INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Does the use of systemic antimicrobials as an adjunct to mechanical treatment provide a beneficial effect in the treatment of periodontitis? A systematic review and network meta-analysis protocol

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Review question / Objective: **Does the use of systemic antimicrobials as an adjunct to mechanical treatment provide a beneficial effect in the treatment of periodontitis?**
Condition being studied: **Untreated periodontitis.**
Information sources: **We will search the following electronic bibliographic databases: EMBASE, PubMed, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials - Central), LILACS database, Scopus database and Web of Science database. There will be no language restrictions and no years restrictions. We will use the PICOS strategy for the research question construction and evidence search. The searches will be rerun just before the final analyses and further studies retrieved for inclusion. The reference lists of the articles identified will be cross-checked. Furthermore, studies from the 'grey literature' will be screened through the following trial registry platforms: Current Controlled Trials (http:// http:// www.controlled-trials.com), ClinicalTrials.gov (http:// www.clinicaltrials. gov), and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search/search). A manual search will be done in the relevant journals of Dentistry.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 October 2020 and was last updated on 17 October 2020 (registration number INPLASY2020100057).

INTRODUCTION

Review question / Objective: **Does the use of systemic antimicrobials as an adjunct to mechanical treatment provide a beneficial effect in the treatment of periodontitis?**

Condition being studied: Untreated periodontitis.

METHODS

Participant or population: We will include studies examining adult humans (18 years or older) diagnosed with untreated chronic and aggressive periodontitis (Armitage, 1999) and periodontitis stages III and IV (Caton et al, 2018). Studies with smoking and diabetic subjects will be also included. None restrictions about sex, gender or ethnicity will be applied on the population of study.

Intervention: Use of antibiotics as adjuncts to non-surgical treatment of periodontitis (scaling and root planning).

Comparator: Scaling and root planing (SRP) alone or SRP plus a single protocol or a combination of antibiotic protocols to the treatment of periodontitis.

Study designs to be included: Randomized controlled clinical trials.

Eligibility criteria: Studies will be selected according to the PICOS criteria (Participant, Intervention, Comparator, Outcomes and Study Design) outlined in the referred sections. Additionally, we will exclude studies with pregnant or breastfeeding women, periodontitis treatment previous, antibiotic therapy in the previous 6 months, need for antibiotic pre-medication for dental treatment and long-term administration of anti-inflammatory medications.

Information sources: We will search the following electronic bibliographic databases: EMBASE, PubMed, The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials - Central), LILACS database, Scopus database and Web of Science database. There will be no language restrictions and no years restrictions. We will use the PICOS strategy for the research question construction and evidence search. The searches will be rerun just before the final analyses and further studies retrieved for inclusion. The reference lists of the articles identified will be cross-checked. Furthermore, studies from the 'grey literature' will be screened through the following trial registry platforms: Current Controlled Trials (http://http://www.controlled-trials.com), ClinicalTrials.gov (http://www.clinicaltrials.gov), and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search/search). A manual search will be done in the relevant journals of Dentistry.

Main outcome(s): The primary outcome will be: mean reduction in probing depth (PD) and gain in clinical attachment level (CAL) in initially deep sites, percentage of sites with bleeding on probing (BOP) and reduction in mean number of sites with PD ≥ 5 mm post treatment.

Data management: The studies will be imported into Endnote X9 software (Thompson Reuters, Philadelphia, PA, USA) where duplicates will be automatically removed. All analyses will be performed using the software R version 3.6.2 or updated Mac OS X computer system. The package "netmeta" will be used to run network meta-analysis. This package is available from the Comprehensive R Archive Network (CRAN).

Quality assessment / Risk of bias analysis: Two review authors will independently assess the risk of bias. We will use the Cochrane tool for assessing risk of bias. Sequence generation - Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. Allocation concealment - Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment. Blinding of participants, personnel and outcome assessors - Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Incomplete outcome data - Describe the completeness of

outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors. Selective outcome reporting - State how the possibility of selective outcome reporting was examined by the review authors, and what was found. Other sources - State any important concerns about bias not addressed in the other domains in the tool.

Strategy of data synthesis: A pairwise meta-analysis for direct evidence and a network meta-analysis for direct and indirect evidence of eligible comparisons will be accomplished. We will provide a quantitative and narrative synthesis. We will provide summaries of intervention effects for each study by calculating standardized mean differences or mean differences. We will pool the results using a fixed or random-effects meta-analysis. Heterogeneity will be assessed using both the χ^2 test and the I^2 statistic. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. In addition to the heterogeneity assessment using the I2 statistic, the assumption of transitivity and similarity based on clinical and methodological characteristics will be assessed. The inconsistency will be explored using the Net Heat Plot. We will also assess evidence of publication bias.

Subgroup analysis: None.

Sensibility analysis: None.

Language: No language restrictions.

Country(ies) involved: Brazil.

Keywords: Periodontitis/ Chronic periodontitis (ChP)/ Aggressive periodontitis (AgP)/Scaling and root planning (SRP)/Antibiotic/Antimicrobials/ Systematic review/ Network meta-analysis.

Dissemination plans: The results of this systematic review will be disseminated through peer reviewed journal.

Contributions of each author:
Author 1 - Monike Santoro - The author will draft the protocol and the manuscript; contribute to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. The referent author will develope the search strategy, the risk of bias assessment and screening of search studies against eligibility.
Author 2 - Samira Regina Fraga - The author will draft the protocol and the manuscript; contribute to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. The referent author will develope the search strategy, the risk of bias assessment and screening of search studies against eligibility.
Author 3 - Barbara Marques - The author will draft the protocol and the manuscript; contribute to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. The referent author will develope the search strategy, the risk of bias assessment and screening of search studies against eligibility.
Author 4 - João Vitor Canellas - The author will read, perform the risk of bias assessment, provide statistical expertise, supervise, provide feedback and approve the final manuscript.
Author 5 - Eduardo Tinoco - The author will read, supervise, provide feedback and approve the final manuscript.