Oral Fluoroquinolone Use and the Risk of Acute Liver Injury: A Nationwide Cohort Study

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Background. Antibiotics are considered to be among the most frequent causes of drug-related acute liver injury (ALI). Although many ALIs have mild and reversible clinical outcomes, there is substantial risk of severe reactions leading to acute liver failure, need for liver transplant, and death. Recent studies have raised concerns of hepatotoxic potential related to the use of fluoroquinolones.

Methods. This study examined the risk of ALI associated with oral fluoroquinolone treatment compared with amoxicillin (419 930 courses, propensity score matched 1:1). The information on drug use was collected from a national, registry-based cohort derived from all Swedish adults aged 40–85 years.

Results. During a follow-up period of 60 days, users of oral fluoroquinolones had a >2-fold risk of ALI compared to users of amoxicillin (hazard ratio, 2.32 [95% confidence interval {CI}, 1.01–5.35). The adjusted absolute risk difference for use of fluoroquinolones as compared to amoxicillin was 4.94 (95% CI, .04–16.3) per 1 million episodes.

Conclusions. In this propensity score–matched study, fluoroquinolone treatment was associated with an increased risk of ALI in the first 2 months after starting treatment.

Keywords. ALI; DILI; fluoroquinolones; hepatotoxic; liver injury.

Many hepatotoxic drug reactions are predictable or dose dependent, and thus preventable to some degree. Other hepatotoxic drug reactions, however, are unpredictable and independent of dose and duration of treatment. This type of event is commonly referred to as an idiosyncratic drug-induced liver injury (DILI) and is considered the main cause of acute liver injury (ALI) [1]. These rare but potentially life-threatening events are associated with clinical outcomes ranging from minor elevations in liver enzymes to transient liver failure, need for liver transplant, and death. Due to the innate unpredictability of idiosyncratic drug reactions as well as the difficulty in establishing causality, they are often not discovered until the drug is released to the general public and used in larger populations. In a summary of 5 large prospective and retrospective studies on DILI, anti-infectives were the most common attributable cause, accounting for proportions ranging from 27% to 65% of all cases of DILI [2]. Population-based estimates for all DILIs have been reported in studies conducted in France (2002) and Iceland (2013) with an incidence rate of 13.9 and 19.1 per 100 000, respectively [3, 4]. In the latter study, it was estimated that 1 in 2300 users of amoxicillin-clavulanate and 1 in 1369 users of nitrofurantoin developed liver injuries.

Fluoroquinolones are a family of broad-spectrum antibiotics covering an array of both gram-positive and gram-negative bacteria. It is one of the most widely used classes of systemic antibiotics, reaching almost 23 million unique prescriptions per year in the United States alone [5]. The fluoroquinolones exhibit antibacterial properties by inhibiting the bacterial DNA synthesis by targeting the microbe's DNA topoisomerase and DNA gyrase [6]. Although the drug is not generally considered to interact with host DNA, adverse effects such as tendinopathy and QT-interval prolongation are well established [7–9]. There have been safety concerns with regard to hepatic toxicity in the past decades. Owing to case reports of a possible association with ALI, trovafloxacin and temafloxacin were both withdrawn in the 1990s [10, 11]. A few observational studies have been published reporting an up to 3-fold increase in risk of ALI associated with fluoroquinolone treatment. However, these estimates are primarily based on case-control studies with limited ability to control for underlying differences in health status, so it cannot be ruled out that the observed increased risk is not attributable to fluoroquinolone use. Furthermore, considering the potential severity of hepatotoxic drug reactions and the widespread use of fluoroquinolones, further investigation is warranted.

We conducted a nationwide register-based cohort study in Sweden to assess whether oral fluoroquinolone treatment was associated with an increased risk of ALI.

