Fluoroquinolones to treat uncomplicated acute cough in primary care: predictors for unjustified prescribing of antibiotics

Attila Altiner1*, Stefan Wilm2, Karl Wegscheider3, Martin Sielk4, Silke Brockmann4, Angela Fuchs4, Heinz-Harald Abholz4 and Jürgen in der Schmitten4

1Department of General Practice, Medical Faculty, University of Rostock, 18055 Rostock, Germany; 2Department of General Practice and Family Medicine, University of Witten/Herdecke, Alfred Herrhausen-Str. 50, 58448 Witten, Germany; 3Department of Medical Biometry and Epidemiology, University of Hamburg, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany; 4Department of General Practice, Heinrich-Heine-University Duesseldorf, University Hospital Duesseldorf, Moorenstr. 5, 40225 Duesseldorf, Germany

*Corresponding author. Tel: +49-381-494-2480; Fax: +49-381-494-2482; E-mail: altiner@med.uni-rostock.de

Received 20 December 2009; returned 30 January 2010; revised 7 April 2010; accepted 9 April 2010

Background: Despite efforts to ensure more accurate prescribing of antibiotics for respiratory tract infections, inappropriate selection of antibiotic treatment remains a big issue. We tried to ascertain which factors best predict the nature of fluoroquinolone prescribing for acute cough in primary care.

Methods: Random effects logistic regression models were applied to the baseline prescription data taken from a cluster-randomized controlled trial based on 104 general practitioners (GPs) and 2745 patients.

Results: Significant predictors for the prescription of fluoroquinolones from both patient and GP data were identified. Predictors from a patient’s perspective were the severity of illness [odds ratio (OR) 3.56 [95% confidence interval (CI) 2.45–5.19] P < 0.001], the duration of illness before seeing the GP [OR 1.09 (95% CI 1.04–1.14) P = 0.020] and the individual patient’s age [OR 1.01 (95% CI 1.00–1.01) P = 0.015]. Predictors from the GP’s perspective were extent/lack of specific vocational training [OR 3.10 (95% CI 1.54–6.22) P < 0.001], status as a general internist [OR 2.00 (95% CI 1.10–3.70) P < 0.002], the physician’s overall antibiotic prescription rate for acute cough [OR 1.02 (95% CI 1.01–1.04) P < 0.001], the duration of illness before contact with patient [OR 0.81 (95% CI 0.69–0.95) P < 0.010] and the severity of illness [OR 0.27 (95% CI 0.12–0.63) P < 0.002].

Discussion: Whether a fluoroquinolone is prescribed by a GP seems to be determined not only by the patient’s characteristics but also by the GP’s vocational training and overall antibiotic prescribing rate. As the prescription of fluoroquinolones for the treatment of acute coughing can rarely be justified, such prescriptions may serve as a quality indicator for antibiotic prescribing in primary care.

Keywords: respiratory tract infections, prescribing patterns, quality of care

Introduction

Antibiotics are still frequently prescribed for acute cough in primary care throughout most of Europe and North America,1–4 in spite of current guidelines that advise against using antibiotics during the initial treatment of acute cough or other symptoms of uncomplicated respiratory tract infection (RTI) in otherwise healthy adults.5 The over-prescription of antibiotics puts patients at risk of side effects, promotes bacterial resistance and produces unnecessary costs. The question of which antibiotics to prescribe becomes increasingly important, particularly in the case of fluoroquinolone misuse.

Newer fluoroquinolones are broad-spectrum agents that have enhanced potency against many Gram-negative and Gram-positive organisms, and are therefore effective in treating complicated and nosocomial infections. However, a number of bacterial pathogens—including Staphylococcus aureus, enterococci and Streptococcus pyogenes—are becoming increasingly resistant to fluoroquinolones.6 Fluoroquinolones were once considered relatively safe, but several severe side effects have recently come to light, including case reports of spontaneous tendon ruptures or damage. Consequently, the FDA recently upgraded their warnings on the package instructions for all drugs within this class7 and the European Medicines Agency (EMEA) toned down its recommendations for the use of oral moxifloxacin.8

Correspondingly, appropriate guidelines explicitly advise against the prescription of fluoroquinolones during the initial...
stages of treatment of uncomplicated RTI in primary care. Unfortunately, over the past decade fluoroquinolones have been heavily marketed by the pharmaceutical industry as a ‘routine’ treatment for acute respiratory infections across Germany and other European countries and they seem to be used frequently for RTIs in Europe. We therefore analysed which factors predict fluoroquinolone prescribing for acute cough in primary care and put the results into perspective regarding the use of fluoroquinolone prescriptions as a quality indicator for antibiotic prescribing.

