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What Interventions are Efficacious in Managing Aggressive Periodontitis?

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Abstract:

Background: Aggressive periodontitis (AP) is a severe, rapidly progressing form of periodontitis affecting less than 1% of the general population. Due to the significant morbidity associated with this disease, effective treatment and management of those affected are necessary. **Purpose:** The purpose of this paper is to determine which treatments are efficacious in managing aggressive periodontitis in order to help the practitioner reach an evidence-based, patient centered decision regarding treatment. **Search Strategy:** A comprehensive literature search was conducted utilizing computerized databases, including PubMed, Ovid/Medline, Blackwell Synergy, The Cochrane Library and Google Scholar. Additionally, dental health professionals were consulted. **Selection Criteria:** Five randomized controlled studies met the inclusion criteria of this review, which includes but are not limited to: dealt with aggressive periodontitis, a minimum duration of six months, and measured at least two of the following as outcome measures: periodontal probing depth (PPD), clinical attachment loss (CAL), bleeding on probing (BOP), or gingival recession. Two review articles met the inclusion criteria for acceptance into the current review. These include but are not limited to: independent examination of AP, consisted primarily (>80%) of RCTs, covered the treatments in question: antimicrobial therapy, surgical therapy or both and measured either PPD or CAL. **Results:** Scaling and root planing (SRP) has limited effectiveness in deeper pockets seen in AP, thus adjunctive therapy is often warranted to achieve the best result for the patient. Specifically, the use of systemic antibiotics or surgery in addition to SRP shows a significant improvement in clinical attachment levels and reduction of periodontal probing depths. **Conclusion:** While it is clear that either antibiotics or surgical procedures provide a significant benefit for the patient with aggressive periodontitis as an adjunct to SRP, there is currently limited evidence to provide a specific recommendation for use of any particular treatment regimen.

Periodontitis is a disease characterized by the inflammation of the supporting structures of the teeth, resulting in loss of bone and decreased periodontal support of the teeth. While chronic periodontitis affects approximately 40% of the adult population, less than 1% of the population is affected by a much more severe form of the periodontitis that is termed aggressive periodontitis (formerly Early Onset Periodontitis, Localized Juvenile Periodontitis). Both localized and generalized forms of aggressive periodontitis (AP) exist, defined based on the areas of the dentition affected; the treatment of the two forms does not differ greatly, thus we will not distinguish further between them.

In contrast to chronic periodontitis, aggressive periodontitis generally affects young healthy individuals, with the most common age of onset between puberty to twenty years of age

¹. It is a rapidly progressing disease associated with specific microflora, namely *Actinobacillus actinomycetemcomitans* and *Porphyromonas Gingivalis*, both of which are gram negative organisms with the ability to invade host epithelial tissue. The microflora associated with the disease and their ability to invade host tissues has important implications for treatment². Aggressive periodontitis also displays a strong genetic influence and shows familial and racial aggregation; the disease is eight times more prevalent in the African-American population than in Caucasians^{3,4,5,6}. Genetics contributes to other risk factors of the disease, as individuals with polymorphonuclear or neutrophil deficiencies or other genetic disorders are at increased susceptibility for the disease.

Aggressive periodontitis is a unique disorder that causes significant morbidity to those affected. The disease results in the destruction of the periodontal ligament and alveolar bone, which can lead to an increase in tooth mobility and eventual tooth loss. Furthermore, other symptoms like increased tooth sensitivity, pain during mastication, and periodontal abscess formation are common⁷. Thus, the impact on the patient physically, psychologically, esthetically, and economically is great.

Due to the significant impact of aggressive periodontitis, the need for treatment is evident. Though the conventional treatment of periodontal disease involves frequent scaling and root planing (SRP), adjunctive therapies may be warranted to deal with the invasive nature of the organisms associated with aggressive periodontitis. Currently, the standard approach to therapy for both localized and generalized aggressive periodontitis include scaling and root planing in the early stages of disease and adjunctive systemic antibiotic regimens in conjunction with local mechanical therapy (SRP), with or

without surgery in later phases⁸. The surgical procedures, which are most often utilized in pockets with depth greater than 5 mm, are either regenerative (growing new bone and periodontal tissues around the affected teeth) or resective (removal of bony deformities caused by invading infection) and are usually followed by a course of antibiotic therapy. Extraction, which may or may not be followed by transplantation, has also been attempted in the treatment of localized aggressive periodontitis with mixed results and limited reports in the literature. Lastly, there is the option of no treatment⁸. In this case, the tooth will be lost as both the periodontal ligament and the surrounding alveolar bone are destroyed by the inflammatory process.

As many options for treatment of aggressive periodontitis exist, the dental practitioner must become educated on the evidence in the literature to help guide their treatment options and apply them appropriately to individual patients. The purpose of this paper is to determine which treatments are efficacious in managing aggressive periodontitis in order to help the practitioner reach an evidence-based, patient centered decision regarding treatment.