METHODS

Study Design

We conducted a register-based cohort study based on a historical cohort of all Swedish adults 40–85 years of age, July 2006–January 2014, linking individual data from national healthcare registries. We investigated the risk of ALI in users of oral fluoroquinolones by collecting individual information and prescription data for patients either seeking medical care for, or having as a cause of death, diagnoses of ALI within 60 days after start of drug use. We considered each prescription as a separate event, meaning an individual could contribute with >1 prescription to the study. Index date was based on date of filling a study drug prescription. To control for confounding by indication, we used an active comparator design with amoxicillin as the reference drug. Amoxicillin has a safe hepatic profile with relatively few case reports describing liver-related injuries [12, 13]. In addition, it has medical indications overlapping those of fluoroquinolones. To control for potential differences in baseline health status, we used a propensity score–matched design comprised of a large number of covariates. Linking of registries was done using the national unique personal identification numbers assigned to all Swedish citizens.

Data Sources

Prescription data on fluoroquinolones (Anatomical Therapeutic Chemical [ATC] code J01MA) and amoxicillin (ATC code J01CA04) was collected using the Swedish Prescribed Drug Register, which contains comprehensive coverage (date of filling prescription, size of prescription, dosage, etc) of all drugs dispensed at Swedish pharmacies from July 2005 onward [14]. Outcome data were collected from the National Patient Register, which holds information on all hospital admissions, outpatient visits, and emergency department visits as well as from the National Cause of Death Register, which holds information on all causes of death according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*). In addition, data for estimations of baseline differences in health (ie, demographic data and information on healthcare and drug usage) were collected from the National Patient Register as well as from the Total Population Register, which holds demographic information on all Swedish residents [15].

Study Cohort

From the source population of all Swedish adults, 40–85 years of age in the July 2006 to January 2014 time period, we identified all treatment courses of oral fluoroquinolones or amoxicillin. We excluded courses in patients who had filled a prescription for any of the study drugs in the past 2 months, had multiple filled prescriptions of different study drugs on the date of filling prescription (index date), or had been hospitalized in the past 2 months. To reduce confounding, we also excluded courses in patients with a history of acute hepatitis (including infectious) in the past 2 months who had previously been diagnosed with hepatic or biliary cancer, previously diagnosed with any other hepatobiliary disease (including chronic hepatitis) or liver transplant, with a history of human immunodeficiency virus/AIDS, and with predefined end-stage illness, who may have had a high pretreatment risk of ALI. To assure adequate covariate ascertainment, we also excluded courses from patients with no prescriptions for any drug in the past year preceding the index date. See Supplementary Table 1 and Figure 1 for details.

Propensity Score Model

To reduce the influence of confounding from differences in baseline health status, we used propensity score matching. Logistic regression, including a total of 43 covariates as predictors, was used to calculate the propensity to receive fluoroquinolone therapy. The greedy 1 to >5 digit propensity score–matching algorithm was used to match fluoroquinolone and amoxicillin use on a 1:1 ratio [16]. To estimate covariate balancing after matching, we used standardized differences, considering a value ≤0.10 as being well balanced [17]. Missing values were present in the "region of residence" category (0.2%) and were handled by including a missing value category [18]. A complete list of predictors included in the propensity score calculation is included in Supplementary Table 2.

Follow-up and Outcome

Data from the Drug Induced Liver Injury Network between 2004 and 2010 indicate that the majority of adverse events occur within weeks after start of treatment [19]. Therefore, the main analysis and follow-up interval was determined as 1–60 days after filling a prescription. Follow-up started on the date of filling prescription of an index drug and ended on end of study (1 January 2014), participant reaching age 86, hospitalization or death due to any of the primary outcome diagnoses, or 60 days after filling the prescription, whichever occurred first. The 60-day risk period was divided into 10-day intervals, to explore the timing of events.

The primary outcome, ALI, was defined as toxic liver disease (*ICD-10* codes K710, K711, K712, K716, K719), or acute and subacute liver failure (*ICD-10* codes K720, K729), recorded either in the National Patient Register or in the National Cause of Death Register [20, 21]. The *ICD-10* codes are listed in Supplementary Table 3.

