
CLINICAL PRACTICE GUIDELINES
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LIGNES DIRECTRICES DE PRATIQUE CLINIQUE

Ciprofloxacin: an oral quinolone for the treatment of infections with gram-negative pathogens

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Objective: To optimize the use of ciprofloxacin, a synthetic fluoroquinolone, in community and hospital practice, and to minimize overprescribing by providing an overview of the literature and recommendations for appropriate use.

Options: First-line treatment for infections in which ciprofloxacin is shown to be effective, treatment with oral ciprofloxacin rather than parenteral therapy with another drug, and step-down therapy with oral ciprofloxacin after initial parenteral treatment.

Outcomes: In order of importance: efficacy, side effects and cost.

Evidence: A MEDLINE search of articles concerning ciprofloxacin, including in-vitro and pharmacokinetic studies using recognized standard methods with appropriate controls and published in recognized peer-reviewed journals, and randomized, controlled, double-blind clinical trials.

Values: The Committee on Antimicrobial Agents of the Canadian Infectious Disease Society (CIDS) and a recognized expert (T.J.L.) recommended use of ciprofloxacin to treat infections against which it has proved effective both in vitro and in randomized controlled trials. They took into account its value as an oral replacement for other drugs given parenterally and development of resistance.

Benefits, harms and costs: With more appropriate use of ciprofloxacin there will be less development of resistant pathogens. For certain infections patients who would otherwise require admission to hospital could be treated at home and patients initially admitted for parenteral therapy could be discharged sooner on oral therapy with ciprofloxacin.

Recommendations: Ciprofloxacin may be considered as first-line treatment for a number of infections in which gram-negative pathogens are proven or strongly suspected, including complicated urinary tract infections, bacterial prostatitis, bacterial diarrhea, selected bone and joint infections, malignant otitis externa, bronchopulmonary infections in patients with cystic fibrosis and selected pneumonia cases.

Validation: The paper was prepared, reviewed and revised by the Committee on Antimicrobial Agents of the CIDS. It was then reviewed and revised further by the Council of the CIDS.

Sponsor: The CIDS is solely responsible for developing, funding and endorsing these guidelines.

Objectif : Optimiser l'utilisation de la ciprofloxacine, un fluoroquinolone synthétique, dans la pratique communautaire et hospitalière, et réduire au minimum les ordonnances excessives en présentant un aperçu des publications et des recommandations sur l'utilisation appropriée.

Options : Traitement de premier recours d'infections à l'égard desquelles la ciprofloxacine a

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démonstré son efficacité, traitement à la ciprofloxacine par voie orale au lieu d'une thérapie parentérale avec un autre médicament et thérapie décroissante par administration orale de ciprofloxacine après un premier traitement parentéral.

Résultats : Par ordre d'importance : efficacité, effets secondaires et coût.

Preuves : Recherche dans MEDLINE d'articles concernant la ciprofloxacine, y compris études in vitro et pharmacocinétiques fondées sur des méthodes normalisées reconnues et sur des contrôles appropriés, publiées dans des journaux reconnus et validées par les pairs, et essais cliniques randomisés, contrôlés et à double insu.

Valeurs : Le Comité des agents antimicrobiens de la Société canadienne des maladies infectieuses (SCMI) et un expert reconnu (T.J.L.) ont recommandé d'utiliser la ciprofloxacine pour traiter les infections contre lesquelles elle a fait ses preuves à la fois in vitro et au cours d'essais randomisés contrôlés. Ils ont tenu compte de sa valeur comme médicament administré par voie orale pour remplacer d'autres médicaments administrés par voie parentérale ainsi que du développement d'une résistance à ce médicament.

Avantages, préjudices et coûts : Une meilleure utilisation de la ciprofloxacine réduira l'apparition d'agents pathogènes résistants. Dans le cas de certaines infections, des patients qui autrement devraient être hospitalisés pourraient être traités à domicile et des patients hospitalisés pour recevoir une thérapie parentérale pourraient ensuite passer à la ciprofloxacine par voie orale et être ainsi libérés plus tôt.