Methods:

A systematic literature search was established to identify, select, and eliminate studies relating to the efficacious treatment modalities of aggressive periodontitis. An initial search using PubMed was performed in order to identify the treatments currently available for aggressive periodontitis. All treatments were reviewed and divided into three main categories: scaling and root planing treatment, antibiotic treatment, and surgical treatment. From these treatments, keywords were established and entered into several electronic databases including PubMed, Ovid/Medline, Blackwell Synergy, The Cochrane Library and Google Scholar. The specific keywords entered in various combinations included: aggressive periodontitis, antibiotics, scaling and root planning, early-onset periodontitis, localized juvenile periodontitis, Amoxicillin, Metronidazole, and Tetracycline. A total of 952 articles were found and eliminated at various stages of the search strategy. Appendix 1 and 2 the articles and their stage of elimination, based on their pertinence to the efficacious management of aggressive periodontitis. In addition to the electronic database search engines, three specialized dental health care professionals in the field of periodontology were consulted: Dr. Eric Freeman, Dr. Robert Turnbull, and Dr. Richard Ellen.

Determination of Relevance using Validity Instruments:

Although the systematic literature review yielded many articles, a total of seven articles were accepted for critical appraisal based on stringent inclusion criteria. The initial search was limited to Randomized Control Trials (RCTs) that dealt with aggressive periodontitis. To be accepted, the study must have had a minimum duration of six months and measured at least two of the following as outcome measures: periodontal probing depth (PPD), clinical attachment loss (CAL), bleeding on probing (BOP), or gingival recession, as these are the most accepted clinical parameters in periodontology. In addition, it was required that the trials involving drug administration were blinded (surgical trials could not be blinded for practical reasons), and the subjects must have been randomly assigned to the specific therapies.

The quality of randomized control trials was then assessed against the CTFPHC "Checklist to Assess Evidence of Efficacy of Therapy or Prevention". Due to the lack of universally accepted criteria for the successful outcome of treatment of aggressive periodontitis, the criterion "was the treatment effect large enough to be clinically important" was eliminated from the checklist. (The issue of "clinical relevance of treatment" will be discussed further in the pages to follow). A score of at least 14/16 was required for inclusion of the study. Five RCTs met all of the inclusion criteria.

For the two review articles that were selected, a different set of inclusion criteria was utilized in order to deem them relevant. To be included, the review article must have consisted primarily (>80%) of RCTs and must have covered the treatments in question: antimicrobial therapy, surgical therapy or both. As well, as the majority of available review articles looked at the more prevalent chronic periodontitis, only those articles that evaluated evidence for aggressive periodontitis separately from chronic periodontitis were selected. Again, included articles must have measured either PPD or CAL, and had to be independently reviewed. Finally, to ensure high quality and relevant review articles, the CTFPHC "Checklist for a Review Article" was used, and a score of 8/10 was required. Two review articles met these inclusion criteria.

Results:

Table 1: Results of Randomized Controlled Trials

Study- RCT Chart	Population	Intervention	Control	Outcome	Appraisal
Xajigeorgiou et al. (2006) ⁹	21F & 22M no antibiotic intake/ periodontal treatment, healthy, with family history of the disease	1. Group 1- SRP+ metronidazole + amoxicillin (N=10) 2. Group 2- SRP+ doxycycline (N=10) 3. Group 3- SRP+ metronidazole (N=12)	Group 4: SRP alone (N=11)	<u>6 months post-treatment:</u> - <i>groups 1 & 3</i> showed a statistically greater <u>reduction of proportion sites with PPD>6mm</u> than SRP alone ($p<0.05$), (80%, 87.8% vs 57.7% in controls) - <u>no difference in PPD</u> between <i>group 2</i> and control - <i>groups 1,2& 3</i> showed a <u>reduction in all pathogens</u> for 6 months ($p<0.05$) while only <u><i>p.gingivalis</i></u> was significantly reduced in <i>group 4</i>	- 14/16 on checklist -Grade B, Level1 -care received outside the study was not identified and controlled for -did not have 80% power
Guerrero et al. (2005) ¹⁰	28F & 13M no antibiotic intake/ periodontal treatment, healthy	1. Group 1- SRP+ metronidazole + amoxicillin (N=20) 2. Group 2- SRP+placebo (N=21) * Used full mouth scaling and root planing in 24 hours	Group 2- SRP + placebo (N=21)	<u>6 months post-treatment in deep pockets (>7mm)</u> - <u>Group 1</u> showed: 1. 1.4 mm (0.8, 2.0 mm) <u>reduction in PPD</u> compared to SRP 2. 1 mm (0.7, 1.3 mm) <u>gain in CAL</u> compared to SRP 3. <u>CAL gains>2mm</u> were reported in 25% of sites in group 1 vs. 16% in group 2 ($p=0.028$)	14/16 on checklist -Grade B, Level I -higher than usual dosage of antibiotics caused AEs in 65% vs. 23% with placebo so may not be worth potential harms -did not control for care outside study
Purucker et al. (2001) ¹¹	28 F&M no antibiotic intake, healthy	1. Group 1- SRP+ local tetracycline fibres (N=15) 2. Group 2- SRP+ amoxicillin/ clavulanic acid (N=13)	Baseline	<u>54 weeks post-treatment:</u> - <u>both groups</u> showed: 1. a significant <u>reduction in PPD</u> (1.5, 2.3mm respectively) and <u>CAL gain</u> (0.7, 1.1 mm respectively) ($p<0.001$) - no statistically significant difference between the 2 groups was found	14/16 on checklist; Grade B, Level I -sample size small (28 people) -care received outside the study was not

