Systematic Review Protocol: Combining antibiotics to curb antibiotic resistance
A systematic review and meta-analysis

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Review title

Combining antibiotics to curb antibiotic resistance: A systematic review and meta-analysis

Anticipated or actual start date

18/12/2018

Anticipated completion date

15/10/2020

Review stage

We have completed preliminary searches, piloting of the study selection process and have completed the formal screening of search results against eligibility criteria.

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Organizational affiliation of the review

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Funding sources/sponsors

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Conflicts of interest

None

Review question

In patients receiving antibiotic treatment is the frequency of bacterial resistance to the administered drugs lower during or after treatment when the number of administered antibiotic substances is increased? I.e. is there a benefit of more antibiotic substances compared to less antibiotic substances regarding developed or acquired antimicrobial resistance.

Searches

The following three electronic databases will be searched: PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL). There will be no restrictions placed on the publication date. For the search there will be no language restrictions even though we intend to only include articles written in English, German or Russian in the review. Final decision for any language restriction will be conducted after the search, where a more informed decision concerning language bias can be determined. In addition to the database search we will systematically screen the reference list of all papers included in the meta-analysis for further relevant papers and studies of related meta-analyses will be checked for eligibility.

Condition or domain being studied

Any condition requiring antibiotic treatment.

Participants/population.

Patients of all ages treated with antibiotics.

Intervention(s), exposure(s)

Antibiotic treatment regimens of at least one antibiotic given over a period of time. Combination of several antibiotic substances, i.e. multiple antibiotics are administered simultaneously over the whole treatment period, are considered. A cycling regime and sequential therapy are not considered as a combination of antibiotic substances, i.e. any change of the type of antibiotic substances during the treatment period is not considered as antibiotic combination therapy. No restrictions are placed on the antibiotic class or additional substances, that are not considered as an antibiotic, administered in the treatment regime. We do not consider additional substances as antiseptics or beta-lactam inhibitors as antibiotics. The administered antibiotic substances have to be the same for all patients within one treatment-arm.

Comparator(s)/control

Antibiotic combination treatment regime, as defined above, with at least one additional antibiotic substance. The antibiotics in the control group do not have to be the same, just the number of administered antibiotic substances has to be increased by at least one. No restrictions are placed on the antibiotic class or additional substances administered in the treatment regime. The administered antibiotic substances have to be the same for all patients within one treatment-arm.

Types of study to be included

Randomized controlled trials (RCTs) and quasi-randomized controlled trials.

Main outcome(s)

1.Proportion of patients with acquisition of antibiotic resistant bacteria. We define an event of acquisition of antibiotic resistant bacteria as the following: a baseline and a follow-up culture are available, and a bacterial species is found to be more resistant against any of the administered antibiotics in the follow-up culture in comparison to the baseline culture. If a resistant bacterial species is detected in the follow-up culture but not in the baseline culture, it is also counted as acquisition of resistant bacteria. We consider all changes to a more

resistant phenotype between the resistance categories ‘susceptible, intermediate and resistance’. Definition of resistance categories and their breakpoints are taken as reported in each study.
In case there are multiple follow-up measurements per patient, we count any acquisition event and may disregard any loss of resistance in later follow-up measurements.

2. Proportion of patients with emergence of resistance. We define this outcome similarly to the proportion of patients with acquisition of antibiotic resistant bacteria. The difference is that the bacterial species must be reisolated at the follow-up measurement and the susceptibility must have changed to a more resistant phenotype in comparison to the baseline culture.

The measure of effect is planned to be odds ratio.

Additional outcome(s)

1. All-cause mortality as reported in each study.
2. Mortality attributable to infection as reported in each study.
3. Treatment failure as reported in each study. The definition of treatment failure of each study will be stated.
4. Treatment failure due to a change of resistance against the study drugs.
5. Proportion of patients with alterations of the prescribed treatment due to adverse events.
6. Emergence or acquisition of resistance against non-administered antibiotics.

The measure of effect is planned to be odds ratio.

