Fluoroquinolone Utilization in the Emergency Departments of Academic Medical Centers

Prevalence of, and Risk Factors for, Inappropriate Use

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Background: Resistance to fluoroquinolone (FQ) antibiotics has risen markedly in recent years and has been associated with increasing FQ use; however, few data exist regarding FQ use patterns. Designing strategies to limit FQ resistance by optimizing FQ use depends on identifying patterns of inappropriate FQ use. Use of FQs in emergency departments (EDs) has not been studied.

Methods: We studied 100 consecutive ED patients who received an FQ and were subsequently discharged. Appropriateness of the indication for use was judged according to existing institutional guidelines. A case-control study was conducted to identify the prevalence of, and risk factors for, inappropriate FQ use.

Results: Of 100 total patients, 81 received an FQ for an inappropriate indication. Of these cases, 43 (53%) were judged inappropriate because another agent was considered first line, 27 (33%) because there was no evidence of infection based on the documented evaluation, and 11 (14%) because of inability to assess the need for antimicrobial therapy. Although the prevalence of inappropriate use was similar across various clinical scenarios, there was a borderline significant association between the hospital in which the ED was located and inappropriate FQ use. Of the 19 patients who received an FQ for an appropriate indication, only 1 received both the correct dose and duration of therapy.

Conclusions: Inappropriate FQ use in EDs is extremely common. Efforts to limit emergence of FQ resistance must address the high level of inappropriate FQ use in EDs. Future studies should evaluate the impact of interventions designed to reduce inappropriate FQ use in this setting.

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FLUOROQUINOLONE (FQ) antibacterials are important components of the modern antimicrobial armamentarium. Their high potency, broad spectrum of activity, relative tolerability, and availability in both oral and parenteral formulations make FQs extremely useful in many clinical settings.[1] Although the potential for development of resistance to FQs was initially predicted to be very low,[2] recent years have witnessed increased resistance to these agents. Resistance was initially described in organisms such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*,[3,4] which have borderline baseline minimum inhibitory concentrations. The increasing scope and importance of FQ resistance is evident in the recent emergence of resistance in such organisms as *Escherichia coli*, *Klebsiella pneumoniae*, *Campylobacter* species, *Salmonella* species, and *Streptococcus pneumoniae*.[5-8] If these trends continue, the utility of these agents will be greatly diminished.

Devising strategies to limit FQ resistance relies on understanding the factors driving resistance. Several studies have noted an association between FQ use and FQ resistance,[6,9] suggesting that improving use of FQ agents is likely to be an essential component of interventions to address the emergence of FQ resistance. Before such efforts can be implemented, however, patterns of FQ use must be elucidated. It has been strongly suggested that FQ use should be limited to situations in which they offer a clear therapeutic advantage, where other less expensive first-line agents do not exist, or in which such agents are contraindicated.[1] However, it is unclear whether these recommendations are routinely followed. Although a few studies have investigated the use of FQs in hospitalized patients,[5,10] information regarding use in ambulatory settings is extremely limited. Furthermore, evaluation of FQ use in emergency departments (EDs) has not been previously reported, to our knowledge. Information regarding FQ use in the ED is of great importance given the frequent use of antibiotics in this setting[11] and the increasingly important role that FQs play in oral antibiotic therapy.[12]

Table 1. Guidelines for Fluoroquinolone Use

Indication	Comments
CAP	Empiric treatment if 1 of the following were present: 1. Age >60 y 2. Multilobar involvement on chest radiograph 3. Gram-negative bacilli on sputum gram stain 4. Transplant recipient (taking cyclosporine or tacrolimus) 5. Significant comorbidity (at least 1 of the following): a. Known chronic obstructive pulmonary disease b. End-stage renal disease (hemodialysis or peritoneal dialysis) c. Known liver disease (diagnosis of cirrhosis) d. Respiratory rate >30/min e. Decreased BP (systolic BP <90 mm Hg or diastolic BP <60 mm Hg) f. Pa_{O_2} >50 mm Hg
Gastroenteritis	Empiric therapy; definitive treatment for *Salmonella* or *Shigella* infection
Urinary tract infection	Empiric treatment if allergy to first-line therapy (eg, sulfamethoxazole-trimethoprim)
SBP	Prophylaxis
Chronic prostatitis	Empiric therapy; definitive treatment for Enterobacteriaceae infection
Endophthalmitis	Postoperative; definitive treatment for *Pseudomonas aeruginosa* infection in combination with gentamicin sulfate
Malignant otitis externa	Empiric treatment
HIV-associated infections	*Mycobacterium tuberculosis* or *Mycobacterium avium* complex

Abbreviations: BP, blood pressure; CAP, community-acquired pneumonia; HIV, human immunodeficiency virus; SBP, spontaneous bacterial peritonitis.