				<p>2. <u>significant BOP reduction</u> from baseline in both groups ($p < 0.001$) similar</p> <p>At 54 weeks post-treatment: - <u>BOP</u> 28% more reduction in group 2 ($p < 0.01$)</p>	<p>identified and controlled for</p> <p>-patients, health care workers, and study personnel not blind to treatment</p> <p>-no SRP control</p>
Sirirat et al. (1996) ¹²	<p>4F & 2M</p> <p>no systemic medication, healthy</p> <p>*15 pairs of defects-oneside GTR treated, the other side osseous surgery</p>	<p>1. guided tissue regeneration (GTR) with expanded polytetrafluoroethylene membrane (N=15)</p> <p>2. osseous surgery (N=15)</p> <p>* All patients received systemic antibiotics (Amoxicillin) for a week after surgery</p>	Baseline	<p>1 year post-treatment:</p> <p><u>GTR group:</u> - <u>PPD reduction</u> of (2.60±1.30 mm) - <u>CAL gain</u> (2.20±1.42 mm)</p> <p><u>Osseous Surgery group:</u> - <u>PPD reduction</u> 1.73±0.96 - <u>CAL gain</u> 1.20±1.01</p> <p>- both PPD and CAL <u>significantly greater</u> in <u>GTR</u> than osseous surgery group ($p < 0.05$)</p>	<p>15/16 on checklist -Grade B, Level I</p> <p>-patients, health care workers, and study personnel not "blind" to treatment</p>
DiBattista et al. (1995) ¹³	<p>5F & 2M</p> <p>no systemic antibiotics intake, healthy</p> <p>*3 or 4 5mm mesial defects of first molars</p>	<p>1. Surgical debridement (N=5)</p> <p>2. GTR with ePTFE (N=7)</p> <p>3. ePTFE+root conditioning (N=7) (Doxycycline solution)</p> <p>4. ePTFE+root Conditioning (Doxycycline solution)+ composite bone graft (calcium sulfate + DFDBA + doxycycline) (N=7)</p> <p>* All patients received systemic antibiotics (Doxycycline) for a week after surgery</p>	Baseline	<p><u>12 months post-treatment:</u></p> <p>-<u>significant gain in CAL</u> following <i>all four treatments</i>- average gain 3.2 ±1.8 ($p < 0.05$)</p> <p>-<u>no difference</u> among the treatment modalities ($p > 0.05$)</p> <p><u>6 months post re-treatment:</u></p> <p>- <u>CAL gain</u> statistically <i>insignificant</i> (0.8±0.7, $p > 0.05$)</p> <p><u>CAL gain</u> in 0-12 months significantly greater than 12-18 months</p>	<p>14/16 on checklist -Grade B Level I</p> <p>-patients, health care workers, and study personnel not blind to treatment</p> <p>-did not have 80% power</p>

Table 2: Results of Review Articles

Study-Review Articles	Type of Studies Included	Treatments Employed	Results	Appraisal	Conclusion
Haffajee et al. (2003) ¹⁴	26 randomized controlled clinical trials 3 quasi-experimental studies	1. SRP+ systemic antibiotics 2. surgery + systemic antibiotics 3. Antibiotics as a standalone treatment	- for most comparisons, <u>antibiotics increased CAL gain</u> more than control groups (p<0.001) -antibiotics showed an improvement in CAL when used with SRP -borderline significance if antibiotics used with surgery or stand alone -statistically significant <u>CAL</u> improvements for <u>Tetracycline</u> , <u>Metronidazole</u> , and <u>Amox/Met</u>	-10/10 on checklist -CTFPHC rating of "good" internal validity	-enhanced improvement in CAL for at least 6 months for both chronic periodontitis (CP) and aggressive periodontitis (AP) subjects, but <u>patients with AP benefited more from antibiotics</u> -improvement expected regardless of probing depth, though <u>greater improvement in deeper pockets</u> (≥ 6 mm) -insufficient evidence to discuss specific <i>regimens</i> and <i>dosages</i> , or use of antibiotics as <i>monotherapy</i>
Herrera et al. (2002) ¹⁵	25 randomized controlled clinical trials	1.SRP+ systemic antibiotics 2.SRP alone	<u>systemic antibiotics + SRP</u> showed : 1. an improvement in both <u>CAL</u> and <u>PPD</u> change than SRP alone or with placebo groups 2. <u>reduced</u> risk of <u>further</u> decrease in <u>CAL</u> <u>Meta-Analysis</u> for pockets > 6 mm: 1. <u>amoxicillin+ metronidazole</u> showed a statistically significant increase in <u>CAL</u> 2. <u>spiramycin</u> showed a statistically significant difference in <u>PPD</u> decrease vs. controls	-10/10 on checklist -CTFPHC rating of "good" internal validity	- <u>systemic antimicrobials in conjunction with SRP</u> can offer <u>additional benefit</u> over SRP alone in treatment of periodontitis - <u>greater effect in AP</u> than CP

The evidence table provided in Table 1 summarizes the findings of five randomized controlled studies (RCT) with Grade A, level I evidence on the treatment modalities of aggressive periodontitis. As SRP has been recognized for years as an efficacious treatment, it is unethical to deny patients this basic care. As such, the treatments reviewed in the literature include scaling and root planning as a control, with test groups receiving SRP in combination with either local or systemic antibiotics or surgical techniques. The adjunctive antibiotics include local delivery of Tetracycline through the use of a fiber TCF), Amoxicillin/clavulanic acid (AMO + clavulanic acid), Metronidazole (MET), Amoxicillin (AMO), or Doxycycline (DOXY). The surgical techniques studied were both resective, specifically osseous surgery and surgical debridement, and regenerative, including guided tissue regeneration (GTR), expanded polytetrafluoroethylene (ePTFE) membrane, ePTFE plus root conditioning with Doxycycline, and ePTFE plus root conditioning plus composite graft consisting of calcium sulfate + DFDBA (decalcified freeze dried bone allograft) + Doxycycline. Main outcome measures to assess improvement in the periodontal condition were clinical attachment levels (CAL) and/or probing pocket depth (PPD) assessments.

