefore expanding, due to its once-daily schedule, high tolerability and well maintained clinical efficacy.

The efficacy of levofloxacin in UTI has been confirmed in later reports from Kurt G. Naber, MD, PhD and Florian M.E. Wagenlehner, MD, published in 2005 Penetration. Dr. Naber recommended a 3 day course of 250 mg levofloxacin for acute uncomplicated, with a 98% clinical success rate using this schedule. When treating acute uncomplicated pyelonephritis and mild-moderate complicated UTIs a dose of 250–500 mg once daily for 5–10 days was recommended. Finally in patients requiring hospitalization for more severe disease the dose could be increased up to 750 mg daily, due to the excellent safety profile of levofloxacin. The issue of increasing resistance to other commonly used agents was raised, with Dr. Naber noting that resistance, particularly among *E. coli*, against ampicillin and TMP-SMX has resulted in fluoroquinolones as first line treatment. However due to concerns about maintaining the efficacy of these agents it is stressed that they be prescribed carefully, using strategies to minimize the

Table 8. Clinical results for the treatment of acute pyelonephritis among fluoroquinolones and other agents

Study	Drug/route/dosage	Duration	No. of patients	Bacteriological cure rate[a]	Clinical cure rate[b]	Incidence of adverse drug reactions[c]	Significance
Talan DA, et al. (13)	Ciprofloxacin PO 500 mg b.i.d. (with or without an initial ciprofloxacin IV 400 mg)	7 days	128	99% (112/113)	96% (109/113)	24% (46/191)	[a] 95%CI: 0.04–0.16 $p = 0.004$ [b] 95%CI: 0.06–0.22, $p = 0.002$ [c] 95%CI: -0.001–0.2
	vs						
	Trimethoprim–sulfamethoxazole PO 160/800 mg b.i.d. (with or without ceftriaxone IV 1 g)	14 days	127	89% (90/101)	83% (92/111)	33% (62/187)	
Mouton Y, et al. (14)	Lomefloxacin PO 400 mg q.d.	14 days	33	100% (20/20)	65.0% (13/20)	12% (4/33)	[a] $p = 0.05$ [b] NA
	vs						
	Trimethoprim–sulfamethoxazole PO 160/800 mg b.i.d.	14 days	30	88.9% (16/18)	68.4% (13/19)	17% (5/30)	
Richard GA, et al. (15)	Levofloxacin PO 250 mg q.d.	10 days (in the study with ciprofloxacin) 7–10 days (in the study with lomefloxacin)	89	95%	92% (82/89) (82/89)	2% (3/124) (3/124)	
	vs						
	Ciprofloxacin PO 500 mg b.i.d.	10 days	58	94%	88% (51/58)	8% (6/80)	
	vs						
	Lomefloxacin PO 400 mg q.d.	14 days	39	95%	80% (31/39)	5% (3/55)	

Abbreviations: PO = oral, IV = intravenous, b.i.d = twice a day, q.d. = once daily, NA = not applicable.
Adapted from references (13–15).

(Penetration 2002; 11: Table 5)

potential for resistance to develop. Such strategies include reduced prescription of antibiotics, use of a range of different agents, and appropriate dosing to ensure elimination of the causative pathogen. This latter strategy may result in using levofloxacin twice daily when treating organisms such as *Pseudomonas aeruginosa* in order to ensure the minimal bactericidal concentration (MBC) is maintained over a 24 hour period, thereby blocking the growth of first step mutants.

