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Ciprofloxacin

An Updated Review of its Pharmacology, Therapeutic Efficacy and Tolerability

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Synopsis

Ciprofloxacin is a broad spectrum fluoroquinolone antibacterial agent. Since its introduction in the 1980s, most Gram-negative bacteria have remained highly susceptible to this agent in vitro; Gram-positive bacteria are generally susceptible or moderately susceptible. Ciprofloxacin attains therapeutic concentrations in most tissues and body fluids. The results of clinical trials with ciprofloxacin have confirmed its clinical efficacy and low potential for adverse effects.

Ciprofloxacin is effective in the treatment of a wide variety of infections, particularly those caused by Gram-negative pathogens. These include complicated urinary tract infections, sexually transmitted diseases (gonorrhoea and chancroid), skin and bone infections, gastrointestinal infections caused by multiresistant organisms, lower respiratory tract infections (including those in patients with cystic fibrosis), febrile neutropenia (combined with an agent which possesses good activity against Gram-positive bacteria), intra-abdominal infections (combined with an antianaerobic agent) and malignant external otitis. Ciprofloxacin should not be considered a first-line empirical therapy for respiratory tract infections if penicillin-susceptible Streptococcus pneumoniae *is the primary pathogen; however, it is an appropriate treatment option in patients with mixed*

infections (where S. pneumoniae *may or may not be present) or in patients with predisposing factors for Gram-negative infections.*

Clinically important drug interactions involving ciprofloxacin are well documented and avoidable with conscientious prescribing. Recommended dosage adjustments in patients with impaired renal function vary between countries; major adjustments are not required until the estimated creatinine clearance is <30 ml/min/1.73m^2 (or when the serum creatinine level is ≥2 mg/dl).

Ciprofloxacin is one of the few broad spectrum antibacterials available in both intravenous and oral formulations. In this respect, it offers the potential for cost savings with sequential intravenous and oral therapy in appropriately selected patients and may allow early discharge from hospital in some instances.

In conclusion, ciprofloxacin has retained its excellent activity against most Gram-negative bacteria, and fulfilled its potential as an important antibacterial drug in the treatment of a wide range of infections. Rational prescribing will help to ensure the continued clinical usefulness of this valuable antimicrobial drug.

Overview of Antibacterial Activity

Ciprofloxacin is very active *in vitro* against most Gram-negative bacteria including Enterobacteriaceae (especially enteropathogens such as *Escherichia coli*, *Salmonella* spp. and *Shigella* spp.), *Neisseria* spp., *Moraxella catarrhalis* and *Haemophilus* spp., with MIC_{90} (minimum concentration of ciprofloxacin inhibiting 90% of strains) values much lower than the susceptibility cut-off value (1 mg/L). Reports from a number of European centres of increasing resistance to ciprofloxacin among Enterobacteriaceae are of concern.

Ciprofloxacin remains active *in vitro* against *Pseudomonas aeruginosa*. Progressively decreasing susceptibility among *P. aeruginosa* has been reported in Europe and North and South America, predominantly in hospital or nursing home settings in patients with identifiable risk factors. Epidemiological studies suggest that this decreased susceptibility is the result of selection and horizontal transmission of fluoroquinolone-resistant clones. Decreased susceptibility of *Campylobacter* spp. to ciprofloxacin has been reported in Spain, Finland, The Netherlands and Greece.

The majority of methicillin-susceptible strains of *Staphylococcus aureus* are susceptible to ciprofloxacin while most methicillin-resistant *S. aureus* (MRSA) strains are resistant (MIC_{90} ≥4 mg/L). The drug has been shown to select for ciprofloxacin-resistant coagulase-negative staphylococci when it is used as prophylaxis in neutropenic patients and as treatment in patients with chronic ambulatory peritoneal dialysis (CAPD) peritonitis.

Streptococcus pneumoniae, including penicillin-resistant strains, are generally susceptible or moderately susceptible (MIC_{90} 1 or 2 mg/L). Like most fluoroquinolones, ciprofloxacin has little activity against anaerobic bacteria.

Pharmacokinetic Properties

Ciprofloxacin has an approximate bioavailability of 70% after oral administration. Maximum plasma concentrations (C_{max}) between 0.8 and 3.9 mg/L are achieved 1 to 2 hours after oral administration of single 250 to 750mg doses. The drug has a large apparent volume of distribution (2.1 to 5 L/kg after oral or intravenous administration) and is concentrated in many body tissues and fluids, including bile and kidney, liver, gallbladder, prostate and lung tissue.

Ciprofloxacin is largely excreted unmetabolised in the urine and faeces, although small amounts of metabolites have been detected. Transintestinal elimination appears to be the predominant route of gastrointestinal elimination, but

bile excretion also occurs. The elimination half-life ($t_{1/2}\beta$) is approximately 3 to 5 hours.

As a result of age-related decrease in renal function, renal clearance of ciprofloxacin is decreased, and thus C_{max}, $t_{1/2}\beta$ and AUC values are increased in elderly versus younger patients. Similar variations in these parameters for ciprofloxacin have also been noted in patients with renal impairment.

Therapeutic Efficacy

With its broad spectrum of antibacterial activity and ability to achieve therapeutic concentrations in most body fluids and tissues, ciprofloxacin has proved useful in the treatment of a wide variety of infections.

Clinical and bacteriological cure rates for uncomplicated urinary tract infections were >90% with 3- to 7-day ciprofloxacin regimens (500 mg/day; >90% of patients were female), and were slightly lower with single-dose regimens. A 3-day course of low-dose ciprofloxacin (100mg twice daily) was as effective as cotrimoxazole (trimethoprim-sulfamethoxazole) [3- and 7-day regimens], nitrofurantoin (7 days) and ofloxacin (3 days) in this indication. Cure rates ranged from 76 to 96% in complicated urinary tract infections, and ciprofloxacin was as effective as cotrimoxazole, ceftazidime, aminoglycosides and other fluoroquinolones.

Ciprofloxacin showed efficacy similar to that of ceftriaxone, ceftazidime and fleroxacin and greater than that of imipenem-cilastatin in patients with pneumonia (mostly nosocomial). In patients with acute exacerbation of chronic bronchitis, rates of cure/improvement were generally >90% and were similar to those achieved with rufloxacin, cotrimoxazole, amoxicillin (with and without clavulanic acid), ceftibuten, cefixime, cefuroxime axetil and cefaclor. Although the use of fluoroquinolones in the treatment of lower respiratory tract infections in which *S. pneumoniae* is a suspected pathogen is an issue of concern, a recent review showed that the clinical and bacteriological efficacy of ciprofloxacin are similar to that of traditional agents in these infections, including those caused by *S. pneumoniae*.

Ciprofloxacin was as effective as cefuroxime axetil and amoxicillin-clavulanic acid, respectively, in the treatment of acute and chronic sinusitis. Clinical and bacteriological cure rates with ciprofloxacin in patients with chronic otitis media ranged from 58 to 70% and were higher than with amoxicillin-clavulanic acid in one study. High cure rates were observed in the treatment of malignant otitis externa (>95%); compared with historical controls, ciprofloxacin markedly shortened the hospital stay in this infection.

Single-dose, 3- or 5-day ciprofloxacin regimens produced cure or marked improvement in approximately 90% of patients with travellers' and non-travellers' diarrhoea and shigellosis (including infections caused by multiresistant strains). Ciprofloxacin was also shown to be effective in controlling institutional outbreaks of salmonellosis, but microbiological relapse rates varied between studies; prolonged faecal excretion of salmonellae is a concern. Cure rates of 100% were reported in patients with typhoid fever, including those with up to 40% multiresistant strains, in most studies. 14-day regimens may be more effective than 7-day regimens in patients with symptoms for ≥10 days duration. Ciprofloxacin produced cure rates of 100% in patients with cholera and reduced symptom duration.

Ciprofloxacin treatment of skin/skin structure infections was as effective as cefotaxime, ceftazidime and other fluoroquinolones in moderate to severe infec-

tions. Increased resistance to MRSA would appear to limit its usefulness as first-line empirical therapy in these infections, most notably in institutions where MRSA predominate. Ciprofloxacin is effective in the treatment of osteomyelitis, where it has been used as sequential therapy to facilitate early discharge from hospital.

Ciprofloxacin monotherapy is probably not appropriate in patients with febrile neutropenia. The ideal regimen in this infection remains to be defined, but ciprofloxacin-containing combination regimens appear to be at least as effective as standard regimens. Ciprofloxacin has demonstrated usefulness as prophylaxis in patients with neutropenia; however, this practice potentially limits its future usefulness as empirical treatment and increases the potential for development of resistance.

In a limited number of comparative trials, ciprofloxacin, in combination with an antianaerobic agent, has demonstrated efficacy similar to that of amoxicillin/clavulanic acid plus metronidazole and that of imipenem-cilastatin in intra-abdominal infection. In patients undergoing CAPD, ciprofloxacin (25 to 50 mg/L per dialysate bag) appeared to be more effective than oral ciprofloxacin in the treatment of peritonitis. Its clinical activity against Gram-positive pathogens in this setting has not been encouraging and further clarification is needed. Ciprofloxacin monotherapy showed similar efficacy to standard combination regimens in the treatment of pelvic inflammatory disease, endometritis and gall-bladder infections; anaerobic pathogens accounted for the majority of treatment failures in ciprofloxacin-treated patients with gynaecological infections, indicating that the addition of an antianaerobic agent may be appropriate in these infections.

Data, mostly from noncomparative trials, indicate that sequential intravenous and oral ciprofloxacin is effective in the treatment of bacteraemia/sepsis in non-neutropenic patients. Oral and intravenous ciprofloxacin has been used successfully as preoperative prophylaxis in patients undergoing urological, biliary tract, vascular or colorectal surgery.

Clinical and bacteriological cure rates of 99.5% have been reported in gonococcal infections following single-dose ciprofloxacin (100 to 2000mg; 69% received 250mg) administration. It is as effective as standard agents and other fluoroquinolones. Clinical cure rates of 92 to 100% have been reported in patients with chancroid following single-dose ciprofloxacin (500mg). Because of its moderate activity against *Chlamydia trachomatis*, ciprofloxacin is not recommended for treatment of non-gonococcal urethritis.

Although not currently approved for use in patients <18 years old, ciprofloxacin produced clinical improvement in >90% of respiratory tract infections and demonstrated efficacy similar to that of combination intravenous regimens in paediatric patients with cystic fibrosis. Additionally, nearly 100% of children with life-threatening multiresistant typhoid fever were cured with ciprofloxacin.

Pharmacoeconomic Considerations

Oral ciprofloxacin treatment is effective in some infections which would otherwise require parenteral therapy and can be used as sequential therapy after parenteral antibacterial agents. Accordingly, a number of investigators have shown cost savings with oral ciprofloxacin in hospitalised patients, based on the assumption that the more expensive parenteral regimen would have continued had oral ciprofloxacin not been available. Treatment with oral ciprofloxacin also allowed

early discharge of some patients, thereby substantially reducing overall treatment costs.

In two prospective randomised trials conducted in the US, sequential ciprofloxacin therapy reduced antibacterial drug costs by approximately 45% compared with parenteral therapy and reduced hospitalisation costs by 20%. Retrospective cost analyses applied to recent prospective clinical trials showed that intravenous ciprofloxacin was more cost effective than ceftazidime in patients with nosocomial pneumonia and 40% less costly than initial treatment with imipenem-cilastatin in patients hospitalised with severe pneumonia.

Used appropriately, ciprofloxacin can be less costly and/or more cost effective than traditional parenteral regimens in selected clinical settings. More well designed studies would be helpful in further defining the most cost-efficient use of this antimicrobial agent.

Tolerability

Evidence from clinical trials and postmarketing surveillance studies confirms the good tolerability of oral ciprofloxacin. Overall, ciprofloxacin-related adverse events were reported in approximately 9% of patients, and led to treatment withdrawal in 1.5% of patients. Gastrointestinal adverse events, mainly nausea, diarrhoea, vomiting, dyspepsia, anorexia or abdominal pain, were reported in ≈5% of ciprofloxacin recipients. CNS (mostly dizziness, headache, restlessness or tremors) and dermatological (mostly rash or pruritus) adverse events were the next most frequently reported events (≈2 and ≈1% of patients, respectively). Most events were mild to moderate in severity; serious adverse events occurred in <1% of patients. Ciprofloxacin is rarely associated with phototoxicity. Careful examination of adverse event data has revealed no evidence of temafloxacin-like adverse reactions.

With the exception of local reactions at the site of administration (1% of 5010 patients from clinical trials), the tolerability profile of intravenous or sequential intravenous and oral ciprofloxacin appears similar to that of oral ciprofloxacin. Ciprofloxacin appears to be well tolerated in elderly (>65 years) and younger patients. Although the use of ciprofloxacin is restricted in patients <18 years old because of concerns over cartilage damage, accumulated data in >1500 paediatric patients treated with ciprofloxacin suggest a similar tolerability profile in children/adolescents and adults.

Ciprofloxacin is rarely associated with clinically relevant changes in laboratory parameters. Metabolic or nutritional disorders occur in ≈4% of patients; alterations are mostly elevations in serum glutamic oxaloacetic transaminase and/or glutamic pyruvic transaminase levels (incidence of ≈1.5% each). Changes in renal function are rare, with elevated serum creatinine and blood urea nitrogen levels occurring in 0.25% of patients.

Drug Interactions

Concurrent administration of ciprofloxacin and theophylline can increase plasma concentrations of the latter, which may increase the potential for theophylline-related adverse events. Multivalent cation-containing preparations (e.g. aluminium- or magnesium-based antacids, iron-, calcium- or zinc-containing preparations, enteral nutrition products, didanosine and sucralfate) can substantially reduce the bioavailability of ciprofloxacin.

Dosage and Administration

Oral and intravenous ciprofloxacin are normally administered in twice-daily regimens. Recommended dosages of oral ciprofloxacin are 500 to 1500mg daily, depending on the site and severity of infection. Intravenous dosages usually range

from 400 to 800mg daily and are infused over at least 60 minutes to minimise venous irritation; higher dosages (up to 1200 mg/day) have been used in patients with serious life-threatening infections. Duration of treatment depends on infection severity but is usually 7 to 14 days, or at least 2 days after disappearance of signs and symptoms of infection. Shortened regimens have been used in some infections, e.g. 3 to 7 days' treatment in infectious diarrhoea, 3 days' treatment (100 or 250mg twice daily) in acute uncomplicated cystitis and single-dose treatment in patients with acute uncomplicated gonococcal urethritis. Bone and joint infections generally require longer treatment durations (e.g. 4 to 6 weeks or longer).

The international dosing guidelines in renally impaired patients recommend maximum oral and intravenous ciprofloxacin dosages of 1000 and 800 mg/day, respectively, in patients with a creatinine clearance between 31 and 60 ml/min/1.73m^2 (or a serum creatinine level of between 1.4 and 1.9 mg/dl), and 500 and 400 mg/day, respectively, in patients with a creatinine clearance ≤30 ml/min/1.73m^2 (or a serum creatinine level of ≥2 mg/dl). Ciprofloxacin is not currently approved for use in pregnant or lactating women, or in children and adolescents <18 years of age.

Plasma theophylline concentrations should be monitored and dosage adjustments made as appropriate with concurrent administration of ciprofloxacin. If concomitant administration of multivalent cation-containing preparations cannot be avoided, ciprofloxacin should be administered at least 2 hours before or 6 hours after administration of these products.

Ciprofloxacin was one of the first fluoroquinolone antibacterial drugs to become available for the treatment of systemic infections and is the benchmark compound with which other fluoroquinolones are compared. Since the previous review of ciprofloxacin in *Drugs*,[1] numerous studies have monitored its *in vitro* antimicrobial activity and evaluated its clinical efficacy in a broad range of infections. In particular, with the introduction of the intravenous formulation, clinical experience with ciprofloxacin in the treatment of serious infections has expanded. Thus, this review updates information from the previous article, and assesses the impact of widespread use of ciprofloxacin on its clinical usefulness.

1. Overview of Antibacterial Activity

The primary mechanism of action of ciprofloxacin, like other fluoroquinolones, is inhibition of bacterial DNA gyrase (a type II topoisomerase), which disrupts bacterial DNA replication.[1] Inhibition of topoisomerase IV has recently been identified as an additional potential target of fluoroquinolone activity and resistance mechanisms.[1-5]

According to National Committee for Clinical Laboratory Standards (NCCLS) recommendations, a minimum inhibitory concentration (MIC) of ≤1 mg/L indicates susceptibility to ciprofloxacin, 2 mg/L indicates moderate susceptibility and ≥4 mg/L indicates resistance in *in vitro* susceptibility studies.

At the time of the previous review,[1] ciprofloxacin was reported to be active against all Enterobacteriaceae except certain *Providencia* spp. Other Gram-negative organisms highly susceptible to the drug included *Acinetobacter* spp., *Neisseria gonorrhoeae*, *N. meningitidis*, *Moraxella (Branhamella) catarrhalis* and *Haemophilus* spp. MIC_{90} (minimum concentration inhibiting the growth of 90% of strains) values for *Pseudomonas aeruginosa* ranged between 0.12 and 1 mg/L, but other *Pseudomonas* spp. were less susceptible.