Recommandations : La ciprofloxacine peut être considérée comme traitement de premier recours dans le cas de certaines infections où l'on a démontré ou où l'on soupçonne fortement la présence d'agents pathogènes gram-négatifs : infections compliquées des voies urinaires, prostatite bactérienne, diarrhée bactérienne, certaines infections osseuses et articulaires, otite externe maligne, infections bronchopulmonaires chez des patients souffrant de fibrose kystique et certains cas de pneumonie, par exemple.

Validation : Le document a été préparé, revu et révisé par le Comité des agents microbiens de la SCMI et examiné et revu ensuite par le Conseil de la SCMI.

Commanditaire : La SCMI est seule responsable de l'élaboration, du financement et de l'aval de ces lignes directrices.

Ciprofloxacin (1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-[1-piperazinyl]-3-quinolonecarboxylic acid hydrochloride monohydrate) is a welcome addition to the antimicrobial armamentarium of Canadian physicians. In molecular structure it is related to other quinolones including nalidixic acid, norfloxacin, ofloxacin and enoxacin, but it differs from them in having a cyclopropyl residue at the 1 position of the quinolone nucleus (Fig. 1).

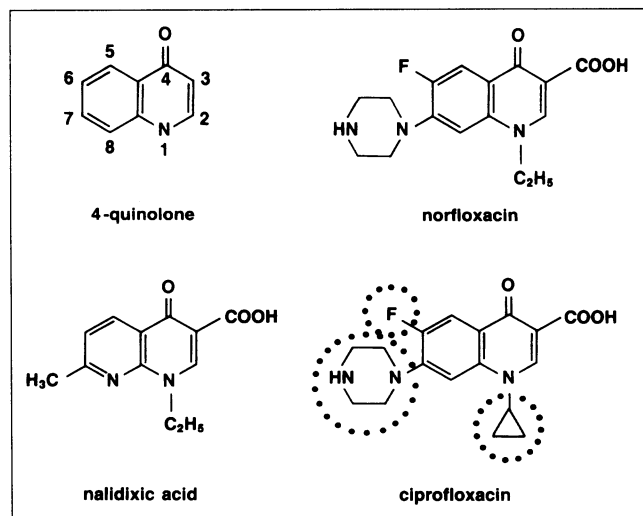


Fig. 1: Chemical configurations of the 4-quinolone nucleus, nalidixic acid, norfloxacin and ciprofloxacin (6-fluorine, 7-piperazine and 1-cyclopropyl moieties circled).

Because of relatively poor gastrointestinal absorption, nalidixic acid and norfloxacin are used to treat only urinary tract and intestinal infections.¹ Ciprofloxacin offers better absorption, wide distribution in tissues and a broad spectrum of in-vitro activity against enteric gram-negative bacilli, *Pseudomonas aeruginosa* and staphylococci.² These features of ciprofloxacin allow the physician to treat orally several infections that previously required parenteral therapy. This translates into two very real advantages: patients with certain infections no longer need to be admitted to hospital for parenteral therapy, and in certain cases patients in hospital can be discharged earlier on oral therapy.

Of the new quinolones ciprofloxacin is the most potent by weight against most gram-negative bacilli.²⁻⁶ This article summarizes its effectiveness and makes recommendations for clinical practice based on results of published clinical trials and symposia.

Methods

This article was prepared in a number of stages designed to ensure an unbiased and critical approach. A recognized content expert (T.J.L.) identified by the Committee on Antimicrobial Agents of the Canadian Infectious Disease Society (CIDS) prepared a first draft, which followed a standardized format for articles concerning a specific drug, with the following headings:

mechanism of action, in-vitro activity, pharmacokinetic features, clinical trials, side effects, dosage and recommendations.

Appropriate published sources of evidence were identified by a MEDLINE search. For the section dealing with clinical trial data we paid particular attention to study design and gave greatest credence to randomized, controlled, double-blind trials. Consideration was also given to position papers, consensus statements and reviews concerning ciprofloxacin.

The first draft was reviewed by committee members, revised and reviewed again. After a second revision the article was forwarded to the CIDS Council for review. The committee chairman then made any further revisions that were required.