Gastrointestinal Infections

TYPHOID FEVER

Public health issues seen in the developing world are often different to those seen in Western countries. One such problem is typhoid fever. In 1994 Dr. Fu Wang reported on the use of ofloxacin in typhoid fever, which she described as an important global health issue. At that time chloramphenicol was the most commonly used agent, followed by TMP-SMX and ampicillin as alternative therapies. However due to a lack of full coverage and toxicities these agents do not provide the clinician with optimal therapy. New fluoroquinolones were able to overcome these limitations, providing a broad antimicrobial spectrum, with particularly high activity against most Gram-negative pathogens and *Enterobacteriaceae* including *S. typhi* and other *Salmonella* spp. Strains resistant to chloramphenicol, TMP-SMX and ampicillin were susceptible to ofloxacin, which had an MIC_{90} against *S. typhi* of 0.008–0.25 mg/l. Ofloxacin's rapid oral absorption and penetration into most tissues including the gall bladder, bile and phagocytes provided additional benefits in typhoid treatment. In addition, when ofloxacin was compared with other agents including norfloxacin, ciprofloxacin, pefloxacin, enoxacin and chloramphenicol, it achieved consistently better results than the comparators. Ofloxacin also provided the clinician with the additional advantage of being an effective treatment of carriers, making it the agent of choice in treating typhoid caused by chloramphenicol-resistant strains.

This role was further investigated by R. H. H. Nelwan, MD in a 2005 article reviewing the use of fluoroquinolones in typhoid. Due to its intracellular penetration it is able to target typhoid bacilli inside macrophages, resulting in increased bacterial clearance. Results from a trial of levofloxacin were reported, which evaluated 53 adult hospitalised patients with 48 enrolled in the study. They were treated with 500 mg levofloxacin once-daily for one week. Following treatment all patients demonstrated an excellent response (Table 9) (16), with fever subsiding a mean of 2.43 days after treatment in cases of confirmed disease and in 2.22 days in probable cases. In contrast the average time for reduction of fever in cases treated with chloramphenicol was 4–5 days or 5–7 days for those receiving TMP-SMX or ampicillin. Levofloxacin was also well tolerated with possible skin reactions only reported in 2 patients (4.2%). While the development of resistance following insufficient typhoid treatment with the earlier fluoroquinolones was a concern, with the advent of newer more effective agents such as levofloxacin this is not so prevalent. In addition levofloxacin is effective in a shorter duration of treatment which further reduces the potential for resistance to develop. However in areas with nalidixic acid resistance Dr. Nelwan recommended levofloxacin should possibly be used in a longer duration of therapy.

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R. H. H. Nelwan, MD
Professor, Chief, Division of Tropical and Infectious Diseases, Department of Internal Medicine, Faculty of Medicine University of Indonesia, Jakarta, Indonesia

SKIN & SOFT TISSUE INFECTIONS (SSTI)

Levofloxacin and its parent compound have long been recognized as being useful therapeutic agents for the management of bacterial SSTI. A review article in the 1998 issue of Penetration by Antonio Nicodemo, MD. Dr. Nicodemo noted that most of these infections are caused by Gram-positive pathogens, although in more complicated cases, especially those in patients with co-morbidities such as diabetes, Gram-negatives start to play a more prominent role. It is therefore important that antimicrobials possess a broad antimicrobial spectrum in order to cover all likely pathogens. With penetration into the relevant tissues achieving a high concentration at infected sites, a prolonged elimination half-life allowing once-daily dosing and with the possibility of IV to PO switch therapy, levofloxacin provides

Table 9. Clinical results of treatment

Treatment results	Definite cases *n*	(%)	Probable cases *n*	(%)
Clinical efficacy				
Response	21	(100)	9	(100)
Failure	0		0	
Defervescence after treatment				
1 day	4	(19.0)	1	(11.1)
2 days	6	(28.6)	6	(66.7)
3 days	10	(47.6)	1	(11.1)
4 days	0		1	(11.1)
5 days	1	(4.8)	0	
Mean (days)	2.43		2.22	

(Penetration 2005; 36: Table 3)

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the clinician with an exceptional antibiotic aimed at managing these infections. To evaluate its efficacy Dr. Nicodemo performed a multicenter, prospective, randomized, double-blind trial, with levofloxacin administered at a dose of 500 mg once daily for 7 days versus ciprofloxacin 500 mg orally twice daily for ten days. Patients had uncomplicated SSTI including abscess, impetigo, furuncle, and pyoderma. 253 patients were evaluated (129 levofloxacin and 124 ciprofloxacin) with clinical success in 96.1% and 93.5% respectively. Microbiological eradication rates were also higher for levofloxacin at 93% versus 90% for the twice daily ciprofloxacin. These results confirmed the efficacy of once-daily levofloxacin, which was noted to have greater compliance. Additionally, in situations where the patient is hospitalized early switch therapy is associated with potential cost reductions through earlier patient discharge.