Among Gram-positive organisms, *Staphylococcus aureus* (including penicillin- and methicillin-resistant strains), *S. epidermidis*, and *S. saprophyti-*

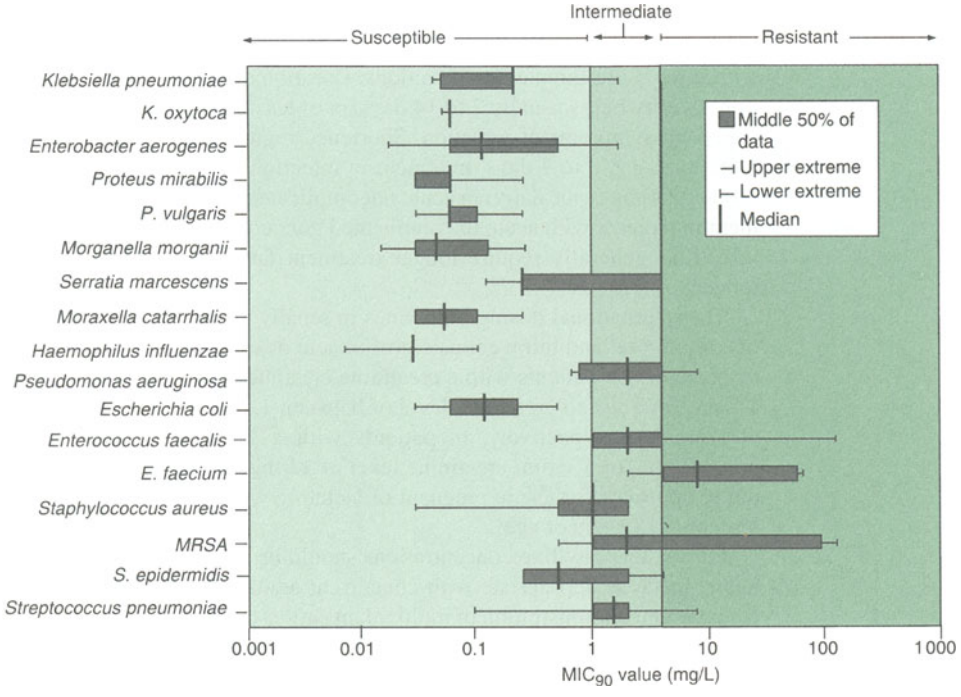

Fig. 1. Overview of the antimicrobial activity of ciprofloxacin. Box-plot illustrating MIC_{90} (minimum inhibitory concentrations required to inhibit the growth of 90% of strains) data for ciprofloxacin against various Gram-negative and Gram-positive bacteria. Each box represents the middle 50% of MIC_{90} values for a given organism. Each plot was constructed using a minimum of 10 MIC_{90} values calculated from a minimum of 15 (but usually >30) clinical isolates. References for bacteria: *Klebsiella pneumoniae*,[6-20] *K. oxytoca*,[6,7,10,11,14-18,21] *Enterobacter aerogenes*,[7-10,13-19,21-24] *Proteus mirabilis*,[6-8,11,13-19,22,25-28] *P. vulgaris*,[6,8,11,15,17,18,26,29-32] *Morganella morganii*,[6-8,11,14-18,25,26,31-33] *Serratia marcescens*,[6-8,10,12-18,20,22,27] *Moraxella catarrhalis*,[6-8,14,23,25,26,28,34-37] *Haemophilus influenzae*,[6-8,11,14,18,25,26,28,36] *Pseudomonas aeruginosa*,[6,15-18,38-41] *Escherichia coli*,[15-18,34,38,40-44] *Enterococcus faecalis*,[6,8,10-12,14-18,28,33,45-48] *E. faecum*,[6,8,14,16,17,45-49] *Staphylococcus aureus*,[6-8,10,11,15-18,26,31,32,36,50,51] MRSA,[6,10,11,15,17,34,48,52-54] *S. epidermidis*,[6,8,11,15,16,28,31,36,48] *Streptococcus pneumoniae*.[6-8,10,18,23,25-27,31,35,36,45,52,55-64] *Abbreviation:* MRSA = methicillin-resistant *Staphylococcus aureus*.

cus were susceptible to ciprofloxacin while *Streptococcus* species were reported to be moderately susceptible.[1]

1.1 *In Vitro* Antibacterial Activity

1.1.1 Enterobacteriaceae

Ciprofloxacin has largely retained its *in vitro* activity against Enterobacteriaceae (fig. 1). Most isolates of *Serratia marcescens* remain susceptible to the drug (MIC ≤4 mg/L),[65,66] but increasing resistance of this organism is of clinical concern.[67] Although ciprofloxacin resistance among *Providencia* spp. has been reported in Australia[68] and in the US (70% of 110 strains of *P. stuartii* were susceptible),[69] susceptibility rates among *Providencia* spp. ranged from 91 to 97% (n = 1357 isolates) in a large US surveillance study.[65]

Ciprofloxacin is very active against *Salmonella* spp. No or minimal resistance (≤2%) has been reported in studies from various geographical locations including India,[70] Brazil[71] and Spain.[72] The drug is active against strains resistant to other drugs, including chloramphenicol, ampicillin and tetracycline.[70,73]

Shigella spp. are also highly susceptible to ciprofloxacin; the drug had an MIC_{90} of 0.008 mg/L against 117 isolates collected from various geographical locations including the US (78

strains), Bulgaria (27), Mexico (4) and Guatemala, Egypt, Thailand and West Africa (2 strains each).[74] Similar results were obtained in studies from Spain[75,76] and Saudi Arabia.[77]

There have been several reports from individual centres of increasing resistance to ciprofloxacin among Enterobacteriaceae (mainly *E. coli* and *S. marcescens*) in Spain.[78-82] An increased incidence of ciprofloxacin resistance was associated with increased usage of the drug,[79,80] while prior fluoroquinolone use appeared to be a significant risk factor for fluoroquinolone resistance in *E. coli* in community and hospital settings and in neutropenic and non-neutropenic patients.[81-83] However, reports from the UK[84] and France[85] indicated that despite increased fluoroquinolone use over 3- and 5-year periods, respectively, decreased susceptibility of *E. coli* was not observed. Differences in local antimicrobial policies and/or observance of treatments may in part account for these differences between countries.[85]

Recent reports from a number of European centres of the emergence of fluoroquinolone-resistant *E. coli* in cancer patients with neutropenia who received fluoroquinolone prophylaxis suggest the need to reassess the benefits and risks of prophylaxis with this drug class.[86-88]

1.1.2 Pseudomonas *and* Strenotrophomonas *(Xanthomonas) spp.*

The activity of ciprofloxacin against *P. aeruginosa* has diminished somewhat since the previous review. MIC_{90} values obtained in most *in vitro* studies fall between 1 and 4 mg/L (fig. 1). Jones et al.[67] reported an overall susceptibility rate of 85% among 1003 *P. aeruginosa* isolates from 43 US medical centres while other recent US studies reported higher overall susceptibility rates (95[89] and 92%,[65] respectively) among 8517 and 14 208 isolates. Longitudinal studies have reported progressively decreasing susceptibility to ciprofloxacin among *P. aeruginosa* in Europe and North and South America (see reviews by Dalhoff,[90] Kresken et al.,[91] and Goldstein and Acer[92]), most frequently in hospital or nursing home settings in patients with identifiable risk factors.[90] The results from epidemiological studies indicate that in nearly all cases one predominating fluoroquinolone-resistant clone was selected and horizontally transmitted. Thus, the sudden rise in resistant isolates observed in single institutions is probably due to specific hospital epidemiology factors contributing to the spread of resistance rather than the selection of mutationally resistant strains.[90,91,93]

Ciprofloxacin exhibited good activity (MIC_{90} 0.2 mg/L) against 35 cefoperazone-resistant (MIC_{90} 75 mg/L) strains of *P. aeruginosa*.[94] Synergistic *in vitro* activity against *P. aeruginosa* has been reported for combinations of ciprofloxacin and ceftazidime, aztreonam and azlocillin.[95,96]

MIC_{90} values for ciprofloxacin against 123 strains of *Strenotrophomonas (Xanthomonas) maltophilia* ranged between 0.5 and >16 mg/L; most isolates were not susceptible to the drug (MIC_{90} 16 mg/L).[97] Lesco-Bornet et al.[98] reported a similar activity range (0.5 to 16 mg/L) against 75 isolates of this organism but a lower MIC_{90} value (4 mg/L).

1.1.3 Other Gram-Negative Bacteria

Ciprofloxacin has excellent activity (MIC_{90} ≤0.06 mg/L) against *H. influenzae*, including β-lactamase–producing strains (fig. 1).

At the time of the previous review, most *Campylobacter* spp. were considered to be susceptible to ciprofloxacin (MIC_{90} values ≤0.62); however, decreased susceptibility to the drug among *Campylobacter* spp. has been reported in Spain,[99,100] Finland,[101] The Netherlands[102] and Greece.[103] *Vibrio cholerae* strains are very susceptible to ciprofloxacin (MIC_{90} 0.008 to 0.06 mg/L).[34,104,105]

Neisseria gonorrhoeae remains largely susceptible to ciprofloxacin (MIC_{90} <0.01 mg/L); however, fluoroquinolone resistance in this pathogen has been reported in the US (in Hawaii,[106] Ohio,[107] Colorado[108] and Washington[109]). While the strains identified in Hawaii and Colorado were probably imported from Asia (where strains with increased MIC values have also been reported), those isolated in Ohio and Washington may have developed locally.[110]

Ciprofloxacin has good and modest activity against *Mycobacterium fortuitum* (MIC_{90} 0.06 to 0.7 mg/L) and *M. tuberculosis* (MIC_{90} 0.5 to 4.3 mg/L), respectively, but is less active against *M. chelonei* (MIC_{90} 1 to 12.5 mg/L) and *M. avium* complex (MIC_{90} 1 to 100 mg/L).[111] *Chlamydia trachomatis* strains are moderately susceptible to ciprofloxacin (MIC_{90} 2 mg/L).[26,112-114]

1.1.4 Gram-Positive Bacteria

S. aureus and *S. epidermidis* remain susceptible to ciprofloxacin; however, the MIC_{90} values for these bacteria are often close to the breakpoint for susceptibility (≤1 mg/L) [fig. 1]. In a large US study, 91% of 17 978 methicillin-susceptible strains were susceptible to ciprofloxacin.[65] High-level fluoroquinolone resistance (up to 100%) has been reported for methicillin-resistant *S. aureus* (MRSA) [section 1.2.3].

The MIC_{90} values of ciprofloxacin for S. pneumoniae, including penicillin-resistant strains,[7,27,57,63] are generally close to the susceptible and moderately susceptible breakpoints (i.e. MICs of either 1 or 2 mg/L) [fig. 1].[65] With the exception of 2 studies in figure 1,[6,7] mean MIC_{90} values for this pathogen were ≤2 mg/L; the number of resistant strains tended to be low.

Most strains of *Enterococcus faecalis* are susceptible to ciprofloxacin while *E. faecium* is largely resistant (fig. 1). A significant increase in the proportion of ciprofloxacin resistance among enterococcal isolates was reported by one US institution [2 of 138 (1.4%) isolates in 1985/86 compared with 88 of 578 (15.2%) isolates in 1989/90; $p < 0.0001$].[115] Increased resistance among enterococci has also been reported in Germany; however, similar to the phenomenon observed with *Pseudomonas* spp. (section 1.1.2), strain subtyping indicates that cross infection is an important factor in the development of resistance to fluoroquinolones in enterococci.[116]

1.1.5 Anaerobic Bacteria

Ciprofloxacin, like most fluoroquinolones, has little activity against anaerobic bacteria such as *Bacteroides fragilis* group (reported MIC_{90} range 4 to 64 mg/L), *Fusobacterium* spp. (2 to 32 mg/L), *Peptostreptococcus* spp. (0.5 to 4 mg/L) and *Clostridium* spp. (4 to 32 mg/L) [reviewed by Appelbaum[117]].

1.2 Mechanisms of Resistance

Bacterial resistance to fluoroquinolones is chromosomally mediated.[118] Two mechanisms of fluoroquinolone resistance have been identified: mutation of DNA gyrase, the target site of the drug class; and mutations of chromosomally encoded drug influx and efflux systems that affect intracellular drug accumulation (see reviews by Bryan and Bedard,[119] Piddock,[120] Watanabe et al.[121]) and Wiedemann & Heisig[122]). Mutations altering the gyrase A subunit (*gyrA*) continue to be the most reported cause of resistance although few fluoroquinolone-resistant bacteria have been analysed for the presence of mutations of the gyrase B subunit (*gyrB*).[120]

Spontaneous mutations conferring resistance to fluoroquinolones are relatively infrequent, occurring at a frequency of between 10^{-6} and 10^{-11} *in vitro* depending on the bacterial species, the drug and drug concentration.[92,123] Clinical fluoroquinolone resistance is rarely found in intrinsically highly susceptible organisms such as Enterobacteriaceae.[122] For example, at least three mutation steps are necessary to yield *E. coli* mutants that are highly resistant to fluoroquinolones; thus, assuming a mutation frequency of 10^{-9}, detection of one such mutant requires at least 10^{27} cells. In contrast, species with moderate intrinsic susceptibility (e.g. *C. jejuni*, *P. aeruginosa* and *S. aureus*) require only one mutation to become clinically resistant.[122]

Emergence of ciprofloxacin-resistant organisms has been noted to occur in situations where large numbers of organisms are present, or when penetration of the drug into the infected tissue is poor.[124] In addition, many investigators have cited prior use of a fluoroquinolone agent to be highly predictive of the isolation of ciprofloxacin-resistant organisms.[125]

Patterns of resistance differ between community-acquired and nosocomial pathogens. While re-

sistance among community-acquired pathogens is minimal, resistance among nosocomial pathogens is becoming increasingly troublesome.[92] The incidence of resistance to fluoroquinolones varies between species, clinical settings and countries, and is related to local epidemic spread of a few clones.[92] Data from a long term longitudinal study of the susceptibility of urinary pathogens clearly demonstrate these differing resistance rates between community and nosocomial isolates (fig. 2).

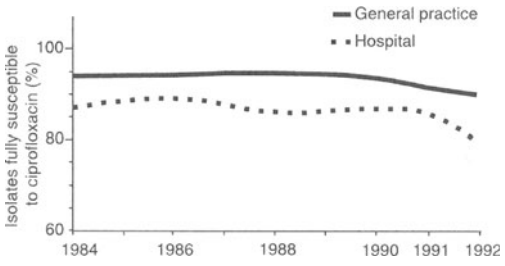

Fig. 2. Differing resistance patterns for ciprofloxacin among community and nosocomial isolates. Longitudinal comparison of ciprofloxacin susceptibility patterns between general practice and nosocomial isolates.[126]

1.2.1 Enterobacteriaceae

Molecular typing of various Enterobacteriaceae revealed identical *eco*RI restriction patterns in 26 ciprofloxacin-resistant *S. marcescens* and also in 10 *P. mirabilis* isolates while various different patterns were seen in ciprofloxacin-susceptible strains. However, several ciprofloxacin-susceptible strains had a pattern matching that of the resistant isolates, suggesting that mutation of ciprofloxacin-susceptible isolates to ciprofloxacin-resistant isolates had occurred.[127]

Mutations affecting both the target site (DNA gyrase) and the intrabacterial accumulation of ciprofloxacin have been demonstrated in *E. coli*. Although various examples of the latter type have been identified, most result from downregulation of the expression of the OmpF porin channel, which impedes entry of the drug into the bacterial cell.[120]

Cross-resistance between fluoroquinolones and β-lactam antimicrobials (with or without an aminoglycoside) has been reported in some Enterobacteriaceae (*E. cloacae*, *S. marcescens*, *C. freundii*, *K. pneumoniae*, *P. stuartii* and *E. coli*).[123,128,129]

1.2.2 Other Gram-Negative Bacteria

It seems likely that modifications to DNA gyrase are largely responsible for conferring resistance to *P. aeruginosa*.[130,131] Ciprofloxacin monotherapy has been associated with selection of *P. aeruginosa* resistant to ciprofloxacin and the structurally unrelated carbapenem imipenem.[132] This phenomenon has also been observed in laboratory studies.[123,133,134] Conversely, fluoroquinolone resistance in *P. aeruginosa* can also be produced by exposure to β-lactam antimicrobials (imipenem, ceftazidime and cefpirome).[123,128] However, Fass et al.[135] suggest that development of such cross-resistance is rare in clinical practice.

1.2.3 Staphylococcus aureus and Coagulase-Negative Staphylococci

Reports of fluoroquinolone-resistant *S. aureus* have been documented in many countries including the US,[65,136,137] Canada,[138] Brazil,[139] Germany[116] and Australia.[140] Both DNA gyrase mutations and drug penetration alterations have been attributed to ciprofloxacin-resistant *S. aureus*.[120] Resistance is largely confined to MRSA isolates and is caused by initial colonisation or infection with ciprofloxacin-resistant MRSA followed by horizontal transmission of resistant clones, occurring most frequently in hospital or nursing home settings.[90,92,141-144]

Strains of MRSA are almost invariably resistant to multiple drugs.[145] Exposure of MRSA to subinhibitory concentrations of ciprofloxacin *in vitro* can promote the development of low-level resistance to structurally unrelated antimicrobial agents (imipenem, tetracycline, fusidic acid and gentamicin).[134] According to Barry et al.,[146] spontaneously occurring staphylococcal mutants resistant to ciprofloxacin can be selected in patients if the concentration of the drug at the site of infection is close to (within 1 dilution) the MIC for the strain; thus, ciprofloxacin serum and tissue concentra-

tions that are typically attained during therapy may be optimal for the selection of staphylococci resistant to the drug. This is supported by *in vivo* animal data; in mice infected with ciprofloxacin-susceptible *S. aureus*, administration of ciprofloxacin selected stably ciprofloxacin-resistant mutants at a frequency inversely proportional both to the dosage of the drug and to duration of administration.[147]

Clinical use of ciprofloxacin [notably when used as prophylaxis in neutropenic patients and as treatment in patients with chronic ambulatory peritoneal dialysis (CAPD) peritonitis] has been shown to select ciprofloxacin-resistant coagulase-negative staphylococci.[89,148-156]

2. Pharmacokinetic Properties

The pharmacokinetic properties of ciprofloxacin are well established and have been previously reviewed;[1,157,158] they are summarised in table I. Both high pressure liquid chromatography (HPLC) and microbiological diffusion assays have been used to quantify ciprofloxacin concentrations in biological fluids. There is generally equal sensitivity and good agreement between the two methods.[158]

2.1 Absorption

The absolute bioavailability of oral ciprofloxacin is approximately 70%.[158] Food has been shown to prolong time (t_{max}) to reach maximum plasma concentration (C_{max}); however, this is not thought to be clinically relevant.[1,158] Following oral administration of single doses (250 to 750mg) of ciprofloxacin to healthy volunteers, mean C_{max} values ranging from 0.8 to 3.9 mg/L were reached within 1 to 2 hours (table I).

Oral ciprofloxacin is not predictably absorbed in critically ill patients up to 36 hours following major abdominal surgery[163] or in febrile post-chemotherapy patients.[164] Drug absorption does not appear to be affected in patients with diabetic gastroparesis[165] or in febrile hospitalised patients.[166]

Table I. Pharmacokinetic properties of ciprofloxacin. Overview of some pharmacokinetic properties of oral (PO) and intravenous (IV) ciprofloxacin after single dose (unless otherwise specified) administration to healthy volunteers. With the exception of C_{max} and AUC values for oral (750mg) and IV (400mg) ciprofloxacin, all data were obtained from a review by Vance-Bryan et al.[158]

Pharmacokinetic variable	Value
t_{max}	1-2h
Bioavailability	≈70%
C_{max}	
PO	
250mg	0.8-2.0 (1.4[a]) mg/L
500mg	1.5-2.9 (2.3-3.5[a]) mg/L
750mg	2.0-3.9[159-161] (3.6[161][a]) mg/L
IV[b]	
200mg	2.8-3.8 mg/L
400mg	3.4-6.7 mg/L[159-162]
Vd/F (after PO or IV dose)	2.1-5.0 L/kg
$t_{1/2\beta}$	≈3-5h
CL/F	≈25-86 L/h
CL_R/F	≈15-30 L/h
AUC	
PO	
250mg	3.0-8.6 mg/L • h
500mg	7.0-12.7 mg/L • h
750mg	8.8-19.2 mg/L • h[159]
IV[b]	
200mg	3.0-7.7 mg/L • h
400mg	8.1-14.2 mg/L • h[159-162]
Protein binding	≈30%

a Administered every 12h for ≥7 doses.

b 200 and 400mg doses infused over 30 and 60 min, respectively.

