Risk of Acute Liver Injury Associated with the Use of Moxifloxacin and Other Oral Antimicrobials: A Retrospective, Population-Based Cohort Study

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STUDY OBJECTIVE To estimate the incidence and relative risk of a hospitalization or emergency visit for noninfectious liver injury in users of eight oral antimicrobials—amoxicillin, amoxicillin-clavulanic acid, clarithromycin, cefuroxime, doxycycline, levofloxacin, moxifloxacin, telithromycin—compared with nonusers of these antimicrobials.

DESIGN Retrospective, observational cohort study with a nested case-control analysis.

DATA SOURCE HealthCore Integrated Research Database.

PATIENTS Adults with continuous health plan enrollment for at least 6 months before study entry who had a new dispensing of a study antimicrobial between July 1, 2001, and March 31, 2009. Cases had diagnoses indicating noninfectious liver injury during follow-up. To control for potentially confounding risk factors, 10 controls at risk for liver injury during follow-up were matched to each case by age, sex, and event date (liver injury date of the case), and analyses were adjusted for medical history, concomitant drugs, and health care service use.

MEASUREMENTS AND MAIN RESULTS Two physician reviewers (blind to exposure) validated the cases. Among 1.3 million antimicrobial users, we identified 607 cases of liver injury, including 82 cases of severe hepatocellular injury and 11 cases of liver failure. Liver injury incidence in nonusers of study antimicrobials was 35/100,000 person-years (95% confidence interval [CI] 29–42/100,000 person-years). For valid cases, the adjusted relative risk among current users of multiple antimicrobials was 3.2 (95% CI 1.6–6.7). Levofloxacin had the highest relative risk for current single use (3.2, 95% CI 1.8–5.8). Relative risks were also elevated for amoxicillin-clavulanic acid (2.5, 95% CI 1.3–5.0), doxycycline (2.5, 95% CI 1.2–5.2), moxifloxacin (2.3, 95% CI 1.1–4.7), and amoxicillin (2.3, 95% CI 1.1–4.7).

CONCLUSION The results support a comparatively high adjusted relative risk of liver injury among patients exposed concurrently to multiple antimicrobials and modest elevations in the risk for several antimicrobials used alone; however, we found little evidence of any strong effect of commonly used antimicrobials on the risk of liver injury.

KEY WORDS antinfective agents, drug-induced liver injury, epidemiology, fluoroquinolones, moxifloxacin, levofloxacin, amoxicillin, telithromycin.

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Acute noninfectious liver injury is rare in the general population, with an estimated incidence of 2.4–14.8 cases/100,000 person-years.1–7 Antimicrobials are a relatively frequent cause, in part because they are commonly used.8 The risk of liver injury is particularly high among patients who received isoniazid9 or pyrazinamide8 for tuberculosis. Many other antimicrobials, including β-lactams, macrolides, ketolides, fluoroquinolones, sulfonamides, and tetracyclines, have also been implicated.8

The present study fulfilled a regulatory requirement related to the potential for hepatotoxicity with use of moxifloxacin, a fluoroquinolone used to treat respiratory, pelvic, skin, and complicated intraabdominal infections. An unpublished United States insurance claims study using the PharMetrics database, with no validation of end points, estimated the risk of severe liver injury requiring hospitalization among moxifloxacin users at 16.9/100,000 prescriptions, more than 2-fold higher than with amoxicillin-clavulanic acid.10 A warning concerning hepatic toxicity was added to the moxifloxacin U.S. labeling in 2007.11 In Europe, moxifloxacin was restricted to second-line indications in 2008, and prospective cohort and nested case-control study, with regulatory authorities, we conducted a retrospective cohort and nested case-control study,

controlling for potentially confounding risk factors, and estimated the incidence and relative risk of liver injury among antimicrobial users and nonusers in a broad study population.

Methods

Study Design, Data Source, and Patient Population

We conducted a retrospective, observational cohort study of adults in the HealthCore Integrated Research Database who had a new dispensing of a study antimicrobial between July 1, 2001, and March 31, 2009. To reduce end point misclassification, we included an extensive case validation process.

HealthCore, Inc., is a wholly owned subsidiary of WellPoint, Inc. (Indianapolis, IN), one of the largest health benefits companies in the United States and an independent licensee of the Blue Cross and Blue Shield Association, serving members who are geographically dispersed throughout the United States. Participating insurance plans are based in 14 states, but members of those plans may reside in states different from where their plan is based. Participating insurance plans are geographically dispersed throughout the United States. The database contains fully adjudicated paid claims with dates of service for all emergency department, inpatient, and outpatient encounters for members with eligibility at the time of service, including visits with primary care physicians and specialists. Claims for medical services are associated with diagnoses using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding. Inpatient and outpatient medical records for health plan members with claims data in the database can be abstracted in a deidentified manner for health research purposes. In August 2009, the database contained claims information on 31 million people, mostly insured through employer-based programs. Information from the database has been used extensively in conducting pharmacoepidemiology research16–20 and it constitutes part of the Sentinel Network developed under mandate of the U.S. Congress to detect and confirm drug safety signals rapidly and quantitatively.21

Study Eligibility

Eligible new users of the study antimicrobials were at least 18 years old with continuous health plan enrollment (both medical and prescription
coverage) for 6 months or more before study entry, defined as the first date of dispensing of oral amoxicillin, amoxicillin-clavulanic acid, clarithromycin, cefuroxime, doxycycline, levofloxacin, moxifloxacin, or telithromycin, with no use of any study antimicrobial within the previous 6 months. We omitted parenteral formulations, which had little use in the database, and nonsystemic formulations.

We excluded patients with acute or chronic infectious hepatitis, chronic alcoholism or alcoholic cirrhosis, or human immunodeficiency virus infection or acquired immunodeficiency syndrome before entry. Late pregnancy and the puerperium were temporary exclusions from study person-time. Follow-up terminated with diagnosis of liver injury, occurrence of an exclusion diagnosis, health plan disenrollment, death, or end of the study period, whichever occurred first.

To use resources for case validation efficiently, we randomly sampled from the base population to create new user cohorts approximately the same size as the entire moxifloxacin group at entry. However, because individuals aged over 65 years are underrepresented in the database, we oversampled eligible patients in this age group.

