

A New Dosing Paradigm: High-Dose, Short-Course Therapy for Community-Acquired Pneumonia

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The goals of optimal antimicrobial therapy are to treat infection effectively, to improve the clinical condition of the patient, and to prevent the emergence of resistant bacterial strains. For ideal drug usage the World Health Organization recommends administering the correct drug by the best route, in the right amount, at optimum intervals for the appropriate period, and after an accurate diagnosis. This article discusses the use of high-dose, short-course fluoroquinolone therapy as an effective option for patients with community-acquired pneumonia. Clinical Cornerstone® Monograph. Copyright © 2004 Excerpta Medica, Inc.

“We know everything about antibiotics except how much to give.”— Maxwell Finland

There is limited scientific information concerning the optimal duration of therapy for most infections (1). For ideal drug usage the World Health Organization (2) recommends using the correct drug administered by the best route, in the right amount, at optimum intervals, for the appropriate period, and after an accurate diagnosis. Usual-course therapy for community-acquired pneumonia (CAP) is steered by a number of national guidelines. For example, the Infectious Diseases Society of America (3) recommends treatment of *Streptococcus pneumoniae* until the patient is afebrile for 72 hours while advocating treatment of gram-negative bacilli, *Staphylococcus aureus*, and “atypical” organisms for 2 weeks. The Canadian Infectious Disease Society and Thoracic Society (4) guidelines advise treatment

KEY POINT

High-dose, short-course regimens have the potential to reduce the emergence of antibacterial resistance in the pathogen as well as other commensal flora, both in the patient being treated and in the wider population.

for 1 to 2 weeks. The British Thoracic Society (5) guidelines advise treatment for 7 to 21 days, subject to clinical judgment. Unfortunately, as the guidelines comment, “the precise duration of treatment ... is not supported by robust evidence” (5), and authors are “not aware of controlled trials” (3) to support

their recommendations. The American Thoracic Society (6) standard is 7 to 14 days, but with the appropriate agents the duration of treatment may be shortened to 5 to 7 days for outpatients.

PRINCIPLES OF SHORT-COURSE THERAPY FOR CAP

It is possible that high cure rates can be achieved using high-dose, short-course therapy when a potent, rapidly acting antibacterial agent is used. The efficacy of this approach is based on achieving optimal pharmacodynamic parameters for each antimicrobial agent. For agents that affect bacteria by concentration-dependent killing, rapid bacterial killing and a decrease in the potential for adaptive resistance can be best achieved by exposing the pathogen to adequate serum concentrations of antibiotic over time (expressed as area under the concentration-time curve [AUC]), and maximizing peak serum concentration (C_{max}) parameters. Other potential benefits include avoidance of adverse effects, improved patient and health care worker convenience and compliance, and improved cost-effectiveness. The concept “hit hard and fast ... then leave ASAP” describes this policy. For this approach to be successful, careful consideration of the pharmacokinetic and pharmacodynamic parameters of a particular drug is required.

In addition to eradicating the pathogen and therefore resolving the clinical syndrome, high-dose, short-course regimens have the potential to reduce the emergence of antibacterial resistance in the pathogen concerned as well as other commensal flora, both in the patient being treated and in the wider population. Bacterial resistance to common respiratory pathogens, including *S pneumoniae*, is increasing worldwide and, particularly in some areas, possibly to a critical level due to both point-mutation-mediated and gene-mediated resistance in pathogenic and commensal organisms (7). An important reason for the recommendation of high-dose, short-course treatment at sufficient dose is the evidence that it may reduce the emergence of resistant strains, whereas prolonged or low-dose regimens of antibiotics may be associated with increased rates of drug resistance.

In one observational study of French school-children, pharyngeal carriage of penicillin-resistant *S pneumoniae* was associated with a prescription of a β -lactam antibiotic in the preceding 30 days (odds ratio [OR], 3.0; 95% confidence interval [CI], 1.1–8.3), particularly when the dose of β -lactam antibiotic was lower than the clinically recommended amount (OR, 5.9; 95% CI, 2.1–16.7) or the treatment duration was longer than 5 days (OR, 3.5; 95% CI, 1.3–9.8) (8).