**Methods**

**Sample**

We used the baseline prescription data taken from a cluster-randomized controlled trial evaluating an educational intervention that was designed to improve antibiotic prescribing by modifying the communication between doctor and patient.

**Primary care physicians**

One hundred and four primary care physicians out of 99 primary care practices from across nine regions in the North Rhine and Westphalia–Lippe districts—representing German areas of high, medium and low population density—enrolled all patients visiting their surgeries with acute cough during a 6 week period. The participating general practitioners (GPs) can be divided into three types based on their vocational training, although all serve an identical function within the German healthcare system: GPs with GP-specific vocational training; general internists with specialist training in internal medicine; and physicians without vocational training (abandoned in 2002).

**Patients**

A total of 2745 eligible patients were included. According to the inclusion criteria, patients had to be at least 16 years of age, understand the German language, it had to be the first consultation for this particular bout of coughing and they should not have had another episode of coughing during the previous 8 weeks. The only exclusion criteria were underlying chronic pulmonary diseases like asthma or chronic obstructive pulmonary disease, immune deficiency and malignant diseases. Study documentation included data on the patient’s age, gender, duration of cough before consulting a GP, smoking status, presence of fever and the results of any examinations carried out. Study-specific documentation exceeded routine data and provided specific details of all prescriptions to combat ‘acute cough’, inclusion of drug samples (including antibiotics) dispensed by GPs and the severity of the disease as subjectively rated by the GP [score 1–4 (1 = mild, 2 = moderate, 3 = moderate/severe, 4 = severe)].

**Statistical analysis**

We applied random effects logistic regression models to the data. This is a particular type of special case of the more general family of multilevel models. These models are appropriate if cluster effects are to be expected that can result in optimistically biased $P$ values if not taken into consideration. In the case at hand, it has to be assumed that physicians treat their different patients according to the same rules so that prescriptions of the same physician will be more alike than prescriptions of different physicians. We thus modelled the patients as random terms (lower level) nested in physicians taken as random as well (upper level). This modelling approach allows the strength of a cluster effect to be expressed by the intra-class correlation coefficient (ICC), which is the ratio of the variance between average physician rates and the total variance between patients. Tentatively, we added practice as a third level to study whether there were similarities between physicians within the same practice with respect to their prescription behaviour and used a
maximum likelihood test to compare the approaches. Finally, we studied two models. The first model was applied to the complete sample using antibiotic prescribing as a response (dependent variable). The second model was applied to the subgroup of patients who were prescribed an antibiotic using fluoroquinolone prescribing as a response. In both cases the same covariates were used for model building. At the patient level: gender; age; gender × age (interaction); smoker/non-smoker; fever; and duration and severity of illness. At the GP level: gender of physician; age of physician; vocational training background; any special interest in complementary medicine (including herbal treatments and homeopathy); population density in the catchment area of the practice; unemployment rate in the catchment area; average ratio of women; average ratio of smokers; average age of patients; and, as variables measuring the local and temporal intensity of infections, average ratio of patients with fever, average duration of cough, average severity of condition and overall number of antibiotic prescriptions (for fluoroquinolone analysis only).

We performed a model search by backward elimination of non-significant factors. The two final models are presented, with odds ratios (ORs), 95% confidence intervals (CIs) and P values. Calculations were carried out using STATA/SE 10.0.

**Ethical approval**

Ethical approval was obtained from the Ethics Committee of the Medical Faculty of the University of Duesseldorf, No. 2398. Patient consent was not required.

