Abstract: Aggressive periodontitis is a relatively rare periodontal condition that can result in significant attachment loss over a short period of time. As the disease is difficult to manage, owing to its rapid progression and severity, a variety of adjuncts have been advocated in its management. The authors outline concepts of the aetiology and pathogenesis of aggressive periodontitis and how the different treatment regimens relate to the current understanding of the disease process.

Clinical Relevance: There is a wide variety of treatment regimens advocated for the treatment of aggressive periodontitis. General dental practitioners and specialists should be aware of the relative advantages and disadvantages of these and how they relate to the disease process.

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Aggressive periodontitis (AP) has been defined as a group of rare, often severe, rapidly progressive forms of periodontitis which are often characterized by an early age of onset and a tendency to aggregate in families. It has been characterized as having the following major features:1

- Non-contributory medical history;
- Rapid attachment loss and bone destruction;
- Familial aggregation of cases.

Other features or characteristics of AP often include:

- Low levels of bacterial plaque;
- Increased proportions of certain bacteria, in particular Aggregatibacter actinomycetemcomitans (Aa);
- Defects in neutrophil function;
- Root abnormalities;
- Hyper-responsive macrophage phenotype; and, possibly,
- Viral infection.2

It is well established that AP

<table>
<thead>
<tr>
<th>Localized Aggressive Periodontitis</th>
<th>Generalized Aggressive Periodontitis</th>
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<tbody>
<tr>
<td>Circumpubertal onset</td>
<td>Usually affecting patients of less than 30 years of age</td>
</tr>
<tr>
<td>Localized first molar/incisor with interproximal attachment loss on at least two permanent teeth one of which is a first molar, and involving no more than two teeth localized to first molars/incisors</td>
<td>Generalized interproximal attachment loss affecting at least three permanent teeth other than first molars and incisors</td>
</tr>
<tr>
<td>Robust serum antibody response to infecting agents</td>
<td>Clear episodic nature of destruction of periodontal attachment and associated structures</td>
</tr>
<tr>
<td>Poor serum antibody response to infecting agents</td>
<td>Table 1. Diagnostic criteria for aggressive periodontitis.</td>
</tr>
</tbody>
</table>
can be further classified as localized or generalized (Table 1) (Figures 1–4). The localized form usually occurs around puberty and often affects first molars and then central incisors, although it is not always exclusive to these teeth.

Features of the generalized form include:
- An occurrence below the age of 30 years;
- Generalized interproximal bone loss affecting at least three permanent teeth other than the first molars and incisors;
- A clear episodic nature of periodontal attachment loss; and
- A poor serum antibody response to infecting agents.3–6

Although these two subdivisions may have some substance in their criteria, the differences between localized and generalized may not be so obvious. The prevalence of AP varies according to the population studied and ranges from 0.1% in Caucasians to up to 22% in Afro-Caribbeans.7,8

The aim of this paper is to investigate how our understanding of the aetiology of AP has influenced treatment options and outcomes.

Aetiology of aggressive periodontitis

There has been considerable research into the role of Aa in the aetiology of AP and this has had a significant impact upon treatment. *Aggregatibacter actinomycetemcomitans* possesses a large number of virulence factors which may be relevant in the pathogenesis of AP. These factors are shown in Table 2.

In addition to such virulence factors, there is also a body of evidence to suggest that Aa can ‘invade’ the gingival...
Virulence Factor | Role in Aggressive Periodontitis (AP)
--- | ---
Leukotoxin | Affect PMN functions by suppressing chemotaxis and increasing superoxide generation
Collagenases | Breakdown of connective tissue and loss of attachment
Endotoxins | Drives inflammatory response in gingival connective tissue
Fibroblast inhibitory factor | Prevents fibroblast adhesion to root surface and other structures
Soluble heat labile factor | May inhibit the growth and proliferation of other micro-organisms associated in the plaque biofilm

Table 2. Virulence factors arising from Aggregatibacter actinomycetemcomitans (Aa) and possible roles in pathogenesis of AP.

Aetiology of AP and treatment options

The association between Aa and AP has led to extensive investigations into the efficacy of antibiotics in the management of this condition. In most instances, the antibiotics have been prescribed as adjuncts to either a surgical or non-surgical approach. Other treatment options that have recently been evaluated in the management of AP include:

- Antimicrobial photodynamic therapy;
- Nd:YAG laser treatment; and
- A systemic 7-day course of etoricoxib, a COX-2 inhibitor.

These studies will be commented upon later.