Abbreviations: AUC = area under the plasma concentration-time curve; C_{max} = peak plasma concentration; CL/F = apparent clearance; CL_R/F = apparent renal clearance; h = hours; min = minutes; t_{max} = time to C_{max}; $t_{1/2\beta}$ = terminal elimination half-life; Vd/F = apparent volume of distribution.

Following single-dose intravenous administration of ciprofloxacin 200 and 400mg, respectively, C_{max} values ranged from 2.8 to 3.8 mg/L and 3.4 to 6.7 mg/L (table I).

2.2 Distribution

The relative penetration of ciprofloxacin into various body tissues and fluids is outlined in table II. The drug achieves very high concentrations (>6 times greater than the corresponding plasma concentration) in urine and bile, and in kidney, gall-

bladder and liver tissue (reviewed by Campoli-Richards et al.[1] and Bergan[167]). It also penetrates well into lung tissue; bronchial mucosa (sampled during fibreoptic bronchoscopy) versus plasma concentration ratios in patients with pneumonia receiving treatment with intravenous ciprofloxacin 200 mg/day ranged from 10.1 to 26.3.[168] Ratios were slightly lower (6.24 and 2.75 to 4.97, respectively) with single-dose intravenous (200mg)[169] and oral (250 to 750mg)[169,170] ciprofloxacin.

Table II. Penetration of ciprofloxacin into body tissues and fluids. Percentage of penetration was calculated from areas under the concentration-time curves (AUC), with the exception of vitreous body tissue and cervix (sampled at 1 to 3h) and prostate and seminal fluid (sampled at 12h)[167]

Tissue/body fluid	Percentage of plasma concentration
Ascitic fluid	80
Bile	100-1000
Bone	50-200
Bronchial secretion	100-150
Cervix	50-400
CSF (inflamed meninges)	30-50
CSF (noninflamed meninges)	5-10
Endometrium	300-500
Fat	50-100
Gallbladder wall	100-500
Kidney	1000-5000
Lung	200-1000
Lymph node	60-120
Lymph, peripheral	70
Muscle	200-400
Myometrium	250
Nasal secretion	75-100
Ovary	50-250
Pancreatic juice	10-40
Peritoneal exudate	50-100
Peritoneum	100
Pleural exudate	100-150
Prostate	300-1000
Prostate fluid	200-1000
Seminal fluid	110-120
Sinus mucosa	160
Skin	50-100
Skin blister (cantharidine-induced)	120
Skin blister (suction)	60-85
Sputum	60-150
Tears	20-50
Tonsil	90-300
Uterus	100-150
Vagina	100-180
Vitreous body	10-20

Early studies (reviewed by Bergan[167]) and two more recent Japanese studies[171,172] indicate that ciprofloxacin is concentrated in prostatic tissue and fluid. In contrast, Naber et al.[173] found that ciprofloxacin concentrations in prostatic fluid were lower than corresponding serum levels. The drug is concentrated in semen.[173,174]

Ciprofloxacin is not concentrated in ocular tissues. Ratios of aqueous humour to serum concentrations were <0.25 after intravenous[175] or oral[176] ciprofloxacin administration. Similarly, intravitreal ciprofloxacin concentrations were consistently lower than corresponding serum concentrations after administration of one or two 750mg oral doses to volunteers.[177,178] In a further study which investigated the penetration of orally administered ciprofloxacin into aqueous humour, and vitreous and subretinal fluid, averaged intraocular ciprofloxacin concentrations equated to ≈15% of average serum values.[179]

2.3 Elimination

The elimination half-life ($t_{½\beta}$) of ciprofloxacin is about 3 to 5 hours. Renal clearance accounts for about two-thirds of total serum clearance of ciprofloxacin and has been shown to exceed creatinine clearance, indicating that tubular secretion is an important elimination mechanism.[158] Transintestinal elimination and biliary clearance account for the remaining one-third of total ciprofloxacin clearance.[180,181] In most studies, the percentage of ciprofloxacin excreted unchanged in the urine ranged from 25 to 35%.[158]

Approximately 94% of a radiolabelled 259mg oral dose of ciprofloxacin was recovered in the urine and faeces within 5 days of administration to healthy volunteers. Similar results were recorded after administration of a radiolabelled 107mg intravenous dose. The drug does not appear to be extensively metabolised; unchanged ciprofloxacin was the major moiety recovered from both urine and faeces. Small amounts of 4 metabolites were

detected; all had some antibacterial activity, but less than that of the parent compound (reviewed by Campoli-Richards et al.[1]).

2.4 Pharmacokinetic Properties of Ciprofloxacin in Specific Patient Populations

As a result of age-related decline in kidney function, renal clearance of ciprofloxacin is lower, and thus AUC and C_{max} are higher, and $t_{1/2\beta}$ is longer, in elderly than in younger patients.[1,157,158,162]

The $t_{1/2\beta}$ of ciprofloxacin in patients with end-stage renal failure is approximately twice that recorded in healthy volunteers; AUC and C_{max} may also be elevated. Furthermore, there is wide interpatient variability in the half-life of the drug in patients with severe renal failure. Ciprofloxacin is not cleared to a clinically relevant extent by CAPD and haemodialysis, and does not require any further dosage adjustments in these patients.

Hepatic dysfunction appears to have little effect on the disposition and elimination of the drug. The pharmacokinetics of ciprofloxacin in patients with AIDS appear to be similar to those of healthy volunteers.[182]

In a study which assessed the pharmacokinetics of single-dose oral ciprofloxacin (15 mg/kg) in infants (aged 5 to 14 months; n = 7) and children (aged 1 to 5 years; n = 9), mean $t_{1/2\beta}$ (2.7 *vs* 1.3 hours), AUC (16.1 vs 5.3 mg/L • h) and mean residence time (4.6 *vs* 2.4 hours) values were significantly higher in infants than in children.[183] No significant differences in C_{max}, t_{max} or absorption half-life were observed between the 2 groups. The authors suggested that, because ciprofloxacin elimination appears to be particularly rapid in children aged 1 to 5 years, shorter dosage intervals (every 8 hours) than those required by infants, older children or adults (every 12 hours) may be appropriate in this group.[183]

Rubio et al.[184] assessed the pharmacokinetics of sequentually administered intravenous (10 mg/kg every 8 hours) and oral (20 mg/kg every 12 hours) ciprofloxacin in 11 children aged 6 to 12 years with cystic fibrosis. Mean C_{max} and t_{max} values following intravenous and oral administration, respectively, were 5 mg/L and 1 hour and 3.2 mg/L and 2.5 hours. Compared with the pharmacokinetic values presented in table I, ciprofloxacin elimination appears to be slightly more rapid in this patient group ($t_{1/2\beta}$ ≈2.5 hours and total clearance ≈25 L/h/1.73m^2). Accordingly, the authors from a recent study conducted to derive dosage regimens in paediatric patients with cystic fibrosis suggested the following: oral ciprofloxacin 20 to 28 mg/kg and 15 to 20 mg/kg twice daily in younger (weight range 14 to 28kg) and older children (weight range 28 to 42kg), respectively, and intravenous ciprofloxacin 10 to 15 mg/kg twice daily.[185]

3. Therapeutic Efficacy

Ciprofloxacin has been studied in a wide range of infections and a large amount of data has become available since the last review.[1] In this section emphasis has been given, where possible, to well designed randomised comparative studies with sufficient patient numbers. The 'Guidelines for the Clinical Evaluation of Anti-Infective Drug Products'[186] were used as a starting point for study selection. Studies which evaluated >1 type of infection were generally not included. Data from the previous review[1] will be overviewed where appropriate. Unless specified otherwise, definitions of terminology for drug efficacy in this section are as follows:

- *Clinical cure:* resolution of all signs and symptoms of infection without recurrence.
- *Clinical improvement:* signs and symptoms of infection show improvement from baseline.
- *Bacteriological eradication:* complete eradication of the pathogen without recurrence, reinfection or superinfection.

MIC data are widely used as an index of antibacterial activity; however, because of interpatient differences in antimicrobial pharmacokinetics, attempts have been made to integrate pharmacokinetic and MIC data in order to make assessments or predictions on therapy outcomes.[187] Measures such as AUC over the MIC [area under the inhibitory time curve (AUIC)], C_{max} to MIC ratio, and time above the MIC have been proposed to inte-

grate these parameters. In the case of ciprofloxacin, therapeutic failure, possibly associated with underdosing (200mg intravenously every 12 hours in these cases), has been described in patients with pneumonia[188] and *S. aureus* infections.[189] Forrest et al.[190] showed that the probability of a favourable clinical outcome in acutely ill patients with pneumonia improved with AUIC ratios >125 and suggested that most clinical failures with ciprofloxacin treatment are the result of high MICs of infecting bacteria, low AUC or both. Thus, increasing ciprofloxacin dosages to achieve more favourable AUIC ratios appears to improve clinical outcome. Therefore, studies using lower intravenous ciprofloxacin dosages (400 to 600 mg/day) may represent undertreatment in some infections, compared with more recent studies which used higher dosages (800 to 1200 mg/day); however, the same caveat can be applied to comparator antimicrobials in these studies. Clearly, development of a useful parameter with which to optimise antimicrobial therapy is a worthwhile pursuit and warrants further study.

3.1 Urinary Tract Infections

Ciprofloxacin possesses excellent *in vitro* activity against most urinary pathogens (section 1.1) and attains high drug concentrations in the urine (section 2.2), its main route of elimination. Accordingly, the drug has been extensively studied in patients with uncomplicated and complicated urinary tract infection (UTI). Ciprofloxacin (usually 250mg twice daily for 7 to 10 days) has demonstrated efficacy similar to that of cotrimoxazole (trimethoprim-sulfamethoxazole) in the treatment of either uncomplicated or complicated UTI, and norfloxacin, cinoxacin and intravenous mezlocillin in the treatment of complicated UTI.[1] The results from a number of comparative studies of ciprofloxacin are presented in sections 3.1.1 and 3.1.2.

3.1.1 Uncomplicated

Acute uncomplicated UTI (or cystitis) is frequently caused by *E. coli* (80% of cases), predominantly affects otherwise healthy females and is among the most common types of infection encountered in general practice.[191] It is worth noting that, when administered for 7 to 14 days, nearly every marketed oral antimicrobial agent with activity against Gram-negative bacteria will cure uncomplicated UTI. Because of the potential for improved patient compliance, decreased cost and reduced occurrence of adverse effects, short-course therapy (either single-dose therapy or multiple-dose administration over 1 to 3 days) has been evaluated in this indication. The best short-course therapy results have generally been obtained with cotrimoxazole and fluoroquinolones; 3-day regimens are usually associated with slightly higher cure rates and fewer recurrences than single-dose regimens.[191,192]

In two single-dose studies which compared ciprofloxacin 250mg with 500 or 750mg, 7-day clinical cure rates were similar (range 81 to 93%) for all 3 regimens.[193,194] However, 28-day cure rates were lower in the 250mg group compared with the 500mg group in one study (62 *vs* 79%)[193] and were significantly lower in the 250mg group compared with the 750mg group in the other study (68 *vs* 92%; $p < 0.001$).[194] Similarly, bacteriological eradication rates at 4 to 9 days post-therapy were significantly lower for single-dose ciprofloxacin 500mg (n = 107) compared with a 7-day ciprofloxacin 250mg twice daily regimen (n = 103) [89 *vs* 98%; 90% confidence interval (CI), 0.029 to 1.138].[195] No significant differences in eradication rates were noted between patients (n = 105 or 106) who received ciprofloxacin 100mg twice daily for 3 days (93%) or 250mg twice daily for 3 (90%) or 7 days (92%).[195] The authors of this trial suggested that ciprofloxacin 100mg twice daily for 3 days was the minimum effective dosage for the treatment of uncomplicated UTI in women.

Data from studies comparing ciprofloxacin with other antimicrobials in >100 evaluable patients (>90% female) with uncomplicated UTI are summarised in table III. For all drugs, rates of both clinical cure and bacterial eradication at 5 to 9 days post-treatment were generally >90%. Although no significant differences were noted between treat-

Table III. Summary of multicentre prospective randomised double-blind studies (with >100 evaluable patients in each treatment group) comparing ciprofloxacin (CIP) with other antimicrobials in patients (>90% female) with acute uncomplicated urinary tract infection (UTI)

Drug regimen (no. of patients evaluated)	Efficacy (% of patients)		Reference
	clinical cure[a]	bacteriological eradication[b]	
CIP 100mg bid × 3 days (229)	93	94	196
CTR 160/800mg bid × 3 days (228)	95	93	
OFL 200mg bid × 3 days (231)	96	97	
CIP 100mg bid × 3 days (168)	95	88	197
CTR 160/800mg bid × 7 days (174)	97	93	
FT 100mg bid × 7 days (179)	93	86	
CIP 500mg sd (114)	91	92	198
NOR 400mg bid × 3 days (112)	94	92	
CIP 500mg sd (182)	90	81	199
PEF 800mg sd (175)	87	81	
CIP 250mg bid × 7 days (120)	98	96	200
FLE 400mg sd (172)	94	85	
FLE 200mg od × 7 days (180)	97	96	
CIP 500mg od × 3 days (151)	97	92	195
CIP 500mg od × 5 days (151)	97	90	
NOR 400mg bid × 5 days (142)	97	94	

a Defined as disappearance of all presenting signs and symptoms associated with UTI at 5 to 9 days post-therapy.

b Defined as elimination of, or $\leq 10^4$ CFU/ml in urine, initial pathogens at 5 to 9 days post-therapy.

Abbreviations: bid = twice daily; CFU = colony-forming units; CTR = cotrimoxazole (trimethoprim-sulfamethoxazole); FLE = fleroxacin; FT = nitrofurantoin; NOR = norfloxacin; od = once daily; OFL = ofloxacin; PEF = pefloxacin; sd = single dose.

ments in any study, single-dose regimens were associated with slightly lower rates of bacterial eradication (range 81 to 92%) than 3-, 5- or 7-day regimens (range 86 to 97%) [table III].

Ciprofloxacin 100mg twice daily for 3 days was as effective as cotrimoxazole (3- and 7-day regimens), nitrofurantoin (7-day) and ofloxacin (3-day) [table III]. However, recurrence rates at 4 to 6 weeks were significantly lower for ciprofloxacin than cotrimoxazole and nitrofurantoin (9 *vs* 22 and 18%, respectively; $p < 0.05$).[197] In addition, ciprofloxacin recipients reported significantly fewer drug-related adverse events (nausea and dermatological events in particular) than cotrimoxazole recipients in both trials (26 *vs* 35%[196] and 48 *vs* 63%[197]).

3.1.2 Complicated

Complicated UTIs are generally associated with urinary catheters or functional and/or structural abnormalities of the urinary tract and are more difficult to treat than uncomplicated UTI or cystitis because of the increased prevalence of resistant pathogens.[191,192] The results from recent prospective randomised comparative trials of ciprofloxacin in >50 evaluable patients are summarised in table IV.

Clinical cure rates for oral ciprofloxacin 250 to 500mg twice daily for 7 to 21 days ranged from 76 to 96% and were similar to those of cotrimoxazole (64%), lomefloxacin (99 and 92%), norfloxacin (72%) and parenteral aminoglycosides (82%) [table IV]. In one trial in patients (94% catheterised) from a chronic-care facility, the short term bacterial eradication rate (defined as sterile urine culture) was significantly higher in ciprofloxacin than aminoglycoside recipients (63 *vs* 15%; $p < 0.0001$).[205] However, the overall bacteriological response rate at 28 to 30 days was similar for both treatment groups (23 *vs* 21%), reflecting the recurrent nature of UTIs in catheterised patients. In addition, sequential ciprofloxacin therapy (200mg intravenously every 12 hours for a mean of 4 days, then 500mg orally twice daily for a mean of 6 days) achieved clinical and bacteriological efficacy similar to that of intravenous ceftazidime 500mg every 8 hours (mean 9 days) in patients with moderately severe UTI requiring hospitalisation (100 *vs* 92%) [table IV].[204]

3.2 Respiratory Tract Infections

Evaluation of antimicrobial agents in the treatment of respiratory tract infections is difficult for the following reasons:[207]

Table IV. Summary of prospective randomised comparative studies with oral ciprofloxacin (CIP) in >50 evaluable patients with complicated urinary tract infection (UTI)

Drug regimen (no. of patients evaluated)	Efficacy (% of patients)		Reference
	clinical cure[a]	bacteriological eradication[b]	
Comparisons with fluoroquinolones			
CIP 500mg q12h × 10-14 days (70)	96	96	201
LOM 400mg q12h × 10-14 days (72)	99	97	
CIP 500mg bid × 7-14 days (70)	87	96	202[c]
LOM 400mg od × 7-14 days (72)	92	97	
CIP 500mg q12h × 14-21 days (29)	79[d]		203[e]
NOR 400mg bid × 10-21 days (29)	72[d]		
Comparisons with other antibacterials			
CIP 200mg IV q12h × ≥2 days (mean 4 days), then 500mg bid × ≤12 days (mean 6 days) [38]	100	100	204
CAZ 500mg IV q8h × ≥4 days (mean 9 days) [39]	92	92	
CIP 500mg q12h × 7-10 days (37)	81	63*	205[f]
GM or TM 1-1.7 mg/kg IM/IV q8h × 7 days (28)[g]	82	15	
CIP 250mg bid × 10 days (34)	76	82	206
CTR 160/800mg bid × 10 days (36)	64	86	

a Defined as disappearance of all presenting signs and symptoms associated with UTI at 5 to 9 days post-therapy.

b Defined as elimination of, or $\leq 10^4$ CFU/ml in urine, initial pathogens at 5 to 9 days post-therapy.

c Multicentre (34) study.

d Clinical and microbiological cure.

e Multicentre (2) study.

f 92 and 96% of patients in the ciprofloxacin and aminoglycoside groups, respectively, were catheterised (Foley, suprapubic or external condom catheters).

g GM was the agent of first choice (n = 12) and TM was administered if *Pseudomonas aeruginosa* was a suspected pathogen (n = 14). Two patients received amikacin (no dose specified) for suspected GM-resistant pathogens.

Abbreviations and symbols: bid = twice daily; CAZ = ceftazidime; CFU = colony-forming units; CTR = cotrimoxazole (trimethoprim/sulfamethoxazole); GM = gentamicin; IM = intramuscular; IV = intravenous; LOM = lomefloxacin; NOR = norfloxacin; od = once daily; q8,12h = every 8,12 hours; TM = tobramycin; * $p < 0.0001$ CIP versus GM/TM.

