BY SARAH DUERDEN

A CRITICAL REVIEW OF THE EVIDENCE FOR THE USE OF SYSTEMATIC ANTIBIOTICS AS ADJUNCTS IN NON-SURGICAL PERIODONTAL THERAPY

Introduction

Periodontitis is a multifactorial disease affecting the supporting tissues of the tooth including gingiva, periodontal ligament fibres and alveolar bone.[1] The aetiology of periodontal diseases is bacteria.[2] Oral biofilms are structurally organised communities embedded within an extracellular matrix on dental and mucosal surfaces.[3] These biofilms are present in health and provide benefits such as protection, support and are responsible for natural development of host physiology. However, disease can occur when there is a shift associated with the bacterial species balance within the biofilm.[3]

Red complex bacteria are strongly associated with severe chronic periodontitis (CP) and include *Porphyromonas gingivalis (P.gingivalis)*, orange complex is closely associated with the red complex[4] and *Aggregatibacter actinomycetemcomitans* (AA), included within the green complex, is strongly associated with aggressive periodontitis (AgP) and has a less frequent association with CP.[5] *P. gingivalis* appears to be one of the key aetiological factors in the progression and pathogenesis in the inflammatory aspect of periodontitis and is referred to within the keystone pathogen hypothesis, which suggests that bacteria, present in low abundance, can cause an environmental disturbance changing the environment from a symbiotic environment to a dysbiotic environment.[6]

It is advised that treatment for periodontitis follows the British Society of Periodontology (BSP) S3 guidelines which consist of improved oral hygiene and professional mechanical plaque removal (PMPR)[7,8] During the mechanical removal of the bacterial biofilm disruption occurs reducing the bacterial burden and reducing inflammatory responses[8] however, in some cases treatment response is limited[5] leading to a rationale for the use of adjunctive local or systemic antimicrobials to reduce the number of target bacteria in the difficult to access sites.[7] Thus, overcoming the protective nature of the biofilm, suppressing pathogenic bacteria and helping the biofilm to return to a symbiotic state associated with health.[9] Bacterial species found in the biofilm next to the epithelial cell surface of a periodontal pocket include members of the red complex bacteria which are quite susceptible to systemic antimicrobial agents due to their proximity to gingival crevicular fluid and the absence of protective glycocalyx.[10] For systemic antibiotics to be effective against bacteria within biofilms it has been suggested antibiotic strength 500 times greater than the usual dose is required.[11]

Adjunctive systemic antibiotics have been indicated in the treatment of chronic periodontitis (CP) and aggressive periodontitis (AgP).[12] Several antibiotics and antibiotics combinations have been suggested in the treatment of periodontitis including: tetracycline; clindamycin; doxycycline; minocycline; azithromycin (AZ) (categorised as agents which act by inhibiting protein synthesis); amoxicillin (AM) (act by inhibition of cell wall synthesis); metronidazole (MET); and ciprofloxacin (act by inhibition of DNA synthesis).[13] Advantages of systemic antibiotics in the treatment of periodontal diseases include ease of use and moderate cost effectiveness, however, systemic antibiotics can impact on the whole system, cause some adverse effects and pose a danger of superinfections and resistance.[5] Adverse effects range from frequent nausea, vomiting, gastrointestinal intolerance and rashes to infrequent photosensitivity, convulsions/confusion, peripheral neuropathy, furred tongue and intercranial hypertension, depending on which drug is prescribed.[5]

Aim

The aim of this paper is to update readers' knowledge of adjunctive systemic antibiotics and critically evaluate the scientific evidence related to this topic to provide clinical recommendations. The objectives below have been prepared to achieve the aim:

1. Identify keywords and search relevant databases to identify current research articles.
2. Critically appraise and discuss the identified articles to construct an informed conclusion regarding the use of adjunctive systemic antibiotics.

Methodology

Keywords - systemic antibiotics, non-surgical periodontal therapy (NSPT), scaling and root planning (SRP) - alongside each antibiotic name were identified and several databases were searched including Dentistry and Oral Sciences Source and Medline with full text. SRP was identified as a keyword in order to identify all available evidence as, although it is no longer a term used to describe any aspect of NSPT, some papers still refer to this term. Boolean operators AND and OR were used along with truncation to search articles included with each facet and to search words together.[14]

Results and discussion

Various sources of information were located including several recent systematic reviews (SR). Five studies were selected for

critical review (Fig.1). The studies included within the SR's all used antibiotics as adjunctive therapy to mechanical biofilm removal.

Herrara et al (2008)[15] reviewed published studies regarding the role of antibiotics as a monotherapy in the treatment of periodontitis and quality of debridement of the biofilm in relation to the efficacy of adjunctive antibiotics. Results of included studies suggested the use of antibiotic monotherapy in the treatment of periodontitis was not supported and antibiotic effect was increased after disruption of the biofilm. This supports the American Academy of Periodontology (AAP) suggestion, based on the concept of 'good medical practice' that antibiotics should only be used as adjunctive therapy.[16] In relation to the quality of debridement, the analysed studies suggested clinical outcomes could be influenced by the quality of debridement and point of antibiotic administration.[15] However, due to the limited studies available, heterogeneity of the studies and small sample sizes, caution should be taken in interpretation.

