Adverse Health Events Associated with Antimicrobial Drug Resistance in Campylobacter Species: A Registry-Based Cohort Study

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(See the editorial commentary by Jones and Schaffner, on pages 1029–31.)

Background. Resistance to clinically important antimicrobial agents, particularly fluoroquinolones and macrolides, is increasing among Campylobacter isolates, but few studies have explored the human health consequences of such resistance.

Methods. In a registry-based cohort study, we determined the risk of invasive illness and death associated with infection with quinolone- and erythromycin-resistant Campylobacter strains, while adjusting for comorbidity. We linked data from the Danish Surveillance Registry for Enteric Pathogens with data from the Civil Registration System and National Health Registries.

Results. Of 3471 patients with Campylobacter infection, 22 (0.63%) had an adverse event, defined as invasive illness or death, within 90 days of the date of receipt of samples. Patients infected with quinolone-resistant Campylobacter strains had a 6-fold increased risk of an adverse event within 30 days of the date of receipt of samples, compared with patients infected with quinolone- and erythromycin-susceptible Campylobacter strains (adjusted odds ratio [AOR], 6.17 [95% confidence interval [CI], 1.62–23.47]). However, infection with erythromycin-resistant strains was associated with a 1.5-fold risk of an adverse event within 90 days of the date of receipt of samples (AOR, 5.51 [95% CI, 1.19–25.50]).

Conclusions. The present study provides evidence of the human health consequences of resistance to clinically important agents among Campylobacter infections and the need for increased efforts to mitigate such resistance.

Campylobacter species are the most frequent cause of bacterial gastroenteritis in many countries [1, 2]. Most often, they cause a self-limiting diarrheal illness, and patients do not usually require antimicrobial treatment. Treatment may be prescribed for patients with severe and prolonged gastroenteritis, suspected septicemia, or other invasive manifestations, as well as for patients who have a severe underlying illness. Drugs of choice typically include a fluoroquinolone for early empirical treatment in adults [3] and a macrolide for treatment after the microbiological diagnosis has been established [1, 4].

In recent years, fluoroquinolone and macrolide resistance has emerged, and fluoroquinolone-resistant Campylobacter strains, in particular, are now common in many countries [1, 5, 6]. Although there is increasing evidence of adverse events associated with antimicrobial drug resistance in Salmonella infection [7–9], limited information exists on the clinical consequences of resistance in Campylobacter infection. A major methodological problem is that the number of well-defined, severe, and relevant outcomes is bound to be limited in most studies. These outcomes include duration of illness, complications (e.g., gastrointestinal perforation or invasive illness), long-term (chronic) sequelae (e.g., Guillain-Barré syndrome or other severe reactive ill-
illness. 

If a Campylobacter isolate was found on >1 occasion from the same person during a period of 6 months, only the first positive sample was registered. As part of this laboratory-based surveillance system, monitoring for macrolide and quinolone resistance in Campylobacter species was initiated in 1996. From 1996 through 1998, a random sample of 10 strains/month was tested, but, from 1999 onward, all Campylobacter strains were tested for susceptibility. The present study includes all Campylobacter isolates examined at the SSI during the period 1 January 1996–31 December 2000.

Antimicrobial susceptibility testing was performed by tablet diffusion on Danish blood agar (SSI Diagnostica) by use of Neosensitabs (Rosco) [15]. Isolates were considered to be resistant if they had an inhibition zone of <27 mm for nalidixic acid or erythromycin.

Registry linkage study. All live-born children and citizens of Denmark are assigned a personal identification number within the Danish Civil Registration System (CRS) [16] that uniquely identifies each person. Demographic data—including vital status, emigration or immigration status, and address of residence—are kept in the CRS. For every patient, we randomly selected 10 persons from the CRS who were matched for age, sex, and county of residence and who were alive on the date when the sample was received. We obtained information on date of death or emigration for patients and for the persons selected from the general population. Finally, data were obtained from the national registry of patients on all hospital admissions, outpatient clinic attendances, and discharge diagnoses within 5 years of entry in the study until 90 days after entry [17]. This allowed us to control for preexisting illness (comorbidity) and to ascertain a diagnosis of invasive illness during the episode of campylobacteriosis. The national registry of patients contains data on all patients discharged from non-psychiatric departments since 1 January 1977 and on outpatient attendances since 1 January 1995. Diagnoses are coded according to the International Classification of Diseases (ICD) 8 or ICD 10 (from 1993 onward).

The outcome variable in the present study was a diagnosis of either invasive illness or death (an adverse event). A person with a diagnosis of sepsis, endocarditis, aneurysm, meningitis, pneumonia, abscesses, pancreatitis, or hepatitis in the national registry of patients within 90 days of the date of receipt of samples (the study period) was classified as having invasive illness [18].

Because of the logistics of the surveillance program, the date of receipt at the SSI is 1–7 days after the sample-collection date, and this date was not available in all cases. Therefore, we included patients who had an adverse event between 7 days before and 90 days after the date of receipt of samples.

Statistical methods. The sample of 10 control subjects/patient selected from the general population was used to calculate the comorbidity index [18–20]. Using data from the national registry of patients and the cancer registry, we first calculated the relative mortality associated with the different diagnostic groups included in the comorbidity index (e.g., metastatic cancer, hematologic malignancies, HIV, and liver disease). The index was defined as the logarithm to this relative mortality. For each patient, the comorbidity weight was then calculated as the sum of indices corresponding to the number and severity of coexisting illnesses within 5 years of entry in the study. Because data from outpatient clinics were only available from 1995, and to avoid possible bias when adjusting for comorbidity, data
Table 1. *Campylobacter* infections, Denmark 1996–2000—details on age, sex, and comorbidity, according to antimicrobial susceptibility pattern, in 22 patients with invasive illness or fatal outcome.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, years</th>
<th>Comorbidity</th>
<th>Resistance to</th>
<th>Outcome</th>
<th>Time to adverse event, days (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>80</td>
<td>Peripheral vascular illness</td>
<td>No</td>
<td>No</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>81</td>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Septicemia</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>79</td>
<td>Hematologic malignancy</td>
<td>No</td>
<td>Yes</td>
<td>Meningitis</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>27</td>
<td>Renal disease</td>
<td>No</td>
<td>Yes</td>
<td>Septicemia</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>37</td>
<td>Congestive heart failure</td>
<td>No</td>
<td>No</td>
<td>Septicemia</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>35</td>
<td></td>
<td>No</td>
<td>No</td>
<td>Septicemia</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>85</td>
<td>Non-COPD pulmonary illness</td>
<td>Yes</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>73</td>
<td></td>
<td>No</td>
<td>Yes</td>
<td>Death</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>29</td>
<td>Cerebral tumor</td>
<td>No</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>69</td>
<td>Biliary tract disease</td>
<td>No</td>
<td>Yes</td>
<td>Aneurysm</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>88</td>
<td>COPD</td>
<td>Yes</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>82</td>
<td>Movement disorders</td>
<td>Yes</td>
<td>Yes</td>
<td>Death</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>54</td>
<td>Metastatic colon tumor</td>
<td>No</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>91</td>
<td>Non-COPD pulmonary illness</td>
<td>Yes</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>88</td>
<td>Urothelial tumor</td>
<td>No</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>89</td>
<td></td>
<td>No</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>79</td>
<td>Dementia</td>
<td>No</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>18</td>
<td>F</td>
<td>85</td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>73</td>
<td></td>
<td>No</td>
<td>No</td>
<td>Death</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>67</td>
<td>Dementia</td>
<td>Yes</td>
<td>Yes</td>
<td>Death</td>
</tr>
</tbody>
</table>

**NOTE.** COPD, chronic obstructive pulmonary disease.

\(^a\) Time from receipt of sample at the laboratory.

form outpatient clinics were restricted to within 1 year of entry in the study.

To investigate the relative risk of invasive illness or death associated with antimicrobial resistance, we used a logistic regression model that adjusted for age, sex, and comorbidity. The analyses were conducted by use of the PROC GENMOD procedure in SAS (version 8.2; SAS Institute). Odds ratios are expressed as the odds of an adverse event in persons infected with antimicrobial-resistant *Campylobacter* strains, compared with those for patients infected with quinolone- and erythromycin-susceptible *Campylobacter* strains.

**RESULTS**

Of the isolates responsible for the 14,443 culture-confirmed *Campylobacter* infections reported during January 1996–December 2000, 3541 (24.5%) were tested for antimicrobial drug susceptibility, and a positive match to the CRS was obtained for 3471 (98.0%). A total of 2506 *Campylobacter* isolates (72.2%) were quinolones and erythromycin susceptible, 760 (21.9%) were quinolone resistant, 109 (3.1%) were erythromycin resistant, and 96 (2.8%) were quinolone and erythromycin resistant.

Information on travel history was available for 3380 (97.4%) patients; 554 (16.4%) of these had a history of travel within 2 weeks of the onset of illness. Spain, Thailand, and Turkey were the most common destinations. A total of 2826 (83.6%) patients had acquired the infection domestically.

Among the isolates responsible for travel-associated infections, 268 (48.4%) were quinolone resistant, compared with 550 (19.5%) responsible for domestically acquired infections (P < .001). The prevalence of quinolone resistance was particularly high among patients returning from Thailand (81.3%), India (71.1%), and Spain (62.5%).