**Exposure Classification**

We defined “current use” of each antimicrobial as the prescribed duration plus 30 days. “Recent use” extended for 90 days after the end of current use; subsequent time was classified as “nonuse.” Patients could again contribute person-time of use if they had a subsequent dispensing of the same antimicrobial. Because antimicrobials are generally prescribed for short periods, most follow-up time would have been classified as nonuse; therefore, we truncated accrual of nonuse person-time after 90 days (i.e., nonuse extended from 121–210 days after the end of prescribed use). This truncation should not bias effect estimates because the background event rate during the subsequent (excluded) nonuse person-time should be similar to that during the nonuse person-time evaluated.

To refine the analysis of each antimicrobial, we defined “current single use” as current use of a study antimicrobial with no current or recent use of any other, “recent single use” as recent use of a study antimicrobial with no current or recent use of any other, “current single use with recent use” as current use of an antimicrobial with recent use of one or more of the others, “current multiple use” as current use of more than one antimicrobial, and “recent multiple use” as recent use of more than one antimicrobial with no current use of another. The referent category was “nonuse” of any study antimicrobial.

**Case Screening and Validation**

We screened for potential cases based on ICD-9-CM emergency department or hospital discharge claims diagnoses indicating liver injury (570.xx, acute and subacute necrosis of liver; 572.2x, hepatic coma; 573.3x, hepatitis unspecified). Criteria for the primary study outcome, liver injury, were based on those from an international consensus meeting: alanine aminotransferase level more than 2 times the upper limit of normal; total bilirubin level more than 2 times the upper limit of normal; or any increase of aspartate aminotransaminase, alkaline phosphatase, and total bilirubin level with at least one measurement of more than 2 times the upper limit of normal. Severe liver injury was defined according to a modification of Hy's Law criteria: alanine aminotransferase level at least 3 times the upper limit of normal and total bilirubin level at least 2 times the upper limit of normal. Liver failure was defined as liver injury with any degree of mental alteration (encephalopathy) and either an increase in prothrombin time or an international normalized ratio more than 2 without anticoagulation, adapted from previous literature. Severe liver injury and liver failure cases are subsets of the primary outcome (liver injury).

For validation, the corresponding medical records were abstracted by trained reviewers by using a standardized form to collect anonymized information on liver test results, diagnoses, imaging and pathology results, and deaths (which were also ascertained in the Social Security Administration death master file). Two authoring physicians, blinded to patients' antimicrobial exposure, reviewed the abstracted information. Potential cases were “valid” if they met the liver test criteria and had no excluded diagnosis, “noncases” if the information indicated that they did not meet all case criteria or had any excluded diagnosis, and “uncertain” if the information available was insufficient.

**Incidence Estimation**

We estimated crude and age-sex–standardized incidence rates and 95% confidence intervals.
(CIs) with nonuse person-time as the standard because it reflects the background rate among the study cohort. Standardized incidence rate ratios (by age and sex) and 95% CIs were also calculated.

Case-Control Analysis

Ten controls at risk for liver injury during eligible person-time were matched to each case by age and sex. Each control was randomly selected on the liver injury date of the case (event date) to which it was matched (incidence density sampling). We used conditional logistic regression to estimate odds ratios, representing incidence rate ratios, described herein as relative risks. We controlled for prior liver disease (other than exclusion diagnoses), diseases of the biliary tract or pancreas, concurrent use of potentially hepatotoxic drugs, and measures of health care utilization (hospitalization days, outpatient visits, and unique prescription drugs during the 6 months before the event date).

The main analysis combined valid and uncertain cases (as defined earlier). Separately, we also analyzed only valid cases. Finally, since many cases had diseases that could cause liver test abnormalities unrelated to the study antimicrobials, we also analyzed only cases without such diagnoses.

Human Subjects Protection

The protocol followed current pharmacoepidemiology research guidelines and was granted exemption from informed consent requirements by the RTI International institutional review board.

Results

Study Cohort and Patterns of Antimicrobial Use

We identified 1,299,056 eligible patients. Demographic characteristics at cohort entry are summarized by antimicrobial exposure in Table 1. A smaller proportion of telithromycin users were aged 65 years or older, and smaller proportions of moxifloxacin and levofloxacin users were in the youngest age categories. There were more women than men among users of all antimicrobials.

The numbers of patients and person-years of current and recent use of each of the antimicrobials during follow-up are presented in Table 2. Nearly 14% of patients were currently exposed to more than one study antimicrobial at any time during follow-up.

Altogether, 1,056,239 patients (81.3% of cohort members) contributed nonuse person-time during follow-up, totaling 350,873 person-years; the remaining 18.7% had fewer than 120 days of eligible follow-up time after the end of prescribed use of a study antimicrobial without further use of the same antimicrobial to which they were already exposed or to another study antimicrobial.

Cases of Liver Injury

In screening, we found 715 potential cases of liver injury. Case validation results are shown in Figure 1. Of the 420 cases with adequate records, 312 were valid and 108 were not cases; 295 were of uncertain status (as defined earlier).

Of the 312 valid cases, 82 (26.3%) had sufficiently abnormal liver test results to qualify as cases of severe liver injury, and 11 (3.5%) had liver failure. Medical record review indicated that of the 312 valid cases, 221 (70.8%) had diagnoses that could have caused liver test abnormalities (e.g., cholecystitis, metastatic cancer, congestive heart failure, sepsis) and 63 (20.2%) had diagnoses of noninfectious hepatitis with no other diagnoses that would plausibly cause abnormal liver test results.

Since 74% of potential cases with adequate records were valid, we combined the 312 valid cases with the 295 uncertain cases in the main analyses. Of these 607 cases, 32 (5.3%) were known to have died.

