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**CAUSE-RELATED THERAPY OF
PERIODONTITIS AND PERI-IMPLANT
MUCOSITIS WITH ADJUNCTIVE USE OF
SUBGINGIVAL LOCALLY
DELIVERED ANTIBIOTICS.**

ABSTRACT

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ABSTRACT

Periodontal disease is a significant oral condition that contributes to the global burden of chronic diseases. It is highly prevalent worldwide and poses a major public health concern. Periodontal diseases, including gingivitis and periodontitis, are likely the most prevalent diseases among humans. According to the recent Global Burden of Disease Study (GBD, 1990–2010), severe periodontitis is the 6th most common disease globally, affecting approximately 743 million people with an overall prevalence of 11.2%. Additionally, the global burden of periodontal disease increased by 57.3% between 1990 and 2010.

Periodontitis is the primary reason why adults around the world lose their teeth. This condition puts individuals at risk of losing multiple teeth, becoming edentulous (having no teeth), and experiencing chewing difficulties. This condition consequently affects their nutrition, quality of life, and self-esteem. Additionally, periodontitis has significant socio-economic consequences and leads to high healthcare costs. Oral epidemiologists and clinicians have faced a persistent challenge in accurately and consistently measuring the extent of periodontal diseases. The unification of case definitions poses a challenge, as the heterogeneity of these definitions impacts the comparability of results and can result in either an overestimation or underestimation of disease prevalence.

In 1987, the World Health Organization (WHO) recommended using pocket probing depth (PPD) as a criterion for detecting severe cases of periodontitis. Important oral health investigations, such as the 2009 Adult Dental Health Investigation in the United Kingdom and the National Health and Nutrition Examination Surveys in the United States, have also measured attachment loss (AL) along with PPD.

Periodontitis could be prevented, accurately diagnosed, and effectively treated and managed through appropriate professional care and long-term secondary prevention. At present, there are multiple cultural and socio-economic obstacles that hinder the public from accessing appropriate preventive measures, obtaining early diagnosis, and obtaining treatment, consequently limiting significant advancements in enhancing periodontal health.

Through the studies carried out within the research and the results obtained, the thesis aims to study the particularities of adjunct antibiotic use in treatment for patients with stage III-IV periodontitis and peri-implant mucositis in different patient groups. The goal was to find out how well and whether additional treatment plans suggested in specialized literature work for different patient groups with severe forms of periodontitis and peri-implant mucositis. The research was conducted in a private clinic and in the Discipline of Periodontology in the Faculty of Dental Medicine at UMFT "Victor Babeș" Timișoara.

Recent years have witnessed significant advancements in periodontology, encompassing both clinical practice and medical research, paving the way for more precise diagnosis and tailored treatment of periodontal diseases based on their severity and complexity. The first progress was achieved in 2018 with the New Classification Scheme of Periodontal and Peri-implantation Diseases and Conditions based on a multidimensional staging and grading system. The second step forward is the release of the S3 Level Clinical Practice Guideline (CPG) for treatment stages I–III, stage IV, and the one for the prevention and treatment of peri-implant disease. These guidelines were created by experts from the European Federation of Periodontology (EFP) and are available from 2018, 2022, and 2023, respectively. They make it easier to find the best treatment plan for each patient by using the suggested methods. The third progress made in the

research field by the international consensus report, The Implant Dentistry Core Outcome Set and Measurement (ID-COSM), focused on clinical research design and reporting standardization in clinical trials.

However, there aren't any studies that compare locally applied antibiotics or systemically applied antibiotics as adjuncts to subgingival instrumentation in patients with severe loss of periodontal support who were recently classified as having stage IV periodontitis. Recently, the CPG for stage I-III periodontitis issued an open recommendation regarding the use of antiseptics within Step 2 in specific cases as an individualized treatment approach based on the case's needs and characteristics. So, we aimed to include in the special part of the doctoral thesis a study that would compare the effects of a single subgingival application of a gel with piperacillin plus tazobactam to a gel with doxycycline gel 14% and a placebo gel during subgingival instrumentation (SI). The study would look at the effects from both a clinical and microbiological point of view. This topic is a continuation of the research activities of the Discipline of Periodontology group at UMFVBT.

The first arm of the personal research is represented by the study evaluating the clinical and microbiological effects of a single subgingival application of piperacillin plus tazobactam gel as adjunctive to subgingival instrumentation in the second step of therapy compared to the use of a slow-release doxycycline gel (14%) and a placebo gel in a population of 62 subjects. All sites that presented an indication for treatment were instrumented at baseline and subsequently at 3 and 6 months. At baseline, in addition, in the test group, a gel with piperacillin plus tazobactam gel was applied subgingivally; in the first control group, a gel with slow-release doxycycline gel was applied; and in the second control group, a placebo gel. We also selected 4 non-adjacent reference sites for each subject, searched them for statistical data analysis, and

collected microbiological samples at baseline and at the end of the study (6 months).