Thirty-five (6.3%) of the travel-associated *Campylobacter* isolates and 163 (5.8%) of the domestically acquired isolates were erythromycin resistant (P = .61). The prevalence of erythromycin resistance was high among patients returning from India (15.8%) and Spain (10.0%).

Overall, we identified 5 persons (0.14%) who died within 30 days of the date of receipt of samples. Within 90 days of the date of receipt of samples, 22 patients (0.63%) had an adverse event—15 died (0.43%), and 7 (0.20%) were diagnosed with invasive illness (table 1). The median age of patients with an adverse event was 78.8 years (range, 0.5–90.6 years), whereas patients with no record of an adverse event had a median age of 27.4 years (range, 0.2–92.3 years). Comorbidity was more common among patients with an adverse event—14 (63.6%) of 22 patients—than among the 614 patients (17.8%) without such an event (P < .001).
Patients infected with a quinolone-resistant *Campylobacter* strain had a 3-fold (95% confidence interval [CI], 0.99–9.39) increased risk of adverse events within 90 days of infection, after adjustment for sex, age, and comorbidity, compared with patients infected with quinolone- and erythromycin-susceptible *Campylobacter* strains (table 2). However, there were no additional cases of invasive illness or deaths among patients infected with quinolone-resistant *Campylobacter* strains during the 30–90 days of the date of receipt of samples. Therefore, we also examined the effect of infection with quinolone-resistant *Campylobacter* strains within 30 days of the date of receipt of samples. During this period, patients quinolone-resistant *Campylobacter* infection had a 6.17-fold (95% CI, 1.62–23.47-fold) increased risk of adverse events, after adjustment for sex, age, and comorbidity, compared with patients infected with quinolone- and erythromycin-susceptible *Campylobacter* strains.

Among patients infected with erythromycin-resistant *Campylobacter* strains, we found a 5.51-fold (95% CI, 1.19–25.50-fold) increased risk, after adjustment, of invasive illness or death within 90 days, compared with patients infected with quinolone- and erythromycin-susceptible strains (table 2). None of these 22 patients had a history of travel abroad within the 2 weeks before infection. Therefore, we performed a subanalysis among the 2826 persons with domestically acquired infection. Patients infected with quinolone-resistant *Campylobacter* strains had a 9.68-fold (95% CI, 2.23–42.04-fold) increased risk of adverse events within 30 days of infection, adjusted for sex, age, and comorbidity.

Information on antimicrobial treatment was only available for a subset of 163 patients infected with erythromycin-resistant *Campylobacter* strains. Fifty-two (31.9%) patients had been prescribed an antimicrobial drug within 30 days of infection. Among these patients, we identified 3 who received a diagnosis of invasive illness or who died—1 received ciprofloxacin and 2 received broad-spectrum penicillin.

**DISCUSSION**

The present study has shown that patients infected with a quinolone- or erythromycin-resistant *Campylobacter* strain have an increased risk of an adverse event, compared with patients infected with quinolone- and erythromycin-susceptible *Campylobacter* strains. Our results corroborate those of other studies from the United States, Thailand, and Denmark [10–12], which showed that infection with quinolone- or erythromycin-resistant *Campylobacter* strains causes a longer duration of illness.

Our data also show that invasive illness and death associated with *Campylobacter* infection are rare events, particularly in comparison with nontyphoidal *Salmonella* infection, the other major cause of foodborne bacterial gastroenteritis in industrialized countries. The overall case-fatality rate in the present study was 0.14% (5 deaths within 30 days of infection), which is lower than that of nontyphoidal *Salmonella* infection but is in line with data from previous studies [18]. Although severe adverse events caused by *Campylobacter* infection are, in general, rare, the relative effect associated with quinolone resistance is of a magnitude similar to the increased mortality associated with quinolone-resistant *Salmonella* infection [20–22].

In the present study, we examined the most severe adverse events—invasive illness and death—associated with quinolone- and macrolide-resistant *Campylobacter* infection. The present study used data from registries created for other purposes, and these data can be regarded as an unbiased sample of the culture-confirmed cases of *Campylobacter* infection. The present study was particularly unique because we were able to include data from the general population, which allowed us to adjust for imbalances in comorbidity.

### Table 2. No. of cases of invasive illness and death among 3471 patients with *Campylobacter* infection, Denmark 1996–2000, according to resistance profile.

<table>
<thead>
<tr>
<th>Resistance/susceptibility profile</th>
<th>0–30 days</th>
<th>0–90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR</td>
<td>Adjusted OR&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adverse event/alive&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Quinolone only</td>
<td>6/754</td>
<td>4.97 (1.40–17.67)</td>
</tr>
<tr>
<td>Erythromycin only</td>
<td>2/107</td>
<td>11.68 (2.12–64.49)</td>
</tr>
<tr>
<td>Both</td>
<td>1/95</td>
<td>6.59 (0.73–59.42)</td>
</tr>
<tr>
<td>Susceptible to quinolone</td>
<td>4/2500</td>
<td>1.00 (95% CI)</td>
</tr>
<tr>
<td>and erythromycin</td>
<td>Total</td>
<td>13/3456</td>
</tr>
</tbody>
</table>

<sup>a</sup> No. of deaths or subjects with invasive illness/no. who survived.