Statistical Analyses

We used Cox regression to calculate hazard ratios (HRs) comparing the risk of ALI between users of fluoroquinolones and users of amoxicillin. An individual could contribute with person-time from >1 treatment course unless an outcome event occurred or study end (January 2014) or end of follow-up (60 days) was reached, ensuring that the courses never overlapped. HRs were also estimated in subgroups of participants
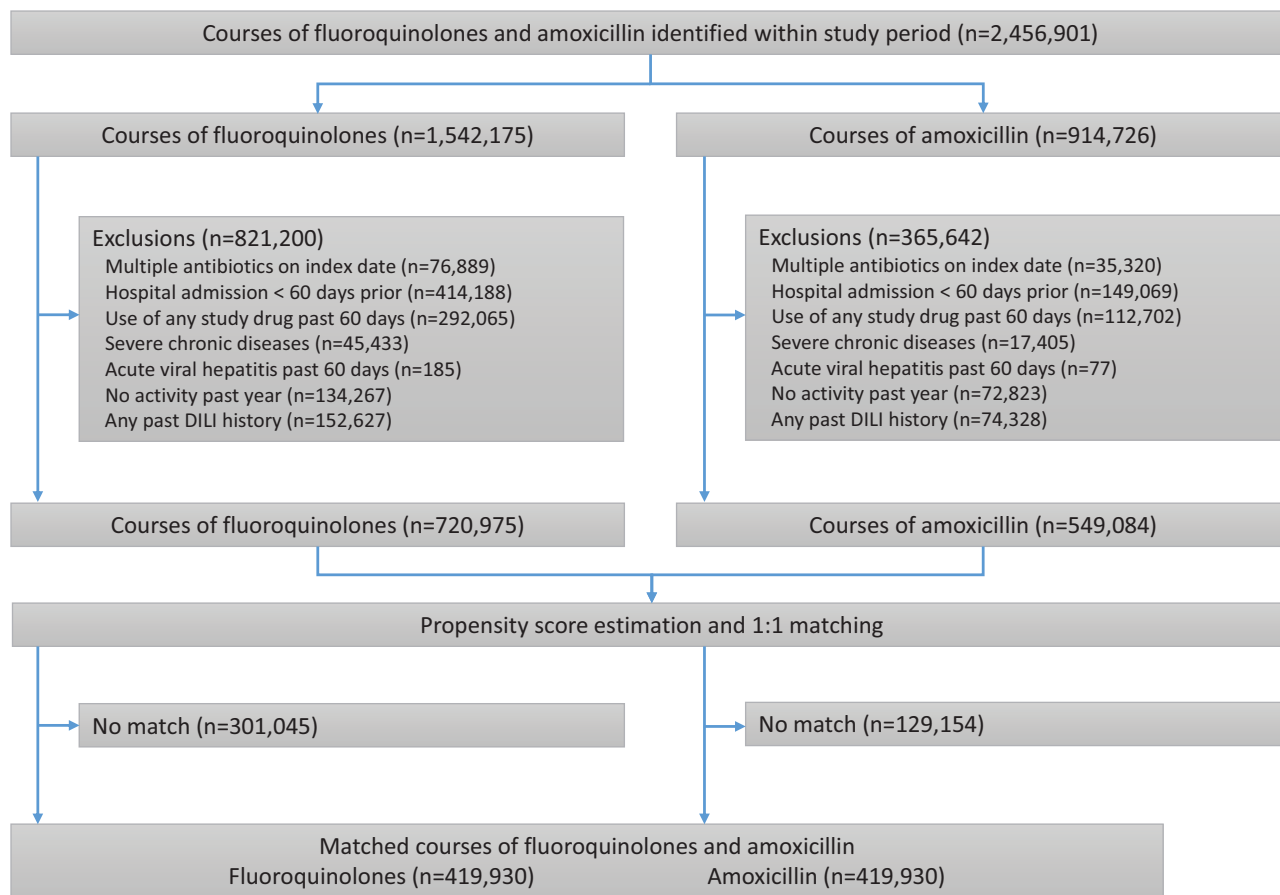
Figure 1. Flowchart of included study drug courses, exclusions, and matched courses based on national registry data in Sweden, 2006–2014.