Adjunctive antibiotics in the treatment of generalized aggressive periodontitis were investigated by Guerrero et al. (2005). In this double-blind randomized controlled trial study, both treatment and placebo-control groups received a full-mouth scaling and root planning. The test subjects received an adjunctive course of systemic antibiotics consisting of AMO+MET three times a day for 7 days while the control group received a placebo. Six months post-treatment, in deep pockets (≥ 7 mm) the treatment group showed an additional improvement of 1.4 mm (95% CI: 0.8, 2.0 mm) in probing pocket depth and 1 mm (95% CI: 0.7, 1.3 mm) in clinical attachment gain compared to the placebo-control group. Furthermore, CAL gains ≥ 2 mm was reported in 25% of sites in test patients, compared with 16% in the placebo group ($p=0.028$) and PPD reduction of 2 mm or more were observed in 30% of sites in treated and 21% of sites in control group.

Similarly, in another RCT by Xajigeorgiou et al. (2006), the effect of various antimicrobial agents on generalized aggressive periodontitis was studied. Six weeks after full mouth SRP, three groups were given systemic antibiotics (MET+ AMO, DOXY, MET) and one group acted as control (SRP alone). Six months after baseline, clinical and microbiological outcome measures were recorded. Xajigeorgiou et al. (2006) found that systemic administration of MET+AMO or MET alone resulted in a statistically significant

reduction of the proportion of sites with a baseline PPD>6mm than the SRP control group six months post-treatment ($p<0.05$); no significant difference was found between the DOXY and control groups. While SRP resulted in a small reduction of the investigated microbial species in all four groups, an additional significant reduction was found in the groups that received antimicrobial therapy for the duration of six months ($p<0.05$). Six months after baseline measurement, the control group showed a significant reduction in *P. gingivalis* only ($p<0.05$). The results of these two studies indicate that systemic antibiotics, specifically Metronidazole with or without Amoxicillin, significantly improve the clinical outcomes of patients with aggressive periodontitis by reducing the PPD, increasing CAL, and reducing the etiologic agents associated with the disease, with particular improvements seen in deeper pockets¹⁶.

In a randomized controlled study of both local and systemic antimicrobial delivery, Purucker et al. (2001) studied the effect of SRP+TCF versus SRP+AMO/clavulanic acid in 30 patients with aggressive periodontitis. Within each treatment group, PPD decreased significantly from baseline to week 54: 6.2 ± 1.5 mm to 4.7 ± 1.4 mm for SRP+TCF and 6.5 ± 1.4 mm to 4.2 ± 0.6 mm for SRP+AMO/clavulanic acid ($p<0.001$); however, no statistically significant difference in PPD was found between the two groups. Similarly, a small but significant improvement was observed in CAL from baseline to week 54 within each group, but no significant difference was noticed between the groups: 12.0 ± 1.8 mm to 11.3 ± 1.8 mm for SRP+TCF and 12.3 ± 1.5 mm to 11.2 ± 1.2 mm for SRP+AMO/clavulanic acid ($p<0.001$).

Purucker et al. (2001) also found a significant reduction in frequency and percentage of bleeding sites in both groups ($p<0.001$); however, at 54 weeks after baseline, a greater reduction in BOP was observed in the SRP+AMO/clavulanic acid group compared to the SRP +TCF group (BOP 31.67% for SRP+TCF versus 3.85% for SRP+AMO/clavulanic acid) ($p<0.01$). Overall, these results indicate that the local delivery of Tetracycline by a fiber or the systemic administration of Amoxicillin/clavulanic acid given 3 months after scaling and root planning produced a similar outcome over the 9-month observation period, as no significant difference in the clinical outcome measures was found between the two groups; however the difference in BOP between the two groups at 54 weeks post-baseline may indicate that there is limited long term benefit of local Tetracycline fibers as a treatment for aggressive periodontitis.

In an RCT comparing regenerative (GTR) and resective (osseous surgery) surgical techniques for the treatment of aggressive periodontitis, Sirirat and colleagues (1996) employed a paired-defect design

within the same patient. With this study design, each patient served as their own control thus the response to surgery and healing could be better controlled and evaluated, as wide individual variation in ability to recover from surgery exists. The follow-up examination was conducted 1 year following surgery, and significant improvement in probing reduction and clinical attachment level in both GTR and osseous surgery treated groups was found. A greater probing depth reduction of 2.60 ± 1.30 mm and clinical attachment gain of 2.20 ± 1.42 mm was observed in the GTR group compared to the osseous surgery group that showed a probing reduction of 1.73 ± 0.96 mm and attachment gain of 1.20 ± 1.01 mm ($p < 0.05$). These findings suggest that clinical attachment can be regained in intrabony defects treated with either resective (osseous surgery) or regenerative (GTR) surgical techniques, although a greater improvement in attachment may be observed with guided tissue regeneration.