In a randomized, controlled study of amoxicillin for respiratory illness in children in the Dominican Republic, 795 outpatients were randomized to receive high-dose (90 mg/kg of body weight) amoxicillin for 5 days or a lower dose (40 mg/kg) for 10 days. Rates of nasopharyngeal carriage of penicillin-resistant *S pneumoniae* were measured at intervals up to 28 days. Children receiving high-dose, short-course therapy were significantly less likely to develop nasopharyngeal isolates of penicillin-resistant *S pneumoniae* (24% of children) than children receiving the standard course (32%) (relative risk [RR], 0.77; 95% CI, 0.60–0.97; $P = 0.03$) (9). The short-course, high-dose regimen was less likely to lead to resistant pneumococcal strains in households with ≥ 3 children (RR, 0.72; 95% CI, 0.52–0.98). An added benefit was that completion rates of treatment were also higher with the high-dose, short-course therapy than with the standard course (82% vs 74%; $P = 0.02$).

The primary evidence of the efficacy of high-dose, short-course antibiotic regimens comes from a variety of sources, which include a number of in vitro studies measuring minimum inhibitory concentrations (MICs) or time-kill rates for various antibiotics (10–13). Other researchers have used animal models to observe the effect of antibiotics on infection rates (14). Studies in humans have also demonstrated rapid reduction of pathogens with oral penicillin. For example, *S pneumoniae* disappeared from sputum by the second day, and bacteremia ceased within 24 hours of starting treatment (15). In addition, eradication of pathogens in nosocomial pneumonia occurred by the third day of treatment (16).

EARLY EXPERIENCE IN TREATING PNEUMOCOCCAL PNEUMONIA

In the early years of antibiotic use, short-course regimens were recommended in standard texts. For example, recommendations provided in the *Textbook of Medicine*, edited by Cecil and McDermott, recommended intramuscular penicillin 15,000 to 20,000 units every 3 hours for 5 to 7 days (17); Harrison et al, 2 decades later, recommended 60,000 to 600,000 units every 6 hours until the patient was afebrile for 48 to 72 hours (18). In 1944, 10,000 to 25,000 units of intramuscular penicillin every 3 hours for 1 to 4 days was advocated. In 1948, 200,000 to 300,000 units of penicillin twice in the first 24 hours and then once each day for 6 days or until the patient was afebrile for 48 hours was advocated (19). Another regimen evaluated was 600,000 to 1.2 million units of benzathine penicillin G as a single dose, although this was not as effective as the longer regimen, with cure rates of 73% and >90%, respectively (19).

Clinical evidence for this approach has come from more recent studies on length of illness and treatment for pneumonia. In one study of 73 patients admitted to a teaching hospital in Zaria, Nigeria (20), pneumonia was confirmed by chest radiograph. The mean age of those admitted was 30 years (range, 12 to 60 years). Antibiotics were prescribed empirically; 65 patients received penicillin, and 8 patients received tetracycline or chloramphenicol. The main pathogen isolated was *S pneumoniae* (38 patients, 19 of whom were bacteremic). Antibiotics were given until patients were afebrile for 24 hours. The average duration of treatment was 2.5 days (range, 1 to 6 days) with a 100% cure rate. This study demonstrates that antibiotics for CAP can be stopped safely when patients have been afebrile for 24 hours.

Halm et al (21) demonstrated that most patients hospitalized with pneumonia achieve clinical stability following treatment within 3 days and, even when applying the most conservative definition of stability, by 1 week. Stability was defined according to a number of clinical criteria. For example, the median time to stability was 2 days for heart rate (<100 beats/min) and systolic blood pressure (≥ 90 mm Hg) and 3 days for respiratory

rate (<24 respirations/min) and temperature (<37.2°C). More severely ill patients took longer to recover, but, once clinical stability was achieved, further deterioration requiring intensive monitoring or care was unlikely.