classified according to sex and age. To estimate homogeneity between the subgroup estimates, we used likelihood ratio tests. As a secondary analysis, Cox regression was used to estimate HRs for all-cause mortality to assess residual confounding from differences in disease severity or underlying health status. Proportional hazards assumption was assessed by evaluating the interaction between treatment status and time scale using Wald test [22]. We estimated the absolute rate difference for the 60-day period as (hazard ratio − 1) × incidence in the amoxicillin group, presented as number of cases per 1 million treatment episodes [23]. The adjusted absolute difference in risk per 1 million episodes of fluoroquinolone use was estimated by multiplying the sum of the adjusted HR minus 1, with the crude rate in users of amoxicillin (see Supplementary Materials for details). All statistical tests were 2-sided where a 95% confidence interval (CI) not overlapping 1.0 and a *P* value < .05 were considered statistically significant. Statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, North Carolina).

Ethical Considerations

The study was approved by the Regional Ethics Committee in Lund (Dnr: 2013/717).

RESULTS

Cohort

During the study period, we identified 1 542 175 courses of oral fluoroquinolone treatment and 914 726 courses of amoxicillin use. The inclusion criteria were met for 720 975 courses of oral fluoroquinolone treatment and 549 084 courses of amoxicillin use. The cohort flowchart is displayed in Figure 1. After applying propensity score matching in a 1:1 ratio, there remained 419 930 courses of fluoroquinolones and amoxicillin. The characteristics were well balanced between the users of fluoroquinolones and the users of amoxicillin (Table 1). The most commonly used fluoroquinolone was ciprofloxacin (79.3%), followed by norfloxacin (17.4%), moxifloxacin (1.78%), levofloxacin (1.11%), and ofloxacin (0.47%). The mean follow-up time in the main (1–60 days) interval was 58.1 days (standard deviation [SD], 8.5 days) in the amoxicillin group and 57.6 days (SD, 9.4 days) in the fluoroquinolone group. Due to switch to another antibiotic, 14.6% of amoxicillin users and 21.3% ciprofloxacin users were censored. Among users of amoxicillin and ciprofloxacin, 10.4% and 12.9%, respectively, were censored due to hospitalization. The difference in proportion of hospitalization in ciprofloxacin users was attributed to admissions for