Data extraction (selection and coding)

Study selection:
The selection of publications will be conducted in two stages. Two reviewers will independently screen title and abstract of all publications for eligibility. This first stage of screening is broad in order to capture as many publications investigating the main ouctomes as possible. Title and abstracts will be screened according to the following criteria:
1. (quasi-) RCTs,
2. The requirements for the intervention arms are met.
3. Human study
In the second stage the full text will be screened by the same two reviewers independently. Articles will be included if data for any of the two main outcomes is reported. We include trials if the testing for the main outcomes was done systematically for the whole study population or just for a subset of the study population. We exclude papers based on the main outcome only at the second stage, since it is not always clear from the abstract if relevant data are reported in a study. As e.g. (Bliziotis et al. 2005) found in their meta-analysis, RCTs are usually not designed in particular to study the emergence of antibiotic resistance as one of the main outcomes.

Data extraction:
The data of the selected studies will be extracted independently by two reviewers into a predefined excel sheet including information about the following domains: characteristics of trials, patient characteristics, infection related variables, interventions, outcome characteristics, results and information for the risk of bias assessment.
The reason for exclusion of studies, which are reviewed in full text and found as irrelevant, will be noted. Authors will be contacted for missing or unclear data for the main outcome. After one month waiting time with no response from authors, those studies will be summarized separately if possible.

Any disagreement between the reviewers will be clarified between the two reviewers if necessary, with a third one.

Risk of bias (quality) assessment

The study quality will be assessed by two reviewers independently using the classification scheme for bias described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT 2011):

I. Selection bias
- Random sequence generation
- Allocation concealment
II. Performance bias
- Blinding of participants and personnel III. Detection bias
- Blinding of outcome assessment
IV. Attrition bias
- Incomplete outcome data
V. Reporting bias
- Selective reporting
VI. Other bias
-Other sources of bias

The risk of bias will be classified as high, low or unclear according to the criteria suggested by the Cochrane manual (Higgins JPT 2011). Justification for the grading will be collected by the two reviewers and any disagreement will be resolved by discussion. If needed a third reviewer will be contacted.

Strategy for data synthesis

We aim for a quantitative data analysis. We are anticipating finding studies with no event in either one or both treatment arms, which we want to include in our statistical analysis. To do so we will analyze the data with a generalized linear mixed-effects model. In case that multiple relevant treatment arms are within one study, we aim to combine treatment arms if plausible. To evaluate heterogeneity for the main outcomes, we will use the between study variance. For the main outcomes heterogeneity will be explored via meta-regression as well as sub-group analysis if possible. The following moderators may be considered:

•The antibiotics used in the treatment arm with less antibiotics are also part of the antibiotic treatment of the comparator group. If possible, we include an additional moderator checking for the same dosage of identical substances.
• The number of antibiotics administered.
• The timespan between the conduction of the trial and the antibiotics are on the market • Administration of additional non-antibiotic drugs
• The participants of a study had to have a specific comorbidity to be included
• The study was conducted in an intensive care unit setting
• Length of antibiotic treatment • Length of study follow-up

A sensitivity analysis will be performed based on the model choice and study quality. In case the data for the main outcomes can be efficiently stratified by individual pathogens, we will perform a sensitivity analysis on inclusion of individual types of pathogens. Further sensitivity analyses will be considered.
We will use the GRADE approach as a method to grade the quality of evidence. Any adjustment of grading will be indicated with a justification.
To test for publication bias visual inspection of the funnel plot and Eggeŕ s test will be applied. Statistical analysis will be conducted with the most recent version of R, (R Core Team 2020).

Analysis of subgroups or subsets

As stated above we do not only intend to perform a meta-regression, but also subgroup analyses for the main outcomes if sufficient data are available:

We will conduct a sub analysis for the main outcomes based on whether the resistance was measured systematically for the whole study population or just for a specific subset of the population.

If the data for the main outcome are reported in such a way that it can be stratified by different pathogens, we intend the following two sub analyses for the main outcomes
• Gram-negative infections,
• Gram-positive infections,
to analyze the different impact of plasmid mediated resistance in gram-positive and negative bacteria.