Mechanism of action and resistance

Ciprofloxacin inhibits the activity of the bacterial enzyme DNA gyrase, which is required for DNA replication and transcription.^{7,8} The drug is bactericidal at or near the minimum inhibitory concentrations for most common gram-negative pathogens.⁹ Also, improved penetration of or uptake by bacterial cells of ciprofloxacin contributes to the drug's enhanced in-vitro activity. However, owing to increased or inappropriate use, ciprofloxacin-resistant strains of enteric gram-negative bacilli are being isolated ever more frequently.^{10,11} Decreased drug permeation of bacterial cells and alteration of the gyrase are mechanisms of drug resistance.

In-vitro activity

Most strains of Enterobacteriaceae are highly susceptible to ciprofloxacin.⁹ This drug is the quinolone most active against *P. aeruginosa*; however, other *Pseudomonas* species are less susceptible.¹² Pathogens that cause diarrheal disease, such as *Salmonella*, *Shigella*, *Aeromonas* and *Plesiomonas* species, are highly susceptible to ciprofloxacin, as are *Neisseria* species, *Haemophilus* species and *Moraxella (Branhamella) catarrhalis* regardless of whether the organisms produce β -lactamase. Ciprofloxacin is at least as active by weight as aminoglycosides, third-generation cephalosporins and aztreonam against gram-negative pathogens. It is active against *Legionella* species in vitro and in an animal model of pneumonia.¹³

The in-vitro activity of ciprofloxacin against staphylococci is consistent regardless of whether organisms are methicillin-resistant.¹⁴ *Streptococcus pneumoniae*, group A streptococci, group B streptococci and enterococci are less susceptible, with minimum inhibitory concentrations of 2 to 4 $\mu\text{g/mL}$, and JK group corynebacteria, *Nocardia* species, *Mycoplasma* species, *Ureaplasma urealyticum* and obligate anaerobes have shown resistance.^{12,14,15} Some intracellular pathogens, such as

Brucella melitensis and *Mycobacterium tuberculosis*, appear to be susceptible, but other mycobacteria vary in susceptibility and resistance.¹⁶

When ciprofloxacin is combined with aminoglycosides against *P. aeruginosa* a synergistic effect is rarely observed. However, synergy is observed in 20% to 50% of isolates of *P. aeruginosa* when ciprofloxacin is combined with an antipseudomonal penicillin.¹⁷ Combinations of ciprofloxacin and β -lactams or aminoglycosides are not synergistic against other organisms; antagonism is rarely observed.

Pharmacokinetic features

After ingestion 60% to 80% of ciprofloxacin is absorbed, with peak serum concentrations at 1 to 1.5 hours. Increased doses produce correspondingly higher serum concentrations; for example, doses of 250, 500 and 1000 mg in adults produce mean peak concentrations of approximately 1.7, 2.3 and 5.9 mg/L respectively.¹⁸ Food has no significant effect on absorption, although eating delays the peak. However, absorption is markedly impaired by concomitant ingestion of sucralfate, ferrous sulfate and antacids containing magnesium or aluminum or both.¹⁹ The serum half-life ranges from 3.4 to 6.9 h; in serum, 16% to 40% of the drug is protein-bound.²⁰

Ciprofloxacin penetrates most body fluids and tissues well. The ratio of maximal site concentration to peak serum concentration is 1.0 for skin blister fluid, 0.95 for bronchial secretions, 3.0 for lung tissue, 10 for bile and 1.9 for prostatic tissue.²⁰ Cerebrospinal fluid concentrations are 10% of peak serum concentrations when the meninges are not inflamed but more than 30% when they are inflamed.²⁰ Intracellular concentrations of ciprofloxacin in polymorphonuclear leukocytes are two to seven times the extracellular concentrations, which suggests that ciprofloxacin is effective against obligate intracellular pathogens.^{21,22}

Half of the bioavailable drug is excreted by the kidneys, and the remainder is eliminated by the liver and probably by intestinal mucosal secretion.²³ Fifteen percent of the drug is eliminated in the feces. Fecal filtrate concentrations in patients receiving doses of 250 to 500 mg range from 300 to 1000 mg/L. Six percent to 12% of any dose is biotransformed into four inactive metabolites. Drug dosages should be reduced by half when the creatinine clearance is less than 0.5 mL/s $\cdot$ 1.73 m².²⁴ Ciprofloxacin is removed slowly by hemodialysis (the extraction coefficient is 0.25).