<sup>b</sup> Adjusted for age, sex, and comorbidity.

**NOTE.** Two and 4 patients emigrated within 30 and 90 days of infection, respectively. Because we did not have complete follow-up data on these patients, they were excluded from the statistical analysis. Also shown are the crude and adjusted relative risk of invasive illness or death within 30 and 90 days of date of the receipt of samples. CI, confidence interval; OR, odds ratio.
Both age and the presence of coexisting illness are important predictors of outcome. The comorbidity index used in the present study was based on diagnoses at discharge and on data from outpatient clinics but did not include data from general practitioners. It could be argued that this weakens the index. However, we assumed that any patient with a preexisting disease that was severe enough to alter the outcome of a foodborne infection was likely to have come into contact with a hospital or an outpatient clinic within the 5 years before infection.

Foreign travel is a major risk factor for the acquisition of quinolone-resistant Campylobacter infection [2, 5, 23, 24]. It is furthermore likely that the average traveler is in better general health than the average patient with domestically acquired infection; therefore, travel may confound the association measurements toward 1. This point was corroborated by the subanalysis that excluded travel-associated cases; the relative risk of an adverse event after infection with quinolone-resistant Campylobacter strains was higher in patients who acquired the infection domestically than in patients who acquired the infection while traveling.

Antimicrobial drug resistance in Campylobacter species may be associated with adverse events in several ways, including reduced efficacy of treatment. This may especially be the case for fluoroquinolones, which commonly are used early during the empirical treatment of severe gastroenteritis in patients with underlying illness or at the extremes of age. This notion is corroborated by the fact that most adverse events occurring after the acquisition of quinolone-resistant Campylobacter infection were observed within 30 days of diagnosis. Unfortunately, we had no data on treatment with quinolones. Therefore, it was impossible to explore the extent to which the increased risk of an adverse event in patients infected with quinolone-resistant strains was caused by reduced efficacy of drugs.

The excess morbidity and mortality associated with erythromycin resistance may, however, have a different explanation. The risk of an adverse event was most convincingly observed within 90 days of the date of receipt of samples.

Information on antimicrobial treatment was available for a subset of patients infected with erythromycin-resistant strains; none of the patients with adverse event had been treated with erythromycin. On this basis, it is unlikely that the adverse effect of erythromycin resistance is caused by therapeutic failure. Erythromycin resistance is more common in Campylobacter coli than in Campylobacter jejuni infection [1], and it has also been suggested that C. coli is more invasive than is C. jejuni [25]. Hence, it is possible that the marked increased risk of invasive illness or death associated with erythromycin-resistant strains is confounded by Campylobacter species. Only 2 strains from patients with an adverse event had been speciated, and they were C. jejuni strains, which suggests that the results are unlikely to be confounded by a possible increased virulence of C. coli. Additionally, strains were available from 17 other patients who died within 1 year of Campylobacter infection, and these strains were all C. jejuni (data not shown). This does not preclude that markers of virulence may be associated with erythromycin resistance. If macrolide resistance is associated with some unknown virulence markers, the use of macrolides in any ecosystem may select such strains. In other words, antimicrobial drug resistance may be of public-health importance even in the absence of evidence of therapeutic failure.

Fluoroquinolones have been part of human medicine since the 1980s, with no or very limited resistance in Campylobacter species. It was not until the license of fluoroquinolones in food-animal production in the early 1990s that resistant Campylobacter strains emerged [1, 2, 26]. Also, in Australia, the use of quinolones has never been approved in food animals; as a result, very few domestically acquired quinolone-resistant Campylobacter infections have been seen [27]. Macrolide resistance is less common, and most studies have not shown a clear trend over time [1, 4]. Nevertheless, a modest increase was observed in studies from Japan, Spain, Sweden, and Thailand [5, 6, 28, 29]. In Denmark, there have been signs of a decreased prevalence of macrolide resistance in Campylobacter species since the ban of antimicrobial growth promoters, including macrolides [10].

In conclusion, the present study has shown that infection with either quinolone- or macrolide-resistant Campylobacter strains is associated with an increased risk of invasive illness or death, compared with infection with drug-susceptible Campylobacter strains. Macrolide and quinolone resistance in Campylobacter species is mainly a consequence of the use of antimicrobials in food-animal production, and our findings emphasize the need for limitation of the use of antimicrobial drugs in agriculture, which is critical to human medicine.

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References