The second piece of personal research in the Special Part is a clinical trial that looked at how well piperacillin plus tazobactam gel worked when used together in people with peri-implant mucositis. Professional mechanical plaque removal (PMPR) of biofilm around implants and prosthetic surfaces is the standard way to treat peri-implant mucositis. We wanted to see what the clinical and microbiological effects were of using piperacillin plus tazobactam gel along with PMPR over a 6-month follow-up period.

The third arm of the research is a retrospective study investigating the effect of locally applied antibiotic adjuncts versus systemic antibiotics in patients with stage III-IV periodontitis. We retrospectively obtained data from patients' personal data sheets, periodontal re-evaluations, and examinations. This retrospective study is important for personal research because it represents a tool for evaluating treatment adjunct selection based on a specific case to reduce the use of systemic antibiotics to prevent antimicrobial resistance.

After obtaining the ethics approval, the necessary data were obtained retrospectively from the personal data sheets of the patients, from the periodontal re-evaluations, and following the examination of the data. Within the statistical analysis (the patient and the group were considered the statistical unit), intra- and inter-group comparisons were made for the clinical (probing depth, clinical attachment level, plaque, and bleeding score) and microbiological parameters of interest. This retrospective study is of interest in the whole context of the personal research carried out during the doctoral studies, focused on severe forms of periodontal disease because it is addressed to that isolated

population of patients who received local or systemic antibiotics as adjuncts to subgingival instrumentation (SI) in step 2 of therapy.

These three studies also provide information on the use of these systemic antibiotics as adjuncts in non-surgical periodontal treatment compared to a novel, locally delivered, slow-released combination of antibiotics to facilitate informed treatment decision-making.

CONCLUSIONS AND PERSONAL CONTRIBUTIONS

In the first part of the thesis, three key aspects regarding the strategies for treating stages III-IV periodontitis and peri-implant mucositis were addressed: the content of step 2 of treatment, the adjuvant antimicrobials associated with it, and the current events in the treatment of stage III-IV periodontitis.

From the three studies conducted in an attempt to clarify the previously mentioned aspects, the following conclusions can be issued:

1. The first Special Part study evaluating the clinical effect obtained from the adjunctive use of piperacillin + tazobactam gel to subgingival instrumentation during Step 2 in patients with stage III-IV periodontitis shows that its adjunctive use alone can provide significant benefits in controlling inflammation in periodontal pockets compared to the placebo group.

2. A single topical subgingival application of piperacillin plus tazobactam gel in combination with subgingival instrumentation can reduce clinical and microbiological outcomes, following a similar dynamic as the doxycycline and placebo groups.

3. The stability of the clinical effect was also observed up to 6 months after administration; the evolution followed a similar dynamic in the three groups.

4. The second study showed that the single use of a slow-release locally applied antibiotic combination of piperacillin and tazobactam gel, adjunctive to PMPR, improved the clinical variables of implants diagnosed with PiM.

6. The adjunctive antibiotic treatment resulted in a higher BoP reduction compared to the control, but there were no significant differences in the changes in other clinical and microbiological parameters.

7. When treating mucositis, the goal was also to prevent the development of PI; this outcome was obtained as none of the patients showed progression to PI during this study. Therefore, the piperacillin and tazobactam gel can contribute to the treatment's success.

8. The results of the third study (retrospective) aimed to evaluate the clinical effects after SI and adjunctive use of systemically administered (SA) AMX + MET (administered for 7 days) either locally delivered (LDD) piperacillin plus tazobactam in Step 2 of periodontal therapy in patients diagnosed with Stage III/IV periodontitis. Statistically significant PD reductions and CAL gains were observed in both groups at 3-month follow-up. Systemic AMX + MET protocol was more efficacious with regard to the reduction of FMBS.

9. This study also provides information on the superiority of these systemic antibiotics as adjuncts in non-surgical periodontal treatment compared to a novel, locally delivered, slow-released combination of antibiotics to facilitate informed treatment decision-making.

10. The objective of using adjunctive antimicrobials is to maximize the efficiency of infection management, limit tissue damage due to the immune response, and optimize the healing process. However, the use of systemic antibiotic (SA) treatment is not commonly embraced due to concerns regarding the escalating issue of bacterial

resistance and the development of adverse effects, such as allergic/hypersensitivity events.

11. Also, the use of systemic antibiotics in periodontal disease treatment can increase concerns regarding the escalating issue of bacterial resistance. Therefore, it is recommended that the use of systemic antibiotics be reduced wherever possible and that the utilization of supplementary systemically administered antibiotics be limited mainly to individuals who would obtain the greatest advantage from them.

12. One of the main benefits of locally delivered antibiotics is the ability to administer lower quantities of topical drugs within the pocket, preventing the adverse effects associated with systemic antibacterial agents. This approach also enhances the exposure of certain microbes to elevated concentrations of the prescription, resulting in more effective therapeutic outcomes.