- Routine specimen collection and culture techniques are often inadequate (causative pathogens can be identified in 60 to 80% of patients at best).
- Specimens are frequently contaminated by indigenous microflora of the oropharynx and the upper airways.
- The microbial aetiology is often polymicrobial.
- Newly recognised pathogens (e.g. *Legionella* spp., *C. pneumoniae*) continue to emerge.

3.2.1 Lower

Because of anecdotal reports of the development of pneumococcal complications (e.g. meningitis, bacteraemia, sinusitis and abscess, as reviewed by Ball & Tillotson[208]), there are concerns with the use of this agent in lower respiratory tract in fections.[209-213]

Results from a meta-analysis of comparative trials with ciprofloxacin, which assessed clinical and bacteriological eradication rates in the treatment of lower respiratory tract infections according to infecting organism, showed higher eradication rates for ciprofloxacin than comparators against *H. influenzae* (94 *vs* 70%; n = 183 isolates), and similar rates against *S. pneumoniae* (n = 100; rates not provided).[214] In a recent review of 37 clinical trials in 3274 patients with lower respiratory tract infections, the overall rates of clinical success and bacteriological eradication for ciprofloxacin (94 and 91%, respectively) were not significantly different from those of comparators (90 and 89%, respectively).[208] Bacteriological eradication rates for *S. pneumoniae* (84 *vs* 91%), *H. influenzae* (98 *vs* 94%) and *M. catarrhalis* (96 *vs* 93%) were also not significantly different between ciprofloxacin and comparators. Treatment failures with ciprofloxacin in these infections have been reported; however, in most instances, these reports were confounded by medical mismanagement (e.g. underdosing of ciprofloxacin or concurrent administration of multivalent cation-containing preparations) and/or co-existing conditions.[208] Nonetheless, because MIC_{90} values for ciprofloxacin against *S. pneumoniae* are close to the susceptibility breakpoint (section 1.1.4) and its acquisition cost is

higher than that of phenoxymethylpenicillin (penicillin V), ciprofloxacin is not an appropriate therapy choice in patients with respiratory tract infections caused only by penicillin-susceptible pneumococci. However, it is an appropriate treatment option in patients with mixed infections (where *S. pneumoniae* may or may not be present) or in patients with predisposing factors for Gram-negative infections (e.g. recent antimicrobial exposure, moderate to severe general disability, residence in a nursing home, hospitalisation or chronic lung disease).

Pneumonia

This diagnosis is often designated as either community-acquired or nosocomial (hospital- or institutional-acquired) pneumonia in order to help determine the most appropriate initial antimicrobial regimen. In community-acquired pneumonia, viruses and *M. pneumoniae* are considered important pathogens in younger patients (aged 5 to 25 years) while bacterial pathogens (mainly *S. pneumoniae* and *H. influenzae*) are more prevalent in older individuals. In patients with nosocomial pneumonia, Gram-negative bacilli are more commonly isolated, particularly in high risk populations (e.g. patients in intensive care units and/or with underlying illnesses).

Data from comparative studies evaluating ciprofloxacin in patients with lower respiratory tract infections are summarised in table V. Most patients in these studies had nosocomial pneumonia and received sequential ciprofloxacin treatment (i.e. intravenous ciprofloxacin for at least 2 to 3 days followed by oral ciprofloxacin for up to 14 days total treatment). Sequential ciprofloxacin was at least as effective as intravenous/intramuscular ceftriaxone[215,216] (91% of patients had community-acquired pneumonia in one study[216]), intravenous ceftazidime[217] and sequential intravenous and oral fleroxacin,[218] with rates of clinical cure/improvement ranging from 50 to 91%. As expected, cure rates tended to be higher in studies which recruited patients with community-acquired pneumonia.[216,217]

Low cure rates were observed for both ciprofloxacin (50%) and ceftriaxone (54%) in a study in hospitalised elderly patients (mean age 79 years) with nursing home-acquired pneumonia.[215] Factors likely to have contributed to these low cure rates included recurrent aspiration of oropharyngeal contents (in >50% of treatment failures), advanced age and the presence of significant underlying diseases [chronic obstructive pulmonary disease (COPD), chronic heart disease, dementia and ≥1 cerebral vascular accident] in most patients.

In a well-designed multicentre study comparing intravenous ciprofloxacin (400mg every 8 hours) with imipenem-cilastatin (1g every 8 hours), a statistically significant difference in clinical cure/improvement rates in favour of ciprofloxacin was thought to be the result of a significantly higher rate of bacteriological eradication of Enterobacteriaceae in the ciprofloxacin group (93 *vs* 66%; p = 0.001).[219] These results are noteworthy in that the majority of patients were critically ill [approximately 80% of patients were mechanically ventilated at randomisation and mean APACHE (Acute Physiology, Age and Chronic Health Evaluation) II scores were 17.6] with severe pneumonia; approximately two-thirds of patients had received non-study antimicrobials prior to enrolment. Importantly, the risk of clinical failure for both regimens was doubled when *P. aeruginosa*, an important respiratory tract pathogen in critically ill patients, was cultured prior to initiation of therapy.[219] Because resistance to this pathogen did not develop earlier than 3 days after initiation of treatment, the authors stated that empirical antimicrobial monotherapy with a potent, broad spectrum agent is a reasonable approach until cultures are obtained. If *P. aeruginosa* is isolated, then combination therapy is recommended to avoid the emergence of resistance.

Acute Exacerbation of Chronic Bronchitis

Chronic bronchitis is characterised by cough and excessive secretion of mucus in patients who have coughed up sputum on most days during 3 consecutive months for >2 successive years.[207,220] Both the role of bacterial infection during episodes

Table V. Summary of prospective randomised comparative studies with ciprofloxacin (CIP) in ≥50 evaluable patients with lower respiratory tract infection (LRTI)

Drug regimen (no. of patients evaluated)	Efficacy (% of patients)		Commonly isolated organisms (no.)	Comments	Reference (study design)
	clinical cure/ improvement[a]	bacterio-logical eradication[b]			
CIP 200-400mg IV q12h (mean 3.4 days) then 750mg PO q12h (total 14 days) [24]	50		*Streptococcus pneumoniae* (6) *Haemophilus influenzae* (5) *Staphylococcus aureus* (2)	Hospitalised patients with nursing home–acquired LRTI. 83 and 92%, respectively, of CIP and CRO recipients had pneumonia	215
CRO 2g IV od (mean 3.9 days) then 1g IM od (total 14 days) [26]	54				
CIP 400mg IV q12h then 500mg PO q12h × ≤14 days (50)	90	94	*S. pneumoniae* (40)[c]	Community-acquired pneumonia in 87/96 (91%) patients.	216 (db)
CRO 1g IV/IM od × ≤14 days (46)	84	100			
CIP 200-300mg IV bid × ≥5 days (mean 6 days) then CIP 500mg PO bid (mean 5 days) [66]	91	93	*Haemophilus* spp. (38) *Pseudomonas aeruginosa* (25) *S. aureus* (22) *Klebsiella pneumoniae* (13) *S. pneumoniae* (12) *Streptococcus* spp. (12)	Hospitalised patients with community-, nursing home– or hospital-acquired LRTI (either pneumonia [91%] or acute bronchitis [9%])	217
CAZ 1-2g IV tid × ≥5 days (mean 7 days) [56]	89	93			
CIP 400mg IV bid × 2-4 days then 500mg PO bid × ≤14 days (49)	67	95	Enterobacteriaceae (29) *H. influenzae* (16) *S. aureus* (16) *Pseudomonas* spp. (10) *S. pneumoniae* (9)	Severe hospital- (58%) or community-acquired (42%) pneumonia	218 (mc)
FLE 400mg IV od × 2-4 days then 400mg PO od × ≤14 days (53)	72	88			
CIP 400mg IV q8h (mean 10.5 days)[d] (95)	69*	69	*P. aeruginosa* (60) *H. influenzae* (43) *S. aureus* (38) *Enterobacter* spp. (31) *Klebsiella* spp. (29) *Escherichia coli* (24)	Severe hospital- (84%) or community-acquired (16%) pneumonia. Eradication rate of Enterobacteriaceae was significantly higher in CIP than IPM recipients [41/44 (93%) *vs* 45/68 (66%); p = 0.001]	219 (db, mc)
IPM 1g IV q8h (mean 10.1 days)[d] (94)	56	59			

a Cure defined as complete resolution of all clinical signs and symptoms of acute infection. Improvement defined as significant reduction in the severity of signs and symptoms of infection.

b Eradication defined as elimination of the causative pathogen(s).

c Represents 35% of isolated pathogens, details of other pathogens not available. This was the causative pathogen in 5/5 and 2/7 failures in CIP and CRO groups, respectively.

d Lower dosages (CIP 400mg IV q12h or IPM 500mg IV q6h) allowed on the basis of impaired renal function or highly susceptible pathogens.

Abbreviations and symbols: bid = twice daily; CAZ = ceftazidime; CRO = ceftriaxone; db = double-blind; FLE = fleroxacin; IM = intramuscularly; IPM = imipenem-cilastatin; IV = intravenously; mc = multicentre; od = once daily; PO = orally; q8,12h = every 8,12 hours; tid = 3 times daily; * $p < 0.05$ CIP versus IPM.

of acute disease (some combination of increasing cough, sputum volume and purulence, and respiratory distress) and the appropriate place of antimicrobial therapy are still emerging, largely because of the non-homogenieity of the populations studied.[210] Indeed, up to 25% of patients fail to respond adequately to primary therapy; however, lack of *in vitro* activity, resistance development, pharmacokinetic inadequacies or individual patient factors may in part account for these poor re-

Table VI. Summary of prospective randomised comparative studies with oral ciprofloxacin (CIP) in >50 evaluable patients with acute exacerbation of chronic bronchitis

Drug regimen (no. of patients evaluated)	Efficacy (% of patients)		Commonly isolated organisms (no.)	Comments	Reference (study design)
	clinical cure/ improvement[a]	bacteriological eradication[b]			
CIP 250mg bid × 10 days (mean) [29]	100	NR	Causative pathogens identified in only 4 patients	Elderly patients (mean age 63-66y)	221 (db)
AM 500mg qid × 10 days (mean) [28]	100	NR			
CIP 500-750mg bid × 7 days (73)	22/70	77	*Haemophilus influenzae* (26) *Streptococcus pneumoniae* (15) *Pseudomonas* spp. (9)	Elderly patients (mean age 62-63y)	222 (sb)
AMX 250-500mg tid × 7 days (67)	10/63	70			
CIP 500mg bid × 9.5 days (mean) [70]	41/44	81	*Streptococcus* spp. (84) *Haemophilus* spp. (59) *Escherichia coli* (16) *Moraxella catarrhalis* (13)	Elderly patients (mean age 62y)	223 (mc)
AMX-CLA 875mg/125mg bid × 9.6 days (mean) [76]	54/37	82			
CFM 400mg od × 9.3 days (mean) [68]	28/53	77			
CIP 500mg bid × 13 days (mean) [28]	71/21	88	*S. pneumoniae* (6) *H. parainfluenzae* (5) *M. catarrhalis* (4)	A significantly higher number CIP *vs* CEC recipients had poor health status (39 *vs* 7%; p = 0.02)	226 (sb)
CEC 250mg q8h × 13 days (mean) [27]	67/9	100			
CIP 500mg bid × 14 days[c]	90	96[d]*	*M. catarrhalis* (64) *H. influenzae* (54) *S. pneumoniae* (28)	Significantly more patients in the CIP group were in fair to poor health at study entry	225 (db)
CXM 500mg bid × 14 days[c]	89	82[d]			
CIP 500mg bid (duration not stated) [153]	84	91[d]	*H. influenzae* (49) *M. catarrhalis* (20) *S. pneumoniae* (10)	Data presented in abstract form; demographic details not available	226 (sb, mc)
CTB 400mg od (duration not stated) [150]	79	90[d]			
CIP 500mg q12h × 7 days (88)	91	82	*H. influenzae* (12) *S. pneumoniae* (9) *M. catarrhalis* (14)	Hospitalised, elderly patients (mean age 65-66y)	227 (sb, mc)
RUF 400mg on day 1, then 200mg od × 4 days (87)	89	79			
CIP 500mg bid × 10-14 days (38)	50/42	76[d]	*H. influenzae* (24) *M. catarrhalis* (16) *H. parainfluenzae* (11) Other Gram-negative organisms (33)	Elderly patients (mean age 65y). More SXT than CIP recipients were excluded from analysis because of resistant organisms (28 *vs* 0%)	228 (sb, mc)
CTR 160mg/800mg bid × 10-14 days (27)	52/37	86[d]			

a Cure defined as complete resolution of all clinical signs and symptoms of acute infection. Improvement defined as significant reduction in the severity of signs and symptoms of infection.

b Eradication defined as elimination of the causative pathogen(s).

c 271 total patients; number of patients in each group not reported.

d Indicates percentage of isolates eradicated.

Abbreviations and symbols: AM = ampicillin; AMX = amoxicillin; bid = twice daily; CEC = cefaclor; CFM = cefixime; CLA = clavulanic acid; CTB = ceftibuten; CTR = cotrimoxazole (trimethoprim-sulfamethoxazole); CXM = cefuroxime axetil; db = double-blind; mc = multicentre; NR = not reported; od = once daily; qid = 4 times daily; q8,12h = every 8,12 hours; RUF = rufloxacin; sb = single-blind; tid = 3 times daily; y = years; * $p < 0.01$ CIP versus CXM.

sults.[210] Nonetheless, *H. influenzae* is the implicated pathogen in more than half of all bacterial exacerbations of chronic bronchitis, with *S. pneumoniae*, and *M. catarrhalis* accounting for a further third. Therefore, antimicrobial therapy with activity against these pathogens is generally prescribed in this setting.

In comparative studies in >50 evaluable patients with acute exacerbation of chronic bronchitis, oral ciprofloxacin was at least as effective as rufloxacin, cotrimoxazole, amoxicillin (with and without clavulanic acid), ceftibuten, cefixime, cefuroxime axetil and cefaclor (table VI). Patients in these studies were generally elderly (aged >65 years) and about 50% were smokers (range 28 to 84%).[227,229-231] Rates of clinical cure/improvement with ciprofloxacin were generally >90% and appeared to be slightly higher than those for amoxicillin (92 *vs* 73%)[222] and cefaclor (92 *vs* 76%).[224] These differences may reflect increased resistance to β-lactam antimicrobials because of increased prevalence of β-lactamase–producing strains of *H. influenzae* (up to 25%) and *M. catarrhalis* (up to 70%) in some areas.[207] Additionally, in one study in which approximately one-third of pathogens isolated were *Streptococcus* spp., no significant differences in clinical efficacy or bacteriological eradication rates were noted between ciprofloxacin, amoxicillin-clavulanic acid or cefixime.[223]

3.2.2 Upper

Sinusitis

Symptoms associated with acute (duration ≤4 weeks) and chronic (duration >3 months) sinusitis are sometimes difficult to differentiate from the common cold, but can include postnasal purulent discharge and facial pain over the infected sinus.[207] Empirical antimicrobial therapy needs to be directed against common causative pathogens, which include *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*.

In a small study in 32 patients with acute sinusitis treated with either ciprofloxacin 500mg twice daily or cefuroxime axetil 250mg twice daily (duration of treatment 10 to 14 days in each group), rates of clinical resolution or improvement (92 *vs* 74%) and bacteriological eradication (100 *vs* 74%) appeared to favour ciprofloxacin, although no statistical analysis was performed.[232] Rates of clinical resolution were equivalent for 10-day courses (same dosages as above) of ciprofloxacin and cefuroxime axetil (87 *vs* 83%) in a larger more recent randomised double-blind trial (n = 453).[233] *H. influenzae* (21%), *S. pneumoniae* (19%), *M. catarrhalis* (14%) and *S. aureus* (9%) were the most commonly isolated pathogens (225 total isolates).

In the treatment of chronic sinusitis, ciprofloxacin (500mg twice daily for 9 days; n = 118) was at least as effective as amoxicillin/clavulanic acid (500mg 3 times daily for 9 days; n = 123), with clinical resolution or improvement reported in 86 and 81% of patients, respectively.[234] Bacteriological eradication rates were 80% in both groups; *S. aureus* (n = 45), *H. influenzae* (n = 35), *S. pneumoniae* (n = 32), Enterobacteriaceae (n = 31) and other streptococci (n = 22) were the most frequently isolated pathogens from sinus fluid aspirates.

Bacterial Otitis

Ciprofloxacin has been evaluated in the treatment of chronic otitis media and malignant external otitis in adults. Chronic otitis media is characterised by mucopurulent otorrhoea; *P. aeruginosa*, *S. aureus* and *P. mirabilis* account for the majority (70 to 90%) of the causative pathogens.[235] Malignant otitis externa is a serious infection caused by *P. aeruginosa* and is notoriously difficult to treat.[236] It is commonly seen in elderly patients with diabetes and can progress to osteomyelitis of the base of the skull.

In a noncomparative study, clinical cure (defined as disappearance of otorrhoea) was reported in 44 of 69 (64%) patients with chronic otitis treated with oral ciprofloxacin 500 or 750mg twice daily for 9 days. When these overall results were analysed by dosage, cure rates were higher in the 750mg group (70 *vs* 59%).[237] Compared with amoxicillin-clavulanic acid (500mg 3 times daily for 9 days), ciprofloxacin (500mg 2 twice daily for

9 days) was associated with significantly higher clinical (58 *vs* 37%; p = 0.04) and bacteriological eradication (70 *vs* 27%; p = 0.003) rates in 76 patients with chronic otitis.[238] *P. aeruginosa* was isolated in approximately one-third of patients in these studies.

In a recent analysis of noncomparative studies and case reports, ciprofloxacin was associated with clinical and bacteriological cure rates of 96 and 99%, respectively, in 84 patients with malignant external otitis.[239] Most patients received ciprofloxacin 1500 mg/day and the average duration of treatment was 3 months. Compared with 68 historical controls in one study, ciprofloxacin recipients (n = 23) had a shorter length of hospital stay (49 *vs* 17 days) and time to bacteriological eradication (15 *vs* 7 days).[240]

3.2.3 In Patients with Cystic Fibrosis

Recurrent respiratory tract infections account for the major cause of morbidity and mortality in patients with cystic fibrosis. The lower respiratory tract of many of these patients is chronically colonised with *Pseudomonas* spp. However, before the infection is classified as chronic (≥6 months continuous colonisation), a period of intermittent colonisation with *Pseudomonas* spp. is observed in most patients.[241] Acute exacerbations of *Pseudomonas* infection in patients with cystic fibrosis generally require hospitalisation and parenteral antimicrobial therapy.

