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Addressing resistance to antibiotics in systematic reviews of antibiotic interventions

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Antibiotics are among the most important interventions in healthcare. Resistance of bacteria to antibiotics threatens the effectiveness of treatment. Systematic reviews of antibiotic treatments often do not address resistance to antibiotics even when data are available in the original studies. This omission creates a skewed view, which emphasizes short-term efficacy and ignores the long-term consequences to the patient and other people. We offer a framework for addressing antibiotic resistance in systematic reviews. We suggest that the data on background resistance in the original trials should be reported and taken into account when interpreting results. Data on emergence of resistance (whether in the body reservoirs or in the bacteria causing infection) are important outcomes. Emergence of resistance should be taken into account when interpreting the evidence on antibiotic treatment in randomized controlled trials or systematic reviews.

Introduction

Antibiotics are one of the most important interventions in healthcare, substantially reducing mortality and morbidity in severe bacterial infections. Many medical procedures could not be safely performed without antibiotics. Resistance of microorganisms to antibiotics threatens to undo these gains, and there is convincing evidence that the consumption of antibiotic drugs induces resistance.[1]

Guidelines and clinical decisions are frequently based on systematic reviews. Between June 2014 and June 2015, approximately 140 systematic reviews on antibiotic treatment were published. However, these systematic reviews on antibiotic treatment often did not address resistance to antibiotics even when data were available in the original trials.[2] The major cost of antibiotic treatment is probably the harm to future patients from emergence of resistance.[3–5] If emerging resistance is ignored in systematic reviews, readers are presented with a skewed view, stressing short-term efficacy and ignoring the long-term consequences to the patient and other people.

Fighting the rise in antibiotic resistance is a global concern. The WHO has recently endorsed a global action plan on antimicrobial resistance with '... five strategic objectives: (i) to improve awareness and understanding of antimicrobial resistance; (ii) to strengthen knowledge through surveillance and research; (iii) to reduce the incidence of infection; (iv) to optimize the use of antimicrobial agents; and (v) to ensure sustainable investment in countering antimicrobial resistance.'[6] Considering resistance to antimicrobials in systematic reviews and in the original trials can address at least three of these goals. Authors of systematic reviews can join this effort. This article outlines a framework for addressing resistance to antibiotics in systematic reviews.

Which systematic reviews?

The types of antibiotic interventions for which resistance should be considered are detailed in Figure 1. We have selected these interventions (and comparisons) based on the potentially divergent influences of the two arms on promoting resistance.

There are three main steps in the expansion of resistance that might be influenced by antibiotic interventions: induction of resistant bacteria in the patient treated with antibiotic drugs; selection of resistant strains in the individual treated; and spread of the resistant bacteria to other people and the surroundings. Because of the short timescale of randomized controlled trials, only the induction and selection of resistant strains are relevant for most systematic reviews on antibiotic treatment. But for some interventions (e.g. large-scale use of antibiotics in a community), both induction and selection of resistance and also spread can be addressed.[7]

Baseline resistance and its influence on outcomes

To be useful to policy development, systematic reviews of antibiotic interventions must consider the influence of antibiotic resistance on the wider applicability of the review results. The development of resistance over time might have lowered the efficacy of drugs that were tested in old trials. New antibiotics will appear superior to old ones if they are evaluated only in areas with resistance to the old comparator drug or in areas where the (old) comparator drug is failing. The comparison of a new, broad-spectrum antibiotic drug with an old drug for which resistance is more abundant adds little to our understanding if the efficacy of the drugs is not compared in the subgroup of patients with susceptible pathogens.

A systematic review may include studies that were done a long time ago or done only in certain regions, with local profiles of resistance. Reviewers need to take these differences into account when interpreting their results and discussing their applicability. They should refer to current patterns of resistance and their distribution. In Figure 2, we make recommendations regarding the data that should be sought and extracted from primary studies into systematic reviews and considered in the interpretation of these studies. If data are missing, systematic description of the absence of important information in the primary studies will encourage those embarking on new primary studies to consider collecting important information relevant to resistance.