To evaluate the use of FQs in the ED, we conducted a case-control study to identify the prevalence of, and risk factors for, inappropriate FQ use, with appropriateness of use judged according to established institutional guidelines.

METHODS

This investigation was conducted at 2 academic medical centers within a larger health care system: (1) hospital A, a 725-bed tertiary care institution with approximately 40 000 ED visits annually, and (2) hospital B, a 344-bed urban community hospital with approximately 26 000 ED visits annually. To calculate the prevalence of inappropriate FQ use and to identify risk factors for inappropriate FQ use, a retrospective case-control study was conducted.

Beginning on August 23, 1999, all consecutive patients who received an FQ in the ED of either hospital and were subsequently discharged were enrolled in the study. Patients who received an FQ in the ED but were subsequently admitted to the hospital were excluded. Eligible patients were identified daily by several pharmacists (L.A.L., N.K., H.P.P.) who reviewed all antibiotics dispensed or prescribed during ED visits. Accrual of patients continued until 50 patients were enrolled at each site. This was accomplished on November 19, 1999.

Determination of appropriateness of FQ use was based on existing health care system guidelines established by the University of Pennsylvania Antimicrobial Management Program (AMP).[13] The AMP was designed to improve clinicians' knowledge about and attitudes toward antimicrobial use. The AMP controls the antimicrobial formulary at our institution (except in the ED) in an effort to restrict the use of broad-spectrum, more expensive agents with unfavorable adverse effect profiles in favor of narrower-spectrum, less expensive agents with better adverse effect profiles. The AMP also restricts agents that have been linked to the emergence of resistant organisms. Antimicrobial use guidelines were first developed in 1993, but are reviewed and updated if needed on a yearly basis. These guidelines were widely available to physicians, nurses, and other health care providers in published pamphlets,[14] through ongoing educational initiatives, and on the Internet (available at: http://www.med.upenn.edu/bugdrug/), to which access was available on various computers throughout the 2 EDs.

The clinical settings in which use of an FQ was recommended by guidelines are shown in **Table 1**. In addition, FQs were considered appropriate for suspected infections in which first-line therapy was not possible because of allergy or other contraindication. The preferred FQ at the 2 EDs was levofloxacin. When an FQ was required for the treatment of febrile neutropenia, ofloxacin was considered the agent of choice. Of note, use of many antimicrobial agents, including FQs, was restricted in all inpatient areas of the 2 hospitals and required approval by the AMP. The EDs, however, were not subject to these restrictions and did not require approval for use of any agent.

To determine appropriateness of therapy according to guidelines, written case descriptions of each patient, prepared by 3 infectious diseases (ID) pharmacists (L.A.L., N.K., H.P.P.), were reviewed independently by 2 ID specialists (E.L., N.O.F.). When the opinions of these 2 reviewers differed, a third ID physician (R.J.M.) provided the deciding opinion. Appropriateness of therapy was based solely on the indication for therapy. Although the route, dose, and duration of therapy were also compared with institutional guidelines, these data were not considered when appropriateness of therapy was determined. We defined an error in duration of FQ therapy to be a greater than 3-day deviation from guidelines and considered a deviation from guidelines in dose of at least 50% to be an error.

Data collected from written and computerized medical records in the 2 EDs included age, sex, race, hospital, medication allergies, presenting complaint, history of present illness, discharge diagnosis, other diagnoses, and treatment plan. All laboratory, microbiology, and radiographic data, as well as characteristics of FQ administration (ie, type of FQ used, dose, route, and duration) were also documented. Laboratory, microbiology, and radiographic study results were confirmed from sources independent of the ED visit record.

Bivariable analysis was conducted to determine the association between risk factor variables and inappropriate FQ use. Categorical variables were compared by means of the χ^2 or Fisher exact test where appropriate. An odds ratio and 95% confidence interval were calculated to evaluate the strength of any association. Continuous variables were compared with the Wilcoxon rank sum test.[15] A 2-tailed *P* value of less than .05 was considered significant. All statistical calculations were performed with Stata version 6.0 (Stata Corp, College Station, Tex).