Table 1. Baseline Characteristics of the Matched Cohort

Characteristic	Amoxicillin, No. (%)	Fluoroquinolones, No. (%)	Standardized Difference
No. in cohort	419 930	419 930	
Male sex	208 235 (49.6)	208 139 (49.6)	<0.10
Age	63.1 (11.5)	63.1 (11.7)	<0.10
Year			
2006–2007	95 462 (22.7)	110 898 (26.4)	<0.10
2008–2009	120 530 (28.7)	115 279 (27.5)	<0.10
2010–2011	109 581 (26.1)	102 154 (24.3)	<0.10
2012–2013	94 357 (22.5)	91 599 (21.8)	<0.10
Region of residence			
Stockholm metropolitan area	106 801 (25.4)	106 637 (25.4)	<0.10
Rest of mid-Sweden	76 341 (18.2)	76 363 (18.2)	<0.10
Southern Sweden metropolitan areas	74 112 (17.6)	74 239 (17.7)	<0.10
Rest of southern Sweden	129 445 (30.8)	129 542 (30.8)	<0.10
Northern Sweden	32 597 (7.8)	32 517 (7.7)	<0.10
Missing	634 (0.2)	632 (0.2)	<0.10
Underlying illnesses/recent procedures			
Acute coronary syndrome	14 541 (3.5)	14 370 (3.4)	<0.10
Other ischemic heart disease	40 093 (9.5)	39 629 (9.4)	<0.10
Heart failure/cardiomyopathy	18 872 (4.5)	18 314 (4.4)	<0.10
Cerebrovascular disease	21 087 (5.0)	21 097 (5.0)	<0.10
Arterial disease	10 516 (2.5)	10 377 (2.5)	<0.10
Respiratory disease	42 375 (10.1)	41 575 (9.9)	<0.10
Cancer	43 811 (10.4)	44 416 (10.6)	<0.10
Cancer in the previous year	29 666 (7.1)	30 206 (7.2)	<0.10
Renal disease	12 061 (2.9)	11 880 (2.8)	<0.10
Rheumatic disease	18 360 (4.4)	18 033 (4.3)	<0.10
Other psychiatric disorder	32 471 (7.7)	32 440 (7.7)	<0.10
Liver procedure	345 (0.1)	373 (0.1)	<0.10
Biliary procedure	220 (0.1)	225 (0.1)	<0.10
Pancreatic procedure	157 (0.0)	152 (0.0)	<0.10
Concomitant drug use			
Platelet inhibitors	94 860 (22.6)	94 677 (22.5)	<0.10
Anticoagulants	27 064 (6.4)	27 037 (6.4)	<0.10
Lipid-lowering drugs	109 269 (26.0)	109 064 (26.0)	<0.10
Oral antidiabetic drugs	32 914 (7.8)	32 767 (7.8)	<0.10
Insulin	21 743 (5.2)	21 634 (5.2)	<0.10
Antidepressants	74 438 (17.7)	74 234 (17.7)	<0.10
Antipsychotics	10 100 (2.4)	10 066 (2.4)	<0.10
Anxiolytics, hypnotics, and sedatives	124 487 (29.6)	124 163 (29.6)	<0.10
Acetaminophen	121 291 (28.9)	121 112 (28.8)	<0.10
Oral corticosteroids	70 061 (16.7)	69 158 (16.5)	<0.10
NSAIDs	131 289 (31.3)	131 086 (31.2)	<0.10
Opiates	95 888 (22.8)	95 592 (22.8)	<0.10
Systemic hormone replacement therapy	66 334 (15.8)	65 228 (15.5)	<0.10
Antibiotic use within the previous 120 days	157 819 (37.6)	159 025 (37.9)	<0.10
No. of concomitant drugs used in the previous year			
1–2	95 612 (22.8)	95 791 (22.8)	<0.10
3–5	128 056 (30.5)	128 209 (30.5)	<0.10
6–9	114 509 (27.3)	114 740 (27.3)	<0.10
≥10	81 753 (19.5)	81 190 (19.3)	<0.10
Healthcare usage			
Hospitalization due to non-hepatobiliary causes in the previous year	141 089 (33.6)	141 323 (33.7)	<0.10
Outpatient contact due to non-hepatobiliary causes in the previous year	236 023 (56.2)	235 664 (56.1)	<0.10
ED visit in the previous 30 days	22 552 (5.4)	23 177 (5.5)	<0.10

Abbreviations: ED, emergency department; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.

urinary tract infections according to discharge codes. The proportional hazards assumption was not violated ($P = .09$).

Main Results

During follow-up, there were 18 events in the fluoroquinolone group and 8 in the amoxicillin group during the main (1–60 days) period (incidence rate, 2.98/10 000 and 1.27/10 000 person-years, respectively). The cumulative incidence for ALI at 60 days was 2.1×10^{-5} in the amoxicillin group and 4.7×10^{-5} in the fluoroquinolone group (Figure 2). There was an increased risk of ALI associated with fluoroquinolone use, with an HR of 2.32 (95% CI, 1.01–5.35). The adjusted absolute risk difference for use of fluoroquinolones as compared to amoxicillin in the 60-day period was 4.94 (95% CI, .04–16.3) per 1 million episodes. The 60-day risk period was divided into 10-day intervals to explore the timing of the association (Table 2); of the 18 cases of ALI in fluoroquinolone users, 12 (67%) occurred in the first 30 days.

Subgroup Analyses

Table 3 includes an overview of the subgroups age and sex; there were no observed differences in these subgroups. There was a trend toward increased risk for men in the older (45–85 years) age group; however, the data did not provide strong enough evidence to support this observation.

