Considering resistance in systematic reviews of antibiotic treatment

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Context: Microorganisms resistant to antibiotic drugs are a threat to the health and chances of survival of patients. Systematic reviews on antibiotic drugs that ignore the topic of resistance present readers with a skewed view, emphasizing short-term efficacy or effectiveness while ignoring long-term consequences.

Objectives: To examine whether systematic reviews of antibiotic treatment consider resistance; if not, to find out whether data on resistance were reported in the original trials; and based on that, to offer a framework for taking resistance into account in systematic reviews.


Study selection: (i) Systematic reviews or meta-analyses of antimicrobial therapy, published during 1996–2000. (ii) Randomized, controlled trials abstracted in systematic reviews that addressed a topic highly relevant to antibiotic resistance.

Data extraction: We examined each systematic review, and each article, to see whether the implications of resistance were discussed; and whether data on resistance were collected.

Results: Out of 111 systematic reviews, only 44 (40%) discussed resistance. Ten reviews (9%) planned or performed collection of data on the response of patients with susceptible or resistant isolates. In 22 systematic reviews (20%), collection of data on induction of resistance was planned or performed. The topic of 41 reviews was judged highly relevant to resistance, and these reviews extracted data from 337 articles, out of which we retrieved 279 articles (83%). In 201 (72%) articles, resistance was discussed or data pertaining to it were collected. Ninety-seven articles (35%) gave actual data on resistance of pathogens to the study drugs, 71 articles (25%) data on efficacy of antibiotic drugs in patients with susceptible and resistant pathogens, and 55 articles (20%) provided data on infection or colonization with resistant strains during treatment.

Conclusions: Most systematic reviews on antibiotic treatment ignored the issue of resistance, although many of the original articles referred to it and some reported relevant data. Reviewers should collect data on resistance and discuss the implications in their discussion and sections concerned with policy implications.

Keywords: meta-analysis, antimicrobial drugs, susceptibility to antibiotic drugs

Introduction

Microorganisms resistant to antibiotic drugs threaten the life and wellbeing of patients.1–4 Convincing evidence links consumption of antibiotic drugs to induction of resistance.5–8 Consumption may be influenced by guidelines and policies, but ultimately it results from many patient–physician encounters.

A strong current in medicine aims to base both policies and patient–physician encounters on evidence. The best evidence comes from randomized controlled trials, and systematic reviews are an excellent way to present a synthesis of the evidence to practitioners and patients. However, randomized, controlled trials of antibiotic drugs have difficulties in taking resistance into account as an outcome. They deal with the efficacy and effectiveness of antibiotic...
reviews, but often without considering resistance, mainly because the timescale of controlled trials cannot be matched conveniently with that of emergence of resistance. There are two steps in the development of resistance: the induction of resistant microorganisms in the major reservoirs of the body during antibiotic treatment, and the spread of resistant microorganisms from one person to another and to the environment. The first step can be addressed in trials of antibiotic drugs.

The events that lead to resistance are relatively rare, and special effort is required to document them (e.g., surveillance cultures). Thus, of six recent guidelines for evaluation of anti-infective drugs in clinical trials, only one addresses explicitly emergence of resistance.

Authors of systematic reviews of antibiotic treatment may face the same difficulties, and thus may choose to disregard resistance. If they do, readers are presented with a skewed view, emphasizing short-term efficacy and effectiveness, whereas medium- and long-term consequences are ignored. Even for a single patient, the induction of future resistance should be taken into account when prescribing antibiotic treatment. In addition, resistance is probably a powerful predictor of clinical failure. Separate analysis of failure in patients with susceptible strains and in patients with resistant strains is important for the interpretation and application of study results.

Here we examine whether recent systematic reviews of antibiotic treatment considered resistance, and if not, whether data on resistance were available in the original trials. Based on that, a framework is offered for considering resistance in systematic reviews. We established whether the reviews addressed three main questions. (i) Does resistance influence response to treatment? Specifically, was a difference in response between patients with susceptible and resistant isolates sought for? Was resistance used to explain heterogeneity between studies? Were the patterns of resistance in different locations considered when discussing implications of the systematic review? (ii) Was the differential effect between arms in trials in causing drug resistance sought? Specifically, were superinfections, re-infections or colonization with resistant pathogens sought as an outcome? (iii) Were the long-term effects on resistance of using a specific regimen discussed?

Methods

Systematic reviews

Inclusion criteria. We included all systematic reviews published during 1996–2000 that looked at systemic administration of antimicrobial drugs, comparing drug to placebo or non-antibiotic drugs or other procedures, drug to drug, or different durations of treatment. Systemic administration was defined as either oral or intravenous administration; or instillation in a body cavity; or inhalation; but not topical treatment. Systematic reviews were defined as such if they contained a clearly formulated question, inclusion criteria, and we retrieved 111 (97%), Figure 1. Our search yielded 334 publications, out of which 115 matched the issue of resistance (category A). We included all randomized controlled trials cited in systematic reviews that addressed a topic highly relevant to the issue of resistance (category A). For each of the articles, we noted the year of publication, and abstracted items on resistance according to a list of questions similar to that used for the systematic reviews.