RESULTS

A total of 100 patients (50 from each ED) were enrolled in the study. Of note, FQs accounted for approximately 25% of all antibiotics prescribed in patients seen in the ED who were subsequently discharged. All charts were available for these patients. The median age (95% confidence interval) of all patients was 45.0 years (41.0-51.0 years); 62% of the patients were female. Of the 77 patients for whom race was indicated, 64 (83%) were African American, 11 (14%) were white, 1 (1%) was Asian, and 1 (1%) was Hispanic. Of 97 patients in whom medication allergy data were available, 23 (24%) reported an antibiotic allergy. Of these 23 patients, 16 (70%) were allergic to penicillin, 5 (22%) were allergic to sulfa agents, 1 (4%) was allergic to both penicillin and sulfa, and 1 (4%) was allergic to sulfa and FQs.

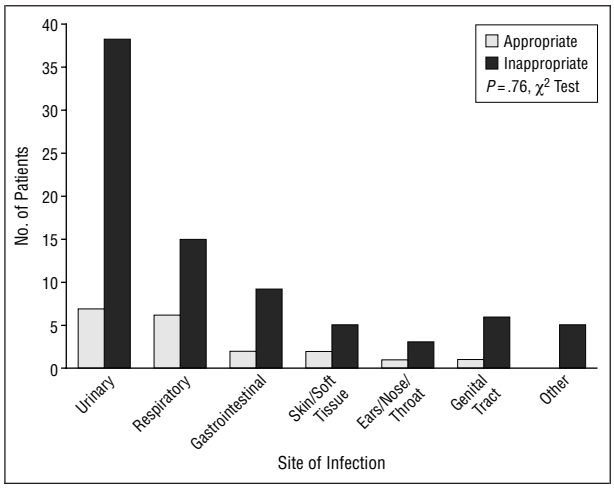
The presumptive infections for which FQs were used are shown in the **Figure**. Of the 45 patients diagnosed as having a urinary tract infection (UTI), 8 had symptoms consistent with pyelonephritis (ie, flank pain, high fever). Eight of 21 patients diagnosed as having respiratory tract infection had evidence of pneumonia by chest radiograph. The 5 patients classified as "other" had presenting complaints of ankle pain, hypoglycemia, allergic reaction, syncope, and dizziness.

Of 100 total patients, 89 received levofloxacin; 9, ciprofloxacin; and 2, ofloxacin. Of the 11 patients in whom ciprofloxacin or ofloxacin was used, 10 were diagnosed as having UTI and 1, as having gastroenteritis. Of the 73 patients in whom the initial route of therapy was indicated, 42 (58%) received parenteral therapy; 30 (41%), oral therapy; and 1 (1%), intramuscular dosing. Of the 42 patients who received parenteral therapy, only 10 (24%) had a documented contraindication for oral therapy (eg, nausea, vomiting, or altered mental status).

The prevalence of inappropriate FQ use based on our institutional guidelines was 81 of 100 (81%). Of the 81 cases of inappropriate FQ use, 43 (53%) were considered inappropriate because another agent was considered first line (most often sulfamethoxazole-trimethoprim for UTIs in patients not allergic to sulfa), while 27 (33%) were inappropriate because there was no evidence of infection based on the clinical evaluation or diagnostic studies. In 11 (14%) there was insufficient evaluation. As shown in the Figure, there were no significant differences in the percentages of inappropriate FQ course when the various sites of suspected infection were compared ($P=.76$).

Of the 100 patients, there were 15 for which the 2 primary reviewers disagreed. Of these 15 patients, the sites of infection were as follows: urinary, 8; skin or soft tissue, 2; genital, 2; gastrointestinal, 2; and respiratory, 1. After review by the third ID physician, FQ use in 8 of these 15 patients was judged to be inappropriate.

As shown in **Table 2**, patients who reported an antibiotic allergy were more likely to have their FQ course judged to be appropriate. In addition, there was a borderline significant association between the ED in which the patient was seen and whether FQ therapy was appropriate. Thirteen (26%) of 50 patients seen in the ED of hospital A were judged to have received appropriate therapy compared with only 6 (12%) of 50 in the ED of hospital B.



Appropriateness of fluoroquinolone use by site of infection.

The dose and duration of FQ therapy was subsequently evaluated in patients for whom the indication for FQ was judged to have been appropriate. Of these 19 cases, only 1 patient was prescribed the correct dose and duration of FQ therapy. Fourteen patients were prescribed both the incorrect dose and duration, 3 patients were prescribed the correct duration but incorrect dose, and 1 patient was prescribed the correct dose but incorrect duration. In general, when dose and duration were incorrect, the dose was higher and the duration was longer than those recommended by guidelines. The most common example was an uncomplicated UTI treated for more than 7 days and/or treated with 500 mg of levofloxacin per day rather than 250 mg.