Incidence Estimates

Age-sex–standardized incidence rates/100,000 person-years and rate ratios (compared with nonuse) are reported in Table 3. The rate of liver injury was highest during current use of multiple antimicrobials. Rates during current single use of each antimicrobial were generally higher than corresponding rates during recent single use except for telithromycin, for which the rates were similar (but based on small numbers). Rates during current single use were somewhat higher for levofloxacin, moxifloxacin, and amoxicillin-clavulanic acid than for the other study antimicrobials and were lowest for telithromycin. There were few cases with current
Table 1. Study Population Characteristics and Antimicrobial Exposure at Cohort Entry

| Characteristic                      | Total (n=1,299,056) | Amoxicillin (n=166,888) | Amoxicillin-clavulanic acid (n=178,047) | Cefuroxime (n=151,238) | Clarithromycin (n=156,774) | Doxycycline (n=181,332) | Levofloxacin (n=181,332) | Moxifloxacin (n=176,934) | Telithromycin (n=79,357) | Current Multiple Use (n=31,692) |
|-------------------------------------|----------------------|-------------------------|-----------------------------------------|------------------------|---------------------------|--------------------------|--------------------------|--------------------------|--------------------------|-------------------------------|
| **Age distribution at cohort entry**|                      |                         |                                         |                        |                           |                          |                          |                          |                          |                               |
| 18–24                               | 115,695 (8.9)        | 17,063 (10)             | 19,137 (11)                             | 16,353 (11)            | 22,200 (13)               | 9915 (5)                 | 9088 (5)                 | 6905 (9)                 | 1807 (6)                 |                               |
| 25–34                               | 201,163 (15.5)       | 26,172 (16)             | 30,728 (17)                             | 25,212 (17)            | 24,298 (15)               | 31,517 (18)              | 21,759 (12)              | 22,488 (13)              | 14,019 (18)               | 4970 (16)                    |
| 35–44                               | 280,137 (21.6)       | 31,535 (19)             | 39,045 (22)                             | 36,157 (24)            | 35,898 (23)               | 35,767 (20)              | 35,346 (19)              | 38,069 (22)              | 20,634 (26)               | 7644 (24)                    |
| 45–54                               | 281,850 (21.7)       | 30,575 (18)             | 35,450 (20)                             | 34,287 (23)            | 34,384 (22)               | 33,201 (19)              | 41,890 (23)              | 44,337 (25)              | 19,801 (25)               | 7936 (25)                    |
| 55–64                               | 203,881 (15.7)       | 21,722 (13)             | 22,102 (12)                             | 23,855 (16)            | 21,397 (14)               | 22,850 (13)              | 37,214 (21)              | 36,267 (20)              | 12,828 (16)               | 5680 (18)                    |
| 65–74                               | 125,061 (9.6)        | 22,321 (13)             | 19,271 (11)                             | 8343 (6)               | 18,466 (12)               | 18,529 (10)              | 17,476 (10)              | 14,905 (8)               | 3406 (4)                  | 2161 (7)                     |
| 75–84                               | 67,474 (5.2)         | 13,485 (8)              | 9080 (5)                                | 4855 (3)               | 7210 (5)                  | 9772 (6)                 | 12,227 (7)               | 8396 (5)                 | 1367 (2)                  | 1108 (3)                     |
| 85+                                 | 23,775 (1.8)         | 3813 (2)                | 3234 (2)                                | 2176 (1)               | 1938 (1)                  | 2998 (2)                 | 5505 (3)                 | 3364 (2)                 | 397 (1)                   | 386 (1)                      |
| **Sex**                             |                      |                         |                                         |                        |                           |                          |                          |                          |                          |                               |
| Male                                | 567,346 (43.7)       | 70,661 (42)             | 81,855 (46)                             | 59,402 (39)            | 69,917 (45)               | 78,201 (44)              | 79,216 (44)              | 78,494 (44)              | 33,859 (43)               | 15,741 (50)                  |
| Female                              | 731,710 (56.3)       | 96,227 (58)             | 96,192 (54)                             | 91,836 (61)            | 86,857 (55)               | 98,593 (56)              | 102,116 (56)             | 98,440 (56)              | 45,498 (57)               | 15,951 (50)                  |
| **Calendar year at cohort entry**    |                      |                         |                                         |                        |                           |                          |                          |                          |                          |                               |
| 2001                                | 46,713 (3.6)         | 6421 (4)                | 5067 (3)                                | 9224 (6)               | 9209 (6)                  | 6963 (4)                 | 4309 (2)                 | 3308 (2)                 | 0 (0)                     | 1592 (5)                     |
| 2002                                | 89,332 (6.9)         | 11,954 (7)              | 11,438 (6)                              | 14,568 (10)            | 17,475 (11)               | 12,939 (7)               | 9781 (5)                 | 8008 (5)                 | 0 (0)                     | 3169 (10)                    |
| 2003                                | 79,682 (6.1)         | 10,454 (6)              | 10,892 (6)                              | 10,678 (7)             | 15,032 (10)               | 11,379 (6)               | 11,069 (6)               | 7450 (4)                 | 0 (0)                     | 2728 (9)                     |
| 2004                                | 162,543 (12.5)       | 22,097 (13)             | 21,547 (12)                             | 17,205 (11)            | 20,704 (13)               | 22,200 (13)              | 23,105 (13)              | 19,011 (11)              | 12,748 (16)               | 3926 (12)                    |
| 2005                                | 265,856 (20.5)       | 32,513 (19)             | 32,166 (18)                             | 25,981 (17)            | 30,385 (19)               | 32,625 (18)              | 34,861 (19)              | 29,967 (17)              | 42,516 (34)               | 4842 (15)                    |
| 2006                                | 235,133 (18.1)       | 29,526 (18)             | 30,891 (17)                             | 23,700 (16)            | 24,244 (15)               | 29,772 (17)              | 34,834 (19)              | 34,694 (20)              | 22,067 (28)               | 5405 (17)                    |
| 2007                                | 220,427 (17.0)       | 27,612 (17)             | 32,846 (18)                             | 24,866 (16)            | 21,225 (14)               | 29,881 (17)              | 34,520 (19)              | 42,389 (24)              | 1937 (2)                  | 5151 (16)                    |
| 2008                                | 160,072 (12.3)       | 21,191 (13)             | 25,759 (14)                             | 19,511 (13)            | 14,584 (9)                | 25,180 (14)              | 23,496 (13)              | 26,341 (15)              | 85 (0)                    | 3925 (12)                    |
| 2009                                | 39,298 (3.0)         | 5120 (3)                | 6821 (4)                                | 5505 (4)               | 3916 (2)                  | 5855 (3)                 | 5357 (3)                 | 5766 (3)                 | 4 (0)                     | 954 (3)                      |

Data are no. (%) of patients.