In a few small noncomparative trials in <25 adults (age range 17 to 27 years)[242,243] or children[244] with cystic fibrosis and acute exacerbations of *Pseudomonas* infection, >90% of patients treated with ciprofloxacin (administered orally 500 to 750mg twice daily or intravenously 4 to 6 mg/kg twice daily for 2 to 4 weeks) showed clinical improvement.[242,243]

Oral ciprofloxacin 750mg twice daily showed efficacy similar to that of combination therapy with intravenous azlocillin (75 mg/kg every 6 hours) plus tobramycin (dosage to achieve peak and trough concentrations of 8 to 10 and <2 mg/L, respectively).[245] Four weeks' treatment with oral ciprofloxacin (maximum dosage 1500 mg/day), administered as sequential therapy in 50 patients who completed 2 weeks' treatment with intravenous aztreonam or ceftazidime (both with amikacin) maintained the clinical improvements observed with initial intravenous therapy.[246] In a recent randomised double-blind trial, 100% of patients (n = 83) treated with sequential ciprofloxacin [10 mg/kg intravenously every 8 hours for 7 days, then 20 mg/kg orally twice daily (maximum 750mg twice daily)] or intravenous ceftazadime plus tobramycin (median duration of therapy 12 and 14 days, respectively) showed clinical improvement.[247] Two clinical relapses were reported in each group; arthralgias were reported in 10 and 11% of patients, respectively, and did not require discontinuation of study medication.

Compared with placebo, early administration of twice-daily oral ciprofloxacin plus inhaled colistin for 3 weeks delayed chronic colonisation with *P. aeruginosa* in patients who had not previously received antipseudomonal antimicrobial therapy.[248] In patients with chronic *Pseudomonas* colonisation, oral ciprofloxacin administered for 10 days every 3 months for 1 year improved symptoms relative to placebo, but did not prevent hospital admissions or reduce the number of courses of intravenous antimicrobials required.[249] However, this approach appears to improve 10-year survival rates relative to more traditional treatment approaches (i.e. treating patients only on an as needed basis).[250,251]

3.3 Gastrointestinal Infections

3.3.1 Acute Infectious/Travellers' Diarrhoea

In a study which evaluated 5 days' empirical antimicrobial therapy in 173 patients with nontravellers' diarrhoea, ciprofloxacin 500mg twice daily shortened the duration of diarrhoea (2.4 *vs* 3.4 days for placebo) and increased rates of cure/improvement relative to cotrimoxazole 160mg/800mg twice daily and placebo (92 *vs* 77 and 60%, respectively).[252] In 3 randomised double-blind trials in patients with travellers' diarrhoea, clinical cure rates for single-dose ciprofloxacin 500 or 750mg (83 to 96%) were not significantly different

from those for ciprofloxacin 500mg twice daily for 3 days (82 to 89%).[253-255] The addition of the antidiarrhoeal agent loperamide (up to 16 mg/day) to ciprofloxacin reduced the mean cumulative number of liquid stools relative to placebo by about 25% at both 24 and 48 hours in one study[254] and by about 50% at both 48 and 72 hours in another study.[255]

Ciprofloxacin 500mg once daily for 1 week (the initial dose was taken on the day before departure and the final dose was taken on the day of return) significantly protected travellers in Tunisia against diarrhoea (94 *vs* 64% for placebo; $p < 0.0001$).[256] Nonetheless, chemoprophylaxis of travellers' diarrhoea is recommended only in special situations (e.g. individuals on special missions or patients who could not tolerate a diarrhoeal episode because of underlying medical conditions).[257-260]

3.3.2 Shigellosis

Ciprofloxacin (1000mg daily for 1 or 2 doses or 500mg twice daily for 3 or 5 days) has also demonstrated good efficacy (cure/marked improvement rates >90% in all treatment groups) in the treatment of confirmed moderate to severe shigellosis, including patients with multiresistant strains.[261-263] Multiple-dose (5 days) therapy was more effective than 1- or 2-dose therapy in patients infected with *S. dysenteriae* type 1.[263] Ciprofloxacin was as effective as ampicillin (500mg every 6 hours for 5 days) in patients with infections caused by ampicillin-sensitive strains of *Shigella* (clinical cure/marked improvement in 95 *vs* 88% of patients), and more effective than ampicillin in ampicillin-resistant infections (95 *vs* 43%).[262] Concurrent loperamide appeared to offer additional benefit, significantly decreasing the number of unformed stools (median 2 *vs* 6.5) and shortening the duration of diarrhoea (median 19 *vs* 42 hours) versus ciprofloxacin alone.[261]

3.3.3 Salmonellosis

In most cases, non-typhoidal *Salmonella* gastroenteritis is self-limiting, resolving within 2 to 5 days.[264] Antimicrobials have traditionally not been used to treat this self-limiting infection because they are often ineffective and may prolong pathogen excretion or encourage the development of resistant organisms.[264]

Despite the good activity of ciprofloxacin against *Salmonella* spp. (section 1.1.1) and its favourable pharmacokinetic properties (penetration into phagocytes and high faecal drug concentrations) [section 2.2], its role in the treatment of salmonellosis is unclear. An early study suggested that ciprofloxacin may be effective in the treatment of *Salmonella* enteritis; however, further analysis of these data revealed bacterial relapse/persistence.[265] In a more recent study, no differences in time to full resolution of infection or rate of pathogen clearance from stools were noted between ciprofloxacin (500mg twice daily for 5 days), cotrimoxazole (160mg/800mg twice daily for 5 days) and placebo in patients with acute uncomplicated *Salmonella* enteritis.[266]

Ciprofloxacin (mostly 500mg twice daily for 5 days) has shown some efficacy in controlling institutional outbreaks of enteric salmonellosis.[267-270] In these studies, stool cultures were negative in most symptomatic and asymptomatic patients within 7 days after therapy initiation. However, microbiological relapse rates varied considerably between studies (range 0 to 64%). Negative stool cultures were reported in 100% of patients at 6 months by some investigators,[268] while short term (2 to 3 weeks after therapy) relapse was reported in 21[269] and 50%[270] of patients in other studies and tended to occur more frequently in previously symptomatic patients. In addition, ciprofloxacin recipients who relapsed showed prolonged faecal excretion of salmonellae relative to placebo.[270] Thus, the role of ciprofloxacin and other fluoroquinolones in this condition remains controversial, because of their lack of efficacy in eliminating *Salmonella* spp. from the faeces.[271] In patients who receive drug treatment, long term follow-up of stool cultures (for ≥3 weeks after therapy completion) in previously symptomatic patients is necessary.

3.3.4 Typhoid Fever

Typhoid fever, an acute febrile illness caused by *S. typhi*, is acquired from an individual who either has acute disease or (more commonly) is a chronic

carrier of the pathogen.[272,273] Resistance to traditional agents used to treat this infection (chloramphenicol, ampicillin or cotrimoxazole) has developed in many regions of the world.[273,274]

In noncomparative trials (total n = 240 patients) with ciprofloxacin (mostly 500mg twice daily administered for 7 to 14 days), clinical cure rates ranged from 96 to 100% in adults with typhoid fever.[275-280] Importantly, 100% cure rates were observed in two studies in which up to 40% of patients were infected with multiresistant *S. typhi* (resistant to chloramphenicol, ampicillin and cotrimoxazole).[277,278] Cure rates were similar for 7-, 10- and 14-day ciprofloxacin regimens; no relapses were reported with 10- or 14-day regimens while a relapse rate of 8% (2 of 25 patients) was reported with the 7-day regimen in one study.[279] One group of investigators recommended the use of longer regimens (≥10 days) in patients with symptoms for ≥10 days prior to seeking treatment.[278]

In 2 small studies (n < 32) which compared the efficacy of shorter treatment courses, ciprofloxacin produced clinical cure rates of 82 *vs* 67%[281] and 100% *vs* 86%[282] for 6-day *vs* 3-day regimens. It is difficult to draw firm conclusions regarding the efficacy of short-course fluoroquinolone therapy for typhoid fever from these studies; therefore, regimens of at least 10 days' duration are recommended until further data on shorter courses are available.[283]

In comparative trials, oral ciprofloxacin was as effective as other quinolones (ofloxacin, pefloxacin, enoxacin and norfloxacin),[284,285] and cotrimoxazole 160mg/800mg twice daily for 10 to 14 days.[286,287] It was more effective than ceftriaxone 3 g/day parenterally for 7 days (cure rates 100 *vs* 73%; p = 0.01).[288] Lower rates of relapse (0 *vs* 10%) and the development of a chronic carrier state (0 *vs* 13%) were reported with oral ciprofloxacin relative to chloramphenicol 2 g/day for 15 days.[284] Ciprofloxacin showed excellent activity against multiresistant *S. typhi*, curing 100% of patients who did not respond to initial treatment with ceftriaxone.[288]

Sequential intravenous and oral ciprofloxacin was life-saving in a study in 18 severely ill children (mean age 6.4 years) with multiresistant *S. typhi* infection, impaired consciousness and a mean duration of illness of 23 days before treatment.[289] 17 of 18 (94%) patients were cured (1 child with severe malnutrition and shock died within 24 hours of admission); children regained consciousness within an average of 2 days and no relapses or carrier states were noted during the 3-month follow-up period. In addition, a 100% cure rate was reported with sequential intravenous and oral ciprofloxacin in a recent case report study in 7 pregnant women with multiresistant typhoid fever; 5-year follow-up revealed no adverse drug effects on child development or cartilage formation.[290]

Ciprofloxacin 750mg twice daily for 28 days eliminated *S. typhi* intestinal carriage in 11 of 12 (92%) patients.[291] Two patients received shortened treatment regimens (10 and 15 days) because of adverse events (allergic reaction and decreased haemoglobin, respectively); cure was maintained in these patients, suggesting that lower dosages and/or shortened regimens might be effective in eradicating *S. typhi* in carriers.

3.3.5 Cholera

Cholera is an acute diarrhoeal disease caused by *V. cholerae* 01. Recently, another strain, *V. cholerae* 0139 (synonym Bengal) has been shown to cause epidemic cholera in southern and eastern India.[292] Correction of fluid and electrolyte disturbances is the standard treatment in patients with cholera; however, antimicrobial therapy generally reduces the severity and duration of diarrhoea as well as the duration of shedding of *V. cholerae*.[293] Tetracycline has traditionally been the treatment of choice but emergence of resistant strains has prompted a search for effective alternatives.

In a randomised double-blind study in 202 adults with moderate to severe cholera (*V. cholerae* 01), microbiological eradication rates (99 *vs* 95%) and duration of diarrhoea (51 *vs* 48 hours) were similar for ciprofloxacin (250mg daily for 3 days) and tetracycline (500mg 4 times daily for 3 days).[294] In a recent trial in 75 adult males with

tetracycline-resistant *V. cholerae* 01 infections, ciprofloxacin 500mg twice daily was as effective as erythromycin (500mg every 6 hours), nalidixic acid (500mg every 6 hours) and pivmecillinam (400mg every 6 hours) and more effective than tetracycline (500mg every 6 hours) as assessed by stool output and bacteriological clearance (3-day treatment regimens for each drug).[295] Single-dose ciprofloxacin 1000mg and single-dose doxycycline 300mg showed equivalent efficacy in 129 males with *V. cholerae* 0139 infections.[296]

Prophylactic single-dose ciprofloxacin 250mg did not prevent *V. cholerae* 01 infection among household contacts during a period of low transmissibility.[297] However, in a subgroup of 30 patients who were already infected at study enrolment (and thus excluded from the above efficacy analysis), ciprofloxacin significantly reduced the bacterial load of *V. cholerae* relative to placebo. The authors suggested that chemoprophylaxis during the beginning of an epidemic (when higher transmission rates are likely) warrants further evaluation.[297]

3.4 Skin/Skin Structure Infections

Ciprofloxacin has been evaluated in the treatment of skin/skin structure infections, particularly those considered difficult to treat (e.g. ulcer, abscess and wound infections). A review of 20 noncomparative studies showed that clinical success (complete or substantial resolution of the signs and symptoms of infection without need for further antimicrobial treatment) was observed in 274 of 358 (77%) ciprofloxacin recipients (44 and 46% of patients received ciprofloxacin 500 and 750mg, respectively, every 12 hours for 5 to 14 days).[298] Approximately 60% of patients in this review had infections which required initial hospitalisation. Rates of bacterial eradication for specific pathogens were 48 and 83% for methicillin-resistant and methicillin-susceptible *S. aureus*, respectively, 72% for *P. aeruginosa* and 100% for Enterobacteriaceae. Superinfection was reported in 8% of patients. Similar cure rates were reported in earlier reviews (≈75%).[1,299]

In the previous review in *Drugs*,[1] ciprofloxacin 750mg twice daily showed efficacy similar to that of cefotaxime 2g 3 times daily in patients with skin/skin structure infections. These results were confirmed in a large (n = 461) randomised double-blind multicentre study in patients (70% with underlying diseases) with culture-proven moderate to severe cutaneous infections requiring hospitalisation.[300] Rates of clinical cure were similar for ciprofloxacin and cefotaxime recipients (81 *vs* 74%). Subsequent studies have shown that sequential intravenous and oral ciprofloxacin was as effective as intravenous ceftazidime,[301-303] and that oral ciprofloxacin was as effective as oral lomefloxacin[304,305] in patients with moderate to severe cutaneous infections. It is worth noting that in most of these trials, agents (e.g. third generation cephalosporins) with less-than-optimal activity against Gram-positive bacteria were used as control drugs; comparisons with agents with better Gram-positive activity are needed.

3.5 Osteomyelitis

Bone infections are difficult to treat and often require surgical intervention. Commonly isolated pathogens include *S. aureus* and *P. aeruginosa* and long term treatment (4 to 6 weeks) with intravenous antimicrobials is usually required.[306]

Previously reviewed data indicated that oral ciprofloxacin 500 or 750mg twice daily for >4 weeks) was effective in treating chronic osteomyelitis (>50% with *P. aeruginosa* infections) in patients who failed to respond to previous antibacterial therapy, with clinical cure rates ranging from 50 to >90%.[1] In more recent noncomparative studies in small numbers of patients (n = 17 to 27), cure rates with oral ciprofloxacin (mostly 750mg twice daily for 5 to 52 weeks) ranged from 62 to 76%;[307-310] a higher cure rate (95%) was reported in another noncomparative study following bone debridement and treatment with ciprofloxacin 750mg twice daily for 1 to 4 months (mean duration of follow-up 27 months) in 20 patients with *P. aeruginosa* osteomyelitis.[311]

Table VII. Summary of prospective randomised comparative trials evaluating ciprofloxacin (CIP) for the empirical treatment of febrile episodes in neutropenic adults. All patients had fever (criterion for most studies was an oral temperature >38.5 or >39°C on 1 occasion or >38°C on 2 or more occasions over a 12h period), neutropenia (polymorphonuclear leucocyte count <0.5 or <1 × 10^9 cells/L or counts expected to fall below these values because of antecedent therapy), and a diagnosis of a primary disease or entity leading to neutropenia.[316] All drugs were administered intravenously unless specified otherwise

Drug regimen	Clinical response with initial regimen,[a] no. of patients (%)		Duration of neutropenia (days)	Comments	Reference (study design)
	all episodes	microbiologically documented episodes			
As monotherapy					
CIP 200mg q12h	15/21 (71)		19 (median)	All patients received GD. 4 and 0 episodes of streptococcal bacteraemia observed in CIP and CAZ groups, respectively (all BMT patients)	315
CAZ 2g q8h	16/25 (64)		18 (median)		
CIP 400mg q12h[b]	24/36 (67)	8/20 (40)	4 (median)	1/8 patients with Gram-positive infections responded to CIP compared with 2/3 in CAZ group	316
CAZ 2g q8h	29/34 (85)*	12/14 (85)*	5 (median)		
CIP 200-300mg q12h	31/48 (65)	9/19 (47)		Study discontinued prematurely because of significantly lower response rates in CIP group. 2/8 patients with Gram-positive bacteraemia responded to CIP compared with 4/4 in PIP/AN group	317 (mc)
PIP 4-5g q6h + AN 500mg q12h	48/53 (91)**	14/16 (88)*			
CIP 300mg bid[b]	25/66 (38)	8/27 (30)	23* (median)	87% of patients received GD. 34% of patients in the CIP group received follow-on oral therapy (750mg bid) after a median 3 days of intravenous therapy	318
AZL 5g tid + NET 2.5 mg/kg bid	28/67 (42)	14/31 (45)	18 (median)		
In combination with other antibacterials					
CIP 200mg q12h + AZL 5g q8h	46/80 (58)	20/34 (59)	>14 (88% of patients)	GD allowed according to protocol; number of patients not stated. Superinfection reported in 0 and 5 patients, respectively, in the CIP + AZL and GM + AZL groups	319 (mc)
GM 0.7-1.7 mg/kg q8h + AZL 5g q8h	30/67 (45)	14/29 (48)	>14 (85% of patients)		
CIP 300mg q12h + AZL 4g q6h then CIP 750mg PO bid[b]	8/25 (32)		12 (mean)	Risk of oto- or nephrotoxicity higher with AN- versus CIP-containing regimens (8 *vs* 1 episode; p = 0.15). 52 and 79%, respectively, of patients in CIP + AZL and CAZ + AN groups received oral CIP as follow-on therapy	320 (mc)
CAZ 2g q8h + AN 7.5 mg/kg q12h	15/30 (50)		12 (mean)		
CAZ 2g q8h + AN 7.5 mg/kg q12h then CIP 750mg PO bid[b]	12/24 (50)		11 (mean)		
CIP 200mg bid + AZL 5g tid	20/37 (54)	5/10 (50)		100% of patients received GD. Isolation of 7 NET-resistant Gram-positive pathogens accounted for low response rate (16%) for NET + AZL in documented infections	321
NET 1.7-2.5 mg/kg q8h + AZL 5g tid	13/36 (36)	2/12 (16)			
CIP 200mg q12h + NET 2.3 mg/kg q8h[b]	68/115 (59)	23/47 (49)	8 (median)	GD used in 6 BMT patients. In patients with Gram-negative bacteraemia, response rates were higher in the CIP group [9/11 (82%) *vs* 3/7 (43%)]	322
PIP 4g q6h + NET 2.3 mg/kg q8h	61/99 (62)	20/42 (48)	7 (median)		
CIP 200mg q12h + TEC 400mg q12h × 1 day then 400-600 mg od	23/38 (61)*	14/23 (61)*	9 (mean)	100% of patients received GD. Gram-positive bacteria accounted for 78% of bacterial isolates in documented infections. Higher clinical response rate observed in CIP + TEC *vs* PIP + GM recipients with *Staphyloccocus epidermidis* infections [10/12 (83%) *vs* 2/8 (25%); p < 0.05]	323
PIP 4g q6h + GM 120mg × 1 dose then 80mg q8h	15/35 (43)	5/17 (29)	9 (mean)		

Table VII. Contd

Drug regimen	Clinical response with initial regimen,[a] no. of patients (%)		Duration of neutropenia (days)	Comments	Reference (study design)
	all episodes	microbiologically documented episodes			
CIP 200mg q12h + P 1.2g q6h	23/51 (46)	15/36 (42)	Not available	100% of patients received GD. *S. epidermidis* was the most commonly isolated pathogen [21/56 isolates (38%)]. A higher incidence of therapy-related adverse effects reported in PIP + NET recipients (28 *vs* 10%).	324
PIP 4g q6h + NET 2 mg/kg q8h	24/46 (52)	16/34 (47)	Not available		

a Defined as neutropenic episode in which the patient survived and became free of all signs and symptoms of infection, without modification of original regimen.

b If a favourable clinical/bacteriological response was observed after 72h, oral ciprofloxacin 750mg twice daily could be initiated in patients able to take oral medications.

