The quest for optimal antimicrobial therapy
Mol, Petrus Gerardus Maria

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2005

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Chapter IV

Academic fluoroquinolone prescribing and resistance - impact of guidelines revisited

Peter GM Mol
Prashant V Nannan Panday
John E Degener
Tjip S van der Werf
Flora M Haaijer-Ruskamp
Rijk OB Gans

submitted
Abstract
An increase in ciprofloxacin prescriptions in our university-hospital was associated with the emergence of drug-resistant enterobacteriaceae. We studied whether guideline-recommended antimicrobials could be used as effectively as ciprofloxacin for empirical treatment of infections. Cultured pathogens are well covered by guideline-recommended antimicrobial agents. These results should favor more adherence to these guidelines.
Fluoroquinolones are often used inappropriately; Lautenbach et al. showed that up to 81% of patients treated in an emergency department received a fluoroquinolone for an improper indication. Various authors report increasing bacterial resistance to fluoroquinolones especially for uropathogens, e.g. Enterobacteriaceae. Despite these observations, ciprofloxacin remains the most commonly prescribed antimicrobial agent for urinary tract infections (UTI) in many hospitals. Moreover, excessive ciprofloxacin use has recently been linked with the emergence of drug-resistant organisms like vancomycin-resistant Enterococci. In our university-affiliated teaching hospital, ciprofloxacin is also often prescribed as a first line agent, i.e. for urinary tract infections, despite the fact that it is not recommended by the hospital guideline for any presentation of UTI. Not unexpectedly, we have observed an increase in quinolone-resistant Enterobacteriaceae in the past decade.

Antimicrobial treatment guidelines, such as the ones used in our hospital, are not only based on evidence-based national and international guidelines, but also on local microbial susceptibility and resistance patterns. We studied whether guideline-recommended agents for initial empirical treatment, i.e. when no in-vitro culture results were yet available to the physician, were indeed as effective as ciprofloxacin, as judged by the in-vitro susceptibility of subsequently isolated pathogens.

The study
Within the framework of an intervention study aimed at optimizing antimicrobial use in our hospital, we collected prospectively patient-, disease-, and drug-therapy data for 795 patients treated with an antimicrobial agent. We included 1,822 antimicrobial prescriptions for patients with an infection admitted to the various departments of medicine, pulmonology, hematology, nephrology, gastro-enterology, general internal medicine and intensive care from February 2001 until February 2002. An independent observer assessed whether prescribing had been in accordance with the hospital guideline recommendations. Prescriptions were assessed according to explicit guideline recommendations for specific clinical indications (or cultured pathogens). The in-vitro test results overruled guideline recommendations if cultured pathogens were insensitive to guideline-recommended agents.

Therapy with ciprofloxacin was classified as adherent, too broad or less effective compared to the guideline recommended antimicrobial drug choice. Ciprofloxacin was assessed as:
a) adherent, when the guideline recommended ciprofloxacin for that specific indication,
b) too broad, when the guideline recommended using a more narrow spectrum agent,
c) less effective, when the expected or cultured pathogens were not sensitive to ciprofloxacin.

The guideline recommended ciprofloxacin only for empirical treatment of urinary sepsis in the presence of a catheter (combined with amoxicillin), enteric sepsis, or skin ulcer associated sepsis (combined with clindamycin), acute pyelonephritis, and acute prostatitis. Ciprofloxacin had a limited place in the guideline for culture-targeted treatment of Salmonella species and Legionella pneumophila.

Changes in the route of administration or dosage, leading to new ciprofloxacin prescriptions were not considered in the analysis. Three patients received ciprofloxacin for two separate disease-episodes during the same hospital admission. Only the initial prescriptions were included in the analysis.

Out of a total of 1,822 prescriptions ciprofloxacin was prescribed 199 times (10.9%) to 144 patients. For all prescriptions a guideline-adherent drug choice was made in 68%. For ciprofloxacin, however, adherence was much lower. It was properly indicated for the treatment of sepsis in only 13 (33%) of 40 patients, in only 7 of 57 (12%) patients with an UTI, and 12 of 24 (50%) patients with respiratory tract infections (RTI); for gastro-intestinal infections ciprofloxacin was the guideline-recommended drug of choice in 8 of 9 patients, whereas only 6 of the remaining 14 patients with another type of infection were treated with ciprofloxacin in accordance with the guideline-recommendations.

**Empirical therapy**

Ciprofloxacin was prescribed as empirical treatment to 82 patients. For only 30 patients, ciprofloxacin was advised by the guideline. For 38 patients ciprofloxacin covered the expected pathogen but a less broad-spectrum agent would have sufficed according to the guideline. For another 14 patients ciprofloxacin did not even cover the expected pathogen(s), which was confirmed in 5 patients when culture results became available (see below) [table 1]

Next, all prescriptions with ciprofloxacin were reassessed after in-vitro culture results became available. For 41 patients (8=sepsis, 15=UTI, 6=RTI, and 12=other infections) appropriate cultures did not disclose any growth of micro-organisms. For six patients ciprofloxacin was the most appropriate therapy when culture results became available. Twenty-one patients were continued on therapy with ciprofloxacin despite the guideline recommending non-fluoroquinolone agents that were confirmed by culture results ('too broad').
Two examples are provided below that illuminate cases where reassessment led to a new classification of 'too broad' therapy.