Comparisons between:

- An antibiotic drug and no treatment, placebo, delayed treatment or a non-antibiotic intervention.
- Antibiotic drugs or combinations of antibiotics.
- Different durations of antibiotic treatment.
- Different dosing of antibiotic drugs.
- Antibiotic de-escalation/escalation strategies.
- Antibiotic prophylaxis.
- Mass programmes of antibiotic drug administration.
- Interventions to improve antibiotic prescribing.

Figure 1. Systematic reviews that should address resistance to antibiotics.

Resistance as an outcome

During antibiotic treatment, bacteria resistant to the administered drug have an advantage and might grow in the main non-sterile reservoirs of the body, such as the bowel, nasopharynx and skin. Documentation of such changes demands surveillance cultures during and after the trial. This step is not taken in many trials, as it requires resources and poses an additional burden to the participants. However, in some trials, surveillance cultures were done[2]; and the results can be incorporated in systematic reviews.

Data on superimposed bacterial infections by pathogens resistant to the study antibiotic during or shortly after treatment should be collected as outcomes. Even if susceptibilities to antibiotics were not reported, bacterial infections during antibiotic treatment suggest resistance to the antibiotic drug. Emergence of resistance in the index pathogen (initially susceptible) during treatment is rare in acute infections but important when it occurs. However, in some cases, treatment is given for chronic infection,

Data to be collected and reported for each trial included in the systematic review:

- Percentage of resistance to the trial drugs in the trial participants.
- Percentage of resistance to the trial drugs at the time and location/s the trials were conducted and in the populations of interest.
- Alongside the main comparisons of the outcomes of interest in all randomized patients by ITT, outcomes should be compared in the subgroups of patients with isolates susceptible to the antibiotic given in the specific arm; in patients with isolates resistant to this antibiotic; and in patients with sterile cultures. Especially in non-inferiority trials, outcomes should be compared in these subgroups in a PP analysis as well.

Interpretation of results:

- Discuss the results of the systematic review in populations of interest in the context of the present distribution of pathogens and their susceptibility to antibiotics compared with the time and location of the trials included in the review.
- Discuss the efficacy of the drugs in the ITT analysis; but also in context of the efficacy in the subgroup of patients with susceptible isolates.

Figure 2. Contextual data about baseline antibiotic resistance to be considered in systematic reviews.

Data to be collected:

- Isolation of resistant bacteria from surveillance cultures of body reservoirs during and after antibiotic treatment.
- Superinfections with resistant pathogens during and after antibiotic treatment.
- Any bacterial superinfection during antibiotic treatment.
- Development of resistance in the index pathogen.
- In relevant studies, change in resistance in the population.

Interpretation of results:

- If resistance-related outcomes are different between the arms of the trial, discuss the implications for policy and practice.
- If no resistance data are available, discuss what is known about resistance to the drugs of interest from other sources and how it can influence policy and practice.

Figure 3. Antibiotic resistance as an outcome to be collected in systematic reviews of antibiotic interventions.

where eradication of the organism is unlikely (e.g. anti-pseudomonal antibiotics for lung infection in cystic fibrosis). It is particularly important to report resistance data in systematic reviews in these conditions, as treatment is often lifelong and selection of resistant organisms is commonplace.[8]

In studies in which a whole population or group of people were exposed to an antibiotic intervention (e.g. azithromycin for trachoma[7] or decontamination of the oropharynx and intestinal tract in intensive care units),[9] the changes in resistance over time in the population are important and should be collected. Figure 3 details the data that should ideally be gathered on resistance as an outcome in trials of antibiotic interventions.

Conclusions

Not all trials report data relevant to antibiotic resistance. Where trials report resistance, these data should be extracted, analysed and used in the interpretation of studies in systematic reviews. Where data on antibiotic resistance are not available, the implications of resistance should be considered in the Discussion section. Systematic reviews can point to areas where crucial data on resistance are missing from the original studies, setting a research agenda.

We offer a framework for data collection and discussion. The same considerations apply to systematic reviews on antiviral and antifungal agents.

We aim to draw on this framework in the development of Cochrane protocols and reviews. We hope that the use of this framework in systematic reviews will encourage researchers to include reference to resistance in the design of their trials and in their reports. We also hope that the readers of these systematic reviews will look for data on resistance and incorporate them in their decisions on treatment and policy.

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