RESISTANCE

The problem of resistance to antimicrobials has been a long standing concern, with the efficacy of many classes of drugs reduced due to this problem. With the advent of the fluoroquinolones clinicians acted to ensure these important drugs would maintain their efficacy through careful and well planned prescribing. Coupled with this were ongoing surveillance studies which provided excellent data on the susceptibility patterns for these agents, monitoring changes as they occurred. One of the first reports showing the susceptibility situation at that time was in the 1995 issue of Penetration which summarized the prevalence of fluoroquinolone resistance in Europe, using ciprofloxacin as the benchmark. Collaborative study results from 1983, 1986, 1989, and 1990 were reported which showcased differences in the overall susceptibility between various species. Resistance rates varied from 0% for *Proteus vulgaris* to 26% for *Providentia stuartii*. During this time the results confirmed that prevalence of resistance to *Enterobacteriaceae* remained below 1%, while resistance to *Pseudomonas* spp. ranged from 0.7% to 7% and for *S. aureus* from 1% to 6.8%. Striking differences were also noted between different European countries with southern areas such as Greece and Spain having much higher resistance rates. This was attributed to freer access to the agents, necessitating a more regimented approach in the future to ensure the durability of these agents.

Clyde Thornsberry, PhD
Chief Scientific Advisor, MRL Pharmaceutical Services, Brentwood, TN, USA.

Further data was added to this debate following a 1999 interview with Clyde Thornsberry, PhD. Dr. Thornsberry drew attention to the problem of PRSP, as well as resistance to β-lactams and macrolides. In contrast he noted that levofloxacin had excellent activity against both penicillin-resistant, β-lactam and macrolide-resistant organisms. It also covered many of the atypical respiratory pathogens. Dr. Thornsberry therefore stressed the need to maintain this exceptional efficacy through prudent usage. Results from a pivotal surveillance study monitoring resistance patterns to respiratory pathogens throughout the US were introduced. In the 1980s, PRSP was at 4–5% in the US which stayed relatively stable until the 1990s when it rocketed to 20% and continued to increase throughout the later 1990s. Even more alarming was the fact that PRSP isolates also tended to be resistant to other agents such as macrolides. This multi-drug resistance was of great concern. 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 evolving resistance among *H. influenzae* and *M. catarrhalis*, where β-lactamase production causes problems. Results from the Tracking Resistance in the United States Today study (TRUST) look specifically at the three respiratory pathogens mentioned. 434 healthcare institutions throughout the US were involved, with MICs performed on all organisms to get true resistance rates. At completion of the first year of the study over 11,368 isolates had been tested and susceptibility measured according to National Committee for Clinical Laboratory Standards (NCCLS) criteria. Results demonstrated that approximately 20% of *S. pneumoniae* were of intermediate sensitivity to penicillin and 14% had high-level resistance, which was described as "alarming" due to the fact high levels of resistance had been practically zero prior to the 1990s. With the high-level resistant strains more likely to be multi-drug resistant it sets the scene for a frightening situation. Using this data as a trend, Dr. Thornsberry extrapolated that the rate of high level PRSP in the US could reach 40% within a few years. In regard to *H. influenzae*, 33.4% were β-lactamase producing, and nearly all *M. catarrhalis* were resistant to ampicillin. However 100% of these isolates retained sensitivity to levofloxacin. The *in vitro* efficacy of levofloxacin against PRSP was further confirmed by a report in the same issue of Penetration by Dr. Bor-Shen Hu, Taiwan. Results confirmed that levofloxacin MIC_{90} against *S. pneumoniae* was 1μg/ml, which was two-fold more potent than ofloxacin and 4-fold more active than ciprofloxacin, with all isolates susceptible to levofloxacin.