COMMENT

This study investigated patterns of FQ use in the ED. Evaluating FQ use solely on the basis of indication, we found that 81% of FQ courses were inappropriate when judged by established institutional guidelines. Furthermore, of the few patients in whom an FQ was prescribed for an appropriate indication, all but 1 received an incorrect dose and/or duration of therapy. Finally, there was a borderline significant association between the hospital in which the ED was located and the prevalence of inappropriate therapy.

In the outpatient setting, antibiotics are often recommended even when there is no clinical indication.[16] Most studies that have investigated appropriateness of FQ use have focused on the hospitalized patient population.[5,10,17] While in-hospital use of FQs is important, the availability of FQs in oral formulation suggests that the impact of their use in the outpatient setting may be even greater. Indeed, a recent study noted that FQs are one of the most common classes of antibiotics used in the ambulatory environment.[12] Increases in FQ prescribing in the wake of recent bioterrorist attacks will almost certainly perpetuate the emergence of FQ resistance.[18] Therefore, the outpatient setting may be particularly important in the emergence of FQ resistance. Recent data demonstrate that, although resistance to most antimicrobials is much higher in inpatients, the prevalence of FQ resistance is often greater in outpatient isolates.[19] Nationally, the focus of efforts to limit the emergence of resistance is shifting to include the ambula-

Table 2. Risk Factors for Inappropriate FQ Therapy

Variable	Inappropriate	Appropriate	OR (95% CI)	*P* Value
General				
Median age (range), y	44 (18-96)	51 (18-76)	. . .	.54*
Sex, No. (%) M	31/81 (38)	7/19 (37)	1.06 (0.39-2.91)	>.99†
Race, No. (%) African American	54/65 (83)	10/12 (83)	0.98 (0.0-4.64)	>.99†
Antibiotic allergy, No. (%)	15/78 (19)	8/19 (42)	0.33 (0.11-0.93)	.06†
Hospital, No. (%) hospital A	37/81 (46)	13/19 (68)	0.39 (0.14-1.09)	.07‡
Type of FQ, No. (%) levofloxacin	60/68 (88)	14/17 (82)	1.61 (0.41-6.42)	.52‡
Parenteral FQ therapy, No. (%)	34/60 (57)	8/13 (62)	0.81 (0.25-2.68)	>.99†
Site of suspected infection, No. (%)				
Urinary tract	38/81 (47)	7/19 (37)	1.51 (0.55-4.12)	.46†
Respiratory tract	15/81 (19)	6/19 (32)	0.49 (0.16-1.45)	.22†
Skin/soft tissue	5/81 (6)	2/19 (11)	0.55 (0.11-∞)	.61†
Genital tract	6/81 (7)	1/19 (5)	1.44 (0.21-∞)	>.99†
Gastrointestinal tract	9/81 (11)	2/19 (11)	1.05 (0.23-∞)	>.99†
Ears/nose/throat	3/81 (4)	1/19 (5)	0.69 (0.09-∞)	.57†
Other	5/81 (6)	0/19	. . .	.58†

Abbreviations: CI, confidence interval; FQ, fluoroquinolone; OR, odds ratio.
*Wilcoxon rank-sum test.
†Fisher exact test.
‡χ^2 Test.

tory setting.[20] The importance of focusing on the ED is supported by a recent study that noted that more than half of patients seen in this setting had taken an antimicrobial agent within the past 48 hours.[21]

Despite the widespread outpatient use of FQs, little is known regarding how FQs are used in these settings. Despite the frequent use of antibiotics in the ED,[11,22] no study to our knowledge has investigated patterns of FQ use in this setting.

We noted that approximately 4 of every 5 ED patients treated with an FQ receive it inappropriately, most often because another agent was considered first line. Our findings suggest that there is vast opportunity to improve on current patterns of FQ use in an effort to curb emergence of FQ resistance. This rate of inappropriate use is somewhat higher than that noted in hospitalized patients, where rates of inappropriate use have ranged from 40% to 71%.[5,10,17] Are there reasons why the ED setting may foster inappropriate use of FQs? Given the knowledge that a significant subset of patients seen in the ED have less access to routine health care,[23] a prescriber might be inclined to use a broader-spectrum agent than necessary because of concern that a patient may not follow up if an infection is inadequately treated. However, an unintended effect of such a practice may be to increase a patient's risk of harboring an FQ-resistant pathogen, since multiple courses of FQ have been associated with FQ resistance.[24] Another unintended effect of such FQ prescribing patterns might be that the patient is less likely to fill a prescription for the more expensive FQ, thus increasing the chance that an infection will go untreated. Future studies devised to characterize physician prescribing behavior would be welcome in better designing effective strategies to reduce inappropriate FQ use.