### Table 3. Prescribed antibiotic substances (n=1285 antibiotic prescriptions)

<table>
<thead>
<tr>
<th>Substances</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>143</td>
<td>11.1</td>
</tr>
<tr>
<td>Amoxicillin + ß-lactamase inhibitor</td>
<td>5</td>
<td>0.4</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>108</td>
<td>8.4</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>438</td>
<td>34.1</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>146</td>
<td>11.4</td>
</tr>
<tr>
<td>Macrolides</td>
<td>366</td>
<td>28.5</td>
</tr>
<tr>
<td>Penicillin</td>
<td>49</td>
<td>3.8</td>
</tr>
<tr>
<td>Others</td>
<td>30</td>
<td>2.3</td>
</tr>
</tbody>
</table>

**Results**

Across the 2745 eligible patients whose cases were documented by the 104 participating GPs the overall antibiotic prescription rate was 46.8% during the period of the trial, resulting in 1285 patients of 101 physicians on antibiotic treatment. Prescriptions of the same physician were more alike than prescriptions of different physicians (ICC 0.31, 95% CI 0.24–0.39). The inclusion of an additional random term for practice did not significantly improve the models. Fluoroquinolones were prescribed in 11.4% of all antibiotic prescriptions. The prescribed fluoroquinolones were moxifloxacin (69%), ciprofloxacin (17%) and levofloxacin (14%). GP and patient characteristics are shown in Tables 1 and 2. The types of antibiotics prescribed are shown in Table 3.

#### ORs for antibiotic prescription (all substances)

The statistical analysis identified significant predictors in the prescription of antibiotics at both patient and GP levels (Table 4). Significant predictors at patient level were the severity of the illness (as rated by the GP) [OR 5.83 (95% CI 4.77–7.12) P<0.001], fever [OR 2.20 (95% CI 1.69–2.86) P<0.001], whether the patient is a smoker or not [OR 1.43 (95% CI 1.14–1.78) P<0.002], the duration of the condition before seeing the GP [OR 1.03 (95% CI 1.01–1.06) P<0.015] and the individual patient’s age [OR 1.01 (95% CI 1.00–1.01) P<0.015]. Significant predictors from a physician’s perspective were the average fever rate [OR 1.03 (95% CI 1.01–1.04) P<0.009] and the average severity of the illness [OR 0.34 (95% CI 0.14–0.81) P<0.016], indicating that physicians tend to prescribe antibiotics more frequently if more patients with fever are present and less frequently if there are more severe cases around, independently of the individual health state of a patient.
**Table 5. Adjusted ORs for the prescription of fluoroquinolones**

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>severity of illness (score)</td>
<td>3.56</td>
<td>&lt;0.001</td>
<td>2.45–5.19</td>
</tr>
<tr>
<td>duration of cough before seeing GP (per day)</td>
<td>1.09</td>
<td>&lt;0.001</td>
<td>1.04–1.14</td>
</tr>
<tr>
<td>age (per year)</td>
<td>1.01</td>
<td>0.018</td>
<td>1.01–1.03</td>
</tr>
<tr>
<td><strong>Physician level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>practitioner without specific vocational training⁶</td>
<td>3.10</td>
<td>0.001</td>
<td>1.54–6.22</td>
</tr>
<tr>
<td>general internist</td>
<td>2.00</td>
<td>0.002</td>
<td>1.10–3.70</td>
</tr>
<tr>
<td>overall antibiotic prescription rate in practice (per day)</td>
<td>0.81</td>
<td>0.010</td>
<td>0.69–0.95</td>
</tr>
<tr>
<td>severity of illness (score) in practice</td>
<td>0.27</td>
<td>0.002</td>
<td>0.12–0.63</td>
</tr>
</tbody>
</table>

⁶Reference category: physician with GP-specific vocational training.