Methods of data collection

Data from the reviews and articles were collected independently by two reviewers. Discrepancies were settled by discussion with a third reviewer. For items that addressed the question whether the issue was discussed, we used three possible answers: discussed; mentioned but not discussed; and not mentioned.

Analysis of data

For statistical analysis of contingency tables, the χ² test or the Fisher’s exact test was used, as appropriate. For changes across years, we used the χ² test for trends. For comparison of a continuous variable between two categories, we used the Wilcoxon sum-rank test. κ was calculated as a measure of agreement.

Results

Systematic reviews

Our search yielded 334 publications, out of which 115 matched the inclusion criteria, and we retrieved 111 (97%). Figure 1. Table 1 describes the topics addressed by these systematic reviews. Forty-one reviews (37%) addressed a topic categorized as highly relevant to resistance; 60 (54%)—possibly relevant; and 10 (9%)—probably not relevant. Examples of topics categorized as highly relevant are treatment of dyspepsia with antibiotics, treatment of acute otitis media in...
children and of acute cough in adults, treatment of patients with cystic fibrosis and decontamination of the gut with systemic antibiotics in the intensive care unit. Examples of topics we considered possibly relevant were: prophylaxis for surgical interventions, treatment and prophylaxis in neoplastic patients and antibiotic regimens before and during birth. Topics considered to be less than relevant were: antibiotic treatment for leptospirosis, prophylactic antibiotics for post-traumatic cerebrospinal fluid fistula and post-operative procedures for improving fertility after pelvic reproductive surgery. Table 2 shows the percentages of reviews addressing each item on resistance, according to classes of relevance.

Only 44 reviews (40%) discussed the implications of resistance, whereas in 67 publications resistance was not discussed, or was mentioned only cursorily. Of those in class A (high relevance), 46% for treating salmonella gut infections.101

Table 1. Topics addressed by the 111 systematic reviews surveyed

<table>
<thead>
<tr>
<th>Topic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peri-surgical and post-trauma infections</td>
<td>17 (15)</td>
</tr>
<tr>
<td>Helicobacter pylori-related conditions</td>
<td>14 (13)</td>
</tr>
<tr>
<td>Respiratory tract infections</td>
<td>14 (13)</td>
</tr>
<tr>
<td>Peri-obstetric events</td>
<td>13 (12)</td>
</tr>
<tr>
<td>Infections in persons with cystic fibrosis</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Infections in neonatal patients</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Prevention of infections in critically ill patients</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Others</td>
<td>24 (22)</td>
</tr>
</tbody>
</table>

The percentage of reviews that discussed resistance increased significantly with the year of publication (P = 0.01), but not the percentage of reviews in which collection of data on resistance was planned or performed (Figure 2). Reviews that addressed longer duration of antibiotic treatment discussed and collected data on resistance more often. The number of reviews that discussed resistance was 25 out of 74 addressing short-term treatment (34%); 14 of 28 reviews addressing variable duration of treatment (50%); and five of nine reviews addressing long-term treatment (56%), P = 0.2.

Forty reviews (36%) addressed prophylaxis, and the remainder treatment. No relation was found between the purpose of antibiotic administration, whether prophylaxis or treatment, and the comparison, whether drug to placebo or drug to drug, and reporting on resistance.

**Articles**

To test whether ignoring issues concerning resistance was caused by lack of data or lack of consideration in the original articles, we looked for the randomized, controlled trials cited in the 41 systematic reviews of topics that are highly relevant to the question of resistance. These 41 reviews had extracted a total of 337 articles and 15 abstracts for review, and we retrieved 279 articles (83%). The articles were published during 1950–2000, half of them after 1993. We found no significant association between discussing or reporting data on resistance and the year of publication.

Of the 279 articles, 201 (72%) discussed the issue of resistance or collected data pertaining to it. Ninety-seven articles (35%) gave actual data on resistance of pathogens to the study drugs, 71 articles (25%) data on efficacy of antibiotic drugs in patients with susceptible and resistant pathogens, and 55 articles (20%) data on infection or colonization with resistant strains during treatment.

Of the 37 reviews in class A that did not collect data on response of patients with susceptible isolates, in 14 (38%) the data were reported in at least one trial quoted by the review. Of the 32 reviews in class A that did not report on isolation of resistant strains during treatment, in 12 (37%) data were reported in at least one trial.
Nineteen reviews in class A addressed treatments with durations equal to or less than 10 days. Fourteen of them (74%) included at least one article that reported on emergence of resistance as an outcome, but only seven of the 14 reviews included a discussion or collection of data on emergence of resistant strains as an outcome.

For both reviews and articles, the agreement between the two people who abstracted the data was high ($\kappa$ for all items $\geq 0.7$, with one exception of 0.6).