Peak serum concentrations are 40% higher in elderly patients; one explanation for this observation is the increased absorption and reduced metabolism in the elderly.²⁵ However, the most likely mechanism is the smaller volume of distribution due to reduced extracellular fluid and fat and diminished renal excretion in the elderly.²⁶

Clinical trials

Urinary tract infections

Ciprofloxacin has been shown to be equivalent to trimethoprim-sulfamethoxazole^{27,28} and superior to nalidixic acid or trimethoprim alone^{29,30} for treating uncomplicated urinary tract infections caused by susceptible organisms. For treating complicated urinary tract infections (upper-tract infections or infections in patients with anatomic abnormalities) ciprofloxacin is comparable or superior to trimethoprim-sulfamethoxazole,^{31,32} and 250 mg is as effective as higher doses.³³

Ciprofloxacin treatment cures 35% to 75% of difficult-to-treat *P. aeruginosa* urinary tract infections associated with anatomic and functional abnormalities, in terms of a 4-week to 8-week follow-up of bacteriologic response.³⁴ Resistance during treatment of *P. aeruginosa* infections has been observed in patients with urinary tract calculi and catheters. In acute and chronic bacterial prostatitis caused primarily by *Escherichia coli* 64% to 77% of infections responded to ciprofloxacin treatment, but infections caused by *P. aeruginosa* or gram-positive pathogens did not respond as often.^{35,36} Additional comparative studies are needed to determine the effectiveness of ciprofloxacin in treating prostatic infections.

Enteric infections

Ciprofloxacin is active in vitro against most bacteria that cause diarrheal diseases, including *Campylobacter jejuni*; however, its usefulness in treating *C. jejuni* infection is not established. It has been shown to be useful in the empiric treatment of diarrheal illnesses caused by bacteria in adults.³⁷ Ciprofloxacin was as effective as trimethoprim-sulfamethoxazole in treating traveller's diarrhea,³⁸ and it cured enteric infection caused by *Shigella* strains resistant to nalidixic acid and trimethoprim-sulfamethoxazole.³⁹ In a noncomparative study, ciprofloxacin eradicated chronic intestinal carriage of *Salmonella* species.⁴⁰ The results of initial comparative evaluations of the drug for the treatment of typhoid fever were favourable.⁴¹ Despite in-vitro susceptibility of *Helicobacter pylori* to ciprofloxacin, treatment of patients with chronic gastritis and ulcer disease associated with *H. pylori* resulted in rapid development of ciprofloxacin resistance.⁴²

Osteomyelitis

Ciprofloxacin cured 65% to 100% of cases of osteomyelitis caused by gram-negative bacilli in four non-comparative trials and one comparative trial.⁴³⁻⁴⁸ Ciprofloxacin-resistant strains emerged in 20% of patients with osteomyelitis caused by *P. aeruginosa*.⁴⁹ Osteomyelitis caused by *Staphylococcus aureus*, streptococci and anaerobes did not respond as well to ciprofloxacin.^{50,51}

As with *P. aeruginosa* infection, the emergence of resistance during treatment was a concern with staphylococcal osteomyelitis.⁵⁰

Upper respiratory tract infections

There are insufficient data to recommend ciprofloxacin for the treatment of routine cases of sinusitis and acute or chronic otitis media. However, this drug has been shown to be useful in treating malignant otitis externa caused by *P. aeruginosa*.^{52,53}

Lower respiratory tract infections

Ciprofloxacin was comparable to ampicillin, trimethoprim-sulfamethoxazole or doxycycline in treating acute exacerbations of chronic bronchitis and alleviated 80% of acute exacerbations of bronchopulmonary infections caused by *Pseudomonas* species in teens and young adults with cystic fibrosis.^{2,54} Organisms frequently became resistant during treatment; cessation of treatment allowed the strains to become susceptible again.