Patients counted as being exposed to each antimicrobial are those exposed to a single antimicrobial at cohort entry. Patients with current use of more than one antimicrobial at cohort entry are counted only in the column for current multiple use. Because of the sampling plan, the numbers of patients exposed to each of the antimicrobials at entry were similar except for those exposed to telithromycin, which was prescribed considerably less commonly than any of the other drugs.
use of a single antimicrobial with recent use of at least one other antimicrobial; these rates were quite variable. Rate ratios (compared with non-use) mirror all of these findings.

In the stratified analysis, the incidence rate of liver injury during nonuse was lowest among patients aged 25–34 years (11, 95% CI 3.7–26) and increased to a peak among patients aged 85 years or older (137, 95% CI 66–251). The rate among women (37, 95% CI 29–46) was slightly higher than that among men (33, 95% CI 25–44).

The incidence rates and rate ratios for severe liver injury were greater than those for the primary outcome (Table 3). The highest incidence rate was observed for current multiple use; those for recent multiple use were lower than those for current multiple use, and those for current single use were somewhat higher for levofloxacin, moxifloxacin, and amoxicillin-clavulanic acid than for the other antimicrobials.

Case-Control Analyses

Characteristics of the cases and controls are presented in Table 4. Cases were more likely than controls to have a history of chronic diseases, including congestive heart failure, chronic pulmonary disease, diabetes mellitus, renal disease, and malignancy. Severity of concomitant

Table 2. Antimicrobial Exposure During Follow-Up for the 1,299,056 Study Patients

| Antimicrobial                          | No. of Patients | Current Use (Person-Years) | Recent Use (Person-Years) |
|----------------------------------------|----------------|---------------------------|--------------------------|
| Amoxicillin                            | 352,614        | 56,886                    | 109,142                  |
| Amoxicillin-clavulanic acid            | 309,593        | 43,922                    | 85,272                   |
| Cefuroxime                             | 182,786        | 25,179                    | 47,647                   |
| Clarithromycin                         | 245,865        | 34,524                    | 66,206                   |
| Doxycycline                            | 254,535        | 49,998                    | 65,446                   |
| Levofloxacin                           | 331,891        | 52,383                    | 97,197                   |
| Moxifloxacin                           | 226,375        | 29,373                    | 58,374                   |
| Telithromycin                          | 95,887         | 10,745                    | 24,210                   |
| Multiple study antimicrobials<sup>c</sup> | 180,116        | 15,915                    | 40,374                   |

Data in this table are shown for all the patients in the study. However, patients could have had exposure to more than one study drug during their follow-up and thus could be counted in the multiple study antimicrobials group as well as in one or more single antimicrobial lines; therefore, the numbers in the “No. of Patients” column add up to more than the total number of patients in the study.

<sup>a</sup>Current use is defined as the prescribed duration of the antimicrobial plus 30 days.

<sup>b</sup>Recent use is defined as a duration of 90 days after the end of current use of the antimicrobial.

<sup>c</sup>Multiple study antimicrobials is defined as current use of two or more study antimicrobials on the same day or recent use of two or more study antimicrobials on the same day.
| Antimicrobial Exposure | Person-years (n=1,117,323) | Liver Injury | Incidence Rate | 95% CI | Incidence Rate Ratio | 95% CI | Severe Liver Injury | Incidence Rate | 95% CI | Incidence Rate Ratio | 95% CI |
|-----------------------|-----------------------------|--------------|----------------|-------|---------------------|-------|---------------------|----------------|-------|---------------------|-------|
| Nonuse                | 350,873                     | 123          | 35.1           | 29.1–41.8 | REF                 | REF   | 82                  | 2.6            | 1.2–4.9 | REF                 | REF   |
| Current single use    |                             |              |                |       |                     |       |                     |                |       |                     |       |
| Amoxicillin           | 44,555                      | 23           | 51.0           | 32.2–77.0 | 1.45                | 0.93–2.28 | 4                  | 9.4           | 2.5–24.3 | 3.67                | 1.12–12.0 |
| Amoxicillin-clavulanic acid | 35,529                | 30           | 86.0           | 57.8–123.1 | 2.45                | 1.64–3.67 | 5                  | 13.1          | 4.2–31.2 | 5.10                | 1.70–15.31 |
| Cefuroxime            | 21,456                      | 14           | 70.3           | 37.3–120.2 | 2.01                | 1.13–3.56 | 2                  | 11.5          | 1.2–41.0 | 4.48                | 0.93–21.63 |
| Clarithromycin        | 25,593                      | 16           | 64.4           | 36.3–105.3 | 1.84                | 1.08–3.13 | 1                  | 6.8           | 0.2–30.8 | 2.67                | 0.34–21.06 |
| Doxycycline           | 42,994                      | 19           | 46.6           | 27.9–73.0  | 1.33                | 0.82–2.17 | 3                  | 7.4           | 1.5–21.5 | 2.90                | 0.78–10.75 |
| Levofloxacin          | 39,974                      | 38           | 134.3          | 101.2–175.0 | 3.83                | 2.79–5.27 | 10                 | 22.9          | 10.8–42.9 | 8.92                | 3.59–22.17 |
| Moxifloxacin          | 24,901                      | 30           | 116.4          | 78.4–166.7 | 3.32                | 2.22–4.96 | 3                  | 10.6          | 2.2–32.1 | 4.12                | 1.11–15.22 |
| Telithromycin         | 9175                        | 3            | 26.6           | 5.3–83.1   | 0.76                | 0.24–2.38 | 1                  | 8.9           | 0.2–56.2 | 3.45                | 0.44–27.25 |
| Recent single use     |                             |              |                |       |                     |       |                     |                |       |                     |       |
| Amoxicillin           | 87,527                      | 27           | 29.0           | 19.0–42.6  | 0.83                | 0.54–1.26 | 3                  | 3.5           | 0.7–10.4 | 1.36                | 0.37–5.08 |
| Amoxicillin-clavulanic acid | 66,390                | 26           | 42.4           | 27.6–62.1  | 1.21                | 0.79–1.85 | 2                  | 3.0           | 0.3–11.2 | 1.18                | 0.25–5.68 |
| Cefuroxime            | 38,510                      | 12           | 28.9           | 14.8–51.5  | 0.82                | 0.45–1.50 | 1                  | 2.1           | 0.1–14.1 | 0.83                | 0.11–6.57 |
| Clarithromycin        | 48,097                      | 12           | 25.1           | 12.9–43.9  | 0.72                | 0.39–1.30 | 1                  | 2.8           | 0.1–13.7 | 1.09                | 0.14–8.59 |
| Doxycycline           | 54,641                      | 18           | 31.6           | 18.6–50.1  | 0.90                | 0.55–1.48 | 1                  | 1.8           | 0.0–10.2 | 0.71                | 0.09–5.64 |
| Levofloxacin          | 73,615                      | 57           | 70.9           | 53.4–92.4  | 2.02                | 1.47–2.78 | 8                  | 10.0          | 4.3–20.1 | 3.91                | 1.50–10.22 |
| Moxifloxacin          | 46,732                      | 25           | 52.6           | 34.0–77.8  | 1.30                | 0.97–2.31 | 5                  | 10.0          | 3.2–23.7 | 3.91                | 1.31–11.70 |
| Telithromycin         | 19,404                      | 4            | 29.2           | 15.0–80.6  | 0.83                | 0.24–2.89 | 0                  | 0.0           | 0.0–19.3 | 0.00                | 0.00–NE |
| Current multiple use  | 13,915                      | 37           | 234.3          | 164.8–323.9 | 6.69                | 4.63–9.67 | 7                  | 44.7          | 18.0–92.5 | 17.44               | 6.50–46.84 |
| Recent multiple use   | 40,374                      | 36           | 88.4           | 61.9–122.7 | 2.52                | 1.74–3.66 | 8                  | 19.8          | 8.5–39.3 | 7.72                | 2.98–20.01 |