A number of studies have established the efficacy of short-course therapy for respiratory tract infections, including acute exacerbation of chronic bronchitis, pneumonia, and even atypical pneumonias. The clinical response rates of single-dose, 3-day, and 5-day regimens of azithromycin are comparable to the 90% effectiveness of standard 10-day regimen (22–26). These data for azithromycin cannot generally be applied to other agents since azithromycin has a prolonged half-life.

KEY POINT

High-dose, short-course fluoroquinolone therapy is a potential option for CAP because of the favorable pharmacodynamic and pharmacokinetic properties of the fluoroquinolones.

HIGH-DOSE, SHORT-COURSE FLUOROQUINOLONE THERAPY

Pharmacokinetics and Pharmacodynamics

High-dose, short-course fluoroquinolone therapy is a potential option for CAP because of the favorable pharmacodynamic and pharmacokinetic properties of fluoroquinolones. They are able to maximize concentration-dependent killing of susceptible bacteria by achieving higher C_{max} and AUC/MIC values (27,28), which leads to increased bactericidal activity and enables eradication and treatment of difficult pathogens (**Figure 1**) (29).

Improved antibacterial activity with increased penetration in various tissues and fluids may prevent resistance and the emergence of resistant strains through a reduction in drug exposure to patient and environment. The tolerability of increased fluoroquinolone dosing remains a concern so that high doses of any fluoroquinolone must

be safe and well tolerated before it can be considered for high-dose therapy.

Gotfried et al (30) compared the steady-state plasma, epithelial lining fluid, and alveolar macrophage concentrations of levofloxacin 750 mg or 500 mg daily for 5 doses with ciprofloxacin 500 mg twice daily for 9 doses. Venipuncture, bronchoscopy, and bronchiolar lavage were performed in 36 healthy adult subjects at 4 hours, 12 hours, or 24 hours after the last administered dose of antibiotic. Levofloxacin 750 mg achieved higher levels in respiratory tissue (epithelial lining fluid and alveolar macrophages) and plasma compared with levofloxacin 500 and ciprofloxacin 500 (Figure 2) (30). The higher dose of levofloxacin also showed better activity in vitro against ciprofloxacin-resistant *S pneumoniae* compared with the lower dose; kill-curves are shown in Figure 3 (31).

High-dose, short-course therapy with fluoroquinolones therefore maximizes the pharmacodynamic and pharmacokinetic profile of the drug while maintaining tolerability, allowing dosing flexibility, and providing a therapeutic option for

complicated clinical situations associated with problematic pathogens.

CLINICAL EFFECTIVENESS AND SAFETY OF HIGH-DOSE, SHORT-COURSE LEVOFLOXACIN FOR CAP

Despite its pharmacokinetic and pharmacodynamic properties, the question of whether levofloxacin is safe and effective in clinical practice needs to be addressed. Dunbar et al (32) compared high-dose,

KEY POINT

A literature search performed in March 2004 using the operators fluoroquinolones, high-dose therapy, and community-acquired pneumonia, failed to identify any articles. A similar search performed using the names of specific fluoroquinolones (ciprofloxacin, gatifloxacin and levofloxacin) yielded citations related to the use of levofloxacin in this setting.