Abbreviations and symbols: AN = amikacin; AZL = azlocillin; bid = twice daily; BMT = bone marrow transplant; CAZ = ceftazidime; GD = gut decontamination; GM = gentamicin; mc = multicentre; NET = netilmicin; P = benzylpenicillin (penicillin G); od = once daily; PIP = piperacillin; PO = orally; q6, 8,12h = every 6,8,12 hours; TEC = teicoplanin; tid = 3 times daily; * $p < 0.05$ *vs* comparator; ** $p < 0.01$ *vs* comparator.

Comparative data are limited, but cure rates were similar for oral ciprofloxacin (750mg twice daily) and conventional intravenous therapy with a broad spectrum cephalosporin (usually ceftazidime) or nafcillin plus an aminoglycoside (77 *vs* 79%) in 59 patients with biopsy-proven osteomyelitis.[312] Overall, *S. aureus* (25%) and *P. aeruginosa* (21%) were the most commonly isolated pathogens. In a recent study, cure rates at 2 years were similar for oral ciprofloxacin or lomefloxacin (69 *vs* 65%) in 31 patients with acute or chronic osteomyelitis.[313]

3.6 Infections in Febrile Neutropenic Patients

Febrile episodes in neutropenic patients represent a challenging clinical situation where patients are at risk of death because of infection and/or progression of their underlying malignancy. Historically, infections caused by Gram-negative bacteria (i.e. *E. coli*, *K. pneumoniae* and *P. aeruginosa*) predominated and empirical therapy was directed towards these pathogens.[314] However, there is an increasing prevalence of infections due to Gram-positive bacteria (staphylococci and streptococci) which has been in part attributed to the increased use of indwelling intravascular catheters and the use of prophylactic regimens for selective intestinal decontamination. Therefore, empirical antimicrobial regimens vary from centre to centre, depending upon resistance patterns and changes in frequency of infecting pathogens. In addition, the infecting pathogen is often not defined (in up to 50 to 70% of cases). This, combined with the fact that there is no consensus on the optimal way by which to assess antimicrobial efficacy in febrile neutropenia, makes evaluation of empirical therapy difficult. Factors such as definition of clinical success (whether initial regimen modification is judged a treatment failure or not), type and stage of cancer, type of chemotherapy, presence or absence of indwelling catheters, use or nonuse of prophylactic antimicrobial regimens and duration of neutropenia are important considerations when evaluating study results.[314]

3.6.1 Treatment

Ciprofloxacin monotherapy and combination therapy have been evaluated as empirical treatment of febrile episodes in neutropenic patients (table VII). In these studies, all patients had fever (criteria for most studies was an oral temperature >38.5 or >39°C on 1 occasion or >38°C on 2 or more occasions in a 12-hour period), neutropenia (polymorphonuclear leucocyte count <0.5 or $<1 \times 10^9$ cells/L or counts that were expected to fall below

these values because of antecedent therapy), and a diagnosis of a primary disease or other factors (usually chemotherapy) leading to neutropenia.[314] All drugs were administered intravenously except in a few studies in which the protocol allowed switching to oral ciprofloxacin in appropriate patients (generally ≥72 hours of intravenous ciprofloxacin in patients with a good clinical response who were able to take oral medications). This change was feasible in approximately 50% of patients in applicable studies.[320,322] Because of the difficulties encountered in interpretation of efficacy data for empirical regimens which have been modified, clinical response has been defined as success without modification of the initial regimen in this review.

The results from studies which compared ciprofloxacin monotherapy with ceftazidime monotherapy or with combination therapy (piperacillin plus amikacin or azlocillin plus netilmicin) suggest that this approach may not provide adequate coverage for Gram-positive organisms in febrile neutropenic patients. Ciprofloxacin was significantly less effective than ceftazidime[316] and piperacillin plus amikacin[317] in both total and microbiologically documented episodes (table VII); these differences appeared to result from poorer efficacy of ciprofloxacin in patients with Gram-positive bacteraemia. Indeed, one study was discontinued prematurely because of the statistically significantly lower response rate with ciprofloxacin monotherapy (65 *vs* 91%; $p = 0.002$).[317] It is worth noting that the percentage of positive responses obtained with ciprofloxacin (65%) was not different from the expected response rates for both regimens used in the pre-trial statistical calculations.[317] In addition, the 91% response rate in piperacillin plus amikacin recipients appears to be markedly higher than rates reported in other comparative trials which evaluated this combination (44 to 53%)[325-327] or piperacillin plus an aminoglycoside (33 to 62%);[322,323,328,329] therefore, the possibility of a type I statistical error should be considered. The low ciprofloxacin dosage (200mg twice daily) used in these monotherapy studies may also have contributed to the overall disappointing response rates.

Studies which assessed ciprofloxacin as part of a combination regimen are also outlined in table VII. The addition of an agent with activity against Gram-positive bacteria markedly lowered the rate of ciprofloxacin treatment failures against these pathogens. This point was illustrated in a study by Kelsey et al.[323] in which Gram-positive bacteria accounted for 78% of isolates in bacteriologically documented infections; clinical response rates with ciprofloxacin plus teicoplanin were significantly higher than those observed with piperacillin plus gentamicin, both overall (61 *vs* 43%; $p < 0.05$) and in patients with *S. epidermidis* infections (83 *vs* 25%; $p < 0.05$). In addition, preliminary results from a study comparing ciprofloxacin with ceftazidime (with teicoplanin added if catheter-related infection was suspected) showed a higher incidence of Gram-positive bacterial superinfections with ciprofloxacin monotherapy than with ciprofloxacin plus teicoplanin.[330]

Results from an outpatient study which compared 8-hourly oral ciprofloxacin 750mg plus clindamycin 600mg with 8-hourly intravenous aztreonam 2g plus clindamycin 600mg in low-risk neutropenic patients (those without comorbidity requiring hospitalisation) are encouraging.[331] Clinical cure rates were similar in both groups (88 *vs* 95%) and the cost of the oral regimen was markedly lower than that calculated for the intravenous regimen [median $US2302 *vs* $US7336 (cost year not stated); $p < 0.0001$]; however, a higher than expected incidence of renal toxicity in the oral group (acute renal failure in 4 of 43 episodes) necessitated early discontinuation of the study.

Similar response rates (and no nephrotoxicity) were observed in patients who received the same intravenous regimen described above or oral ciprofloxacin (500mg 3 times daily) plus amoxicillin-clavulanic acid (90 *vs* 87%).[332] In addition, results from a recent study in low-risk neutropenic patients showed similar clinical response rates (95 *vs* 94%; $n = 103$ febrile episodes) for an oral regimen of ciprofloxacin (750mg twice daily) plus

phenoxymethylpenicillin (1 million units 4 times daily) compared with an intravenous regimen of carbenicillin (500 mg/kg/day) or ceftazidime (100 mg/kg/day) plus amikacin (15 mg/kg/day).[333] No clinically significant adverse events were reported in this trial and the median cost of therapy (excluding labour costs and laboratory fees) per patient was markedly higher for the intravenous compared with the oral regimen ($US704 *vs* $US116; cost year not stated).

3.6.2 Prophylaxis

The use of prophylactic oral antimicrobials to reduce the incidence of proven infection in patients with neutropenia has become standard practice in a number of centres (see review by Del Favero and Menichetti[334]). Oral cotrimoxazole (with or without nonabsorbable antimicrobials) has been shown to reduce the incidence of Gram-negative infections. Major drawbacks with this agent include frequent adverse effects, prolongation of neutropenia and emergence of resistant bacterial strains. Because of their broad spectrum of antimicrobial activity and pharmacokinetic properties, fluoroquinolones have been evaluated as prophylactic agents for antimicrobial prophylaxis in neutropenic patients. Indeed, a recent meta-analysis of 2027 patients suggested that fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin and pefloxacin) alone were more effective than control groups (cotrimoxazole, oral nonabsorbable antimicrobials and placebo) in preventing overall microbiologically documented infections, Gram-negative bacteraemia and febrile mortality, but not Gram-positive bacteraemia.[335] Addition of agents with better Gram-positive activity (e.g. penicillins, vancomycin or macrolides) significantly reduced Gram-positive bacteraemia.

Oral ciprofloxacin, used for prophylaxis against infections caused by Gram-negative bacteria, was significantly more effective than placebo in patients undergoing bone marrow transplantation (BMT),[336] and was as effective as cotrimoxazole plus colistin in patients with acute leukaemia[337-339] or in those undergoing BMT.[340] Ciprofloxacin was also better tolerated (fewer withdrawals because of adverse events) than cotrimoxazole[337-340] and produced a significantly lower incidence of *C. difficile* enterocolitis in one study (0 *vs* 10 patients; p = 0.001).[340] In another study, ciprofloxacin recipients (n = 117) had fewer cases of bacteraemia caused by Gram-negative bacteria; however, cotrimoxazole recipients (n = 113) had significantly fewer infective complications of any kind, a lower mean number of infective events and a slower overall onset of fever than ciprofloxacin recipients.[341]

In comparative studies with other fluoroquinolones, ciprofloxacin was more effective than norfloxacin,[342] ofloxacin[343] or pefloxacin[343] in reducing the incidence of infections caused by Gram-negative bacteria. Despite the potential advantages offered by ciprofloxacin compared with other regimens in general, potential problems associated with increased bacterial resistance, limitation of future use as empirical therapy in patients who have already received prophylaxis with a fluoroquinolone and the increasing prevalence of Gram-positive infections warrant consideration. Recent reports of the emergence of fluoroquinolone-resistant *E. coli* in patients with cancer and neutropenia from a number of patients in European centres who received fluoroquinolone prophylaxis suggest the need to reassess the benefits and risks of prophylaxis with this drug class (section 1.1.1). However, in a recent editorial, Ball[344] suggested that patients in countries where community resistance is not a problem should continue to derive the benefits of fluoroquinolone prophylaxis until epidemiological evidence indicates otherwise.

3.7 Intra-Abdominal and Gynaecological Infections

3.7.1 Peritonitis Associated with Peritoneal Dialysis

Peritonitis is a frequent and serious complication of long term peritoneal dialysis. Commonly isolated organisms in this infection include *S. epidermidis* (45%), *S. aureus* (14%), Enterobacteriaceae (10%) and *P. aeruginosa* (5%).[345] An intraperitoneal regimen of vancomycin plus an aminoglycoside is generally recommended as ini-

tial therapy, with modification once microbiological culture results become available. Oral and intraperitoneal ciprofloxacin has been evaluated in the treatment of peritonitis associated with CAPD in a few noncomparative studies, and in comparative studies with standard therapy.

In noncomparative studies, clinical cure (defined as the absence of symptoms of peritonitis and clear dialysate effluent) rates ranged from 75 to 83% of episodes following treatment with intraperitoneal ciprofloxacin (25 or 50 mg/L in each bag of dialysate for 5 or 7 days).[346-348] Not surprisingly, cure rates (clinical and microbiological) were higher in Gram-negative (19 of 20; 95%) than in Gram-positive infections (39 of 58; 67%).[348] A cure rate of 83% (n = 115 episodes) was reported in a study which used a sequential intraperitoneal (50 mg/L in each bag of dialysate for 5 days) and oral (500mg orally 3 times daily for 10 days) ciprofloxacin regimen.[349]

Results for orally administered ciprofloxacin in CAPD peritonitis are inconclusive; clinical cure was reported in 25 of 33 episodes (76%) at a dosage of 750 to 2000 mg/day for 8 to 16 days[350] and in 1 of 10 patients (10%) at a dosage of 500 to 750mg twice daily for 10 days.[351] The authors of the latter study suggested that the wide interpatient variations in ciprofloxacin concentrations and impaired activity of the drug in dialysate fluid may have been responsible for the poor results in this study.[351]

Compared with intraperitoneal ciprofloxacin (200mg intraperitoneal loading dose then 25 mg/L in each bag of dialysate for 10 days), oral ciprofloxacin (750mg twice daily for 10 days) produced lower cure rates (67 *vs* 42%; 24 episodes in each group).[352] Resistant Gram-positive bacterial infections accounted for about half of the treatment failures/relapses in this study. Other reports suggest that the use of ciprofloxacin in the treatment of CAPD peritonitis has resulted in the emergence and spread of ciprofloxacin-resistant coagulase-negative staphylococci.[150,154]

A high cure rate (94%) has been reported with single-dose intraperitoneal vancomycin (30 mg/kg with a 6-hour dwell time) followed by initiation of oral ciprofloxacin 750mg every 12 hours.[353] In this study, ciprofloxacin was continued for 10 days only in patients with culture-negative or Gram-negative infections (n = 16); however, it was unclear from the study results whether the remaining patients received single or multiple doses of ciprofloxacin while awaiting culture results.

In comparative studies, oral ciprofloxacin 1 to 2 g/day in 2 to 4 divided doses was as effective as intraperitoneal regimens of vancomycin plus gentamicin (45 *vs* 65%; p = 0.17)[354] or vancomycin plus netilmicin (76 *vs* 72%).[355] Although the difference in cure rates between the regimens in the former study was not significant, ciprofloxacin was less effective than the standard regimen against Gram-positive infections (31 *vs* 60%), particularly those caused by coagulase-negative staphylococci (14 *vs* 100%). Ten days' therapy with intraperitoneal ciprofloxacin (20 mg/L in each dialysate bag) was as effective as standard therapy (intraperitoneal vancomycin plus gentamicin) [cure rates 95 *vs* 80%].[356] The authors of this trial suggested that, because high ciprofloxacin dosages are needed to achieve acceptable drug concentrations in the peritoneal cavity and there is wide interpatient variation in these concentrations, intraperitoneal ciprofloxacin administration may be preferred over oral administration.

3.7.2 Intra-Abdominal Infections

Intra-abdominal infections are nearly always polymicrobial in nature, involving both aerobic and anaerobic organisms that colonise the gastrointestinal tract.[357] Standard antimicrobial regimens include combination therapy with an aminoglycoside plus an antianaerobic agent (e.g. metronidazole or clindamycin) or monotherapy with an agent with a broad spectrum of activity which includes activity against anaerobes (e.g. imipenem-cilastatin).

Rates of cure/improvement at 5 days were similar for ciprofloxacin plus metronidazole and amoxicillin-clavulanic acid plus metronidazole (97 *vs* 90%) in 78 patients with established intra-abdominal infection (following a surgical proce-

dure in approximately two-thirds of patients).[358] Ciprofloxacin plus metronidazole was more effective than cefotaxime plus gentamicin and metronidazole in 79 post-surgical patients with intra-abdominal infection (cure/improvement rates were 77 *vs* 57%; $p < 0.05$).[359]

Results from a recent double-blind multicentre trial in 691 patients with intra-abdominal infections (330 of whom were valid for efficacy assessment) suggest that ciprofloxacin plus metronidazole is therapeutically equivalent to imipenem/cilastatin.[360] In this study, patients with sufficient clinical improvement, based on APACHE II scores and ability to tolerate oral feeding, were eligible for blinded conversion to active or placebo oral therapy with continued intravenous placebo or active treatment. No significant differences in clinical success rates were noted between intravenous ciprofloxacin plus metronidazole (93 of 111; 84%), sequential intravenous and oral ciprofloxacin plus metronidazole (91 of 106; 86%) or imipenem-cilastatin recipients (91 of 113; 81%).

Clinical cure/improvement with sequential intravenous (200mg every 12 hours) and oral ciprofloxacin (750mg every 12 hours) was observed in 28 of 32 (88%) patients with acute biliary tract infections (cholecystitis, cholangitis or both).[361] In a comparative study in 90 patients with acute suppurative cholangitis, rates of clinical cure were similar for intravenous ciprofloxacin (200mg every 12 hours) and combination therapy with ceftazidime (1g twice daily), ampicillin (500mg 4 times daily) and metronidazole (500mg 3 times daily) [85 *vs* 77%].[362] The mean durations of fever (1.7 *vs* 2.4 days) and hospitalisation (6.6 *vs* 7.7 days) were both significantly ($p < 0.05$) shorter in the ciprofloxacin group.

3.7.3 Gynaecological Infections

Empirical antimicrobial treatment regimens of acute pelvic infections in women should include drugs with activity against resident anaerobic and aerobic bacterial flora of the lower genital tract as well as activity against nonresident pathogens such as *N. gonorrhoeae* and *C. trachomatis*.[363,364] Sequential intravenous and oral ciprofloxacin monotherapy has been compared with standard combination regimens in a small number of trials in women hospitalised with acute pelvic infections, mostly pelvic inflammatory disease (PID) or endometritis.

In studies with 40 to 70 evaluable women with acute PID, clinical cure rates for ciprofloxacin (range 94 to 97%) were similar to those achieved with clindamycin plus gentamicin (95 and 97%)[365,366] or cefoxitin plus doxycycline (87%),[367] and slightly higher than those obtained with metronidazole plus doxycycline (70%).[368] In one study, a significantly lower percentage of post-treatment cultures were negative in ciprofloxacin- than clindamycin plus gentamicin-treated patients (14 *vs* 42%; $p < 0.02$); anaerobes accounted for the majority of microbiological failures in the ciprofloxacin group.[366]

In two studies in women with postpartum endometritis (≈95 evaluable patients in each study), no significant differences in cure rates were noted between ciprofloxacin and clindamycin plus gentamicin recipients (85 *vs* 74%[369] and 71 *vs* 85%[370]). Anaerobic pathogens and *E. faecalis* accounted for the majority of treatment failures in the ciprofloxacin-treated patients in these studies. Accordingly, some investigators suggested that ciprofloxacin monotherapy may not be suitable in these infections and recommended the addition of an antimicrobial agent with antianaerobic coverage (e.g. clindamycin or metronidazole).[366,370]

3.8 Bacteraemia/Septicaemia

Data concerning non-neutropenic patients are limited, but clinical and bacteriological cure rates from noncomparative trials consistently exceeded 90% with intravenous or sequential intravenous and oral ciprofloxacin in the treatment of Gram-negative bacteraemia/septicaemia.[371-374] In a recent comparative trial in 234 patients with sepsis, sequential ciprofloxacin (400mg intravenously every 12 hours for 3 to 5 days then 500mg orally every 12 hours for a total of 7 to 20 days) was more effective than parenteral cefotaxime (1g intravenously or intramuscularly every 6 hours for 7 to

20 days) as measured by clinical outcome (95 *vs* 87% patients cured; p = 0.036).[375] A similar number of Gram-positive (n = 129) and Gram-negative (n = 119) pathogens were isolated at baseline; the most common sources of infection were pulmonary (34%), urinary (32%) and gastrointestinal (9%).