**Comment and recommendations**

Resistance to antibiotic drugs is a grave concern. Systematic reviews on antibiotic treatment could address two aspects of this problem. Firstly, to ask whether the advantage of one treatment over another is due to resistance. Secondly, whether the treatments compared have a differential influence on the induction of resistance during treatment.

Sixty percent of the systematic reviews published during 1996–2000 did not discuss resistance and did not plan to collect data relevant to resistance from the original articles. In topics with a high relevance to resistance, the percentage of reviews ignoring resistance was only slightly lower, 54%. Disregarding the issue of resistance could not be explained entirely by lack of consideration or data in the original articles. In $\sim40\%$ of reviews addressing topics highly relevant to resistance and not discussing resistance at all, some of the original articles included data on it. Data available in about a third of articles were not collected or used.

It was interesting to note that the percentage of reviews discussing resistance increased with time, whereas no such trend was found in original articles.

A few caveats should be kept in mind. We counted publications and not studies, and this is incorrect from a statistical point of view, as some of the counting units are not independent. The reason was that we addressed the presentation and discussion of results as regards resistance, and that might change from publication to publication even using the same database. We categorized systematic reviews as to their relevance to resistance by title, in order to avoid being biased by the consideration that resistance was given in the full review or abstract. We retrieved only 83% of the articles and none of the abstracts included in the class A systematic reviews. The missing articles might have changed our results, but are unlikely to have introduced a bias. Even if none of them reported on resistance, the trends we described would have remained similar.

The reviews surveyed here address a wide spectrum of clinical questions. Important questions relate to practice in the community (antibiotic treatment for bronchitis, sinusitis, otitis media, cough, sore throat, dyspepsia); and to groups of patients at special risk: patients in intensive care units, with neutropenia, or with cystic fibrosis. These reviews are likely to be among the first choices for a physician looking for evidence to decide on antibiotic treatment. Using their conclusions for evidence-based practice would often mean ignoring the problem of resistance.

**Issues of resistance addressed in systematic reviews have clinical implications. For example, knowledge of the local patterns of resist-
Pneumonia in patients in the intensive care unit, 75, 76 and, ignoring be used in favour of combination therapy. In patients with cystic fibrosis, on the other hand, the use of combination therapy might have slowed the emergence of resistance strains, probably because the duration of treatment was longer. 51

Antibiotic prophylaxis might have reduced the incidence of pneumonia in patients in the intensive care unit, 75, 76 and, ignoring resistance, this evidence could be construed as an indication to use broad-spectrum antibiotics for this purpose. A true balance demands data on induction of resistance, and thus adverse effects that will be caused by resistant pathogens in future patients to be included in the considerations.

As a minority of comprehensive reviews demonstrates, systematic reviews can address questions on resistance to antibiotic drugs, and these issues are relevant to clinical practice. Based on these reviews, 34, 48, 51, 94, 101, 106, 116, 127 we recommend that systematic reviews on antibiotic treatment should:

**Extract information on baseline resistance and influence of resistance on outcome for each trial.** Ideally, data collected from each study on antibiotic drugs for the control and treatment group should contain the outcome/s of interest for:

1. All the patients who were randomized (on an ‘intention to treat’ basis).
2. Patients stratified into those with: (i) isolates that were susceptible to the antibiotic drug given in that specific group; (ii) resistant isolates; (iii) no microbiological diagnosis.

When the data are not available in sufficient detail (either from the original article or from the authors), the percentage of identified pathogens and the percentage of pathogens susceptible to the study drug/s should be used to try and explain heterogeneity. If even these data are not available, the resistance in the region and at the time of the trial could be used to examine how far they might explain heterogeneity.

**Report on resistance as outcome.** Data on the development of resistance during treatment in the pathogen/s of infection, on super-infections, re-infections or colonization with resistant microorganisms should be collected as outcomes.

**Discuss the applicability and implications for practice and research.** The discussion should consider resistance on three counts:

1. How do local patterns of resistance influence applicability of the results of the review?
2. If any data on differential effects in the arms of the trials on resistance are available, how should these influence practice?
3. How should future trials be designed to clarify the role of resistance and to test ways of overcoming or sidestepping it?

Full consideration of resistance in systematic reviews on antibiotic treatment will assure a truer balance for the choice of antimicrobial therapy. It could also improve the handling of resistance in future controlled trials.

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**References**

1. From the Centers for Disease Control and Prevention. (1999). Four pediatric deaths from community-acquired methicillin-resistant *Staphylo-
4. Zaidi, M., Sifuentes-Osorio, J., Rolon, A. L. et al. (2002). Inade-
microbial resistance: a population perspective. *Emerging Infectious Dis-
eses* 8, 347–54.
bial Chemotherapy* 24, 983–92.
tion*. *Clinical Infectious Diseases* 15, Suppl. 1, 55–32.
tion*. *Clinical Infectious Diseases* 15, Suppl. 1, 962–88.