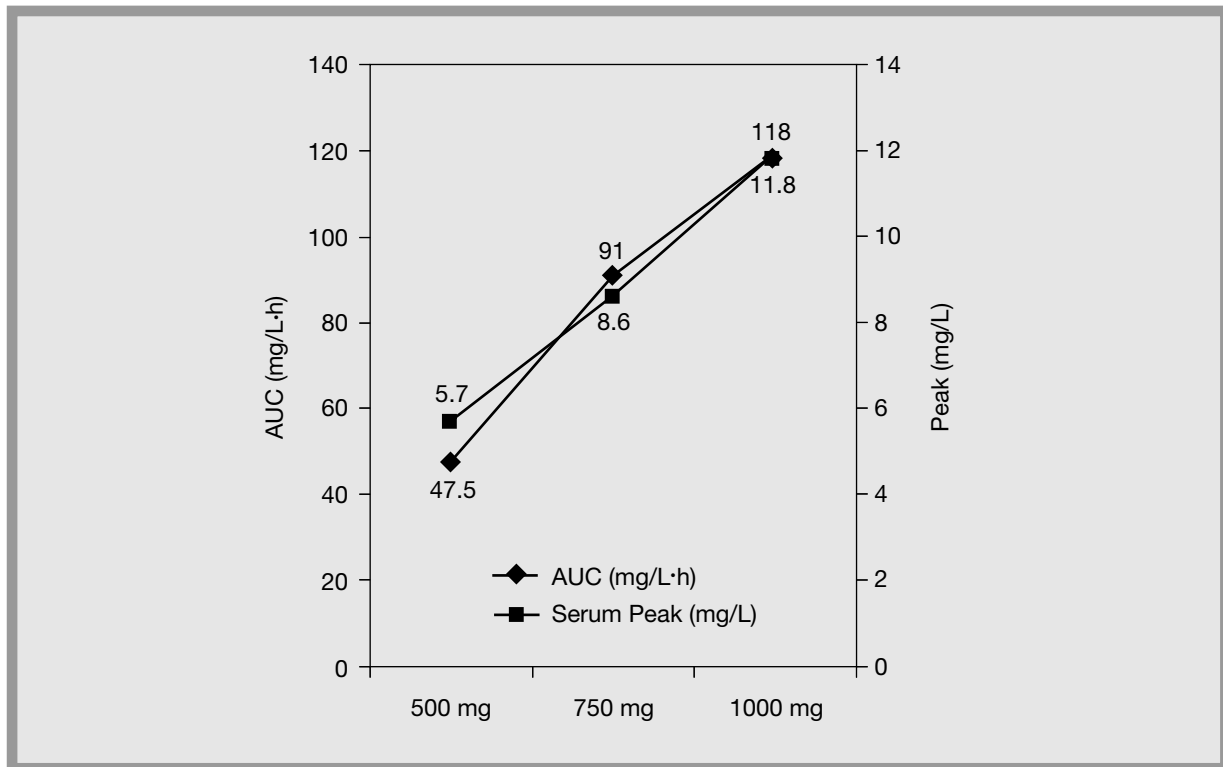


Figure 1. Rationale for high-dose (750 mg) levofloxacin. Levofloxacin prescribing information; June 2003. AUC = area under the concentration-time curve. Adapted with permission (29).

short-course levofloxacin (750 mg daily for 5 days) with a standard regimen (500 mg daily for 10 days) in patients with CAP (**Table I**). The baseline characteristics of patients in each group were similar. The high-dose, short-course regimen was as effective as the standard regimen. It was also clinically effective against >90% of infections due to *S pneumoniae* strains and 100% of infections with *Haemophilus influenzae* and *Legionella* spp.

The high-dose, short-course levofloxacin regimen was significantly more effective than standard treatment in controlling fever within 3 days of starting treatment (**Table II**) (33). Shortness of breath and purulent sputum also tended toward rapid resolution with the 750-mg dose, compared with the 500-mg dose, but not to a statistically significant degree.

For inpatients, in addition to more rapid defervescence, the high-dose regimen provides in