Bor-Shen Hu, MD
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In 2003, Penetration published an update on surveillance results, presented by Mark E. Jones, PhD, Clyde Thornsberry, PhD, James A. Karlowsky, PhD and Daniel F. Sahm, PhD. They noted that the variability of resistance among the three major respiratory pathogens was best illustrated by the International Surveillance results covering the 1997–98 period in Asia and Europe. Results from this survey showed that PPRSP varied dramatically, even within Europe, 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 followed, with over 70% of Chinese isolates and almost 60% of French isolates resistant to the both azithromycin and clarithromycin. Pneumococcal resistance to TMP-SMX varied, with high levels of resistance in China but not in Japan.

In results from a US surveillance study in 1999, 21.4% were resistant to azithromycin with the majority also being resistant to penicillin. TMP-SMX resistance was 30.3% and this was strongly linked to penicillin-resistance. 16.2% of isolates demonstrated high level resistance to penicillin and 19.3% had intermediate resistance. Comparing these results to those from a similar study carried out in 1997–98 showed that the percentage of high level resistance to penicillin had increased from 12.7 to 16.2%, although the overall total was similar.

Results from these trials also confirmed that despite the widespread use of ciprofloxacin over the preceding ten years there were only a few reports of reduced fluoroquinolone susceptibility, most of these from Canada. A second International Surveillance study was carried out in 13 countries around the world, demonstrating that resistance to levofloxacin was uncommon with MIC_{50}s and MIC_{90}s of 0.5µg/ml and 1.0 µg/ml, respectively in all countries. No resistance to levofloxacin was 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%). Table 10 summarizes the susceptibility patterns from selected countries (Table 10) (17–19). Levofloxacin was highly active against *Legionella pneumophila*, with activity superior to the macrolides and far greater than doxycycline. It was also active against *M. catarrhalis* and *H. influenzae*. In the TRUST study no resistance to levofloxacin was seen in nearly 2,000 *H. influenzae* isolates and levofloxacin was of equal or greater activity than the macrolides against 1,000 isolates of *Moraxella catarrhalis*. Multi-drug resistance was also monitored and revealed that isolates with MDR phenotypes were increasing. However resistance to levofloxacin was still relatively low in most countries. The clinical efficacy of these resistance results was confirmed in a 2005 Penetration article by Burke A. Cunha, MD, who showed that levofloxacin has been used to treat therapeutic failures of CAP due to *S. pneumoniae* initially treated with β-lactams, ciprofloxacin or macrolides. As noted by Dr. Cunha, even after years of extensive use worldwide, it is exceedingly rare to document 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 500 mg levofloxacin or a shorter 5 day course of the higher dose 750 mg schedule.

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Focus Technologies, Inc., Hilversum, the Netherlands

SEQUENTIAL IV/PO THERAPY

As early as 1992, reports were filed relating to the use of parenteral, followed by oral, ofloxacin in the management of pneumonia. It was rapidly apparent that although the oral administration of ofloxacin, and subsequently levofloxacin, were extremely effective, that for some serious infections intravenous therapy was required. The question then arose of when to switch from IV to oral therapy and in this regard ofloxacin and levofloxacin were seen as leaders amongst other fluoroquinolones. Due to their excellent oral bioavailability (almost 100%) neither ofloxacin nor levofloxacin required dose adjustment when changing from parenteral to oral therapy. This ease of switch provided an added advantage for these two agents that both already possessed many benefits. The clinical utility of such sequential therapy was reported by S. Ragnar Norrby, MD, PhD, for dealing with hospitalized patients with lower respiratory tract infections. Dr. Norrby noted that the ease of sequential therapy with levofloxacin allowed earlier discharge from hospital and less need for costly intensive home care compared with ceftriaxone and then reported study results from trials comparing levofloxacin IV and/or PO versus ceftriaxone followed by cefuroxime axetil. The first by File et al. randomized patients to either received 500 mg levofloxacin once daily IV or PO, or to receive ceftriaxone 1–2 g once or twice daily and/or cefuroxime axetil 500 mg b.i.d. Patients receiving cephalosporins could also receive erythromy-