Efficacy of adjunctive systemic antibiotics in the management of AP

A synopsis of the various studies that have evaluated the efficacy of adjunctive antibiotics in the management of AP is shown in Table 3. For the most part, the antibiotics have been used as an adjunct to a non-surgical approach for the underlying periodontal condition. The number of patients recruited into such studies have, of necessity, been small. AP is a relatively rare condition and this is reflected in the number of patients that have been evaluated. The follow-up period is likewise variable, and ranges from 6 to 18 months. The latter would be an exceptional timeframe for most periodontal studies of similar design.

The antibiotics evaluated include tetracyclines, clindamycin, amoxicillin, metronidazole (also used in combination) and azithromycin. Outcome measures have mainly emphasized the reduction of probing pocket depths, although some studies primarily focused on suppression of Aa.

It is clear from the outcomes of the various studies reported in Table 3, that the benefits of systemic, adjunctive antibiotics in the management of AP is equivocal. The combination of amoxicillin and metronidazole does appear to be the most efficacious in this regard. By contrast, systemic tetracycline may have little value over the conventional non-surgical approach.

Issues that can affect the efficacy of systemic antibiotics in the management of AP include timing of the course of antibiotics and compliance. Both issues have been evaluated. Timing options for the prescription of systemic antibiotics could be immediately prior to the non-surgical root surface instrumentation (RSI), immediately after the debridement, or up to 3 months post-treatment. Prescribing immediately after RSI has been compared with taking a course of antibiotics 3 months after treatment. The antibiotic used in this study was the amoxicillin/metronidazole combination. The authors showed that prescribing this combination after RSI was of greater benefit, in terms of probing pocket depth reduction, than the 3 month prescription.

Compliance with any antibiotic regimen is also an important factor that can affect efficacy of these drugs as adjunctive agents in the management of AP. Poor compliance will result in fluctuating blood levels which will impact upon the bactericidal capacity of the antibiotics. Indeed, patients with good compliance show greater reduction in probing depths for sites >7mm.

The metronidazole/amoxicillin combination does appear to be the most widely investigated adjunctive antimicrobial regimen in the management of AP. Data from Table 3 suggest that the additional benefits of this combination results in a further 0.5–1.00mm additional mean reduction in probing pocket depth, when compared to a non-surgical approach alone. This will approximate to an additional 20–25% benefit. Other periodontal parameters have been evaluated in the various clinical trials and these are reported in Table 3.

The apparent periodontal benefits of the combination of amoxicillin and metronidazole need to be balanced against adverse effects arising from either agent. Of particular concern is the development of bacterial resistance and gastrointestinal disturbances. Duration of the course for this combination in the periodontal perspective is in the range of 7–10 days, and the longer the patient is exposed to the drugs, the greater the risk of adverse effects. In the studies cited in Table 3, adverse events were recorded in some of the investigations. Further to these immediate complications, the long-term development of antibiotic resistance by periodontal pathogens has been reported. In this study, patients who had used antibiotics within the previous year demonstrated antibiotic resistance in particular against metronidazole.

Other adjuncts used in the management of aggressive periodontitis

Laser therapy using the Nd:YAG laser has been compared with a conventional
A surgical approach in the management of AP. A split mouth design was used in this study and the results showed no difference between treatments with respect to periodontal outcomes. The authors suggested that the use of the Nd:YAG laser could be more useful for those patients who have disorders of haemostasis or anxiety about having surgery. The Nd:YAG laser has a significant antibacterial action and this may contribute towards its efficacy in the management of AP.

The antimicrobial properties of the laser have also been compared with conventional non-surgical management in patients with AP. This study used a split mouth design and, at a 3-month evaluation, there were no differences between the treatments in relation to a variety of periodontal parameters.

Irrespective of the pathogenesis of AP, there is still, in most patients, a significant inflammatory component within the periodontal tissues which RSI alone can dramatically reduce (Figures 5 a, b). Non-steroidal anti-inflammatory drugs (NSAIDs) have been used as adjuncts in the management of chronic periodontitis. The adjunctive benefits of these drugs is somewhat limited in terms of reducing periodontal measures. Animal models have shown that COX-2 inhibitors have the potential to reduce the inflammatory component of periodontal disease. A clinical trial in patients with chronic periodontitis also indicated that the adjunctive use of a COX-2 inhibitor (loxoprofen) provided additional benefits in reducing deep periodontal pockets (>7 mm) over root surface instrumentation alone. In contrast to this finding, when the COX-2 inhibitor (etoricoxib) was used as an adjunct to non-surgical management in patients with AP, no additional clinical benefits were found. This finding may reflect the nature of AP, especially the possible limited role of plaque-induced inflammation in its pathogenesis.