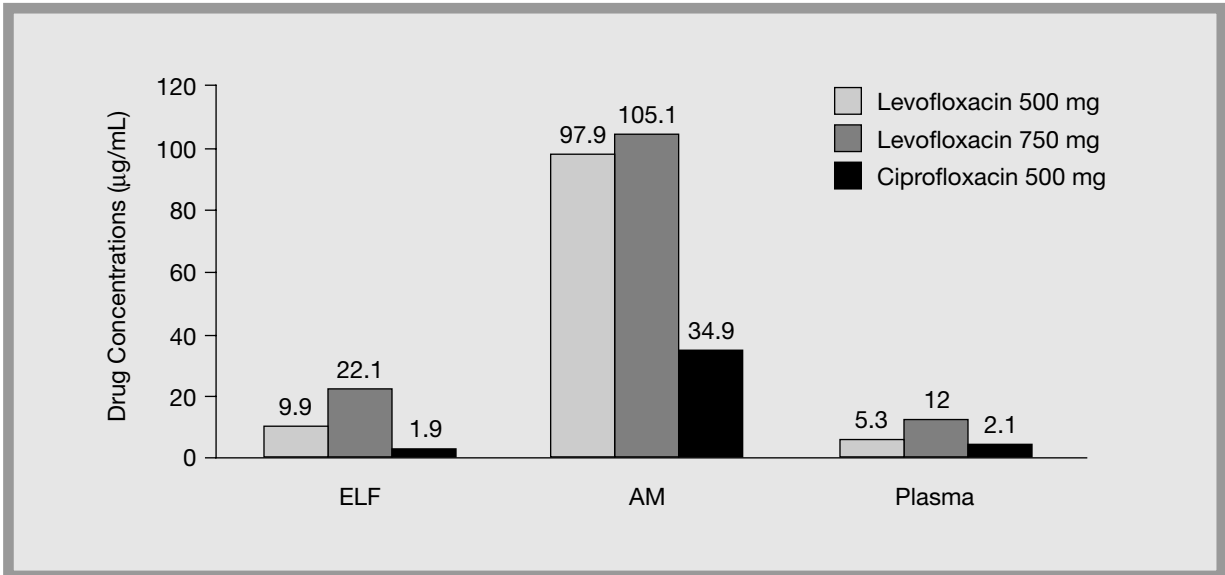


Figure 2. Pharmacokinetics: respiratory tissue and fluid. ELF = epithelial lining fluid; AM = alveolar macrophage. Adapted with permission (30).

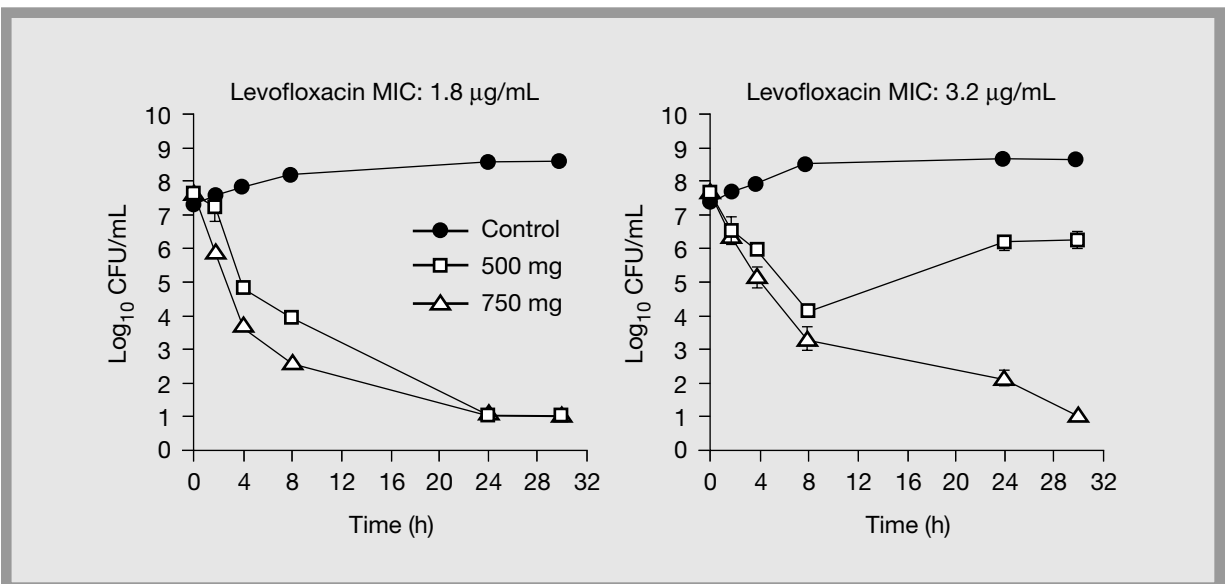


Figure 3. Levofloxacin (750 and 500 mg) against ciprofloxacin-resistant *Streptococcus pneumoniae*. CFU = colony-forming unit; MIC = minimum inhibitory concentration. Adapted with permission (31).

most cases a quicker switch from intravenous therapy to oral therapy. Although the median time to switch is 2.35 days, the shorter course of treatment may translate into shorter hospitalization and therefore potential cost savings (Table III).