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Table 10. Activity of azithromycin, penicillin, TMP–SMX and levofloxacin against isolates of *Streptococcus pneumoniae* from Brazil, China, Germany, Hong Kong, Italy, Mexico, Spain and the US[a]

Country	Antimicrobial	MIC (µg/ml)		Susceptible (%)	Intermediate (%)	Resistant (%)
		Range	MIC_{90}			
Brazil (*n* = 448)	Azithromycin	≤ 0.03– > 4	0.06	94.9	0.4	4.7
	Levofloxacin	0.25–2	1	100	0	0
	Penicillin	≤ 0.03–4	0.25	77.2	19.9	2.9
	TMP–SMX	≤ 0.015– > 4	> 4	44.9	16.5	38.6
China (*n* = 214)	Azithromycin	≤ 0.03– > 4	> 4	32.2	1.4	66.4
	Levofloxacin	0.25– > 8	1	96.7	0	3.3
	Penicillin	≤ 0.03– 4	0.12	84.6	13.1	2.3
	TMP–SMX	0.03– > 4	> 4	26.6	8.9	64.5
Germany (*n* = 560)	Azithromycin	≤ 0.03– > 4	2	85.2	1.4	13.4
	Levofloxacin	0.25– > 8	1	99.8	0	0.2
	Penicillin	≤ 0.03–8	0.06	94.1	5.2	0.7
	TMP–SMX	≤ 0.015– > 4	1	86.8	8.4	4.8
Hong Kong (*n* = 175)	Azithromycin	≤ 0.03– > 4	> 4	29.1	26.3	44.6
	Levofloxacin	0.5–8	1	92.0	0.0	8.0
	Penicillin	≤ 0.03–4	4	36.0	13.7	50.3
	TMP–SMX	0.03– > 4	4	34.3	7.4	58.3
Italy (*n* = 491)	Azithromycin	≤ 0.03– > 4	> 4	66.8	1.8	31.4
	Levofloxacin	0.03–2	1	100	0	0
	Penicillin	≤ 0.03–4	1	79.2	11.4	9.4
	TMP–SMX	≤ 0.015– > 4	4	66.2	12.8	21.0
Mexico (*n* = 271)	Azithromycin	≤ 0.03– > 4	> 4	69.7	1.1	29.2
	Levofloxacin	≤ 0.004– > 8	1	98.5	0	1.5
	Penicillin	≤ 0.03–8	2	44.3	37.6	18.1
	TMP–SMX	0.03– > 4	> 4	47.6	7.7	44.6
Spain (*n* = 492)	Azithromycin	≤ 0.03– > 4	> 4	67.3	0.4	32.3
	Levofloxacin	0.12– > 8	1	98.4	0	1.6
	Penicillin	≤ 0.03–8	2	47.4	27.8	24.8
	TMP–SMX	0.03– > 4	> 4	45.3	10.4	44.3
US (*n* = 9,499)	Azithromycin	≤ 0.015– > 32	8	73.4	3.1	23.4
	Levofloxacin	≤ 0.06– > 8	1	99.4	0.1	0.5
	Penicillin	≤ 0.03– > 8	2	65.9	18.1	16.0
	TMP–SMX	≤ 0.06– > 4	> 4	65.4	5.3	29.3

[a] Susceptible, intermediate-resistant and resistant categories interpreted using breakpoint criteria defined by National Committee for Clinical Laboratory Standards (2002) (17).