CI = confidence interval; NE = not estimable; REF = reference category.

*Incidence rates are per 100,000 person-years. Standardization is by age and sex. Data are not shown for 29,068 person-years of exposure in which patients had current use of a single study antimicrobial and concurrent recent use of at least one other study antimicrobial, nor for 37 cases of liver injury (8 of which were severe liver injury) that occurred during this person-time.
diseases was specified as in the Deyo-Charlson Comorbidity Index.30
The exposure and covariate distributions of the cases and controls and adjusted relative risks for liver injury for both valid and uncertain cases combined (607 cases) are presented in Table 5, Analysis 1. The highest relative risk of any exposure category was associated with current multiple use. Among current single users, the relative risks were somewhat higher for levofloxacin, amoxicillin-clavulanic acid, and amoxicillin than for the other antimicrobials.

Relative risks for liver injury were elevated for prior liver disease, prior disease of the biliary tract or pancreas, congestive heart failure, peptic ulcer disease, metastatic solid tumor, and Deyo-Charlson Comorbidity Index score of 3 or higher. Relative risks of liver injury also increased with increasing number of hospital days, outpatient visits, and unique prescription drugs during the 6 months before the event date.

We restricted a second analysis to only valid cases (312 cases; Table 5, Analysis 2). The pattern of results was similar to that in Analysis 1, but most relative risks were somewhat higher. In this analysis, the relative risk for telithromycin was elevated (with only two exposed cases).

In another approach to control potential confounding, we restricted the analysis to valid cases for which we found no evident cause of abnormal liver test results among their discharge diagnoses (63 cases; Table 5, Analysis 3). Again, the relative risk associated with current multiple use was markedly elevated. Among current single users, the relative risk was highest for telithromycin (based on a single case). The relative risks for levofloxacin, amoxicillin-clavulanic acid, amoxicillin, and moxifloxacin were also elevated; for cefuroxime, clarithromycin, and doxycycline, no cases or only one case occurred in current, singly exposed patients. Due to the smaller number of cases and controls in this analysis, it was not possible to include all components of the Deyo-Charlson Comorbidity Index, but exclusion of cases with diseases such as congestive heart failure and metastatic cancer is expected to accomplish a similar purpose.

Analysis 4 (Table 5) focused on cases of severe liver injury. The patterns were similar to those in previous analyses, with the highest relative risk again observed among patients with current multiple use. Relative risks were elevated for current single use of all the antimicrobials, but were higher for levofloxacin, amoxicillin-clavulanic acid, amoxicillin, and telithromycin than for the others.

Among 11 cases of liver failure, five patients had current or recent single use of levofloxacin, whereas among 607 cases of liver injury overall, only 115 (19%) were so exposed. No liver failure occurred during current or recent single use of moxifloxacin; no cases of liver failure occurred during nonuse, precluding relative risk computation.

Discussion

Automated health databases provide a valuable resource for examining infrequent events like

| Table 4. Characteristics of the Cases and Controls |
|-----------------------------------------------|
| Characteristic | Cases | Controls |
|----------------|-------|----------|
| (n=607)        | (n=6070) |          |
| Sex            |       |          |
| Male           | 274 (45) | 2740 (45) |
| Female         | 333 (55) | 3330 (55) |
| Age (years)    |       |          |
| 18–24          | 23 (4) | 230 (4)  |
| 25–34          | 48 (8) | 480 (8)  |
| 35–44          | 78 (13)| 780 (13)|
| 45–54          | 129 (21)| 1290 (21)|
| 55–64          | 128 (21)| 1280 (21)|
| 65–74          | 99 (16)| 990 (16)|
| 75–84          | 77 (13)| 770 (13)|
| ≥ 85           | 25 (4) | 250 (4)  |
| Event year     |       |          |
| 2001           | 6 (1) | 60 (1)   |
| 2002           | 23 (4) | 230 (4)  |
| 2003           | 35 (6) | 350 (6)  |
| 2004           | 51 (8) | 510 (8)  |
| 2005           | 112 (18)| 1120 (18)|
| 2006           | 105 (17)| 1050 (17)|
| 2007           | 117 (19)| 1170 (19)|
| 2008           | 128 (21)| 1280 (21)|
| 2009           | 30 (5) | 300 (5)  |
| Comorbidities  |       |          |
| Myocardial infarction | 73 (12)| 194 (3)  |
| Congestive heart failure | 154 (25)| 367 (6)  |
| Peripheral vascular disease | 71 (12)| 257 (4)  |
| Cerebrovascular disease | 114 (19)| 529 (9)  |
| Dementia        | 15 (2) | 69 (1)   |
| Chronic pulmonary disease | 233 (38)| 1298 (21)|
| Rheumatologic disease | 41 (7) | 141 (2)  |
| Peptic ulcer disease | 42 (7) | 112 (2)  |
| Mild liver disease | 28 (5) | 11 (0)   |
| Mild-to-moderate | 133 (23)| 775 (13)|
| diabetes mellitus |       |          |
| Hemiplegia or paraplegia | 9 (1)  | 29 (0)   |
| Moderate or severe renal disease | 86 (14) | 152 (3)  |
| Diabetes with complications | 47 (8)  | 166 (3)  |
| Malignancy       | 164 (27)| 565 (9)  |
| Moderate-to-severe liver disease | 17 (3)  | 1 (0)    |
| Metastatic solid tumor | 62 (10)| 111 (2)  |