The results of initial trials evaluating ciprofloxacin for the treatment of pneumonia caused by gram-negative bacilli were encouraging,⁵⁵⁻⁵⁷ and oral ciprofloxacin may be useful as "step-down" therapy for such infections. In one study of lower respiratory tract infections in nursing home residents, oral ciprofloxacin appeared to be as safe and effective as intramuscular cefamandole. However, the sample was small. Additional studies are needed to assess fully the role of ciprofloxacin in treating infections acquired in nursing homes.⁵⁸

Ciprofloxacin's use in treating pneumococcal pneumonia has not been well evaluated. On the basis of data from in-vitro studies the drug is not recommended for this condition. Furthermore, pneumococcal bacteremia⁵⁹ and meningitis⁶⁰ have developed in patients during ciprofloxacin treatment of pneumococcal pneumonia, which indicates marginal efficacy of the drug against *S. pneumoniae*.

Ciprofloxacin is active in vitro against *Legionella* species and is effective in animal models. It has been recently recommended as a possible second-choice agent for the treatment of legionnaire's disease.⁶¹

Sexually transmitted diseases

Ciprofloxacin is highly effective in treating gonococcal urethritis regardless of whether the organisms are penicillin-resistant. However, it is not as effective as tetracycline or doxycycline in treating nongonococcal urethritis in which *Chlamydia trachomatis* is the main pathogen.^{62,63} A ciprofloxacin dosage of 500 mg every 12 hours for 3 days has effectively treated chancroid infections caused by *Haemophilus ducreyi*.⁶⁴ Ciprofloxacin is not effective in treating syphilis.

Soft-tissue infections

In two randomized trials involving infected skin ulcers, abscesses, wound infections, cellulitis and burn wounds caused mainly by *S. aureus* and gram-negative bacilli, 750 mg of ciprofloxacin given orally every 12 hours was comparable to 2 g of cefotaxime given intravenously every 8 hours.^{65,66} These studies had insufficient numbers of patients with group A streptococcal infections to establish the efficacy of ciprofloxacin against this pathogen. Foot infections in patients with diabetes mellitus have responded to ciprofloxacin treatment;^{67,68} however, obligate anaerobes, particularly *Bacteroides* species, were recovered less often in this study than in other studies of foot cellulitis in patients with diabetes. Additional treatment to cover obligate anaerobes may be required in such cases.

Prophylaxis of infection

Ciprofloxacin has been used preventively in a number of situations. A single dose of 500 mg is highly effective in eradicating pharyngeal carriage of *Neisseria meningitidis*.^{69,70} The frequency of gram-negative rod bacteremia in granulocytopenic patients is reduced with ciprofloxacin prophylaxis;^{71,72} however, infection with coagulase-negative staphylococci or viridans-group streptococci remains a problem. Ciprofloxacin prophylaxis against infection in severely granulocytopenic patients should still be regarded as experimental. Ciprofloxacin has been used successfully to reduce septic complications of prostatic surgery.⁷³

Replacement of intravenous therapy

In patients with serious infections caused by gram-negative bacilli who have responded well to initial intravenous therapy, ciprofloxacin may be extremely useful for continued treatment, thereby simplifying and reducing the cost of intravenous therapy. Oral quinolones are less expensive than intravenous drugs and do not require as much nursing care. Patients so treated will benefit from early discharge from hospital. In treating polymicrobial infections, however, physicians should consider the need to continue treatment for copathogens (e.g., gram-positive cocci and anaerobes) when "stepping down" from intravenous to oral therapy.

Side effects

The results of clinical trials and European postmarketing surveys show that ciprofloxacin is well tolerated and has a low frequency of adverse reactions.²⁰ Most side effects are not severe enough to necessitate drug withdrawal. Gastrointestinal side effects are the most common: 2.1% of patients suffered from nausea and vomiting, 0.3% experienced abdominal pain and 1.2%

had diarrhea.²⁰ Central nervous system reactions included dizziness (experienced by 0.4% of patients), headache (0.3% of patients), and insomnia and hallucinations (0.1% of patients). Seizures in predisposed individuals are rare. Because of higher peak serum concentrations in the elderly, clinicians should be vigilant regarding possible side effects in these patients. Elevated levels of hepatic enzymes have been seen in only 2.0% of recipients, and eosinophilia and leukopenia are uncommon. Rashes, which may be triggered by light, have been reported in 1.0% of patients in postmarketing surveys. Anaphylaxis is rare.