1) For five patients empirical therapy was initially considered adherent, but with culture results available therapy was reassessed as 'too broad'. For example, one of these patients presented with acute gastro-enteritis (blood in stools) with the most probable causative organisms in the Netherlands being *Campylobacter, Salmonella, Shigella, or E. coli*. Ciprofloxacin was in this case the guideline recommended empirical drug choice. When finally *Aeromonas hydrophilia* sensitive to cefuroxim was cultured, a targeted narrower spectrum agent would have sufficed, hence the reclassification 'too broad'. Thus, those five patients illustrate the infectious disease ground rule of starting with broad spectrum antimicrobial therapy to sub sequentially streamline therapy to an appropriate narrow spectrum agent based on available culture- and sensitivity-test findings.

2) The second example concerns one patient whose initial empirical therapy with ciprofloxacin was assessed less effective. However, when culture-results became available therapy was considered ‘too broad’. For this patient with an epididymitis and a urinary catheter in situ the guideline recommended amoxicillin and tobramycin to cover the expected causative organisms - *enterococci and enterobacteriaceae* -. Initial therapy with ciprofloxacin failed to cover expected *enterococci*, hence the classification less effective therapy. Ciprofloxacin’s antimicrobial spectrum, however, was reassessed as too broad for the finally cultured *E. coli* that was sensitive to amoxicillin.

<table>
<thead>
<tr>
<th>Table 1. Adherence of ciprofloxacin to guideline-recommended therapy of empirically treated patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial empiric choice</strong></td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Adherent</td>
</tr>
<tr>
<td>Too broad</td>
</tr>
<tr>
<td>Less effective</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

§ Empirical therapy was reassessed after *in-vitro* culture results became available

In 14 patients micro-organisms were cultured that were not susceptible to ciprofloxacin. [table 1]

Notably, this therapy with ciprofloxacin was changed to another antimicrobial agent in only nine of 14 patients. Thus, in five cases a ciprofloxacin prescription was continued despite culturing pathogens that apparently necessitated the prescription of another antimicrobial agent. Despite inappropriate therapy all five patients recovered. If the initial empirical drug choice in these patients, however, had been according to the
guideline-recommendations instead of initial treatment with ciprofloxacin, isolated micro-organisms would not have been adequately covered in nine instead of fourteen patients. [table 2]

<table>
<thead>
<tr>
<th>Drug choice</th>
<th>Pathogens covered</th>
<th>N patients (%)</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>27 (66%)</td>
<td>(49% - 80%)</td>
<td></td>
</tr>
<tr>
<td>Guideline</td>
<td>32 (78%)</td>
<td>(62% - 89%)</td>
<td></td>
</tr>
</tbody>
</table>

**Culture-targeted therapy**

Ciprofloxacin was prescribed, for the first time, to 62 patients after in-vitro culture results had become available, i.e. culture-targeted therapy. Twenty-one patients were on initial treatment with empirical antimicrobial therapy other than ciprofloxacin, whereas 41 patients were antimicrobial therapy-naive. Narrower spectrum non-fluoroquinolone agents could have been used in the majority (66%) of these culture-targeted prescriptions, and notably, according to culture results, less effective ciprofloxacin therapy was started in five patients.

**Conclusions**

Antimicrobial therapy with ciprofloxacin does not follow guideline-recommendations for the majority of empirical and culture-targeted therapy. This study shows that, small spectrum antimicrobial drugs, e.g., nitrofurantoin, trimethoprim, norfloxacin, and amoxicillin, as recommended by the hospital guideline, can be safely prescribed for initial empirical therapy of most infectious diseases for which clinicians choose coverage with ciprofloxacin. This study also shows that despite in-vitro culture results suggesting ciprofloxacin to be a less effective therapy, the fluoroquinolone was continued for patients whose clinical condition apparently improved. Moreover, we were surprised that with the causative pathogen and its in-vitro susceptibility known, physicians still started presumably less effective antimicrobial treatment. This observation is in sharp contrast with the general assumption that Dutch physicians are keen on using small spectrum antimicrobial therapy and streamlining antimicrobial therapy, because of the consistent teaching on this topic in medical schools. Not surprisingly, ongoing antimicrobial surveillance in our hospital has shown a continuing steady increase in fluoroquinolone resistance especially for uropathogens, from around 2% in 1990 to 10% in 2002. A ‘better safe than sorry’ approach, using broad-spectrum agents, such as ciprofloxacin, is clearly not warranted when a carefully designed guideline, based on local antimicrobial resistance patterns is available. We would thus
like to emphasize step 3 and 6 of the CDC “action steps” to prevent antimicrobial resistance, that is target the pathogen and use your local data, i.e. your antibiogram.

References