Data are no. (%) of patients.
| Category                                      | Analysis 1: Liver Injury | Analysis 2: Valid Cases of Liver Injury |
|----------------------------------------------|--------------------------|----------------------------------------|
| Cases, n (%)                                | Controls, n (%)          | OR 95% CI                              |
| Total no.                                    | 607                      | 6070                                   |
| Nonuse                                       | 123 (20.3)               | 1680 (27.7)                           |
| Current single use                           |                          |                                        |
| Amoxicillin                                  | 23 (3.8)                 | 287 (4.7)                             |
| Amoxicillin-clavulanic acid                  | 30 (4.9)                 | 272 (4.5)                             |
| Cefuroxime                                   | 14 (2.3)                 | 186 (3.1)                             |
| Clarithromycin                               | 16 (2.6)                 | 189 (3.1)                             |
| Doxycycline                                  | 19 (3.1)                 | 278 (4.6)                             |
| Levofloxacin                                 | 58 (9.6)                 | 328 (5.4)                             |
| Moxifloxacin                                 | 30 (4.9)                 | 253 (4.2)                             |
| Telithromycin                                | 3 (0.5)                  | 70 (1.2)                              |
| Recent multiple use                          |                          |                                        |
| Amoxicillin                                  | 27 (4.5)                 | 366 (6.0)                             |
| Amoxicillin-clavulanic acid                  | 26 (4.3)                 | 303 (5.0)                             |
| Cefuroxime                                   | 12 (2.0)                 | 172 (2.8)                             |
| Clarithromycin                               | 12 (2.0)                 | 262 (4.3)                             |
| Doxycycline                                  | 18 (3.0)                 | 266 (4.4)                             |
| Levofloxacin                                 | 57 (9.4)                 | 357 (5.9)                             |
| Moxifloxacin                                 | 25 (4.1)                 | 305 (5.0)                             |
| Telithromycin                                | 4 (0.7)                  | 88 (1.5)                              |
| Current multiple use                         | 37 (6.1)                 | 120 (2.0)                             |
| Recent multiple use                          | 36 (5.9)                 | 183 (3.0)                             |
| Mean age (yrs)                               | 56.5                     | 56.1                                  |
| Prior liver disease                          | 81 (13.3)                | 97 (1.6)                              |
| Prior disease of biliary tract or pancreas   | 202 (33.3)               | 220 (3.6)                             |
| Prior or concurrent use of other potentially hepatotoxic drugs | 407 (67.1) | 3046 (50.2) |
| Individual comorbidities of the Deyo-Charlson Comorbidity Index | | |
| Myocardial infarction                        | 73 (12.0)                | 194 (3.2)                             |
| Congestive heart failure                     | 154 (25.4)               | 367 (6.1)                             |
| Peripheral vascular disease                  | 71 (11.7)                | 257 (4.2)                             |
| Cerebrovascular disease                      | 114 (18.8)               | 529 (8.7)                             |
| Dementia                                     | 15 (2.5)                 | 69 (1.1)                              |
| Chronic pulmonary disease                    | 233 (38.4)               | 1298 (21.4)                           |
| Rheumatologic disease                        | 41 (6.8)                 | 141 (2.3)                             |
| Peptic ulcer disease                         | 42 (6.9)                 | 112 (1.9)                             |
| Mild liver disease                           | 28 (4.6)                 | 11 (0.2)                              |
| Mild-to-moderate diabetes mellitus           | 153 (25.2)               | 775 (12.8)                            |
| Hemiplegia or paraplegia                    | 9 (1.5)                  | 29 (0.5)                              |
| Moderate-to-severe renal disease             | 86 (14.2)                | 152 (2.5)                             |

(continued)
Table 5. (continued)