Ciprofloxacin may interfere with the intrahepatic metabolism of theophylline and caffeine, resulting in excessively high blood levels of xanthine. Like other quinolones, ciprofloxacin causes cystic lesions in the cartilage of immature animals. Although ciprofloxacin has no teratogenic effects in animals, its safety in pregnancy has not been established. Arthropathy in weight-bearing joints during ciprofloxacin treatment has been reported,⁷⁴ but this may be caused by immune complexes.

Dosage

Ciprofloxacin is available in 250, 500 and 750 mg tablets. The median dosage is 500 mg every 12 h. For the treatment of urinary tract infections 250 mg twice daily is as effective as higher dosages. The 500 and 750 mg tablets should be used to treat infections other than those in the urinary and gastrointestinal tracts. The dose should be halved in patients with creatinine clearances of less than 0.5 mL/s•1.73 m², particularly if these patients also have coexisting hepatic insufficiency.

Recommendations

Ciprofloxacin is not recommended for use in children or pregnant women. Indications for first-line treatment with oral ciprofloxacin are summarized in Table 1. On the basis of the available data, ciprofloxacin should be selected for the treatment of infections caused by gram-negative bacilli, either as single pathogens or copathogens. Treatment for gram-positive or anaerobic copathogens may be needed as well. The main advantage of ciprofloxacin is that it offers oral treatment of infections that would normally require parenteral therapy. Despite in-vitro study results showing that methicillin-susceptible and methicillin-resistant staphylococci were susceptible to ciprofloxacin, the drug is not recommended for the treatment of such infections because of the development of resistance and because the drug is bactericidal close to the minimum inhibitory concentration of the staphylococci. For similar reasons ciprofloxacin is not recommended for routine treatment of streptococcal infections.

Physicians should prescribe the drug in selected sit-

uations, keeping in mind its strengths and weaknesses. Ciprofloxacin is preferred for the treatment of complicated upper and lower urinary tract infections as well as uncomplicated pyelonephritis, bacterial diarrhea, intestinal carriage of *Salmonella* species, prostatitis, osteomyelitis caused by gram-negative bacteria and malignant otitis externa. As shown in Table 1, it has a role in treating certain cases of pneumonia acquired in the community, hospital and nursing home, and lung infections caused by *Pseudomonas* species in patients with cystic fibrosis. It should not, however, be used to treat pneumonia in which gram-negative pathogens are not a concern or when *S. pneumoniae* is the likely pathogen. Guidelines for the length of treatment for various infections

are not yet established. As a rule, the type of drug used alters the route of administration but not the treatment time.

Ciprofloxacin is an alternative drug for the treatment of uncomplicated lower urinary tract infections, *Neisseria gonorrhoeae* mucosal infections, chancroid, acute exacerbations of chronic bronchitis, septic arthritis, cellulitis caused by gram-negative bacilli and prophylaxis of infection with *N. meningitidis*.

The drug's efficacy in treating disseminated gonococcal infection, biliary tract sepsis, pneumonitis caused by *Mycoplasma pneumoniae*, tuberculosis, meningitis or endocarditis is not established. It should not be used to treat chlamydial infections or infections caused by obligate anaerobes.

In considering the cost of quinolone drugs physicians should be careful to make the appropriate comparisons. Appropriate use of trimethoprim-sulfamethoxazole or ampicillin is cost-effective. However, ciprofloxacin has the advantage of allowing physicians to treat orally certain infections that previously would have required parenteral treatment. Its cost, therefore, should be compared with that of the parenteral drugs that would normally be used. For the treatment of serious infections with gram-negative pathogens oral ciprofloxacin may be an alternative to continued intravenous therapy after patients have responded to initial parenteral treatment.