Secondary Analyses

There was a difference in the estimated risk of all-cause mortality between the groups in the main (1–60), interval with 609 deaths in the fluoroquinolone group compared to 796 deaths in the amoxicillin group (HR, 0.79 [95% CI, .72–.88]). The difference was primarily seen in the 1- to 30-day period (HR, 0.70 [95% CI, .61–.79]) and not in the 31- to 60-day period (HR, 1.02 [95% CI, .85–1.22]).

DISCUSSION

In this nationwide propensity score–matched cohort study from Sweden, we found a 2-fold increased risk of ALI associated with fluoroquinolone treatment within a 60-day period
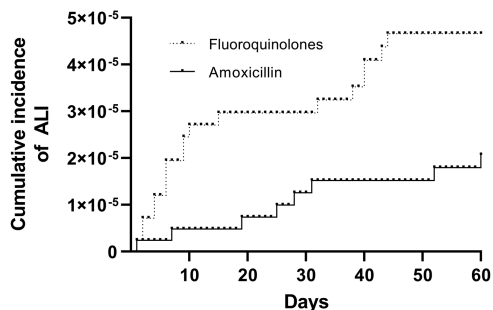
Figure 2. Cumulative incidence of acute liver injury (ALI), fluoroquinolones vs amoxicillin, 1–60 days.

Table 2. Number of Events of Acute Liver Injury Within the 60-Day Risk Period, Divided Into 10-Day Intervals Since Treatment Start

Interval, d	Oral Fluoroquinolones[a] (n = 419 930)	Oral Amoxicillin (n = 419 930)
1–10	11	2
11–20	1	1
21–30	0	2
31–40	4	1
41–50	2	0
51–60	0	2

Data are presented as number of events.
[a]Fluoroquinolone episodes were propensity score matched 1:1 with amoxicillin on 43 different covariates.

after start of treatment. The absolute risk was estimated to be 5 additional events of ALI per 1 million episodes of treatment.

Despite previous safety concerns, only a few studies have assessed the association with ALI in a larger clinical setting [24]. A nested case-control study from Canada including only elderly participants (>66 years of age) reported an odds ratio (OR) of 2.2 for moxifloxacin and an OR of 1.9 for levofloxacin compared to clarithromycin during a follow-up period of 30 days [25]. However, the study lacked information on concurrent drug use and cause of death, factors that potentially confound the outcome of interest. In a retrospective cohort study based on an American insurance claims database, an increased risk for ALI was reported for current use, both for levofloxacin (Relative Risk [RR], 3.2) and for moxifloxacin (RR, 2.3) compared to controls at risk for liver injury [26]. In this study, however, no active comparator drug was used, so it cannot be ruled out that the observed increased risk was attributable to either the acute infection itself or other unmeasured factors associated with filling an antibiotic prescription. In addition, there was a substantial difference in baseline characteristics between cases and controls that were matched on age and sex alone. Furthermore, a North American case-control study based on Veterans Affairs data investigated the risk of ALI associated with fluoroquinolones,

Table 3. Subgroup Analyses of Risk of Acute Liver Injury With Oral Fluoroquinolones Compared With Amoxicillin Use

Analyses	Fluoroquinolones		Amoxicillin			
	Cases of ALI, No.	IR per 10 000 PY	Cases of ALI, No.	IR per 10 000 PY	HR (95% CI)	P Value
Main interval (1–60 d)	18	3.0	8	1.3	2.32 (1.01–5.35)	
Sex						
Women	6	1.9	4	1.2	1.54 (.43–5.46)	.42
Men	12	4.1	4	1.3	3.11 (1.00–9.65)	
Age, y						
40–64	8	2.4	6	1.7	1.37 (.47–3.94)	.14
65–85	10	3.7	2	0.7	5.22 (1.14–23.83)	

Abbreviations: ALI, acute liver injury; CI, confidence interval; HR, hazard ratio; IR, incidence rate; PY, person-years.

and reported an increased risk in users of ciprofloxacin (OR, 1.3) but not in users of levofloxacin and moxifloxacin [27]. The control group in this study was based on patients admitted for myocardial infarction, resulting in a noticeable difference in baseline characteristics between the groups. Also, the cohorts were predominantly male, which could further reduce the external validity. Nevertheless, our results align with these reports, supporting our findings. In addition to previous reports, our study provides some degree of characterization of the timing of this association, suggesting that the risk associated with fluoroquinolones might be most pronounced in the first 10 days after start of treatment; this would correspond to when treatment is ongoing [28].