In another randomized controlled study of surgical techniques for the treatment of aggressive periodontitis, DiBattista et al. (1995) compared the efficacy of guided tissue regeneration compared to surgical debridement. The clinical attachment gain reported from baseline to 12 months post-surgery was 3.2 ± 1.9 mm for DEBR, 3.1 ± 1.4 mm for ePTFE, 3.0 ± 1.5 mm for ePTFE plus root conditioning, and 3.1 ± 2.7 mm for ePTFE plus root conditioning plus composite graft; the average attachment gain for all sites combined from baseline to 12 months post surgery was 3.2 ± 1.8 mm. Although a clinically and statistically significant improvement from baseline to 12 months post-surgery was found within each treatment modality, no statistically significant difference was found among the treatment modalities ($p > 0.05$).

Residual defects were re-treated at 12 months with a composite graft, and they were evaluated at 6 months post re-treatment (i.e. 18 months post-baseline); the attachment gain from re-treatment was statistically insignificant (0.8 ± 0.7 mm, $p > 0.05$). Furthermore, the greatest gain in attachment occurred from baseline-6 months for all parameters, and the attachment level gain from baseline-12 months was significantly greater than that achieved from 12-18 months. The results of the study by DiBattista et al. (1995) demonstrate that all tested treatment modalities, including surgical debridement alone, in conjunction with systemic antibiotics (Doxycycline), were efficacious in the management of aggressive periodontitis and that re-treatment does not enhance clinical reattachment significantly. The studies by Sirirat et al. (1996) and DiBattista et al. (1995) are consistent with results of other studies demonstrating

that regenerative surgical techniques on deeper bony defects provided gains of clinical attachment >2mm.

Two review articles evaluated the literature of management of aggressive periodontitis with respect to SRP alone or in conjunction with systemic antibiotics or surgery, the summary of which is presented in Table 2. In the meta-analysis of 29 studies including 26 RCTs and 3 quasi-experimental studies, Haffajee et al. (2003) concluded that systemically administered antibiotics exhibited an increase in periodontal attachment levels compared to control groups ($p < 0.001$). Systemic antibiotics were uniformly beneficial in improving attachment level when used as adjuncts to SRP and were consistently beneficial, although of borderline significance, when used as adjuncts to SRP plus surgery or as a stand alone therapy. Of the antimicrobials included in the meta-analysis, statistically significant improvements in attachment level were found for Tetracycline and Metronidazole, and borderline statistical significance was found for the combination of Amoxicillin plus Metronidazole.

Herrera et al. (2002) reviewed 25 randomized controlled trials and concluded that patients treated with SRP plus systemic antimicrobial groups overall demonstrated more significant improvements in both CAL and PPD than SRP alone or SRP with placebo groups. Due the difficulties in pooling the studies and the lack of appropriate data, only limited meta-analysis could be performed. The meta-analysis that was performed comparing the additional effect of antibiotics compared to SRP alone showed a statistically significant additional benefit for Spiramycin (PPD change) and Amoxicillin/Metronidazole (CAL change) in pockets with baseline PPD > 6mm. Thus, there is consistent evidence that the use of systemic antibiotics with and without SRP and/ or surgery improved clinical attachment levels; however, specific antimicrobial agents should be selected based on patient factors, as there is insufficient data to provide specific recommendations with the limited data available.

Discussion:

Although aggressive periodontitis is not a very prevalent disease, it does have serious repercussions for those affected. As such, a thorough understanding of the etiology, natural course and efficacious treatments of aggressive periodontitis would be invaluable to the dental practitioner in order to educate and treat patients appropriately to obtain the best outcome. Unfortunately, at the current time we

have only a limited understanding of the disease, though our knowledge is evolving rapidly. From the literature available to date, it can be concluded that patients with aggressive periodontitis benefit from adjunctive therapy to the standard scaling and root planing, either in the form of antibiotics or surgery.

In conducting such a review of the literature, it is imperative that the conclusions drawn be based on sound, well designed and carefully conducted studies. Therefore, stringent inclusion and exclusion criteria were applied to all research uncovered, and only those studies deemed to be of the highest quality were included in the review. Articles included are of the strongest appropriate design, the randomized controlled trial. The systematic review articles included also consisted primarily of randomized controlled trials and had a "good" rating on the CTFPHC rating of internal validity. The articles were assessed against the criteria of the appropriate CTFPHC checklists and high scores on the checklists were required for inclusion in the review. The most consistent weaknesses of the studies, as identified by the checklist criteria, were that care outside of the study was not identified or controlled for, and that because of the rarity of the condition, studies did not have a sample size large enough to afford them 80% power. During the assessment of the quality of the article, each paper was reviewed and rated by at least two individuals in the group, and any discrepancies were resolved through discussion. Therefore, because of the high standards applied to data selection and review, we can be confident that the results presented are valid.

Though the validity of the presented articles can be assured, the conclusions presented are based on relatively few studies. At the current time, there is a limited body of high quality literature on therapies for aggressive periodontitis. As well, because the disease is relatively rare, few studies were available that compared all possible treatments of aggressive periodontitis, covering SRP, antibiotic therapy and surgical therapy in different combinations. Furthermore, as not all publications are readily available through OVID, Medline and PubMed, we attempted to maximize our yield by also searching for literature through Google and Google Scholar, as well as consulting experts in the field who could direct us to other sources. Still, due to constraints on our access to literature, in addition to publication bias, the research presented is likely not exhaustive.