3.9 Surgical Prophylaxis

Ciprofloxacin has been evaluated in a number of procedures requiring preoperative antibacterial prophylaxis. As reported in the previous review, oral ciprofloxacin significantly reduced postoperative bacteriuria in patients undergoing transurethral resection of the prostate or urethrotomy.[1] Subsequently, studies have shown intravenous ciprofloxacin 300mg[376-378] and oral ciprofloxacin 500mg[379] to be as effective as cefotaxime 1g (both administered as single doses) in transurethral surgical procedures.

No differences in wound infection rates were observed between intravenous ciprofloxacin and intravenous ceftriaxone[380] or cefuroxime[381] recipients or between oral ciprofloxacin and cefuroxime[381,382] or cefazolin[383] recipients undergoing biliary tract procedures. Similarly, 1- or 2-dose regimens of intravenous ciprofloxacin (plus, respectively, 1 or 3 doses of intravenous metronidazole 500mg) were as effective as cefazolin 2g every 12 hours for 2 days plus metronidazole 500mg every 8 hours for 1 day[384] and single-dose latamoxef (moxalactam) 2g[385] as prophylaxis in colorectal surgery.

In a recent comparison of 1- and 3-day regimens of oral ciprofloxacin plus intravenous metronidazole with 1- and 3-day regimens of intravenous gentamicin plus metronidazole in patients undergoing colorectal surgery (n = 40 to 45 in each group), the overall incidence of postoperative infections (wound, respiratory tract and UTI) was significantly lower in the ciprofloxacin group (15 *vs* 43%; $p < 0.05$);[386] no significant difference was noted between 1- and 3-day regimens. The wound infection rates were similar for 1-day regimens of oral ciprofloxacin 750mg (2 doses) and intravenous cefuroxime (3 doses) in 580 patients undergoing peripheral arterial reconstructions involving the groin (9.2 *vs* 9.1%).[387]

3.10 Sexually Transmitted Diseases

3.10.1 Gonorrhoea

In previously reviewed trials (mostly noncomparative), single-dose ciprofloxacin (usually 100 to 500mg) produced bacteriological cure in 100% of males with gonococcal urethritis.[1] In a more recent review in 1180 patients who received single-dose ciprofloxacin regimens ranging from 100 to 2000mg (69% received 250mg), bacteriological eradication from all infection sites was achieved in 99.5% of patients.[388] Ciprofloxacin was as effective as standard regimens (ceftriaxone, ampicillin or amoxicillin plus probenecid and spectinomycin).[388] In the 815 patients (910 infected sites) in this review who received single-dose ciprofloxacin 250mg, bacterial eradication was observed in 563 (100%) male urethral, 101 (100%) female cervical, 101 (99%) male and female rectal and 47 (96%) male and female pharyngeal infections. No differences in cure rates were observed between ciprofloxacin and other fluoroquinolones (pefloxacin[389] and sparfloxacin[390]) in recent comparative studies.

3.10.2 Non-Gonococcal Urethritis

A review of noncomparative and comparative studies indicated that, like most other fluoroquinolones, ciprofloxacin is generally not as effective in the treatment of urethritis caused by *C. trachomatis* or *U. urealyticum*, as it is for gonococcal infections.[1] In more recent comparative studies, it was less effective than doxycycline in the treatment of *C. trachomatis* infections (cure rate 46 *vs* 75%; p = 0.04)[391] and appeared to be associated with a higher relapse rate (≈40 *vs* 0%) at 4 weeks after treatment.[392]

3.10.3 Chancroid

In the treatment of chancroid genital ulcers, clinical cure rates with single-dose ciprofloxacin 500mg have ranged from 92 to 100%.[393-397] Single-dose ciprofloxacin 500mg was more effective than single-dose cotrimoxazole 640mg/3200mg

(clinical cure rate 76 *vs* 53%; p = 0.04) in a predominantly (≈70%) HIV-positive group of patients. Treatment failure did not appear to be related to HIV status,[398] although it is generally accepted that HIV-positive patients require more prolonged treatment regimens (>5 days) for chancroid than HIV-negative patients.[399]

3.11 Infections in Children

Because of concerns over the potential for fluoroquinolone-induced cartilage damage, limited data regarding ciprofloxacin use are available in paediatric patients. Kubin[400] recently reviewed data from over 1500 paediatric patients aged <18 years, two-thirds of whom had cystic fibrosis and respiratory tract infections. Excellent or marked clinical improvement was achieved with oral ciprofloxacin in >90% of respiratory tract infections in children with cystic fibrosis. Most of the remaining patients had multiresistant typhoid fever; up to 100% were cured with ciprofloxacin. Importantly, arthralgia was infrequently documented (3.2% of 1113 patients with cystic fibrosis) and was always reversible, resolving during ciprofloxacin treatment in many cases (see section 5.3).

A recent consensus report has outlined potential indications complicated by pathological or special conditions in which the use of fluoroquinolones is justified in paediatric patients.[401] These include:

- Bronchopulmonary exacerbations in cystic fibrosis where *P. aeruginosa* is known to be present.
- Complicated urinary tract infections caused by organisms resistant to standard agents.
- Chronic suppurative otitis media (of >6 weeks' duration) in which *P. aeruginosa* has been isolated.
- Epidemic shigellosis, invasive salmonellosis and enteric infections in developing countries, particularly in areas where multidrug resistance is increasing.
- Subacute forms and/or atypical localisations of osteomyelitis in cases that require prolonged oral therapy.
- Other potential indications including prevention of meningitis due to *N. meningitidis* or *H. influenzae* b, prophylaxis in patients with neutropenia, multiresistant Gram-negative sepsis, staphylococcal central nervous system shunt infection or as part of a regimen for multiple drug-resistant mycobacterial disease.

4. Pharmacoeconomic Considerations

Treatment of serious infections generally requires hospitalisation and administration of intravenous antimicrobial agents for 5 to 10 days. Some infections (e.g. osteomyelitis, skin/skin structure infections or bacterial endocarditis) may necessitate hospital stays of up to 6 weeks, often for the sole purpose of receiving intravenous antibacterial treatment. The most costly aspect of patient care in this setting is likely to be costs associated with occupation of a hospital bed.[402] However, other costs need to be considered; these include antimicrobial drug acquisition and administration costs, monitoring costs and costs arising from adverse effects, drug interactions or treatment failure. Since antibacterials often account for a large proportion of hospital pharmacy drug budgets, this therapeutic class is often the target of intense scrutiny, formulary restrictions and/or cost containment measures.

The availability of a number of new and potent oral antimicrobials, including ciprofloxacin, has led to reassessment of the need for parenteral therapy for many infections. In an attempt to reduce overall healthcare costs in patients with serious infections, it is increasingly common for institutions to utilise antimicrobial streamlining or intravenous-to-oral conversion programmes. In these programmes, patients generally receive initial empirical antimicrobial therapy (often combination therapy) and reduction of the number of parenteral antimicrobial drugs or conversion to oral therapy is attempted once the causative pathogen has been identified and the clinical condition has improved (usually after ≈3 days of parenteral therapy).[403-405] The potential economic advantages of converting

from parenteral to oral antimicrobial therapy include:[406,407]

- Generally lower acquisition cost of the oral agent.
- Minimal expertise required for administration.
- Reduced nursing/pharmacy time required for preparation and administration of drugs.
- Avoided costs associated with parenteral delivery.
- Avoidance of parenteral drug wastage and generation of potentially hazardous waste.
- Improved patient mobility/independence/comfort.
- Reduced potential for venous complications (e.g. phlebitis or line infection).
- Reduced duration or avoidance of hospitalisation.

The pharmacoeconomics of oral ciprofloxacin have been reviewed by Balfour and Faulds.[406] When used as sequential therapy, ciprofloxacin reduced antibacterial drug costs by approximately 45% compared with parenteral therapy in two US prospective randomised trials[408,409] and reduced hospitalisation costs by 20%.[408] Cost savings associated with oral ciprofloxacin were based on the costs which would have been incurred if patients had continued to receive parenteral therapy. In addition, initial treatment with oral ciprofloxacin (750mg twice daily) was less costly (≈80%) than intravenous cefamandole 1g 4 times daily in the treatment of elderly institutionalised patients with lower respiratory tract infections.[410]

More recently, retrospective cost analyses have been applied to prospective clinical trials of intravenous ciprofloxacin in patients with pneumonia. Ciprofloxacin (400mg every 12 hours) was less costly than ceftazidime (2g every 8 hours) in patients with nosocomial pneumonia; the incremental costs of ceftazidime per patient or per day were $US516 and $US58, respectively.[411] Increasing the ciprofloxacin dosage to 400mg every 8 hours or decreasing the ceftazidime dosage to 1g every 8 hours produced daily costs similar to those of ceftazidime 2g every 8 hours and ciprofloxacin 400mg every 12 hours.

Treatment with ciprofloxacin 400mg every 8 hours was 40% less costly than initial treatment with imipenem-cilastatin 1g every 8 hours in a randomised double-blind multicentre study in patients hospitalised with severe pneumonia.[412] This difference was largely due to lower drug acquisition costs for ciprofloxacin. Further evaluation of subsequent infections requiring post-treatment antimicrobials from one centre in this study showed that ciprofloxacin-treated patients (n = 14) had fewer post-treatment days in hospital (398 *vs* 532 days), and lower costs associated with post-treatment antimicrobials ($US744 *vs* $US3386) and hospitalisation (estimated $US636 800 *vs* $US851 200) than imipenem-cilastatin–treated patients.[413]

Since costs associated with hospitalisation are likely to represent the largest portion of antimicrobial treatment costs, it is apparent that early discharge of appropriately selected patients would reduce overall treatment costs. Ciprofloxacin, with its broad spectrum of activity and favourable pharmacokinetic profile, permits oral treatment of some infections which would otherwise require parenteral therapy.[406] Accordingly, a number of investigators have shown cost savings with oral ciprofloxacin in hospitalised patients, based on the assumption that the more expensive parenteral regimen would have continued had oral ciprofloxacin not been available.[414-422] For instance, Grasela et al.[418] estimated that 2 to 3 days of hospitalisation were saved in patients with urinary tract, respiratory tract, skin/skin structure, or other infections, and 20 days in those with bone and joint infections. It is important to note that, because of the number of confounding factors associated with discharging patients from hospital (e.g. concurrent illnesses which need further treatment after resolution of infection or situations in which patients are unable to care for themselves at home and are awaiting placement in other facilities), cost savings in these studies may be overestimated.

Many of these cost-avoidance studies were performed in institutions with established antibacterial monitoring programmes which rely upon

clinical pharmacists to perform routine drug monitoring. It has been suggested that these savings, based primarily in the hospital setting, are more reflective of advancement of rational antimicrobial prescribing by clinical pharmacists, rather than of savings from the use of any single antimicrobial agent.[423]

5. Tolerability

5.1 Oral Administration

Results from large (>8800 patients) studies summarising premarketing (phase II/III) and postmarketing (phase IV) adverse event data confirm the generally good tolerability of oral ciprofloxacin. Patients from phase II/III studies received oral ciprofloxacin dosages of ≤500 (34%), 600 (25%), 750 to 1000 (26%) and >1000 (15%) mg/day.[424] The 600 mg/day dosage was used mostly in Japanese patients, whereas the 1000 mg/day dosage was used mostly in patients from the US or Europe. In two phase IV studies, ciprofloxacin 500 and 1000 mg/day were the most commonly administered dosages (administered to 45 and 42% of patients, respectively, in one study,[425] and 58 and 29%, respectively, in the other[426]). Overall, approximately 90% of patients received ciprofloxacin in dosages ≤1000 mg/day and approximately three-quarters of these were treated for a duration of ≤10 days.

Treatment-related adverse events with oral ciprofloxacin were reported in approximately 9% of patients.[424,426] Treatment was discontinued because of adverse events in 1.5% of 9473 patients from phase II/III clinical trials. The most commonly reported adverse events were gastrointestinal disturbances (mostly nausea, diarrhoea, vomiting, dyspepsia, anorexia or abdominal pain); CNS (mostly dizziness, headache, restlessness or tremors) or dermatological (mostly rash or pruritus) events were less common (fig. 3). Serious adverse events occur infrequently with ciprofloxacin and were reported in <1% of patients in the abovementioned studies.

The results from 2 more recent studies largely confirm the good tolerability of ciprofloxacin as outlined above. A large US study which followed 37 233 patients for 45 days after receiving a prescription for ciprofloxacin reported that 393 patients had a recorded diagnosis of a serious drug-induced illness, 29 in which a causal connection with ciprofloxacin could not be confidently ruled out.[427] There were only 7 patients in whom a causal relationship between the reaction and the drug seemed likely; 3 with skin reactions and 1 patient each with thrombocytopenia, headache, nausea and shakes, and hallucinations and palpitations. No life-threatening events (e.g. haemolytic anaemia or anaphylaxis) were attributable to the drug and all patients recovered after drug discontinuation. Furthermore, in a review of fluoroquinolone tolerability that included an analysis of 63 059 oral ciprofloxacin recipients worldwide, the incidences of gastrointestinal, CNS and dermatological adverse drug reactions were 3.4, 1.1 and 0.7%, respectively.[428]

Because of the rigorous protocols employed in phase II/III clinical trials, a higher incidence of adverse events might be expected in these trials than in postmarketing studies. However, the types and incidences of adverse events were similar in patients in phase II/III and phase IV studies (fig. 3).

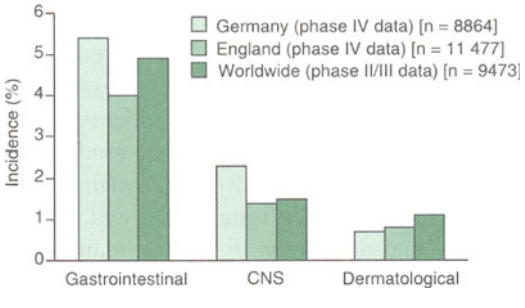

Fig. 3. Overview of commonly reported adverse events with oral ciprofloxacin. Incidence of commonly reported adverse events from worldwide phase II/III clinical trials,[426] and from postmarketing (phase IV) studies conducted in Germany[428] and England.[427] Approximately 90% of patients received ciprofloxacin in dosages ≤1000 mg/day; approximately three-quarters of these were treated for a duration of ≤10 days.

Following the withdrawal of temafloxacin because of a number of serious adverse events (a multisystem syndrome consisting of hypoglycaemia, haemolytic anaemia, renal failure coagulation defects and sensitivity reactions), there has been concern regarding the possibility of such effects occurring with other fluoroquinolones. However, careful examination of adverse event data revealed no evidence of a similar syndrome occurring with ciprofloxacin.[429]

No significant differences in the types and incidences of adverse events have been noted between elderly (>65 years) and younger patients.[157,430,431] Ciprofloxacin is rarely associated with phototoxicity (0.04% of 9473 patients in clinical trials).[424]

Data from comparative clinical trials suggest that oral ciprofloxacin is at least as well tolerated as other commonly used oral antimicrobials, including cotrimoxazole, amoxicillin, ampicillin, doxycycline, cephalosporins[424,430,432,433] and other fluoroquinolones.[201-203,229,231,432,434]

5.2 Intravenous Administration

With the exception of local reactions at the site of administration, the tolerability profile of intravenous or sequential intravenous and oral ciprofloxacin appears similar to that of oral ciprofloxacin. In a recent review of pooled data from over 20 000 intravenous ciprofloxacin recipients, drug-related adverse events were reported in 11.8% of 5010 patients in clinical trials and 4.5% of 16 759 patients in postmarketing surveillance studies.[435] The most commonly administered dosage was 200mg twice daily (52 and 75% of patients in clinical and postmarketing surveillance studies, respectively); gastrointestinal effects (mainly nausea, diarrhoea or vomiting) [4.8 and 2.3%], metabolic and nutritional disorders (mainly elevated liver enzyme values) [2.7 and 1.0%] and dermatological reactions (mainly rash and pruritus) [2.5 and 0.8%] were the most frequently reported adverse events in these studies. In clinical trials, the incidence of these reactions was slightly higher in patients who received 400mg twice daily (8.3, 4.1 and 3.9%, respectively) than in those treated with 200mg twice daily (4.6, 3.0 and 2.4%, respectively). Injection site reactions were reported in 1% of 5010 clinical trial patients.

Therapy was discontinued in 1.8 and 3.2% of patients in postmarketing surveillance studies and clinical trials, respectively.[435] No dose dependency for the incidence of treatment discontinuation was demonstrated. Indeed, only 0.6% of 346 patients who received ciprofloxacin ≥800 mg/day discontinued treatment as a result of adverse events in postmarketing surveillance studies.

Pooled tolerability data are also available from 36 trials comparing intravenous ciprofloxacin (mean 400 mg/day) with ceftazidime (mean 3 g/day).[433] 430 patients received sequential intravenous and oral ciprofloxacin and 140 ceftazidime recipients received oral antimicrobials other than ciprofloxacin following intravenous treatment. No significant difference in the overall incidence of adverse events was noted between ciprofloxacin and ceftazidime recipients (17.3 *vs* 13.6% of patients). The ciprofloxacin group experienced a slightly higher incidence of local/intravenous site (5.6 *vs* 2.7% of patients) and CNS (2.2 *vs* 0.7% of patients) adverse events. Overall, both drugs were well tolerated.