This study has several strengths. First, the cohorts were based on Swedish national registries with near-complete data coverage, assuring that the results have high representativeness. It has been estimated that the underreporting of data in the Swedish National Inpatient Register is <1% [29]. Second, we used several different strategies to minimize confounding. To control for confounding by indication, we used an active comparator drug without known hepatic toxicity [12]. To balance populations on a large range of underlying differences in health factors, we applied a propensity score–matching model. We excluded patients with severe illnesses to reduce the impact of individuals at high-risk of ALI irrespective of fluoroquinolone treatment. Finally, we also excluded individuals with prior antibiotic prescription or hospitalization as well as individuals with previous history of liver-related illnesses (acute and chronic). This reduced the risk of including individuals at higher risk of the outcome due to underlying illnesses as well as to the fact that we have no information on any treatment initiated during hospital stay. However, residual confounding from lifestyle factors such as alcohol consumption or substance abuse cannot be ruled out. A limitation of this study is that the outcome diagnoses were not formally validated. General validation studies from the Swedish Patient Register suggest that 90%–100% of the diagnoses are correctly coded [29]. A positive predictive value (PPV) of 95% for drug-induced hepatotoxicity was reported in a large study based on Canadian health databases [21]. Additionally, the selected outcome diagnoses used in this study were recently validated in a Danish setting (PPV, 74% [95% CI, 60%–85%]) [20]. Nonetheless, misclassification of the outcome (as reflected in a low PPV) would most likely affect exposed and nonexposed nondifferentially and typically bias the estimate toward null, thus not changing our conclusions [30]. Another limitation is that this study lacked information on the duration of treatment; however, current national recommendations suggest treatments in the range of 7–14 days [28]. Additionally, although the study lacked information on the indication of treatment, the distribution of causes of death in the 2 groups were similar, with pneumonia (*ICD-10* code J189)

as the leading cause of death in both groups. The possibility that initial symptoms of ALI are misinterpreted and patients are prescribed fluoroquinolones (ie, protopathic bias) cannot be ruled out. However, it seems unlikely that this would lead to biased results because of the low probability of a bacterial infection being the cause of the patient's clinical status upon presenting with symptoms of liver failure [31].

When analyzing the risk of all-cause mortality in the 2 groups used in our study, we noted a reduced risk among individuals receiving fluoroquinolones primarily in the 1- to 30-day interval. The difference was slight and not present in the second time interval (31–60 days). The difference could be an indication that amoxicillin is prescribed to patients suffering from more severe infections. This scenario is not unlikely considering that amoxicillin is prescribed to a somewhat wider range of indications compared to fluoroquinolones. This observed difference would, however, lead to an underestimation of the main result rather than the opposite. Considering the balance of covariates in the matched cohort and the similarities of causes of death between the 2 groups, this finding should not hamper the main conclusion of this report. In the present study, the majority of treatment courses with fluoroquinolones consisted of ciprofloxacin, which is why the results are primarily applicable to this fluoroquinolone.

In conclusion, this nationwide cohort study found a 2-fold increased risk of ALI associated with fluoroquinolone treatment. The absolute risk is low, which should be taken into consideration when weighing cost vs benefit on an individual level. However, the worldwide and extensive use of fluoroquinolones must also be taken into regard. Further studies are required to elucidate the potential mechanisms behind these reactions. Naturally, the low absolute risk needs to be taken into consideration when weighing cost vs benefit of initiating treatment with these drugs. Nevertheless, the scope of the worldwide and extensive use of fluoroquinolones is substantial and also must be factored into the overall picture.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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