| Category                                      | Analysis 1: Liver Injury |   | Analysis 2: Valid Cases of Liver Injury |   |
|-----------------------------------------------|--------------------------|---|----------------------------------------|---|
|                                               | Cases, n (%) | Controls, n (%) | OR     | 95% CI                  | Cases, n (%) | Controls, n (%) | OR     | 95% CI                  |
| Diabetes with complications                   |             |                 |        |                        |             |                 |        |                        |
| Malignancy                                    |              |                 |        |                        |              |                 |        |                        |
| Moderate-to-severe liver disease              |              |                 |        |                        |              |                 |        |                        |
| Metastatic solid tumor                        |              |                 |        |                        |              |                 |        |                        |
| Acquired immunodeficiency syndrome            |              |                 |        |                        |              |                 |        |                        |
| Deyo-Charlson Comorbidity Index score         |              |                 |        |                        |              |                 |        |                        |
| 0                                             | 176 (29.0)   | 3544 (58.4)     | REF    | REF                     | 100 (32)     | 1850 (59)       | REF    | REF                     |
| 1–2                                          | 159 (26.2)   | 1724 (28.4)     | 1.24   | 0.88–1.75               | 84 (27)      | 874 (28)        | 1.07   | 0.66–1.72               |
| ≥ 3                                          | 272 (44.8)   | 802 (13.2)      | 1.89   | 1.06–3.37               | 128 (41)     | 396 (13)        | 1.80   | 0.77–4.20               |
| No. of hospitalization days                   |              |                 |        |                        |              |                 |        |                        |
| 0                                             | 344 (56.7)   | 5386 (88.7)     | REF    | REF                     | 197 (63)     | 2796 (90)       | REF    | REF                     |
| 1–3                                          | 48 (7.9)     | 237 (3.9)       | 1.25   | 0.81–1.92               | 20 (6)       | 101 (3)         | 0.92   | 0.46–1.84               |
| ≥ 4                                          | 215 (35.4)   | 447 (7.4)       | 2.10   | 1.56–2.83               | 95 (30)      | 223 (7)         | 1.72   | 1.12–2.63               |
| No. of outpatient visits                      |              |                 |        |                        |              |                 |        |                        |
| 0                                             | 45 (7.4)     | 1793 (29.5)     | REF    | REF                     | 23 (7)       | 938 (30)        | REF    | REF                     |
| 1–5                                          | 246 (40.5)   | 3018 (49.7)     | 2.20   | 1.54–3.14               | 142 (46)     | 1538 (49)       | 2.75   | 1.68–4.51               |
| ≥ 6                                          | 316 (52.1)   | 1259 (20.7)     | 3.04   | 2.03–4.54               | 147 (47)     | 644 (21)        | 2.77   | 1.56–4.91               |
| No. of unique prescription drugs              |              |                 |        |                        |              |                 |        |                        |
| 0–2                                          | 36 (5.9)     | 1222 (20.1)     | REF    | REF                     | 23 (7)       | 1538 (49)       | REF    | REF                     |
| 3–5                                          | 95 (15.7)    | 1987 (32.7)     | 1.30   | 0.85–1.99               | 142 (46)     | 644 (21)        | 1.46   | 0.80–2.67               |
| 6–10                                         | 175 (28.8)   | 1871 (30.8)     | 2.12   | 1.37–3.30               | 147 (47)     | 312 (11)        | 2.36   | 1.27–4.40               |
| ≥ 11                                         | 301 (49.6)   | 990 (16.3)      | 3.33   | 2.04–5.43               | 938 (30)     | 312 (11)        | 3.58   | 1.77–7.21               |

| Analysis 3: Restricted Liver Injury |   | Analysis 4: Severe Liver Injury |   |
|------------------------------------|---|---------------------------------|---|
| Category                           | Cases, n (%) | Controls, n (%) | OR     | 95% CI                  | Cases, n (%) | Controls, n (%) | OR     | 95% CI                  |
| Nonuse                             | 63            | 630               | –      | –                       | 82            | 820               | –      | –                       |
| Current use                        |              |                 |        |                        |              |                 |        |                        |
| Amoxicillin                        | 6 (10)        | 34 (5)           | 3.71   | 1.09–12.70              | 7 (8.5)       | 40 (4.9)          | 6.94   | 1.88–25.63              |
| Amoxicillin-clavulanic acid        | 7 (11)        | 31 (5)           | 4.03   | 1.24–13.07              | 5 (6.1)       | 41 (5.0)          | 6.04   | 1.42–25.72              |
| Cefuroxime                         | 1 (23)        | 23 (4)           | 0.40   | 0.04–4.25               | 3 (3.7)       | 23 (2.8)          | 2.12   | 0.32–14.09              |
| Clarithromycin                     | 1 (2)         | 26 (4)           | 0.88   | 0.10–7.85               | 2 (2.4)       | 25 (3.1)          | 2.77   | 0.39–19.69              |
| Doxycycline                        | 0 (0)         | 32 (5)           | 0.00   | 0.00–NE                 | 3 (3.7)       | 34 (4.2)          | 2.54   | 0.48–13.46              |
| Levofloxacin                       | 8 (13)        | 41 (7)           | 3.45   | 1.13–10.57              | 13 (15.9)     | 38 (4.6)          | 7.19   | 0.25–25.22              |
| Moxifloxacin                       | 5 (8)         | 35 (2)           | 2.92   | 0.82–10.44              | 3 (3.7)       | 37 (4.5)          | 3.10   | 0.55–17.33              |
| Telithromycin                      | 1 (2)         | 4 (1)            | 5.70   | 0.44–73.74              | 1 (1.2)       | 9 (1.1)           | 5.67   | 0.41–78.34              |
| Recent single use                  |              |                 |        |                        |              |                 |        |                        |
| Amoxicillin                        | 0 (0)         | 42 (7)           | 0.00   | 0.00–NE                 | 3 (3.7)       | 47 (5.7)          | 2.26   | 0.47–10.93              |
| Amoxicillin-clavulanic acid        | 2 (3)         | 35 (6)           | 1.00   | 0.17–5.90               | 2 (2.4)       | 41 (5.0)          | 6.08   | 0.07–7.13               |
| Cefuroxime                         | 1 (2)         | 26 (4)           | 0.87   | 0.10–7.40               | 1 (1.2)       | 30 (3.7)          | 0.31   | 0.02–4.59               |
| Clarithromycin                     | 3 (5)         | 30 (5)           | 2.18   | 0.50–9.43               | 1 (1.2)       | 28 (3.4)          | 1.62   | 0.16–16.26              |
| Doxycycline                        | 3 (5)         | 18 (3)           | 2.35   | 0.48–11.44              | 1 (1.2)       | 42 (5.1)          | 0.80   | 0.08–7.93               |
| Levofloxacin                       | 2 (3)         | 28 (4)           | 0.80   | 0.13–5.06               | 8 (9.8)       | 39 (4.8)          | 4.92   | 1.25–19.44              |
| Moxifloxacin                       | 3 (5)         | 33 (5)           | 1.07   | 0.23–4.91               | 5 (6.1)       | 56 (6.8)          | 1.25   | 0.27–5.71               |
| Telithromycin                      | 2 (3)         | 6 (1)            | 15.44  | 2.27–105.13             | 0 (0.0)       | 16 (2.0)          | 0.00   | 0.00–NE                 |
| Current multiple use               | 3 (5)         | 7 (1)            | 10.87  | 1.95–60.53              | 7 (8.5)       | 13 (1.6)          | 12.27  | 2.84–53.04              |

(continued)
drug-induced liver injury. To our knowledge, this is the first large, population-based study of liver injury among oral antimicrobial users in a relatively unrestricted population including patients with many illnesses, such as cancer and congestive heart failure, which also could cause liver test abnormalities. Indeed, the incidence of liver injury we observed during nonuse (35.1 cases/100,000 person-years) is higher than background incidence rates estimated by other authors who excluded such diagnoses, which range from 2.4–14.8 cases/100,000 person-years.1–7