To further complicate matters, antimicrobial therapy is routinely given post-surgery; thus, the ability to isolate the benefit from surgical treatment alone is confounded. However, withholding antibiotics

following surgery may be considered unethical, thus more investigation into this confounding factor is needed in order to draw conclusions on the efficacy of these treatments as independent modalities. Also, it is difficult to directly compare different studies and deem one treatment superior to another based on CAL and pocket depths achieved, due to inter-examiner variation during probing. The American Association of Periodontology's accepted value of variation arising during repeated probing of the same site with a manual probe is 0.8mm¹⁷; thus while variability of probing was controlled within each study, the values reported cannot be compared among different studies.

There are also inherent weaknesses of the included studies. Because of the low prevalence of the disease, sample sizes of each study are fairly limited, which also reduces the power of each study. Also, the duration of each study was not long enough to permit conclusions to be made regarding long-term outcomes of each therapy; thus, there is a need for studies with long term follow up. Finally, though each study reported its results in similar terms of periodontal pocket depth and clinical attachment loss, there are no concrete figures accepted universally to quantify successful therapy. The Parameters of Care set out by the American Association of Periodontology simply look for: "significant reduction of clinical signs of gingivitis; reduction of probing depths; stabilization or gain of clinical attachment"⁸. It is for this reason that we excluded the CTFPHC "Checklist to Assess Evidence of Efficacy of Therapy or Prevention" criterion of "Was the treatment effect large enough to be clinically important?" as it is difficult to arbitrarily assign a measure of "clinical significance" when the American Association of Periodontology does not require one to characterize successful treatment.

In a symposium on clinical significance presented in 2002 by Marjorie Jeffcoat, an expert in the field of periodontology, Jeffcoat explains that clinical significance is subjective and varies with the nature of the treatment and trial; specifically, the clinical significance of each treatment modality must be assessed according to the unique nature of each treatment¹⁸. Regarding surgical therapy, the benefit of treatment over SRP alone must outweigh the morbidity of surgery; with antibiotic treatment, the added benefit must outweigh the risk of resistant organisms; and finally, since the effectiveness of SRP is well established it is unethical to conduct a trial with no SRP as the control group. For example, in the study by DiBattista et al. (1995), surgical debridement had equal efficacy to the other more invasive treatment modalities; thus, in assessing the clinical significance of these therapies, one must weigh the morbidity of

all of the treatment options against the additional benefit (or in this case, lack thereof) when selecting a treatment. Furthermore, Jeffcoat (2002) explains that the long term success of the treatment is closely tied to the patient's ability to control plaque in the long term, and that efficacy must therefore be measured relatively soon after treatment as was done in the studies examined here. While this adds credence to the results presented above, it further complicates assessment of treatment types over the long term. Again, as demonstrated in DiBattista et al. (1995), the most gain in clinical attachment was seen in the first 6 months after treatment; thus longer term follow up is required to compare the immediate versus long term benefit of therapeutic intervention, and this is an important factor when considering the clinical significance of treatment.

Therefore, the research available to date allows us to begin to assess the efficacy of the current commonly prescribed therapies for aggressive periodontitis. However, further more comprehensive research is needed to discern the merits of each possible therapy, including studies covering the no treatment option, a larger body of quality studies on surgical therapy as these are currently limited, studies allowing comparison of all treatment options, and studies involving larger sample sizes, if possible. As well, though use of systemic antibiotic therapy shows statistically significant benefits, these must be weighed against the negative repercussions of antibiotic use in terms of adverse effects as well as future resistance of organisms. For example, in the study by Guerrero et al. (2005) there was an increased incidence of adverse events in patients who received a combination of Metronidazole and Amoxicillin due to the higher than usual dose administered, and this is consistent with Herrera et al. (2002) who reported that gastrointestinal adverse effects were found with high doses of antibiotics. Therefore, long term follow up studies are required to further investigate the complications of antimicrobial use. It must also be recognized that the current review is dealing with efficacy of each treatment. In order for results to be applied practically by the clinician, efficacy must eventually be translated to effectiveness. Other factors including cost, patient compliance, and patient individuality in response to different therapies must also be considered in order to help provide the best care to patients.

Conclusions:

The purpose of this paper was to determine which treatments are efficacious in the management of aggressive periodontitis and to help the dental practitioner make an evidence-based, patient-centered decision regarding treatment. From the review of the available literature examining the efficacious treatment of aggressive periodontitis, Metronidazole ± Amoxicillin has consistent evidence to support its use in the treatment of aggressive periodontitis, thus receives a grade I level A recommendation for use as an adjunct to SRP in pockets greater than 6 mm. Although surgical treatment yields a greater average increase in clinical attachment level compared to systemic antibiotics, MET ± AMOX receives the strongest recommendation for treatment due to the quality of studies that have examined its use; specifically, these studies are blinded or double blinded RCTs, contain relatively large sample sizes compared to the studies examining surgical treatments, and the results in support of MET ± AMOX as an efficacious treatment are consistent across the RCTs and the review articles.

Amoxicillin combined with clavulanic acid, as well as surgical techniques (both resective and regenerative surgeries performed on deep pockets) receive a grade I level B recommendation for use as an adjunct to SRP. The available research employing these treatments shows an improvement in the clinical outcome measures examined; however more research on these treatments, including a larger sample size and longer follow up duration, is required in order to increase the strength of the recommendation for use. Additionally, while it appears that regenerative surgery increases clinical attachment more than resective surgery, it would be beneficial to discern which, if any, specific regenerative modalities are most efficacious in managing aggressive periodontitis.