We also noted that, of the patients for whom an FQ was prescribed for an appropriate indication, most received an incorrect dose or duration of FQ therapy (usually too high a dose and too long a duration). This finding also has significant implications for the emergence of resistance, since prolonged courses of FQ therapy have been associated with emergence of resistant strains, regardless of the dose given.[25] The likelihood of FQ drug toxicity may also be affected by inappropriate FQ prescribing. In fact, higher dose and longer duration of FQ therapy both have been associated with a greater risk of adverse events.[26] This may be particularly important for patients seen in the ED, some of whom may have less access to follow-up in the event of drug toxicity.

Finally, nearly two thirds of patients received their initial course of FQ therapy parenterally. However, fewer than 25% of these patients had a documented contraindication to oral therapy. The cost implications of the route of FQ therapy, for both the hospital and the patient, are significant. Of note, the hospital cost of parenteral levofloxacin at the 2 EDs was more than 3 times that of oral therapy.

We found that a history of antibiotic allergy was associated with a decreased risk of inappropriate FQ use. This is likely due to the fact that FQ use was considered appropriate in patients with an allergy to a first-line agent (eg, sulfamethoxazole-trimethoprim). Thus, FQ use in patients with an allergy would have been more likely to be classified as appropriate.

We noted a borderline significant association between inappropriate FQ use and the hospital in which the ED was located. Of note, there is no overlap in the staff of these 2 EDs. The ED at hospital A is associated with an emergency medicine training program, while the ED at hospital B is not. This suggests that prescribing patterns at different EDs may reflect institutional and departmental attitudes toward prescribing and antibiotic selection, rather than specific patient-level factors. Of note, we found no specific patient-level variables to identify situations in which inappropriate FQ use is most likely. These results are, however, based on small numbers of patients and should be confirmed in future investigations.

There were several potential limitations in this study. Although the possibility of selection bias may be of concern, all patients who received an FQ during the study pe-

riod were readily identified and included in the study. Furthermore, all medical records were available for review.

The possibility of misclassification bias may also be of concern. The designation as case or control based on appropriateness of FQ therapy was based on the independent case review of 2 ID physicians. Where discrepancies arose, a third ID physician offered the deciding opinion. While it is possible that differences in interpretation of either the antibiotic use guidelines or the patient case may have led to misclassification, all judgments regarding appropriateness of therapy were rendered without prior knowledge of many of the potential risk factors of interest. Thus, it is unlikely that any differential misclassification bias occurred.

Another potential limitation of this study is that it was conducted at a specific time of year. Inasmuch as there may be seasonal variations in the conditions that cause patients to present to the ED (eg, viral upper respiratory infections) and perhaps the likelihood of an FQ being prescribed, this study represents only those patterns associated with late summer and fall. A study of FQ use patterns conducted throughout the year would help to clarify this issue.

Finally, this study was conducted at 2 large medical centers, and the results may not be generalizable to other institutions. In addition, the EDs in this study represent a specific geographic region, and it is possible that antibiotic use practices differ across regions or across health care systems. Another potential issue of generalizability is that antimicrobial use guidelines may vary from institution to institution depending on such factors as local antimicrobial susceptibility patterns and patient population. We based all decisions regarding whether FQ therapy was appropriate on whether use conformed to existing accepted guidelines at that time. Although these guidelines were developed on the basis of careful review of the literature, contemporary institutional antimicrobial susceptibility patterns, and expert opinion, these guidelines may not conform exactly to those of other institutions. The fact remains, however, that these guidelines were well established and disseminated among the health care providers at our institution. Despite this comprehensive and rigorous effort to optimize use of FQs, we still found that the vast majority of FQ use did not follow these guidelines.

In conclusion, we found FQ use in the vast majority of cases to be inappropriate by established institutional guidelines. Furthermore, in patients in whom the indication for therapy was correct, the dose and duration of therapy were almost always incorrect. Given the well-recognized association between FQ use and emergence of FQ resistance, our results demonstrate that significant improvements can be made in the way in which FQs are used in EDs. Future studies evaluating the impact of interventions designed to improve FQ use in these settings should be encouraged.

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