Surgical management of AP

Interest in a surgical approach for the management of AP has arisen following the evidence that the gingival tissues may be invaded by Aa and other periodontopathogens.

Many of the surgical studies were completed in the 1980s and 90s and often involved only a small number of patients with a limited period of follow-up. In brief, studies have shown that AP can be managed by a surgical approach with or without adjunctive use of systemic antibiotics. For the most part, the adjunctive antibiotics used were tetracyclines. The evidence to support the adjunctive use of these drugs for this purpose is equivocal. Two studies have demonstrated that systemic tetracyclines enhance the surgical approach for the management of AP, whilst a further report showed little or no adjunctive benefit from doxycycline over open flap debridement. There do not appear to be any recent studies comparing the surgical approach with the non-surgical approach for patients with AP.

Regenerative techniques

The periodontal defects associated with AP are often suitable for regenerative procedures. Furthermore, the distribution of such defects also affords the opportunity of evaluating different techniques in the same patient (the so-called split mouth design). An early study compared guided tissue regeneration (GTR) with osseous surgery in 15 patients exhibiting paired defects. These patients were followed up for 12 months and those defects treated with GTR showed a significantly greater (p < 0.05) reduction in probing pocket depth and more attachment gain than those sites treated by osseous surgery. Radiographs also showed greater osseous infill at 12 months in the GTR treated sites.