The clinical implication of more rapid symptom resolution is the potential for a quicker return to normal daily routine, including return to work. In addition, the data suggest that the high-dose, short-course regimen is at least as safe as standard treatment (Table IV) (32).

TABLE I. HIGH-DOSE, SHORT-COURSE LEVOFLOXACIN 750 MG VS STANDARD REGIMEN FOR CAP: CLINICAL SUCCESS

<i>Characteristic</i>	<i>750 mg* (n = 198)</i>	<i>500 mg† (n = 192)</i>
All patients, %	92	91
PSI class I/II, %	93	96
PSI class III/IV/V, %	91	85
<i>Streptococcus pneumoniae</i>	20/22 (91)	18/20 (90)
<i>Haemophilus influenzae</i>	12/13 (92.3)	13/14 (93)
<i>Legionella</i> spp	11/11 (100)	3/3 (100)

Clinically evaluable populations. CAP = community-acquired pneumonia; PSI = pneumonia severity index. *5 days. †10 days. Reprinted with permission (32).

TABLE II. HIGH-DOSE, SHORT-COURSE LEVOFLOXACIN 750 MG VS STANDARD REGIMEN FOR CAP: RESOLUTION AT 3 DAYS

<i>Characteristic</i>	<i>750 mg (n = 198)</i>	<i>500 mg (n = 192)</i>	<i>P value</i>
Fever (symptoms), %	67.4	54.6	0.006
Fever (measured), %	49	36	0.027
Purulent sputum, %	41	31	0.059
Dyspnea, %	35	28	0.132

Clinically evaluable populations. CAP = community-acquired pneumonia. (33)

TABLE III. PHARMACOECONOMIC IMPLICATIONS OF SHORT-COURSE THERAPY

<i>Regimen</i>	<i>Days IV (cost per dose, \$)</i>	<i>Days Oral (cost per dose, \$)</i>	<i>Total Cost (per patient, \$)</i>	<i>Savings (per 500 patients, \$)</i>
750 mg	2.35 (24.00)	2.65 (13.90)	93.23	10,655
500 mg	2.75 (16.00)	7.25 (9.73)	114.54	—

IV = intravenous. Total cost per patient = (No. days IV)(cost per IV dose) + (No. days oral)(cost per oral dose). Savings per 100 patients = difference in total cost per patient × 100. Drug costs = average wholesale price.

TABLE IV. HIGH-DOSE, SHORT-COURSE LEVOFLOXACIN: SAFETY

Characteristic	750 mg (n = 256)	500 mg (n = 265)
Any adverse event, %	58	60
Serious adverse event, %	10	14
D/C due to adverse event, %	7	8
Deaths, %	2	3

Intent-to-treat populations. D/C = discontinued. Reprinted with permission (32).

CONCLUSIONS

Pharmacokinetic and pharmacodynamic parameters can predict outcomes for short-course levofloxacin. A high AUC/MIC or C_{max} /MIC correlates well for outcomes of infections treated with fluoroquinolones. The research shows that high-dose, short-course levofloxacin (750 mg) provides higher pharmacokinetic parameters than a 500-mg course, resulting in more rapid symptom resolution. High-dose levofloxacin therefore is likely to target more pathogens than the low-dose regimen.

The available data indicate that short-course therapy is effective for CAP. The potential exists to improve efficacy and tolerability and to minimize resistance. This approach is also patient-friendly (leading to high compliance) and cost-effective. Therefore, short-course therapy may prove to be an attractive option for patients with CAP.

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