Additional clinical experience, postmarketing evaluation and careful trials comparing the drug with conventional therapy and other quinolones are required. Physicians should know the consequences of overprescribing ciprofloxacin and the risk of drug resistance.

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Table 1: Indications for first-line treatment with oral ciprofloxacin	
Type of infection	Comments
Malignant otitis externa	Usually caused by <i>Pseudomonas aeruginosa</i> . Oral treatment may be used
Bronchopulmonary infections in patients with cystic fibrosis	Treatment should be intermittent or episodic to minimize resistance
Pneumonia acquired in the community	May be used in cases in which infection with a gram-negative bacillus is strongly suspected
Pneumonia acquired in hospital	Useful as a "step-down" therapy to replace intravenous treatment for gram-negative bacilli
Pneumonia acquired in nursing homes	Pneumonia caused by gram-negative pathogens is more common in nursing homes
Bacterial diarrhea including traveller's diarrhea	Quinolones offer excellent coverage. Some physicians may prefer norfloxacin because it is not as well absorbed. There are insufficient data on the efficacy of quinolones in treating infections caused by <i>Campylobacter</i> species
Complicated urinary tract infections (e.g., nosocomial infections and anatomic abnormalities in association with multiresistant gram-negative pathogens)	Useful for outpatient treatment of complicated urinary tract infections, including pyelonephritis. Resistance may develop in patients with anatomic abnormalities or nephrolithiasis
Bacterial prostatitis	May not be effective against pathogens other than gram-negative bacilli or against prostatodynia
Bone and joint infections caused by gram-negative bacilli	Long-term follow-up studies of osteomyelitis treatment are needed to confirm this indication

- tibility data from a 300 bed community hospital. *Am J Med* 1989; 87 (suppl 5A): S12-16
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Conferences continued from page 653

June 26, 1994: International Refractive Surgery Club Meeting (satellite meeting of the 27th International Congress of Ophthalmology)

Toronto

Dr. Spencer Thornton, 307 Mid-State Medical Center, 2010 Church St., Nashville, TN 37203; tel (615) 329-7890, fax (615) 329-7892

June 26-30, 1994: Allied Health Personnel — International Congress of Ophthalmology '94 Conference (held in conjunction with the 27th International Congress of Ophthalmology, organized by the Canadian Ophthalmic Medical Assistants Association, the Canadian Society of Ophthalmic Registered Nurses, the Canadian Orthoptic Society and the Canadian Ophthalmological Society)

Toronto

AHP-ICO '94, c/o Congress Canada Conference Management, 191 Niagara St., Toronto, ON M5V 1C9; tel (416) 860-1772, fax (416) 860-0380

June 26-30, 1994: 27th International Congress of Ophthalmology (hosted by the Canadian Ophthalmological Society)

Toronto

Study credits available.

27th ICO Secretariat, 275 Bay St., Ottawa, ON K1R 5Z5; (general information) tel (613) 563-1994, fax (613) 236-2727; (registration) tel (613) 232-8228, fax (613) 236-2727; (scientific program) tel (613) 829-0084, fax (613) 829-1561

June 27-28, 1994: International Glaucoma Society Meeting (satellite meeting of the 27th International Congress of Ophthalmology, integrated into the Congress program)

Toronto

Dr. Gordon Douglas, 2550 Willow St., Vancouver, BC V5Z 3N9; tel (604) 875-4365, fax (604) 875-4606

July 1-3, 1994: International Society on Metabolic Eye Disease 10th Symposium (satellite meeting of the 27th International Congress of Ophthalmology)

Montreal

Dr. Heskell M. Haddad, International Society on Metabolic Eye Disease, 1125 Park Ave., New York, NY 10128; tel (202) 427-1246, fax (202) 360-7009

July 1-4, 1994: Forum on New Materials — Materials in Clinical Applications (in conjunction with the 8th International Conferences on Modern Materials and Technologies)

Florence, Italy

Official language: English

8th CIMTEC, Forum on New Materials, Topical Symposium VIII, PO Box 174, 48018 Faenza, Italy; tel 011-39-546-22461 or 011-39-546-664143, fax 011-39-546-664138 or 011-39-546-663362

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