Whilst there is a variety of GTR techniques available, there may be a lack of information on the best technique in certain defects. A four-way split mouth study compared surgical debridement alone with expanded polytetrafluoroethylene (ePTFE) membrane alone, ePTFE membrane with root conditioning with doxycycline, and ePTFE membrane with root conditioning and composite graft comprising calcium sulphate, DFDBA and doxycycline. All four techniques were evaluated in seven patients and followed
<table>
<thead>
<tr>
<th>Authors and Year</th>
<th>Design</th>
<th>Duration of Antibiotic</th>
<th>Systemic Antibiotic Used and Dosages</th>
<th>Adverse Events Recorded</th>
<th>Number of Patients</th>
<th>Control Group vs Antibiotic Group</th>
<th>Periodontal Measures</th>
<th>Follow-up</th>
<th>Mean/Median Reduction in Periodontal Pocket Depths</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinoco et al 1998</td>
<td>RCT</td>
<td>8 days</td>
<td>Amoxicillin 1500mg OD and metronidazole 750mg OD</td>
<td>None reported</td>
<td>25</td>
<td>Non surgical management vs antibiotic group</td>
<td>Gingival index, plaque index, probing depth, clinical attachment level, and radiographic levels of crestal bone height</td>
<td>12 months</td>
<td>3mm mean reduction in PPD in test group vs control group at one year</td>
<td>The test group had greater improvement in clinical parameters although the majority of these results were not statistically significant</td>
</tr>
<tr>
<td>Purucker et al 2001</td>
<td>RCT</td>
<td>14 days</td>
<td>Amoxicillin 500mg TDS</td>
<td>None reported</td>
<td>30</td>
<td>Non surgical management with locally applied tetracycline fibres vs antibiotic group</td>
<td>Probing depth, clinical attachment level, and bleeding on probing</td>
<td>15, 30, 41 and 54 weeks later</td>
<td>2mm mean reduction in the test group in comparison to 1.4mm in the control group at 6 month follow-up for bleeding</td>
<td>No statistical difference in any of the clinical parameters in test and control groups, except on probing at week 54, where the reduction in the systemic antibiotic group decreased to 4% in comparison to the local tetracycline decreased to 32%</td>
</tr>
<tr>
<td>Guerrero et al 2005</td>
<td>RCT with placebo</td>
<td>7 days</td>
<td>Amoxicillin (500mg) TDS and metronidazole (500mg) TDS management vs antibiotic group</td>
<td>Nausea, vomiting, gastrointestinal disorder, headache</td>
<td>41</td>
<td>Non surgical</td>
<td>Full mouth plaque score, full mouth percentage bleeding score, probing pocket depth, recession, lifetime cumulative attachment loss</td>
<td>2 and 6 months</td>
<td>1.5mm mean reduction in the test in comparison to 1 mm in the placebo groups at 6 month follow-up</td>
<td>Reduction in pocket depths of greater than 5mm in 74% test group vs 54% of control although this was not statistically significant</td>
</tr>
<tr>
<td>Xaji-georgiou et al 2006</td>
<td>RCT</td>
<td>Between 7 and 14 days depending on the antibiotic</td>
<td>Metronidazole 500mg TDS and metronidazole 500mg TDS and amoxicillin 500mg TDS vs doxycycline 200mg OD</td>
<td>None reported</td>
<td>43</td>
<td>Non surgical management group vs non surgical management with one of 3 different antibiotic groups</td>
<td>Probing depth, probing attachment level, and bleeding on probing</td>
<td>6 weeks and 6 months</td>
<td>Amoxicillin =1.51mm mean reduction doxycycline =0.89mm mean reduction metronidazole =1.85mm mean reduction in comparison to 0.69mm in control groups at 6 month follow-up</td>
<td>Groups treated with metronidazole plus amoxicillin or metronidazole alone resulted in greater reduction in pocket depths in sites of greater than 6mm in depth. Interestingly all bacterial populations reduced significantly apart from Aa</td>
</tr>
<tr>
<td>Kaner et al 2007</td>
<td>RCT</td>
<td>10 days</td>
<td>Amoxicillin (500mg) TDS and metronidazole (250mg) TDS</td>
<td>Gastrointestinal disorder</td>
<td>36</td>
<td>Non surgical management with chlorhexidine chip vs antibiotic group</td>
<td>Clinical attachment level, probing depth, bleeding on probing, suppuration</td>
<td>3 and 6 months</td>
<td>1.91mm mean reduction in the test group in comparison to 1.64mm in control group at 6 month follow-up</td>
<td>Systemic antibiotics significantly reduced clinical parameters in comparison to locally applied chlorhexidine chips</td>
</tr>
<tr>
<td>Moreira et al 2007</td>
<td>RCT</td>
<td>7 days</td>
<td>Metronidazole 250mg TDS and amoxicillin 500mg TDS</td>
<td>None reported</td>
<td>30</td>
<td>Full mouth root planing with antibiotic vs quadrant basic periodontal therapy with antibiotic group</td>
<td>Probing depth, clinical attachment level, bleeding on probing, visible plaque</td>
<td>2, 4 and 6 months</td>
<td>1.3mm reduction in probing depth using full mouth instrumentation in comparison to 1.4mm when using quadrant therapy. Both regimes administered systemic antimicrobials</td>
<td>No additional clinical benefit between full mouth root planing or quadrant basic periodontal therapy when adjunctive antibiotics were used</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Duration</td>
<td>Antibiotic</td>
<td>Comparator</td>
<td>Lesion Days</td>
<td>Lesion Size</td>
<td>Lesion Type</td>
<td>Lesion Site</td>
<td>Lesion Description</td>
<td>Lesion Results</td>
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<tr>
<td>Saxén et al 1993</td>
<td>RCT</td>
<td>10 days</td>
<td>Tetracycline (250mg TDS) vs metronidazole (200mg)</td>
<td>None applicable</td>
<td>27</td>
<td>Non surgical management with no adjuncts vs non surgical management and metronidazole vs non surgical management and tetracycline</td>
<td>Gingival index, gingival bleeding after probing, probing depth, suppuration, radiographic bone loss and selective Aa culturing</td>
<td>6 and 18 months</td>
<td>Mean percentage reduction in pockets of greater than 4mm was greater for metronidazole (from 20.8% to 2.6%) than tetracycline (18.7% to 4.2%) and the control (13.8% to 6%)</td>
<td>Metronidazole was more effective at reducing the presence of Aa than tetracycline</td>
</tr>
<tr>
<td>Palmer et al 1996</td>
<td>RCT</td>
<td>14 days</td>
<td>Tetracycline 250mg QDS</td>
<td>None reported</td>
<td>38</td>
<td>Non surgical management vs non surgical management with adjunctive tetracycline</td>
<td>Pocket probing depths, clinical attachment level, bleeding on probing</td>
<td>3, 6, and 12 months</td>
<td>2.7mm reduction in mean probing depths at 6 months in test group in comparison to 1.95mm in control group</td>
<td>No significant statistical difference in any of the clinical parameters between the test and control groups</td>
</tr>
<tr>
<td>Kamma et al 2000</td>
<td>RCT</td>
<td>7 days</td>
<td>Oridazole 500mg BD</td>
<td>None reported</td>
<td>30</td>
<td>Non surgical management with adjunctive systemic oridazole vs oridazole administered solely</td>
<td>Plaque index, plaque index, suppurative index, attachment level, probing probing depths, bacterial sampling</td>
<td>1 week, 2, 6, and 12 months</td>
<td>2.7mm reduction in mean probing depths at 6 months at instrumented sites in comparison to 1.95mm in non-instrumented sites</td>
<td>Adjunctive oridazole produced beneficial shifts in bacterial populations and clinical improvement when administered in conjunction with instrumentation</td>
</tr>
<tr>
<td>Sigusch et al 2001</td>
<td>RCT</td>
<td>8 days</td>
<td>Metronidazole (500mg BDS) vs clindamycin vs doxycycline</td>
<td>None reported</td>
<td>48</td>
<td>Non surgical management group vs non surgical management with one of 3 different antibiotic groups</td>
<td>Plaque index, sulcus bleeding index, probing depth, clinical attachment level, bacteriological sampling</td>
<td>3 weeks, 6 months and 24 months later</td>
<td>At 6 and 24 months there was a significantly greater reduction of pocket depth in the metronidazole sampling groups and a significantly greater clinical attachment level gain in comparison to the doxycycline and control groups</td>
<td>Greater reduction in pocket depth and increase in clinical attachment level with metronidazole and clindamycin in comparison to control and amoxicillin group and clindamycin</td>
</tr>
<tr>
<td>Haas et al 2008</td>
<td>RCT</td>
<td>3 days</td>
<td>Azithromycin (500mg) once daily</td>
<td>None reported</td>
<td>24</td>
<td>Non surgical management group vs non surgical management and antibiotic groups</td>
<td>Periodontal pocket depth, bleeding on probing</td>
<td>3, 6, 9, and 12 months</td>
<td>2.88mm mean reduction in the test group in comparison to the control (1.85mm) of mean PPD at one year follow-up</td>
<td>More reduction in mean pocket probing depth in test vs control group (2.88 vs 1.85mm) and a higher percentage of attachment gain of 1mm or more of test vs control (81% vs 64%). Although none of these results was statistically significant</td>
</tr>
<tr>
<td>Machtet et al 2008</td>
<td>RCT</td>
<td>2 weeks</td>
<td>Doxycycline 100mg daily with a loading dose of 200mg for 30 days vs amoxicillin 500mg and metronidazole 250mg for 2 weeks</td>
<td>None reported</td>
<td>31</td>
<td>Non surgical management with adjunctive amoxicillin and metronidazole vs non surgical management with adjunctive doxycycline</td>
<td>Plaque index, gingival index, probing pocket depth, clinical attachment level</td>
<td>3 months</td>
<td>0.76mm mean reduction in PPD in amoxicillin and metronidazole group in comparison to 0.72mm in doxycycline group at 3 month follow-up</td>
<td>Both groups showed significant improvements in periodontal measures. Interestingly there was no statistical significance between the two regimens</td>
</tr>
</tbody>
</table>