Table 5. (continued)

| Category | Analysis 3: Restricted Liver Injury | Analysis 4: Severe Liver Injury |
|----------|-----------------------------------|--------------------------------|
|          | Cases, n (%) Controls, n (%) OR 95% CI | Cases, n (%) Controls, n (%) OR 95% CI |
| Recent multiple use | 2 (3) 20 (3) 1.55 0.28–8.59 | 8 (9.8) 31 (3.8) 3.86 1.07–13.98 |
| Mean age (yrs) | 50.4 49.8 1.07 0.95–1.20 | 55.7 55.3 1.05 0.94–1.17 |
| Prior liver disease | 2 (3) 11 (2) 0.50 0.07–3.67 | 9 (11.0) 10 (1.2) 1.52 0.39–5.92 |
| Prior disease of biliary tract or pancreas | 16 (25) 26 (4) 6.09 2.39–15.50 | 29 (35.4) 32 (3.9) 9.05 3.74–21.90 |
| Prior or concurrent use of other potentially hepatotoxic drugs | 37 (59) 285 (45) 1.10 0.53–2.29 | 55 (67.1) 380 (46.3) 1.22 0.59–2.51 |

CI = confidence interval; NA = not available; NE = not estimable; OR = odds ratio; REF = reference category.

aIn addition to the variables shown, Analyses 1 and 2 included variables for current single use with recent use of another antimicrobial (data not shown), whereas in Analyses 3 and 4, current single use of a given study antimicrobial with concurrent recent use of another study antimicrobial was combined with current single use of the antimicrobial to which the patient was currently exposed.

bModel was estimated without this variable.
Moreover, the data source provided information on potential confounders, including previous medical diagnoses, use of other drugs, and rates of utilization of health care services. The highest relative risk of liver injury was associated with current use of multiple antimicrobials. In another study, the risk of liver injury from combined current exposure to nonsteroidal antiinflammatory drugs and other hepatotoxic drugs was more than additive.33

Among current users of single antimicrobials, the highest relative risk was associated with exposure to levofloxacin. Fluoroquinolones are known to be associated with an increased risk of liver injury, but it is difficult to discern the relative risk of hepatotoxicity associated with use of specific fluoroquinolones from the published literature. One report reviewed that hepatotoxicity of moxifloxacin was “not different from what was observed for other fluoroquinolones (excluding trovafloxacin)”34; however, the risk of hepatotoxicity cited was from a single study that did not quantify moxifloxacin use in the study population.35 One study36 reported from the Drug-Induced Liver Injury Network that four cases were attributed to moxifloxacin and one to levofloxacin, but population exposures were not reported, so relative risks were not computed.

The relative risks associated with current single use of moxifloxacin in our primary analysis (1.3, 95% CI 0.76–2.2) and the analysis restricted to valid cases (2.3, 95% CI 1.1–4.7) were both somewhat lower than that reported from the PharMetrics database study (2.58, 95% CI 1.04–6.43).10 The reference exposure in that study was amoxicillin-clavulanic acid, which itself is associated with an elevated risk of liver injury. Our relative risk estimates would have been lower than those we reported if amoxicillin-clavulanic acid had been the reference exposure.

We found that the incidence of liver injury with current single use of amoxicillin–clavulanic acid was slightly higher than that for amoxicillin alone. Other studies have reported similar findings.6, 37 Those studies excluded patients with cancer, gallbladder or pancreatic disease, alcohol-related conditions, pregnancy, viral hepatitis, congestive heart failure, and “other well-defined pathology affecting the liver.” In our adjusted, matched case-control analysis, odds ratios compared with nonuse were similar for the two drugs. Although this could be due to misclassification or residual confounding, it is expected that in a less restricted population there would be less difference between the rates associated with these two drugs because the attributable cases would represent a smaller proportion of the exposed cases.

We did not find an increased risk of liver injury associated with current or recent single use of telithromycin in our main analysis; we did find an elevated risk in the analysis restricted to cases with no other diagnoses known to cause liver test abnormalities (although the number of cases was small). It is possible that changes in telithromycin labeling during the period of our study, including addition of a warning for liver injury in June 2006,38 may have resulted in more cautious prescribing of telithromycin to patients with diseases that can cause liver test abnormalities. The varying findings for telithromycin may have resulted from a lower background risk of liver injury during nonuse in the more restricted population than in the main analysis if there were less confounding by contraindication.39

The adjusted relative risks for liver injury related to recent use of each antimicrobial in the nested case-control analysis were somewhat lower than the corresponding relative risks for current single use but greater than 1 for some of the study drugs (levofloxacin, amoxicillin, amoxicillin–clavulanic acid, and doxycycline), indicating persistence of liver injury risk more than 30 days after prescribed use ends.

The study has several limitations. “Drug-induced” liver injury is a diagnosis of exclusion; therefore, we focused broadly on liver injury without assuming causality. Relatively few cases did not have other diseases or drug exposures that may have contributed to their risk. Despite improved criteria for diagnosis of liver injury, some cases are undiagnosed and others could be missed by screening claims, so we could have underestimated the true population risk. Information in hospital and emergency department medical records needed to validate liver injury is sometimes incomplete or unavailable. We did not have adequate data to control for the clinical indication for the use of each antimicrobial prescription, so there could be residual confounding by indication. Many antimicrobials are potentially hepatotoxic; our decision about which to include were guided by consideration of their labeled indications, by agreement with regulatory authorities, and by availability in the United States.40 We studied only oral antimicrobial use, so these results may not be valid for
exposure by other routes of administration. Finally, we cannot carry out additional analyses (e.g., evaluating specific combinations of antimicrobials) because the study funding was related to a specific regulatory obligation, the protocol and analysis plan were specified and agreed to before analyses were carried out, and additional funding was not available to retrieve archived data and carry out exploratory analyses.

Conclusion

This large study evaluating patients with common comorbidities found modest elevations in the risk of validated liver injury associated with some antimicrobials but little evidence of any strong effect of commonly used antimicrobials on the incidence of acute liver injury. We found a comparatively high adjusted relative risk among patients exposed concurrently to multiple antimicrobials.

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