Abbreviations: MIC_{90} = minimum inhibitory concentration at which 90% of isolates are inhibited, TMP–SMX = trimethoprim–sulfamethoxazole.

Adapted from references (18, 19).

(Penetration 2003; 36: Table 1)

cin or doxycycline at the discretion of the investigator. Only parenteral therapy was given to 2.2% of the levofloxacin group while a further 61% received only oral levofloxacin. In regard to the cephalosporins only 50% received purely oral therapy. Results demonstrated a 96% clinical success rate for levofloxacin versus 90% for the comparator, and a microbiological eradication arte of 98% for levofloxacin versus 85% for the comparator. Another trial, by Marrie et al. (20) evaluated the use of a critical pathway in pneumonia. This compared patients treated with levofloxacin against standard treatment. Primary results included an 18% reduction in the number of bed days used by levofloxacin-treated patients, with an associated reduced mean cost of health care of US$1,700. At the same time the levofloxacin treated group achieved equivalent clinical outcomes. Further evidence supporting the usefulness of IV/PO levofloxacin therapy compared to cephalosporins in CAP was provided by Dr. Manggunnegoro, Jakarta Indonesia. He demonstrated that patients treated with 500 mg once-daily levofloxacin (IV or PO) for 10 days versus IV ceftriaxone 2 g once-daily followed by 500 mg b.i.d. cefuroxime axetil resulted in an 89% success rate for levofloxacin compared to 79% in the comparator group. The mean duration of IV

therapy for levofloxacin was 2.4 days compared to the more lengthy 3.05 days for the comparator. In addition levofloxacin treated patients required less time in hospital and the clinical cure rate at 1–3 days post-therapy was 81% for levofloxacin and 62% for ceftriaxone/cefuroxime axetil. These results confirmed that early switch from IV to PO levofloxacin in hospitalized patients with moderate to severe CAP was successful in 89% and provided a better and cheaper alternative to ceftriaxone/cefuroxime.

SAFETY

Among the fluoroquinolones, levofloxacin has had the advantage of being launched on the excellent safety of its parent compound. In addition it has the confirmatory evidence of a substantial post-marketing surveillance database, available since it was first launched. A review article in 1999 by Andrew T. Chow, PhD delved further into potential drug-drug interactions with levofloxacin, and found it to be a very safe drug. Levofloxacin is only moderately protein bound in plasma, has negligible hepatic metabolism, and is passively excreted by the kidney, features which all contribute to a lack of drug-drug interactions. Levofloxacin however, along with other fluoroquinolones, has the potential to interact with metal cations. Due to this it is important to advise patients not to administer levofloxacin at the same time as aluminium- or magnesium-containing antacids, mineral-containing multivitamin preparations and other drugs containing divalent and trivalent cations.

In 2001 further evidence on safety differences among this class of antimicrobials led to the report from a special roundtable discussion entitled, "Quinolones are not all the Same: Different Safety Profiles". This report clearly demonstrated that after 130 million prescriptions (the total at that time) levofloxacin maintained an exceptional safety record; while at the same time competitor flouroquinolones were being withdrawn due to unacceptable side effects. These included the withdrawal of temafloxacin and grepafloxacin, along with warnings and restricted use of trovafloxacin, and discontinued development of fleroxacin, and clinafloxacin. An update on this important issue was presented by Keith A. Rodvold, Pharm D, FCP, FCCP in the 2006 issue of Penetration. Adverse events associated with the fluoroquinolones have been shown to relate to their specific chemical structures, with phototoxicity and central nervous system effects associated with modifications at positions 1, 5, 7 and 8. Phototoxicity has been shown to be more likely with a halogen at C-8 (lomefloxacin, sparfloxacin, fleroxacin, clinafloxacin and sitafloxacin). In regard to CNS effects, substitution at C-7 appears to create the most problems. Those agents with a 2, 4-difluorophenyl moiety at C-1 have been shown to be more likely to develop severe unexpected adverse events, best illustrated by trovafloxacin-hepatitis; temafloxacin – hemolytic uremic syndrome; and tosufloxacin – eosinophilic pneumonitis.