Locally delivered Tetracycline fibers receives a grade I level I recommendation for use, as only one study with a limited sample size reviewed its use. Therefore, there is insufficient evidence on the efficacy to recommend its use. Additionally, at 54 weeks post treatment the group that received local Tetracycline fibers for treatment had a significant increase in BOP, possibly suggesting recurrence of the disease; thus the long term benefit of this therapy must be investigated further. Doxycycline receives a grade I level C recommendation for use as no significant difference was found between the Doxycycline and placebo groups in the study by Xajigeorgiou et al. (2006), although a significant difference was found in Haffajee's review article; thus, at this point the literature suggests that the risks of adverse events and

antibiotic resistance may not outweigh the benefits of this antimicrobial agent for the treatment of aggressive periodontitis.

In conclusion, while many of these treatments show an improvement in the probing pocket depths and clinical attachment levels of the patients affected by aggressive periodontitis, more extensive research on the management of this disease must be done. While SRP shows some benefit as a stand alone treatment of aggressive periodontitis, it has limited effectiveness in deeper pockets; thus, in treating aggressive periodontitis, either systemic antibiotics or surgical treatment show additional benefits to SRP. The dental practitioner should ultimately make a patient-centered, evidence-based decision for the management of aggressive periodontitis and must weigh the risks and benefits of the chosen treatment for his or her patient.

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Appendix 1

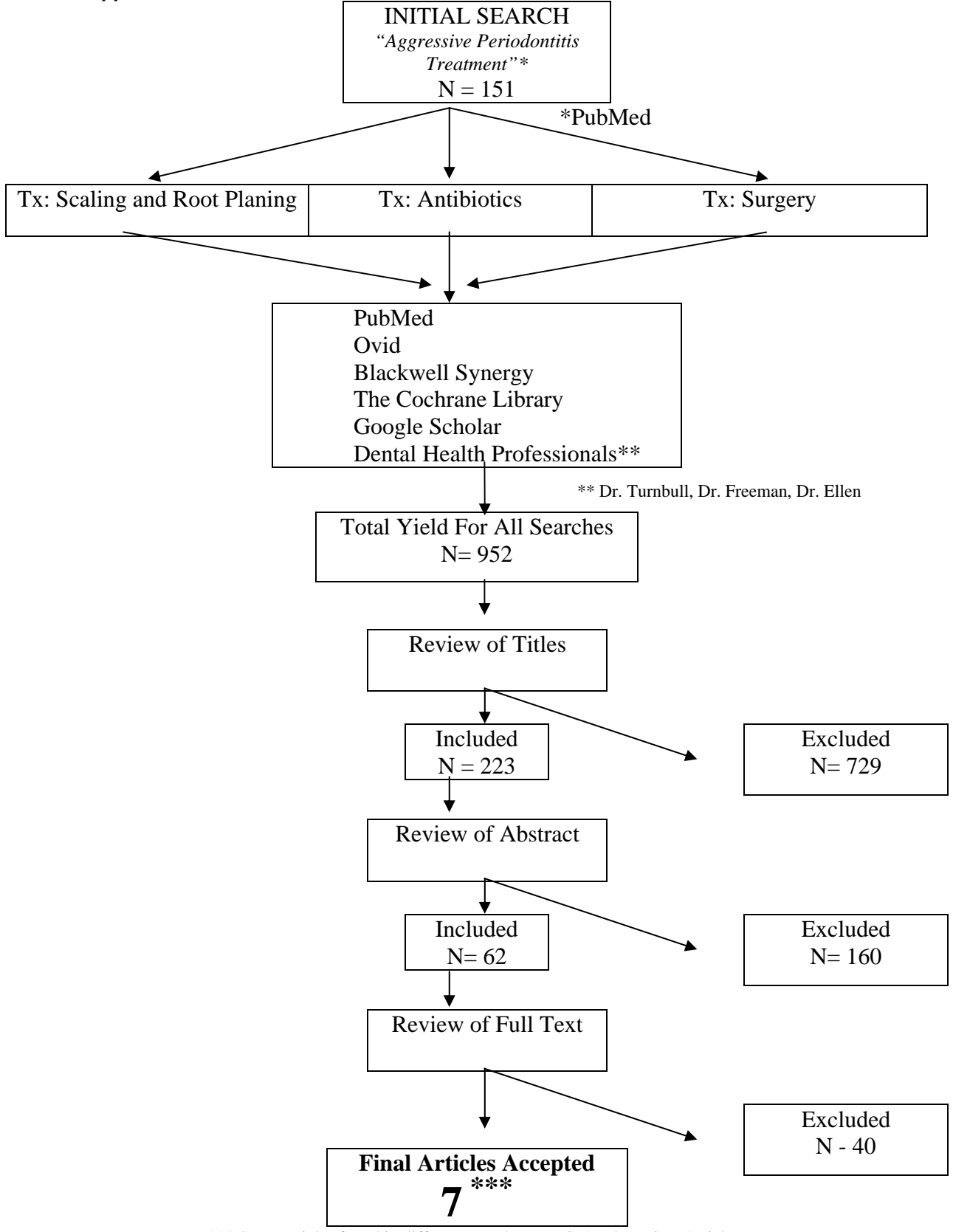
Table 1: Search Results: Aggressive Periodontitis Treatments