Table 3: Illustrating the use of antibiotics in the management of aggressive periodontal disease.
up for a period of 18 months. All four methods of treating such defects in AP patients resulted in a significant gain in attachment as well as an increase in volumetric bone fill, however, there was no difference between the various treatment options.35

A more recent study has investigated the value of resorbable membranes and bioactive glass in the management of periodontal defects in patients with AP.36 A total of 22 defects were treated with the membrane and 20 with the bioactive glass. Patients were followed up for five years. Both techniques provided significant reductions in probing pocket depths and attachment gain. Radiographs showed that there was greater bony in fill in the bioactive glass-treated sites.

There is increasing evidence that regenerative techniques are a suitable option for the management of periodontal defects associated with AP. Although only a few studies have been reported, the evidence to date does show that these techniques afford advantages over conventional flap debridement. The outcome of studies so far suggests that the use of regenerative techniques for the management of AP warrants further investigation.

Supportive care

Two studies have reported on the long-term follow-up of patients with AP who have been treated by different approaches. In the first of these investigations, 13 patients with a diagnosis of AP were reviewed five years after treatment and the provision of supportive care. All patients had initially received a combination of mechanical, surgical and antimicrobial treatments. The patients were enrolled on a regularly scheduled maintenance programme. During the first year, subjects were monitored in 3–6 month recall intervals, which included repeat of oral hygiene instruction and full mouth prophylaxis. At 3 months post-treatment, clinical attachment levels reduced on average by 2.23 mm. At the 5 year review, only 3.2% of the sites in these patients showed further clinical attachment levels reduced on average by 2.23 mm. At the 5 year review, only 3.2%

References