Keestra et al (2015)[17,18] carried out two SR's and meta-analysis on adjunctive systemic antibiotics in patients with untreated chronic periodontitis (CP) (forty-three randomised control trials RCT's) and untreated aggressive periodontitis (AgP) (fourteen RCT's). Both reviews included a clearly focused question and study inclusion was limited to randomised control trials (RCT's) in both SR's in line with current evidence suggesting the main study design to evaluate interventions are clinical trials.[19] Detailed search strategies including databases searched and a hand search of the past 10 years of relevant journals was undertaken in both SR's as 'hand searches through back issues of relevant journals can prove valuable'.[19] In line with current guidance, the reviewers used a preferred reporting items for systematic reviews (PRISMA) diagramme [20] and clearly identified the PRISMA within the article. Two reviewers independently screened papers for inclusion, which follows suggestion from Hedegan and Badenoch (2006)[21] that the use of two independent reviewers reduces bias. Due to the heterogeneity within the studies included within the SR's the reviewers in both Keestra et al (2015)[17,18] papers correctly used a random effects model in the data analysis.[22] The meta-analysis for both Keestra et al (2015) papers showed for PPD, CAL and BOP there was a statistically significant result in favour of adjunctive systemic antibiotics at 3,6,9 and 12 months for the mean, moderate pockets and for deep sites. However, the analysis was limited, since most of the included studies only had follow up periods of 3-6 months and although statistical significance was shown at 9 months only 1 study included a 9-month review. The results were slightly better within deeper sites than the shallower sites and no antibiotic was found to be superior overall.[17,18] From the more detailed breakdown of results within AgP AM/MET was the only antibiotic regime which provided results stable for up to 12 months. AZ did not show statistically significant results after 3 months for PPD and at no interval for CAL and had wide confidence intervals (CI) on the forest plot. However, the SR included ten studies for AM/MET and only included two studies for AZ. Also, the number of studies available to be analysed after 3 months was low with only two studies available at the 12-month analysis and small sample sizes throughout. The effectiveness of AM/MET was compared in CP and AgP where results showed a greater improvement in clinical outcomes for AgP.[17,18]

Zandbergen et al (2016)[9] published a SR with meta-analysis on concomitant administration of AM/MET in the treatment of patients with CP and AgP which included twenty clinical studies. A clear focused question was included with primary and secondary outcomes clearly defined. Although no PRISMA diagramme was located within the article, a further document was located which included the PRISMA diagramme. Data was extracted and analysed using either fixed-effects or random methods. The fixed effects model was correctly used only if there were more than four studies and heterogeneity was interpreted to be less than 40% indicating variability within the studies was negligible.[23] The results showed a statistically significant favouring to adjunctive AM/MET in terms of mean PPD and CAL and the results at deeper sites were slightly better than shallower sites. Sub-analysis was performed using periodontal diagnosis where a similar pattern in treatment effect was observed.[9] However, the RCTs within the SR used differing dosage and regimes and it is not clear if these differences influenced the clinical outcomes as the studies with the most increased treatment effect were those with higher dosages.

Zhang et al (2016)[24] performed a meta-analysis on the clinical effect of adjunctive AZ in the treatment of CP which included nine studies where systemic AZ was administered. A clear focused question was not identified, however, relevant keywords related to the topic were searched in several recommended databases and two authors searched and identified the included studies. The results showed a statistical significance in results in favour of adjunctive systemic AZ in mean reduction of PPD and BOP and mean gain of CAL and when the results were separated into shallow, moderate and deep sites a better clinical response was seen in the deeper sites.[24] However, some low-quality studies with small sample sizes were included within the meta-analysis and some studies had wide CI's on the forest plot. Although the results showed

Figure 1: **Papers reviewed**

Herrara, D, Alonso, B., Leon, R., Roldan, S. & Sanz, M. Antimicrobial therapy in periodontitis: the use of systemic antimicrobials against the subgingival biofilm. Journal of Clinical Periodontology. 2008; 35(8):45-66.

Keestra, J.A.J., Grosjean, I., Coucke, W., Quirynen, M. & Teughals, W. Non-surgical periodontal therapy with systemic antibiotics in patients with untreated aggressive periodontitis: a systematic review with meta-analysis. Journal of Periodontal Research 2015; 50:689-706.

Keestra, J.A.J., Grosjean, I., Coucke, W., Quirynen, M. & Teughals, W. Non-surgical periodontal therapy with systemic antibiotics in patients with untreated chronic periodontitis: a systematic review and meta-analysis. Journal of Periodontal Research 2015;50:294-314.

Zandbergen, D., Slot, D.E., Niederman, R. & Van Der Weijden, F.A. The concomitant administration of systemic amoxicillin and metronidazole compared to scaling and root planning alone in treating periodontitis: a systematic review. Biomed Central Oral Health. 2016;16:1-11.