We also intend to analyze the two main outcomes with respectively the additional requirements:

• Resistance in the combination treatment is detected against all administered antibiotics not only against any of the administered antibiotics.
• Only resistance against antibiotics that both treatment arms have in common are considered.

Additionally, the main outcomes will be analyzed excluding any clinical study focusing solely on Mycobacterium tuberculosis or Helicobacter pylori and a subgroup analysis will be performed.

Type of review

Meta-analysis, Systematic Review, Epidemiologic

Health area of review

Infections and infestations

Language

English

Keywords

Systematic Review, Meta-Analysis, Antibiotic resistance, Combination Therapy, Emergence of Resistance, Acquisition of Resistance, Humans

Search strategy

PUBMED:

((((((((((("Bacterial Infections/Drug Therapy"[mesh]) OR "Bacterial Infections/drug effects"[Mesh]) OR "Bacteria/drug effects"[Mesh]) OR "Bacteria/Drug Therapy"[mesh]) OR (((infection[tiab] OR infections[tiab]) AND bacteria*)))) AND ((((((((((((((((("beta-Lactams/Administration and Dosage"[mesh] OR "beta-Lactams/Therapeutic Use"[mesh])) OR ("Aminoglycosides/Administration and Dosage"[mesh] OR "Aminoglycosides/Therapeutic Use"[mesh])) OR ("Chloramphenicol/Administration and Dosage"[mesh] OR "Chloramphenicol/Therapeutic Use"[mesh])) OR ("Glycopeptides/Administration and Dosage"[mesh] OR "Glycopeptides/Therapeutic Use"[mesh])) OR ("Rifamycins/Administration and Dosage"[mesh] OR "Rifamycins/Therapeutic Use"[mesh])) OR ("Streptogramins/Administration and Dosage"[mesh] OR "Streptogramins/Therapeutic Use"[mesh])) OR ("Sulfonamides/Administration and Dosage"[mesh] OR "Sulfonamides/Therapeutic Use"[mesh])) OR ("Tetracyclines/Administration and Dosage"[mesh] OR "Tetracyclines/Therapeutic Use"[mesh])) OR ("Macrolides/Administration and Dosage"[mesh] OR "Macrolides/Therapeutic Use"[mesh])) OR ("Oxazolidinones/Administration and Dosage"[mesh] OR "Oxazolidinones/Therapeutic Use"[mesh])) OR ("QUINOLONES/Administration and Dosage"[mesh] OR "QUINOLONES/Therapeutic Use"[mesh])) OR ("Lipopeptides/Administration and Dosage"[mesh] OR "Lipopeptides/Therapeutic Use"[mesh])) OR ("Anti-Bacterial Agents/Administration and Dosage"[mesh:noexp]))) OR "Anti-Bacterial Agents/Therapeutic Use"[mesh:noexp]) OR "Anti-Bacterial Agents/Therapy"[mesh:noexp]) OR antibiotic*[tiab])) AND (((((((("Drug Therapy, Combination"[mesh:noexp]) OR "drug combinations"[mesh:noexp]) OR "trimethoprim, sulfamethoxazole drug combination"[mesh:noexp]) OR "Drug Synergism"[mesh:noexp]))) OR (combination[tiab] AND (therapy[tiab] OR therapies[tiab]))) OR

combinationtherap*[tiab])) AND ((("Drug Resistance, Bacterial"[Mesh]) OR "Drug Resistance, Microbial"[Mesh:noexp]) OR resistan*[tiab]))) NOT ((((("Complementary Therapies"[Mesh]) OR "Plant Extracts"[Mesh]) OR bismuth[tiab]) OR "Bismuth"[Mesh]))) AND "Controlled Clinical Trial"[Publication Type]

CENTRAL:

#1 MeSH descriptor: [Bacterial Infections] explode all trees and with qualifier(s): [drug therapy - DT]