**ORS for fluoroquinolone prescription**

Fluoroquinolones were used at least occasionally by 60.4% of GPs prescribing antibiotics. Prescription rates varied considerably between physicians (Figure 1). The statistical analysis identified accurate predictors for the prescription of fluoroquinolones from both patient and GP data (Table 5). Significant predictors from a patient’s perspective were the severity of the illness (as rated by the physician) [OR 3.56 (95% CI 2.45–5.19) P<0.001], the duration of the condition before first consultation [OR 1.09 (95% CI 1.04–1.14) P=0.020] and the individual patient’s age [OR 1.01 (95% CI 1.00–1.01) P<0.015]. Significant predictors at physician level were the physician’s status as a practitioner without specific vocational training [OR 3.10 (95% CI 1.54–6.22) P<0.001], physician’s status as a general internist [OR 2.00 (95% CI 1.10–3.70) P<0.002], the physician’s overall tendency to prescribe antibiotics for acute cough [OR 1.02 (95% CI 1.01–1.04) P<0.001], the duration of cough before first consultation [OR 0.81 (95% CI 0.69–0.95) P<0.010] and the severity of illness (score) [OR 0.27 (95% CI 0.12–0.63) P<0.002].

**Discussion**

The analysis reveals that both physician and patient factors play a role in the prescription of fluoroquinolones, which in our study were at least occasionally prescribed by the majority of the general physicians. Primary care physicians without specific vocational training as well as general internists (who in Germany undergo hospital training only) were more likely to prescribe fluoroquinolones than physicians specifically trained as GPs. Furthermore the frequency with which a GP generally prescribes antibiotics is directly linked to the likelihood of choosing a fluoroquinolone. The higher the overall antibiotic prescription rate of a physician, the greater the odds that the prescribed antibiotic would be a fluoroquinolone. Besides individual physician prescribing habits, a patient’s characteristics both on an individual level and on a physician (and practice) level played an important role in the prescribing of fluoroquinolones for acute cough. The more severely ill an individual patient was rated by his doctor and the lower the overall ‘disease seriousness level’ was at the time in the practice the more likely a prescription of fluoroquinolones was.

The observed phenomena can best be explained by a hypothesis that originates from qualitative research: doctors wrongly imbue fluoroquinolones with particularly strong attributes and erroneously transfer the use of these drugs—normally used to treat certain serious bacterial infections under defined conditions—to the treatment of acute coughing in otherwise healthy patients.¹⁵

**Limitations and strengths**

As the primary care physicians participated voluntarily, the sample may not be representative of all German primary care physicians. However, antibiotic prescriptions were in line with representative data.¹⁶ Furthermore, data were collected during a limited observational period and we cannot therefore explore the impact of seasonal factors, known to play a part in antibiotic prescription patterns in primary care.¹⁷

A particular strength of our study is the utilization of a specific symptom-oriented documentation. If we had relied merely on routine practice data we would not have been able to identify the role of patient factors such as ‘illness severity’ as perceived by the physician. No previous studies on antibiotic prescriptions for patients with acute RTI had analysed this predictor.¹⁸,¹⁹

Another advantage of our study design is the precise limitation of all prescriptions to the symptom ‘acute cough’ and the exclusion of co-morbidities whose inclusion may have undermined the validity of any claims on the back of the very specific research question. Finally, the utilization of random effects logistic regression models allowed full adjustment for the effects caused by clustering of patients with GPs (and practices).

**Conclusions**

Primary care physicians constantly have to juggle the expectations of public health and (presumed) individual patient care, with doctors often prioritizing the latter.²⁰ Research has shown that patients’ perceived expectations and issues surrounding communication may play an important role in the over-prescription of antibiotics in primary care.¹³,¹⁵,²¹

Although several interventions, both at local and national level, have succeeded in reducing unnecessary antibiotic prescriptions, it seems that more concerted efforts are necessary for sustainable changes.¹³,²²–²⁵

The prescription of fluoroquinolones for the treatment of acute coughing can rarely be justified in primary care situations. Therefore, our analysis supports the idea that fluoroquinolone prescriptions can serve as a quality indicator—ideally as part of a set—for antibiotic prescribing in primary care and supports the set of drug-specific quality indicators developed by Coenen et al.²⁵

Understanding the predictors for the inappropriate prescription of antibiotics may help to develop effective and focused strategies for improving the standards of antibiotic use in primary care. Any future interventional studies should aim at ‘demystifying’ the newer broad-spectrum antibiotics and should emphasize the fact that more traditional antibiotics like...
amoxicillin or doxycycline are potent drugs in the case of antibiotic being needed for lower RTI (acute cough).  

**Funding**

This work was supported by the AOK Bundesverband (a statutory health insurance fund).

**Transparency declarations**

None to declare.

**References**