In a recent study, the incidence of adverse events was similar for intravenous ciprofloxacin (400mg every 8 hours) and imipenem-cilastatin (1g every 8 hours) recipients with severe pneumonia (20 *vs* 23%); however, a significantly higher incidence of seizures was reported in the imipenem-cilastatin group (1 *vs* 6%; $p = 0.028$).[219] In addition, ciprofloxacin-based regimens were generally better tolerated than aminoglycoside-containing regimens in febrile neutropenic patients.[320,324]

5.3 Tolerability in Children/Adolescents

The use of fluoroquinolones in patients <18 years old has been restricted because of reports of joint toxicity with these agents in experimental animals. However, in children treated under compassionate use protocols, no unequivocally documented case of fluoroquinolone-induced cartilage toxicity has been recorded.[436]

Accumulated data in >1500 paediatric patients (two-thirds of whom were cystic fibrosis patients with respiratory tract infections) suggest that ciprofloxacin has a similar tolerability profile in children/adolescents and adults.[400] Adverse events were reported in 5 to 15% of patients, with gastrointestinal, dermatological and CNS effects being the most commonly reported; reversible arthralgia was reported in 36 of 1113 (3.2%) patients. Although this rate exceeds that reported in 9473 adults in clinical trials (0.06%),[424] it should be noted that 7 to 8% of patients with cystic fibrosis experience arthropathy which is unrelated to drug therapy.[437] Nuclear magnetic resonance imaging and radiological studies revealed no evidence of joint damage.[400]

Results from a recent study which evaluated the tolerability of ciprofloxacin in 58 children aged 8 months to 13 years with typhoid fever support these findings.[438] No evidence of cartilage damage in nuclear magnetic resonance studies or significant alterations in linear growth was noted during a follow-up period of 19 to 37 months; however, increased serum fluoride levels and urinary fluoride excretion observed following ciprofloxacin therapy in this study warrant further review.

In Vietnamese children aged 1 to 14 years, no evidence of acute joint toxicity or decreased growth velocity was noted with either ciprofloxacin or ofloxacin (3- to 7-day course for typhoid fever) over a 2-year follow-up period.[439] Ciprofloxacin (10 mg/kg orally twice daily for 10 days beginning a week prior to bone marrow transplantation then 7.5 mg/kg intravenously twice daily until the absolute neutrophil count was ≥500 cells/μl) was well tolerated in children (median age 11 years) undergoing bone marrow transplantation; knee effusion and joint pain that resolved without discontinuation was reported in 1 of 23 ciprofloxacin-treated children.

5.4 Effects on Laboratory Parameters

Clinically relevant changes in laboratory parameters occur infrequently with ciprofloxacin treatment. Metabolic or nutritional disorders were reported in 4.4% of 9473 oral ciprofloxacin recipients participating in worldwide controlled clinical trials.[424] Alterations mostly consisted of elevations in serum glutamic oxaloacetic transaminase and/or glutamic pyruvic transaminase levels (incidence of ≈1.5% each); these changes were asymptomatic and no irreversible hepatotoxicity was reported. Changes in renal function were rare, with an incidence of 0.25% for both elevated serum creatinine and elevated blood urea nitrogen levels. The incidence of changes in laboratory parameters was slightly higher in intravenous ciprofloxacin recipients [146 events in 1869 patients (7.8%)]; these alterations also appeared to be of no significant clinical consequence. As stated previously, the slightly higher incidence of adverse events in these patients was probably reflective of their overall poorer health status compared with oral ciprofloxacin recipients.

6. Drug Interactions

Clinically relevant drug interactions involving ciprofloxacin are well documented; the two best-known interactions involve xanthine derivatives and multivalent cations (table VIII). Ciprofloxacin reduces xanthine metabolism and can substantially increase serum concentrations of these substances if coadministered; therefore, monitoring of serum theophylline concentrations is generally warranted with concomitant ciprofloxacin administration. Ciprofloxacin bioavailability is reduced with concurrent administration of multivalent cation-containing preparations (e.g. antacids and supplements containing calcium, iron or zinc). The mean bioavailability of ciprofloxacin was reduced by 53 and 67%, respectively, in hospitalised patients receiving continuous enteral feedings via gastrostomy and jejunostomy tubes.[492] It is recommended that ciprofloxacin should be administered at least 2 hours before or 6 hours after administration of multivalent cation-containing preparations;[466] however, because of interpatient variation in gastric emptying and other uncontrollable variables (e.g. patient compliance), it is probably

Table VIII. Overview of drug interactions with ciprofloxacin (reviewed by Polk,[441] Lomaestro & Baile,[442] and Deppermann & Lode[443])

Drug	Effect	Mechanism	Management
Methylxanthines			
Theophylline[440,443-453]	Increased plasma theophylline concentrations (up to 308%) with possible theophylline toxicity (nausea, vomiting, palpitations, seizures)	Inhibition of cytochrome P450 isoenzyme responsible for metabolism of theophylline	Monitor serum theophylline concentrations when ciprofloxacin is added to treatment, particularly in elderly patients
Caffeine[454-458]	Increased plasma caffeine concentrations; clinically significant adverse effects (nervousness, insomnia) are unlikely unless patient consumes very large quantities of caffeine	Inhibition of cytochrome P450 isoenzyme responsible for metabolism of caffeine	Restrict caffeine intake if excessive
Multivalent cation-containing preparations			
Aluminium- or magnesium-containing antacids[440-442,459-465] Sucralfate[440-442,459,461,463,467-471] Calcium[440-442,460,461,463,472-474] and calcium-rich foods[441,475-477] Iron[440-442,461,463,478-484] Zinc[440,441,461,463,478] Enteral nutrition products[441,485-492] Didanosine[441,493,494]	Reduced ciprofloxacin absorption (up to 99%) which could result in treatment failure	Chelation between metal cations and ciprofloxacin	Avoid concurrent administration if possible or administer ciprofloxacin at least 2h before or 6h after ingestion of metal cation-containing preparations.[467] However, interpatient variability in gastric emptying should be considered. Concurrent administration of enteral nutritional supplements and ingestion of large quantities of dairy products should also be avoided
Warfarin[495-500]	Increased hypoprothrombinaemic effect of warfarin has been reported in a few patients but not substantiated in other studies	Decreased metabolism of warfarin	Monitor prothrombin times or other suitable coagulation tests, particularly in elderly patients with underlying illnesses
Phenytoin[501-504]	Increased or decreased plasma phenytoin concentrations have been reported in a few patients	Inhibition of cytochrome P450 isoenzyme responsible for metabolism of phenytoin (not established)	Monitor phenytoin levels with concurrent ciprofloxacin use
Cyclosporin[505-511]	Transient elevation in serum creatinine levels reported in a few patients but not substantiated in other studies	Unknown	No additional cyclosporin monitoring necessary

best to avoid concurrent administration of multivalent cations with ciprofloxacin whenever possible (table VIII).

In rare instances, ciprofloxacin has been reported to interact with phenytoin, leading to altered levels of serum phenytoin concentrations (table VIII).[466] The concomitant administration of ciprofloxacin with the sulphonylurea glibenclamide (glyburide) has on rare occasions resulted in severe hypoglycemia.[466]

A survey of over 6500 patients treated with ciprofloxacin in clinical practice suggested that interactions with other medications are infrequently encountered.[512] However, results from a recent drug use evaluation of inpatients at a 640-bed hospital indicate otherwise.[513] About one-fifth of patients who received a new medication order for ciprofloxacin also received, concurrently or within 2 hours, at least one medication known to chelate ciprofloxacin, and one-third of patients

had standing orders for a drug known to chelate ciprofloxacin when the order was written. It is likely that this problem is at least as prevalent in outpatient settings.

7. Dosage and Administration

Both oral and intravenous ciprofloxacin are normally administered in a twice-daily regimen. Dosage should be individualised on the basis of the nature and severity of the infection, the susceptibility of the causative pathogen, and the patient's immune status as well as renal and hepatic function. International dosage guidelines for approved indications are outlined in table IX. Therapy duration depends upon infection severity, but the drug is generally continued for at least 2 days after the disappearance of signs and symptoms of infection. The usual treatment duration is 7 to 14 days, although 3 to 7 days' treatment is usually sufficient for conditions such as infectious diarrhoea; bone and joint infections generally require longer treatment durations (e.g. 4 to 6 weeks or longer). Shortened regimens have also been successful in treating acute uncomplicated gonococcal urethritis (250mg single dose) or acute uncomplicated cystitis (100 or 250mg twice daily for 3 days) [see sections 3.10.1 and 3.1.1, respectively].

Because of different medical traditions, dosage recommendations for renally impaired patients may vary slightly between countries. The international dosage guidelines (data on file; Bayer) in renally impaired patients are:

- When creatinine clearance is between 31 and 60 ml/min/1.73m^2 (or when the serum creatinine level is between 1.4 and 1.9 mg/dl), the maximum daily dose of oral or intravenous ciprofloxacin is 1000 or 800mg, respectively.
- When creatinine clearance is ≤30 ml/min/1.73m^2 (or when the serum creatinine level is ≥2 mg/dl), the maximum daily dose of oral or intravenous ciprofloxacin is 500 or 400mg, respectively.

Intravenous ciprofloxacin is usually administered in dosages of 200 to 400mg every 12 hours. Each dose should be infused over 60 minutes; slow infusion of a dilute ciprofloxacin solution (final concentration 1 to 2 mg/ml) through a large vein will minimise venous irritation and patient discomfort.[466] The daily dosage has been increased up to 1200mg (in 3 divided doses) in patients with severe life-threatening infections, particularly those in whom moderately susceptible pathogens (e.g. *Pseudomonas* spp., *S. pneumoniae* or staphylococci) are suspected or in immunocompromised patients.[190,219] Indeed, although this dosage is not currently approved in the US, it is considered equivalent to 1500 mg/day (750mg twice daily) of oral ciprofloxacin.[514,515]

Table IX. Overview of international adult dosage guidelines for oral and intravenous ciprofloxacin administered as a twice-daily (every 12h) regimen; data in parentheses refer to US/Canadian dosage guidelines (data on file; Bayer)

Type of infection	Total daily dose (mg)	
	oral	intravenous
Urinary tract	250-1000	200-400 (400-800)
Respiratory tract	500-1500	400-800 (800[a])
Infectious diarrhoea	500-1000	400
Other infections	500-1500	400-800 (800[a])
Severe life-threatening infections[b]		Up to 1200

a Approved for mild to moderate infections only; however, 1200 mg/day (400mg every 8h) of intravenous ciprofloxacin would be bioequivalent to 1500 mg/day (750mg twice daily) of oral ciprofloxacin.[514,515]

b For example, pneumonia, osteomyelitis, septicaemia, peritonitis.

Ciprofloxacin is not currently approved for use in pregnant or lactating women, or in children and adolescents <18 years of age.[466] However, in paediatric patients in situations where the benefits of ciprofloxacin treatment clearly outweigh the risks, the currently recommended dosage regimens are 30 mg/kg/day (maximum 1500 mg/day) for oral administration and 20 mg/kg/day (maximum 800 mg/day) for intravenous administration, both administered on a twice-daily basis.[516] A recent study suggested slightly higher dosage regimens in paediatric patients with cystic fibrosis (section 2.4).[185]

Although photosensitivity appears to be a rare adverse event (0.04% of 9473 patients in clinical

trials),[424] it is recommended that patients avoid excessive sunlight.[466] In addition, because ciprofloxacin may cause dizziness or lightheadedness, patients should be aware of the possible effect of the drug on driving or other activities that require mental alertness.

When ciprofloxacin and theophylline are administered concurrently, serum theophylline concentrations should be monitored and dosage adjustments made as appropriate (section 6). If concurrent administration of ciprofloxacin and multivalent cation-containing preparations cannot be avoided, ciprofloxacin should be administered at least 2 hours before or 6 hours after administration of these preparations (section 6).

8. Place of Ciprofloxacin in the Treatment of Infections

Previously, Campoli-Richards et al.[1] suggested that ciprofloxacin, with its broad spectrum of antibacterial activity and good tissue penetration, together with the good clinical trial results obtained in several types of infection, offered the potential for a broad clinical application. The nearly 8 years of clinical research and experience gained with ciprofloxacin since this review have served to qualify the use of this agent in many indications.

The role of oral ciprofloxacin in the treatment of urinary tract infections, sexually transmitted diseases (gonorrhoea and chancroid), skin/skin structure and bone and joint infections, multiresistant gastrointestinal infections, Gram-negative lower respiratory tract infections (including those in patients with cystic fibrosis) and malignant external otitis is well established (see section 3). This is in part reflective of its activity against bacteria which are resistant to a wide variety of other commonly used antimicrobials such as β-lactams, tetracyclines, cotrimoxazole and macrolides. In addition, ciprofloxacin has shown good efficacy in the treatment of other infections where Gram-negative pathogens would be expected, including chronic sinusitis, chronic otitis, gallbladder infections, bacteraemia/sepsis, peritonitis associated with CAPD (administered intraperitoneally) and treatment of febrile neutropenia (combined with an agent with activity against Gram-positive bacteria) and in combination with an antianaerobic agent in the treatment of intra-abdominal and gynaecological infections (section 3). Although it is unlikely to replace traditional first-line regimens in these indications, ciprofloxacin is a reasonable alternative in patients who are intolerant of, or who do not respond to, initial treatment.

Ciprofloxacin has also been shown to be effective as oral prophylaxis in patients undergoing urological, biliary tract, colorectal and vascular surgery (section 3.9); however, more studies are needed before oral ciprofloxacin can be recommended over traditional prophylactic regimens.

Ciprofloxacin has shown good efficacy as prophylaxis in patients with neutropenia (section 3.6.2). These results must be weighed against potential problems associated with increased bacterial resistance (most notably reports from a number of European centres of fluoroquinolone-resistant *E. coli* in patients with cancer and neutropenia who received fluoroquinolone prophylaxis), limitation of future use as empirical therapy in patients who have already received prophylaxis with a fluoroquinolone and the increasing prevalence of Gram-positive infections in febrile neutropenic patients.

Intravenous ciprofloxacin is a useful therapeutic option in the treatment of serious infections (in patients unable to take oral ciprofloxacin), especially those in ICU or immunocompromised patients, or those resistant to β-lactam antimicrobials and/or aminoglycosides or in patients intolerant of these drugs. Recent evidence suggests that patients with serious life-threatening infections may require higher intravenous ciprofloxacin dosages (800 to 1200 mg/day) than those used in earlier clinical trials (400 mg/day). In the case of pseudomonal infections, clinicians need to be aware of local susceptibility patterns and to prescribe appropriate drug dosages in order to achieve therapeutic ciprofloxacin concentrations at the infection site;[190,219,514,515] combination therapy is probably warranted in serious life-threatening infections.

The extent of ciprofloxacin resistance among MRSA (section 1.1.4) suggests that the drug can no longer be recommended for treatment of these infections. In institutions where MRSA predominate, ciprofloxacin is probably not an appropriate empirical treatment choice for suspected staphylococcal infections. In addition, because of its limited activity against anaerobes, it should not be prescribed as monotherapy in infections when these pathogens are suspected.

A major issue of concern is the administration of fluoroquinolones in respiratory tract infections in which *S. pneumoniae* is a suspected pathogen. A recent review showed that ciprofloxacin has clinical and bacteriological efficacy similar to that of traditional agents in the treatment of lower respiratory tract infections, including those caused by *S. pneumoniae*.[208] Nonetheless, because of its moderate *in vitro* activity against *S. pneumoniae* (section 1.1.4) and its generally higher acquisition cost relative to phenoxymethylpenicillin, ciprofloxacin should be reserved for patients with mixed infections and those with predisposing factors for Gram-negative infections (section 3.2.1).

Oral ciprofloxacin has not replaced intravenous antimicrobials as initial empirical therapy in patients hospitalised with serious infection; nevertheless, it offers pharmacoeconomic advantages in some cases. Sequential therapy with intravenous ciprofloxacin or other parenteral antimicrobials followed by oral ciprofloxacin can be cost saving in appropriately selected patients (section 4). Additionally, in patients who would otherwise remain hospitalised to receive intravenous antimicrobials (e.g. patients with osteomyelitis or cystic fibrosis), oral ciprofloxacin offers the potential for significant cost savings in those who can be discharged early from hospital.

Extensive clinical experience and postmarketing data have confirmed the good tolerability of ciprofloxacin (see section 5). Although it is still contraindicated in patients <18 years of age, the expanding clinical experience with ciprofloxacin in paediatric patients (mostly with cystic fibrosis) suggests that the drug is effective and well tolerated in this age group with minimal arthropathic potential. In addition, the two most clinically relevant drug interactions associated with ciprofloxacin and most other fluoroquinolones (i.e. reduced metabolism of methylxanthines and decreased absorption in the presence of multivalent cations) are well known and avoidable with conscientious prescribing.

In conclusion, the initial optimism regarding fluoroquinolones has been somewhat tempered by the emergence of resistance in some settings and their variable efficacy in the treatment of serious Gram-positive infections. While newer fluoroquinolones under development appear to possess greater *in vitro* activity against Gram-positive pathogens, and therefore may be able to fill this gap left by older fluoroquinolones,[517] they rarely achieve the antipseudomonal activity of ciprofloxacin. Ciprofloxacin has retained its reliable activity against most Gram-negative bacteria, and remains an important antimicrobial in the treatment of a wide range of infections, particularly difficult-to-treat infections caused by multiresistant Gram-negative pathogens, in patients who are unable to tolerate β-lactam antimicrobials and/or aminoglycosides, or for sequential oral therapy after initial parenteral drugs. Additionally, ciprofloxacin is one of the few antibacterials effective after either intravenous or oral administration. As with any antimicrobial agent, rational use of ciprofloxacin will enable this important antibacterial to maintain its clinical usefulness.

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Errata

Vol. 49, Suppl. 2, page 262: In the third column of table I, the heading should read *Minocycline*.

[Thomas D, Orfila J, Bissac E. Evaluation of the activity of different quinolones in the experimental chlamydial salpingitis mouse model. Drugs 1995; 49 Suppl. 2: 261-3

Vol. 51, No. 3, page 466: In section 1.2.1, the last sentence should read, '24-hour period (median *99%*) . . .'.
page 467: In table I, the reference to Damann et al.[18] should read *Dammann* et al.[18].
page 468: In section 1.2.1, references 18, 19, 20 and 21 should be changed to references 19, 20, 21 and 22, respectively.
pages 468 to 469: In section 1.2.2, references 18 and 19 should be changed to references 19 and 20, respectively.
page 470: In section 1.6, reference 17 should be changed to reference 18.
page 474: In table III, columns 4 and 5 of the first two studies in the section regarding comparisons with ranitidine in patients with duodenal ulcer should read as follows:

Reference	No. of evaluable patients	Dosage (mg/day)	Cumulative ulcer healing rate (% patients)			Epigastric pain relief[a] (% patients)		Overall efficacy
			2wk	4wk	8wk	2wk	4wk	
Baccaro et al.[92]	170	P 40	*83**	*100*				P ≥ R
		R 300	*67*	*97*				
Castro et al.[93]	222	P 40	*75**	*97**				P > R
		R 300	*45*	*75*				

[Fitton A, Wiseman L. Pantoprazole: a review of its pharmacological properties and therapeutic use in acid-related disorders. Drugs 1996; 51: 460-82]