Search Engine	Search Terms	Yield	Rejected at Title Stage	Rejected at Abstract Stage	Rejected at Full Text Stage	Accepted
PubMed	Aggressive Periodontitis AND Antibiotics	53	41	9	1	2
PubMed	Aggressive Periodontitis, scaling and root planning	26	20	2	1	3
PubMed	Aggressive Periodontitis, surgery	60	51	6	2	1
Ovid	Aggressive Periodontitis AND Antibiotics	11	5	4	0	2
Ovid	Aggressive Periodontitis, surgery	19	17	0	1	1
Ovid	Periodontitis treatment	10	9	0	1	0
Blackwell Synergy	Aggressive Periodontitis <i>Limit: Article Title</i>	58	29	21	6	2
Cochrane Library	Aggressive Periodontitis	27	9	8	7	3

Table 2: Search Results: Related Topics of Aggressive Periodontitis Treatments

Search Engine	Search Terms	Yield	Rejected at Title Stage	Rejected at Abstract Stage	Rejected at Full Text Stage	Accepted
PubMed	Early-onset Periodontitis treatment	78	47	21	9	1
PubMed	Early-onset Periodontitis efficacy	4	4	0	0	0
PubMed	Early-onset Periodontitis antibiotics	26	20	6	0	0
PubMed	Early-onset Periodontitis surgery	23	18	3	1	1
PubMed	Localized Juvenile Periodontitis treatment	122	101	18	2	1
PubMed	Localized Juvenile Periodontitis efficacy	7	7	0	0	0
PubMed	Localized Juvenile Periodontitis antibiotics	138	111	23	2	2
PubMed	Localized Juvenile Periodontitis surgery	121	98	18	3	2
Blackwell Synergy	Periodontitis Amoxicillin <i>Limit: Article Title</i>	1	0	0	1	1
Blackwell Synergy	Periodontitis Tetracycline <i>Limit: Article Title</i>	44	39	4	1	0
Blackwell Synergy	Periodontitis Metronidazole <i>Limit: Article Title</i>	43	37	4	2	1
Google Scholar	Aggressive Periodontitis, Meta-analysis, antibiotics	81	66	13	0	2

Appendix 2



*** Same articles found in different searches (5 RCT's, 2 Review Articles)

References

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- ¹ Lang N, Bartold PM, Cullinan M, et al: Consensus Report: Aggressive periodontitis. *Ann Periodontol* 1999; 4:53.
- ² Newman MG, Takei HH, Carranza FA. Carranza's Clinical Periodontology. 9th ed. Philadelphia: W.B. Saunders Company.; 2002:409-413.
- ³ Burmeister JA, Best AM, Palcanis KG, et al: Localized juvenile periodontitis and generalized severe periodontitis: Clinical findings. *J Clin Periodontol* 1984; 11:181.
- ⁴ Melvin WL, Sandifer JB, Gray JL: The prevalence and sex ratio of juvenile periodontitis in a young racially mixed population. *J Periodontol* 1991; 62:330.
- ⁵ Saxby MS: Juvenile periodontitis: An epidemiologic study in the West Midlands of the United Kingdom. *J Clin Periodontol* 1987; 14:594.
- ⁶ Marazita ML, Burmeister JA, Gunsolley JC, et al: Evidence for autosomal dominant inheritance and race-specific heterogeneity in early-onset periodontitis. *J Periodontol* 1994; 65:623.
- ⁷ Manson JD, Lehner T: Clinical features of juvenile periodontitis (periodontosis). *J Periodontol* 1974; 45:636.
- ⁸ American Academy of Periodontology. Parameters of Care Supplement: Parameter on Aggressive Periodontitis. *J Periodontol* 2000; 71: 867-869.
- ⁹ Xajigeorgiou C, Salkellari D, Slini T, Baka A, Konstantinidis A. Clinical and microbiological effects of different antimicrobials on aggressive periodontitis. *J Clin Periodontol* 2006; 33: 254-264.

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- ¹⁰ Guerrero A, Griffiths GS, Niball L, Suvan J, Moles DR, Laurell L, Tonetti MS. Adjunctive antibiotics in the treatment of generalized aggressive periodontitis. *J Clin Periodontol* 2005; 32: 1096-1107.
- ¹¹ Purucker P, Mertes H, Goodson JM, Bernimoulin JP. Local versus systemic adjunctive antibiotic therapy in 28 patients with generalized aggressive periodontitis. *J Periodontol* 2001; 72: 1241-1245.
- ¹² Sirirat M, Kasetsuwan J, Jeffcoat MK. Comparison between 2 surgical techniques for the treatment of early-onset periodontitis. *J Periodontol* 1996; 67: 603-607.
- ¹³ Dibattista P, Bissada NF, Ricchetti PA. Comparative effectiveness of various regenerative modalities for the treatment of localized juvenile periodontitis. *J Periodontol* 1995; 66: 673-678.
- ¹⁴ Haffajee AD, Socransky SS, Gunsolley JC. Systemic anti-infective periodontol therapy. A systemic review. *Ann Periodontol* 2003; 8: 115-181.
- ¹⁵ Herrera D, Sanz M, Jepsen S, Needleman I, Roldan S. A systemic review on the effect of systemic antimicrobials as an adjunct to scaling and root planning in periodontitis patients. *J Clin Periodontol* 2002; 29 (Suppl. 3): 136-159.
- ¹⁷ American Academy of Periodontology. Epidemiology of Periodontal Diseases. *J Periodontol* 2005; 76: 1406-1419.
- ¹⁸ Jeffcoat M. What is clinical significance? *J Clin Periodontol* 2002; 29 (Suppl. 2): 30-32.