Effectiveness of antibiotic stewardship interventions in reducing the rate of colonization and infections due to antibiotic resistant bacteria and \textit{Clostridium difficile} in hospital patients – a systematic review and meta-analysis

Study Protocol

David Baur, Beryl Primrose Gladstone, Federico Foschi, Stefanie Döbele, Evelina Tacconelli
Division of Infectious Diseases, Department of Internal Medicine I, Tübingen University Hospital, Germany

Correspondence:
Prof. Dr. Evelina Tacconelli
Otfried-Müller-Straße 12, D-72076 Tübingen, Germany
Email: evelina.tacconelli@med.uni-tuebingen.de
Tel: +497071 29-85020

Funding: German Center for Infection Research (TTU-HAARBI, Research Clinical Unit)

Planned date of start of study: April 1st 2015
Introduction

Antimicrobial stewardship (ASP) is an essential component of the multifaceted approach to reduce inappropriate usage of antibiotics. Two major goals can be defined: firstly, ASPs should optimize the clinical outcome and minimize unintended consequences (for example adverse drug events, the emergence of resistance or the selection of resistant pathogenic organisms such as *Clostridium difficile*), secondly it should reduce health care costs without degrading the quality of care. There are different interventions to reduce antimicrobial usage and optimize antimicrobial therapy including: antibiotic restriction, audit (pre-approval), education, consultation and guideline implementation. ASPs can play a role in reducing antibiotic resistance (ABR) rates although clear evidence is not available. Davey et al. conducted a systematic review (until 2006) to evaluate the effect of ASP on the improvement of the prescription of antimicrobial drugs. In particular Davey et al. found evidence for *Clostridium difficile* infections (CDIs) to be beneficially impacted by the interventions. Feazel et al. focused on the impact of ASP on the incidence risk of CDI which showed a reduction of 52%. However, these reviews neither provided data on incidence rates of resistance nor were sources of heterogeneity explained.

We plan to conduct a systematic review and meta-analysis to define the effectiveness of ASPs on the incidence of infections and/or colonization due to antibiotic resistant bacteria and *Clostridium difficile* in hospitalized patients.

Objectives

The primary goal of this study is to determine the effectiveness of ASP interventions in reducing the incidence of antimicrobial resistant infections and/or colonization due to antibiotic resistant bacteria and CDIs in hospital patients.

Our secondary outcomes will include the incidence rate ratios (IRRs) sub grouped by study settings, type of ASP intervention, and co-implementation of infection control measures.
Methods

Inclusion and exclusion criteria

Type of interventions
All studies reporting the effect of an ASP intervention on ABR rates among hospitalized patients. ASP is defined as an intervention promoting the optimal selection, and/or dosage, and/or duration of antimicrobial treatment in hospitalized patients. All types of antimicrobial interventions will be included. No limitation on type of resistant bacteria will be performed.

Type of study designs
According to the Cochrane Effective Practice and Organisation of Care (EPOC) Group guidelines, we will include randomised controlled trials (RCTs), non-randomised controlled trials (NRCTs), controlled before-after CBA (studies), retrospective and prospective cohort studies and interrupted time series (ITS) studies with three and more data points before and after the intervention, reporting an ASP intervention (EPOC).

Types of participants
Our review will include all studies that measure the effect of ASP interventions on the antimicrobial resistance rate ratio in hospital patients. All population groups (elderly, children, immunocompromised, etc.), regardless of age, racial and ethnic backgrounds will be considered. Studies reporting interventions on patients in the community or in health care services (long-term care facilities and nursing homes) will be excluded.

Types of outcome measures
The primary outcome is the change in the incidence rates (IRs) of infection/colonization due to ABR bacteria and CDIs among hospitalized patients after the implementation of ASP. The outcome measure is the IRR per 1000 patient-days calculated as the ratio between incidence rates (i.e. number of resistant pathogens isolated and patient-days) of colonization and/or infection due to the targeted antibiotic resistant bacteria or CDI before and after ASP introduction.

Antibiotic class will be stratified according to the WHO drug anatomical therapeutic chemical III level antibiotic classification, and resistance to single antibiotics will be used as unit of analysis. Carbapenem resistance will be reported according to the authors’ definitions. When more than one agent for each class is tested, we will limit extraction to predefined antimicrobial agents for every class in order to avoid double counting of single isolates: in the case of carbapenems, resistance to meropenem will be considered first followed by imipenem; among third-generation cephalosporins, ceftriaxone followed by ceftazidime and cefotaxime; among aminoglycosides, gentamycin and then amikacin; among fluoroquinolones, ciprofloxacin, and levofloxacin.