The most common drug-related adverse events associated with fluoroquinolones relate to the gastrointestinal system, which are reported in 2–20% of cases. The next most common side effects involve the CNS, followed by skin problems. Most of these are mild and do not require discontinuation of therapy (Table 11) (21–26). While anaphylactic reactions have been reported for

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Table 11. Comparative adverse events and discontinuation rates (%) for selected fluoroquinolones

	Ciprofloxacin	Levofloxacin	Gatifloxacin	Moxifloxacin	Gemifloxacin
Gastrointestinal effects					
Nausea	5.0	1.0	3.0–6.0	7.2	2.7
Vomiting	2.0	0.2	2.0	1.0–2.0	0.9
Diarrhea	2.0	1.0	3.0–6.0	5.7–8.0	3.6
Abdominal pain	2.0	0.3	< 3.0	2.0	0.9
CNS effects					
Dizziness	1.0–2.0	0.3	1.0–2.0	3.0	0.8
Headache	1.0	0.1	≥ 0.1–< 3.0	2.0–8.0	1.2
Dermatologic effects	< 1.0	0.3	≥ 0.1–< 3.0	≥ 0.1–< 2.0	2.8
Discontinuation rate	1.2–3.5	1.3–3.7	3.0–5.0	2.0–5.0	2.2

Abbreviation: CNS = central nervous system.
Adapted from references (21–26).

(Penetration 2006; 36: Table 2)

fluoroquinolones these are rare, estimated at 1.2 per 100,000 prescriptions for ciprofloxacin. Other adverse events include musculoskeletal problems, including arthropathy and tendinopathy, which until now have restricted their use to adult patients, although ciprofloxacin is now licensed by the FDA for use in children. Risk factors for tendinopathy include concomitant use of steroids, or those patients with renal failure. Recently there has been concern over effects on glucose metabolism resulting in hypoglycaemia and hyperglycemia. While the risk of these reactions is low, diabetic patients taking insulin or oral glycemic agents are warned to carefully monitor their glucose levels if taking fluoroquinolones. This side effect does appear to occur more often with some fluoroquinolones than others. There is an indication from case reports, post-marketing surveillance and retrospective analysis that gatifloxacin may be more likely to cause glucose metabolic problems, as it accounts for 80% of all glucose homeostasis adverse events and 68% of reported fatalities. Glycemic effects account for 24% of all reported adverse events for gatifloxacin, significantly higher than for ciprofloxacin (1.3%), levofloxacin (1.6%) and moxifloxacin (1.3%).

Prolongation of the QTc interval resulting in cardiovascular complications has also been reported. While this is a class effect for all fluoroquinolones, data shows that the likelihood of individual fluoroquinolones causing cardiovascular adverse effects can be ranked as follows: sparfloxacin>grepafloxacin>moxifloxacin = gatifloxacoin ≫ levofloxacin, ciprofloxacin. There has also been a trend to use higher-dose, shorter course therapy and levofloxacin has been shown to be well tolerated in a 750 mg dose, although the potential safety of gatifloxacin and moxifloxacin in higher doses is not clear. These results, coupled with the long term extensive use of levofloxacin prove it to be one of the safest fluoroquinolones available.

PHARMACOKINETICS/PHARMACODYNAMICS

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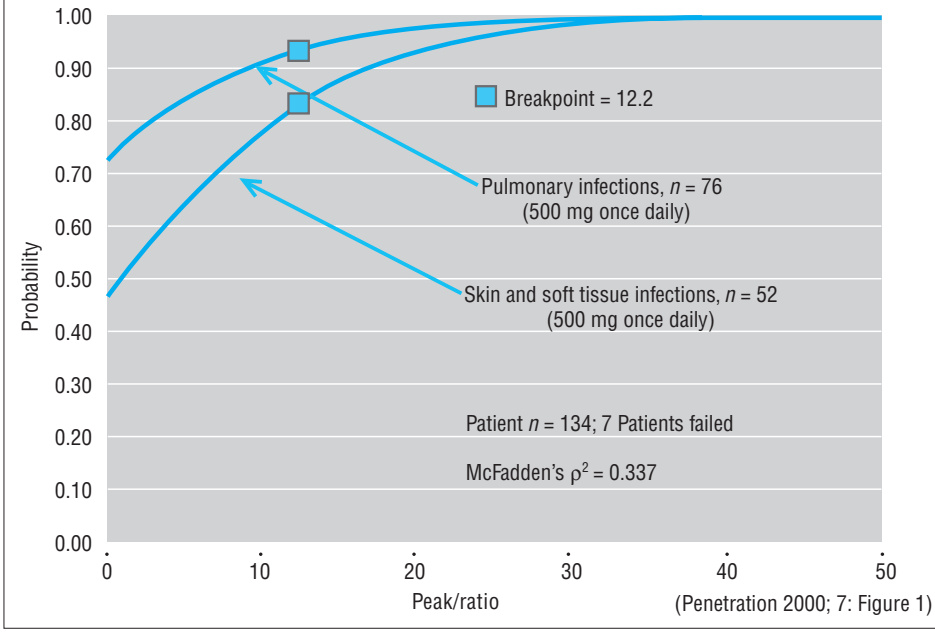
While the clinical efficacy of levofloxacin is well recognized, this has been shown to be based on exceptional PK/PD parameters achieved by this agent. In the 2000 Issue of Penetration, George L. Drusano, MD outlined the pharmacologic variables that are linked to clinical outcome. Fluoroquinolones all exert their bactericidal effect in a concentration-dependent manner. Therefore area under the plasma concentration (AUC)-time curve relative to the MIC (AUC: MIC ratio) is the pharmacodynamically linked variable determining the amount and rate of fluoroquinolone cell kill. To investigate the influence of PK/PD variables on fluoroquinolone activity, Dr. Drusano devised a PK model which found that a once-daily fluoroquinolone dose that achieved a 10:1 Peak: MIC ratio sterilized all organisms and prevented the emergence of resistance. He then used a neutropenic rat model to confirm that Peak: MIC ratio was linked to expected clinical outcome. However this did not fully explain differences in results and he ultimately demonstrated that while a Peak: MIC ratio of greater than 10:1 was able to suppress resistance, if this ratio was not achieved AUC: MIC became linked to outcome. These results supplied the rationale for the development of a once-daily levofloxacin dosing schedule. Dr. Drusano then performed a prospective multicenter study to identify the breakpoint that would be associated with a better likelihood of a good clinical outcome (Figure 4) (27). He demonstrated that if the Peak: MIC ratio was greater than 12:1 optimal results were achieved, a figure that correlates well with the 10:1 ratio determined by PK modeling. Looking at AUC: MIC breakpoint values, Dr. Drusano was able to show that a 50:1 value is associated with excellent outcome. By using

Figure 4. Levofloxacin clinical outcome: probability of a successful outcome.



these two breakpoint values clinicians are able to tailor their treatment to ensure optimal clinical outcome as well as minimizing resistance.

Over the past 15 years levofloxacin has remained a pivotal fluoroquinolone, responsible for effectively treating a wide range of mild, moderate and severe infections, both in the outpatient and hospital setting. While predominantly billed as a respiratory quinolone, levofloxacin has also been of great benefit in treating infections of all body sites, particularly infections of the urinary tract and skin and soft tissue. No other fluoroquinolone has such in-depth safety data available, and this coupled with its exceptional ability to maintain efficacy throughout its long history of use make it arguably the most important and useful fluoroquinolone available.

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