#2 MeSH descriptor: [Bacteria] explode all trees and with qualifier(s): [drug effects -
#3 ((infection):ti,ab,kw OR (infections):ti,ab,kw) AND bacteria*
#4 MeSH descriptor: [beta-Lactams] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU]
#5 MeSH descriptor: [Chloramphenicol] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU]
#6 MeSH descriptor: [Aminoglycosides] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU]
#7 MeSH descriptor: [Glycopeptides] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU]
#8 MeSH descriptor: [Rifamycins] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU]
#9 MeSH descriptor: [Streptogramins] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU]
#10 MeSH descriptor: [Sulfonamides] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU]
#11 MeSH descriptor: [Macrolides] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU]
#12 MeSH descriptor: [Tetracyclines] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU]
#13 MeSH descriptor: [Oxazolidinones] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU]
#14 MeSH descriptor: [Quinolones] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU]
#15 MeSH descriptor: [Lipopeptides] explode all trees and with qualifier(s): [administration & dosage - AD, therapeutic use - TU]
#16 MeSH descriptor: [Anti-Bacterial Agents] this term only and with qualifier(s): [administration & dosage - AD, therapeutic use - TU]
#17 (antibiotic*):ti,ab,kw
#18 MeSH descriptor: [Drug Therapy, Combination] this term only
#19 MeSH descriptor: [Drug Combinations] this term only
#20 MeSH descriptor: [Trimethoprim, Sulfamethoxazole Drug Combination] this term only
#21 MeSH descriptor: [Drug Synergism] this term only
#22 ((combination):ti,kw,ab) NEAR/3 ((therapy):ti,kw,ab OR (therapies):ti,ab,kw)
#23 (combinationtherap*):ti,ab,kw
#24 MeSH descriptor: [Drug Resistance, Bacterial] explode all trees
#25 MeSH descriptor: [Drug Resistance, Microbial] this term only
#26 (resistan*):ti,ab,kw
#27 MeSH descriptor: [Complementary Therapies] explode all trees
#28 MeSH descriptor: [Plant Extracts] explode all trees
#29 (bismuth):ti,ab,kw
#30 MeSH descriptor: [Bismuth] explode all trees
#31 {OR #1-#3}
#32 {OR #4-#17}
#33 {OR #18-#23}
#34 {OR #24-#26}
#35 {AND #31-#34}
#36 {OR #27-#30}
#37 #35 NOT #36

EMBASE:

#26. #24 AND #25
#25. 'controlled clinical trial'/exp
#24. #23 NOT #22
#23. #18 AND #19 AND #20 AND #21
#22. #14 OR #15 OR #16 OR #17
#21. #12 OR #13
#20. #7 OR #8 OR #9 OR #10 OR #11
#19. #5 OR #6
#18. #1 OR #2 OR #3 OR #4
#17. 'herbal medicine'/exp
#16. 'alternative medicine'/exp
#15. 'bismuth'/exp
#14. bismuth:ti,ab,kw
#13. resistan*:ti,ab,kw
#12. 'antibiotic sensitivity'/exp
#11. (combination NEAR/3 (therapy OR therapies)):ti,ab,kw
#10. combinationtherap*:ti,ab,kw
#9. 'antibiotic agent'/exp/dd_cb
#8. 'drug potentiation'/de
#7. 'combination drug therapy'/de
#6. 'antibiotic*':ti,ab,kw
#5. 'antibiotic agent'/exp
#4. (infection:ti,ab,kw OR infections:ti,ab,kw) AND bacteria*
#3. 'bacterial infection'/exp
#2. 'bacterium'/exp
#1. 'prokaryotes by outer appearance'/exp

References

Bliziotis, Ioannis A., George Samonis, Konstantinos Z. Vardakas, Stavroula Chrysanthopoulou, and Matthew E. Falagas. 2005. 'Effect of aminoglycoside and beta-lactam combination therapy versus beta-lactam monotherapy on the emergence of antimicrobial resistance: a meta-analysis of randomized, controlled trials', *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, 41: 149.

Higgins JPT, Green S (editors). 2011. 'Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]', *The Cochrane Collaboration*.

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