Search strategy
All publications reporting the effect of an ASP intervention on incidence of ABR rates among hospitalized patients will be identified by a systematic search of PubMed, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and Web of Science from the inception of the databases till March 31st, 2015 using the following search terms: “antibiotic AND stewardship” OR “antibiotic AND intervention AND Resistance”. Reference lists of retrieved articles will be searched as well. No language restriction will be applied.
Selection process
A two-step selection process will be performed by two independent reviewers. Titles and abstracts of the retrieved articles will be initially screened and non-relevant studies will be excluded. The reasons for exclusion will be noted. In case of disagreement, a third reviewer will be consulted and the decision will be reached by discussion and consensus. Full text of the potential eligible studies will be retrieved and assessed for relevance. The researchers will not be blinded to study authors or location. If the needed data is not extractable from the paper the corresponding author will be contacted.

Data extraction and management
All eligible studies will be managed using a reference management database. A data extraction form will be created including variables related to study design, type of interventions, quality, and outcomes. It will be pilot tested and standardized. Two reviewers will extract the data and perform the risk of bias assessment independently. Any discrepancies and inconsistencies will be cross verified and sorted out by consensus and by discussion with the senior researcher. All the major verifications and decisions will be documented.

Variables to be extracted:

1. Characteristics of study
   - Year, duration, country of study
   - Design
   - Setting (type of hospital, type of ward)
   - Study population
   - Objective
   - Outcome

2. Microbial information
   - Type of bacteria
   - Infection / colonization
   - Type of infection
   - Endemic versus epidemic

3. Characteristics of patients
   - Age (mean), gender, race
   - Co-morbidities
   - Severity of illness

4. Characteristics of intervention
   - Type of intervention
   - Description of intervention
   - Duration
   - Duration of follow up
   - Target antibiotic/s

5. Co-interventions
   - Type of co-intervention
   - Description of co-intervention
   - Infection control measures

6. Characteristics of outcome measures pre- and post-intervention
   - Definition of resistance
   - Total number of patients
   - Number of patients with infection/colonization due to targeted bacteria
   - Number of patients with resistant infection/colonization due to targeted bacteria
   - Incidence rate
   - Total patient-days of follow-up
   - Average (mean/median) days of follow-up
Quality assessment

The quality assessment will be based on an adapted version of the scale developed according to the National Institute of Health's Systematic Evidence Reviews and Clinical Practice Guidelines - Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group (Figure 1). The quality of the eligible trials will be assessed by two researchers independently. Discrepancies will be resolved by discussion and consensus and by consulting a third reviewer.

Figure 1: Quality assessment tool used in the study – adapted version of the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group from the National Institute of Health's Systematic Evidence Reviews and Clinical Practice Guidelines

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Yes</th>
<th>No</th>
<th>Other (CD, NR, NA)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the study question or objective clearly stated?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Were eligibility/selection criteria for the study population prespecified and clearly described?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Were all eligible participants that met the prespecified entry criteria enrolled?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Was the sample size sufficiently large to provide confidence in the findings?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Was the test/service/intervention clearly described and delivered consistently across the study population?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CD, cannot determine; NA, not applicable; NR, not reported
Data synthesis and analysis

The effect of ASP will be studied using a pooled estimate of the IRR among hospitalized patients after the implementation of ASP. If not available the total patient days of follow-up will be calculated from the product of the mean length of follow-up and the number of patients followed for the specific period. The meta-analysis will be performed following the Cochrane Collaboration recommendations and reported according to the PRISMA guidelines. The pooled estimates of IRR and its 95% confidence interval will be obtained by combining the logarithms of the rate ratios using the generic inverse-variance method, with random effect models of meta-analysis. Statistical heterogeneity will be assessed using $I^2$. The data will be synthesized according to type of antibiotic resistant bacteria and type of ASP interventions. In order to study the factors influencing the success of ASP, effect estimates will be synthesized based on co-interventions, study setting, type of infection, place and time-period of study. Sources of heterogeneity will be studied using meta-regression and the overall significance testing carried out using Wald’s test adjusted for Bonferroni correction. Reporting and publication bias will be examined using the funnel plot and tested using Egger’s test. All the statistical analyses will be carried out using STATA version 14.0.

Ethics

As this study includes only a review of published data, no formal ethical approval is required.
Abbreviations:

- **EPOC**: Effective Practice and Organisation of Care
- **ASP**: Antimicrobial Stewardship Program
- **MRSA**: Methicillin-resistant *Staphylococcus aureus*
- **VRE**: Vancomycin-resistant *Enterococci*
- **MDR**: Multidrug-resistant
- **CDI**: *Clostridium difficile* infection
- **ABR**: Antibiotic resistant
- **RCT**: Randomized controlled trial
- **NRCT**: Non-randomized controlled trial
- **CBA**: Controlled before-after study
- **ITS**: Interrupted time series study
- **IRR**: Incidence rate ratio
- **CI**: Confidence interval
- **E. coli**: *Escherichia coli*

References: