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*study*

# Do systemic antibiotics provide additional benefits when *Aa* is present?

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## Background

The European Federation of Periodontology's S3-level guidelines for the treatment of stage I-III periodontitis (Sanz et al. 2020) do not recommend routine use of systemic antibiotics as an adjunct to subgingival instrumentation (SI) because of concerns about patient welfare (side effects) and antimicrobial resistance. In specific situations (e.g., generalised periodontitis, stage III in young adults) the guidelines say that targeted systemic antibiotics may be considered.

Researchers have previously justified the use of systemic antibiotics to improve clinical outcomes in cases where bacterial pathogens such as *Aggregatibactor actinomycetemcomitans (Aa)* are present subgingivally.

But there has been insufficient evidence of the potential benefit of using systemic antibiotics in cases diagnosed as periodontitis stage III and IV, grade B and C when combined with SI compared to SI alone.

The combination of metronidazole and amoxicillin had been reported to be successful in lowering *Aa* to undetectable levels. Until recently (2018), the German Society of Periodontology recommended microbiological testing and the use of systemic antibiotics as an adjunct to SI.

Following this recommendation, the Department of Periodontology of the Johann Wolfgang Goethe University Frankfurt, Germany performed microbiological testing in patients with aggressive or generalised severe chronic periodontitis from 2005 to 2018. Patients were prescribed antibiotics as an adjunct to SI whenever *Aa* was detected.

## Aim

This study investigated the treatment outcomes of patients diagnosed with aggressive or generalised chronic periodontitis (retrospectively classified, under the new classification, as periodontitis stage III and IV, grade B and C) following SI with and without the use of adjunctive antibiotics when *Aa* was detected subgingivally.

## Materials & methods

- Retrospective cohort study consisting of 425 adult patients initially diagnosed with aggressive or generalised severe chronic periodontitis, divided into two groups based on the presence or absence of *Aa*. The test group (AB) with *Aa* present was prescribed antibiotics as an adjunct to SI, while the control group (nAB) received SI alone.
- All patients were treated at the Department of Periodontology of the Johann Wolfgang Goethe University in Frankfurt and were recruited retrospectively after screening the charts of all patients who had received comprehensive periodontal treatment.
- The primary outcome was the "treat-to-target" endpoint: ≤4 sites with probing pocket depth (PPD) ≥5mm, measured by the absolute number of sites with PPD ≤3-4-5mm and ≥6mm.
- The secondary outcome was the frequency of sites with PPD ≤3-4-5mm and ≥6mm at different time points after treatment (T1 and T2).
- Outcomes were evaluated at base (T0), at T1 (after SI; mean 12.4 weeks, range 9.4-15.1 weeks) and at T2 (final secondary periodontal care visit; mean 3.1 years, range 1.4-5.5 years).
- Both groups received SI (sonics scalers and hand instrumentation) in one or two visits.
- The group with *Aa* also received 500mg amoxicillin and 400mg metronidazole thrice daily for seven days.
- All patients rinsed twice daily for one minute with 10ml of 0.12% chlorhexidine (CHX), followed by brushing their teeth and the back of the tongue with a 1% CHX gel. Additionally, all patients received oral-hygiene instructions and professional prophylaxis between six weeks and three months.
- At T1, periodontal surgery was considered, and 111 patients received this treatment: 32 in the AB group and 79 in the nAB group.

**Table 1:** Treatment effect according to "treat-to-target" endpoint and tooth loss following subgingival instrumentation alone vs. subgingival instrumentation and systemic antibiotics

| Parameters | Systemic antibiotics | | *p*-Value |
|---|---|---|---|
| | No (nAB) (*n* = 281) | Yes (AB) (*n* = 144) | |
| "Treat-to-target" endpoint (≤4 sites with probing pocket depths ≥5 mm): (*n*)/frequency (%) | 76 (27%) | 53 (37%) | 0.038 |
| Five to eight sites with probing pocket depths ≥5 mm): (*n*)/frequency (%) | 48 (17%) | 20 (14%) | 0.395 |
| Remaining teeth T0 (*n*): median (lower/upper quartile) | 22 (17/27) | 25.5 (20/28) | <0.001 |
| Remaining teeth T1 (*n*): median (lower/upper quartile) | 22 (17/26) | 24.5 (20/28) | 0.002 |
| Tooth loss T0–T1 (*n*): median (lower/upper quartile) | 0 (0/0) | 0 (0/1) | 0.078 |

**Table 2:** Stepwise backward logistic regression analysis of "treat-to-target" endpoint (yes/no) following subgingival instrumentation alone or subgingival instrumentation and systemic antibiotics

| | Estimate | SE | p-Value |
|---|---|---|---|
| Constant | 2.212 | 1.166 | 0.058 |
| Grade B | 0.640 | 0.307 | 0.037 |
| Adjunctive systemic antibiotics | 0.543 | 0.235 | 0.021 |
| Age (T0) | −0.035 | 0.011 | 0.001 |
| Number of remaining teeth (T0) | −0.093 | 0.020 | <0.001 |
| Current smoker | −0.618 | 0.268 | 0.021 |
| Stage | 0.191 | 0.232 | 0.410 |
| Diabetes mellitus | −0.097 | 0.375 | 0.797 |
| Male sex | −0.050 | 0.224 | 0.824 |

*Note:* $n = 425$; $\chi^2 = 38.013$; $p < .001$.

## Results

- Reasons for excluding 232 participants from the original 657 were highlighted.
- The mean time between T0 and T1 was 12.3 weeks in the AB group and 12.6 weeks in the nAB group.
- From T0 to T1:
  - The proportion of PPD ≤3mm increased in both groups (AB, 81.3%; nAB 79.8%) compared to T0 (AB, 54%; nAB, 53.6%).
  - The proportion of PPD 4-5mm was reduced in both groups (AB, 14.9%; nAB 16.7%) compared to T0 (AB, 29.7%; nAB 30.8%).
  - There was a reduction of PPD ≥6mm in both groups (AB, 1.4%; nAB 3.1%) compared to T0 (AB, 13%; 12.5% nAB).
- From T1 to T2:
  - The number of patients reviewed reduced in both groups (AB, by 23 patients; nAB by 70 patients).
    - There was a further increase in the proportion of PPD ≤3mm in both groups (AB, 89.8%; nAB, 85.2%).
  - The proportion of PPD 4-5mm reduced in both groups (AB, 8.3%; nAB, 13.5%).
  - The proportion of PPD ≥6mm also fell in both groups (AB, 0.6%; nAB, 1%).
- Overall results:
  - All clinical outcomes (based on PPD values/thresholds) improved in both groups from T0 to T1 and from T0 to T2. All differences were found to be statistically significant when compared to those obtained at T0.

## Limitations

- The study was a retrospective analysis of clinical data from a single university centre.
- No sample-size calculation was provided or discussed.
- Imbalances in common confounders between the study groups were reported:
  - Greater number of current smokers in the nAB group than the AB group (p=0.041);
  - Mean age of the AB group was lower than the nAB group (p=0.02).
- AB intake was self-administered, not monitored, and therefore could not be standardised or confirmed.
- Retrospective diagnosis of stages III and IV periodontitis based on old records might have introduced a systematic bias in the categorisation of the study groups.
- The baseline detection of *Aa* governed whether participants were prescribed antibiotics or not. Thus, the two groups cannot be directly compared to each other. For example, participants without detection of *Aa* may have performed better with antibiotics. Therefore, no conclusion can be made regarding the benefit of prescribing systemic antibiotics, whether or not Aa is detected.

## Conclusions & impact

- In cases of severe periodontitis (stage III/ IV, grades B and C), the endpoint of ≤4 sites with PPD ≥5mm was achieved in 37% of the cases with subgingival *Aa* when subgingival instrumentation was combined with systemic antibiotics, while it was also achieved in 37% of the cases where *Aa* was not detected, with subgingival instrumentation alone.
- Logistic regression analyses suggested that cases of periodontitis grade B were associated with better treatment clinical outcomes when compared to other subgroups, especially when assessing patients with stage III, stage IV, and grade C.
- This study provides limited evidence on the clinical benefits of the adjunctive use of systemic antibiotics in the treatment of periodontitis in specific cases where the presence of *Aa* has been detected. Clinicians should follow the recommendation R2.16 from the current EFP guidelines on not recommending routine use of antibiotics as an adjunct to SI.

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