Zhang, Z., Zheng, Y. & Bian, X. Clinical effect of azithromycin as an adjunct to non-surgical treatment of chronic periodontitis: a meta-analysis of randomised controlled clinical trials. Journal of Periodontal research. 2016; 51:275-283.

a statistically significant difference in favour of adjunctive systemic AZ between one and twelve months the overall effect was greatest at one month and decreased over twelve months.[24]

The results within the SR's support previous SR's carried out by Herrera et al (2002)[25] and Haffajee et al (2003)[10] which found adjunctive systemic antibiotics can offer additional benefits to mechanical debridement alone and suggested greater benefit in AgP and deeper sites. However, these results should be interpreted with caution due to the limitations of the reviews, Keestra et al (2015)[17,18] CP article estimated a high risk of bias in over half the papers included and although there was a little more exactitude in Keestra et al (2015) [17,18] AgP and Zandbergen et al (2016)[9] some papers with a high estimation of bias were still included. Also, due to heterogeneity and small sample sizes within the included study populations, no conclusions could be drawn as to which antibiotic to use for each infection, which patients would benefit most, at which point antibiotics should be administered and whether antibiotics should be administered at initial treatment or retreatment. Griffiths et al (2011)[26] carried out a RCT to assess if clinical outcomes were altered if the antibiotics were given at initial treatment or retreatment concluding that at eight months patients who received antibiotics at initial therapy showed statistically significant benefits compared to the group that received the antibiotics at retreatment. However, the initial antibiotics group was assessed eight months after the antibiotic administration whereas the retreatment group was assessed after two months. Therefore, there is potential of time scale skewing in that area.

Although the results within the SR's indicated a statistical significance difference in favour of systemic antibiotics the favouring is small and this raises the question to what point is a value considered clinically significant. The highest mean PPD loss for Keestra et al (2015) CP was -0.49mm, AgP -0.51mm, Zandbergen (2016) -0.47mm and Zhang et al (2015) -0.43mm, however, mean data also includes shallow sites which do not respond as well to systemic antibiotics. Haffajee et al (2003)[10] suggest an attachment level gain of 0.3mm would be equal to seven years of disease progression, however the effects clinically need to be balanced against adverse reactions. Most of the studies included within the SR's found no adverse reactions to the antibiotics and the few studies that did report adverse reactions referenced mild effects with the most common being diarrhoea. However, a small minority of patients do suffer from more serious adverse reactions to adjunctive systemic antibiotics.[25] Bacterial resistance is seen as an adverse reaction with *P.gingivalis* and AA showing an increase in resistance to AM/MET.[27] Hirsch et al, (2012)[28] suggested biofilm bacteria showed more resistance to MET than AZ. The antibiotic regime most documented is AM/MET[7] and there is limited long term research available around adjunctive AZ in the treatment of periodontitis with the most recent published studies regarding AZ being inconsistent.[24] The most common dosage regime for AZ is 500mg once a day for three days, therefore, patient compliance is good due to the short course and AZ also reports low incidence of adverse reactions compared to other antibiotics used in the treatment of periodontitis.[28] Therefore, more research is needed around AZ as a safer antibiotic option.

Within the SR's study populations were not restricted, therefore, confounding factors were not taken into consideration and there was considerable heterogeneity. Confounding factors included systemic diseases, smoking and plaque control, all of which have been indicated as factors in the progression of periodontal diseases.[29] Variability was seen within the type of periodontal condition treated, antibiotic used, dosage and regime, the timing of when the antibiotic was administered, sample size and number of visits taken for mechanical debridement which led to data aggregations within the SR's that may not be optimal. Indirect evidence suggests the antibiotic regime should start on the day treatment starts[7], however, this differed within the studies with some studies not administering antibiotics until the mechanical debridement was over and length of treatment differed within the studies. Also, length of follow up differed among the RCT's, therefore, while the conclusion that statistically significant results in favour of antibiotics were seen, it is not clear how long this effect is maintained. The SR's appraised did not include data longer than 12 months and the two SR's carried out by Keestra et al (2015)[17,18] which hold data for up to 12 months have limited studies included in the twelve-month meta-analysis. No study within the SR's included follow up longer than twelve months, therefore, it is not clear if the result is a long term-maintained effect. Serino et al (2001)[30] carried out a clinical trial over a five-year period to assess the effect of systemic antibiotics in patients with recurrent periodontitis. Seventeen patients were given adjunctive AM/MET and re-examined at one, three and five years. Improvement in PPD and probing attachment level (PAL) was initially seen at one year, was negligible at three years and improvement had been lost at five years. However, the sample was small and over half of the participants were smokers which is a confounding factor in periodontal diseases.[29]

At present there are no definitive guidelines as to the optimal conditions to use adjunctive systemic antibiotics in the treatment of CP and AgP.[31] Due to side effects, and an increase in antibiotic resistance, it is recommended that adjunctive antibiotics are restricted to certain conditions and patients. The studies included to date have referred to CP and AgP when discussing systemic antibiotics in relation to periodontitis which referred to classifications implemented in 1999.[32] However, the 2017 World Workshop classification now exists where the terms CP and AgP have been removed and a staging and grading system for periodontitis was introduced.[32] The papers do refer to moderate or deep sites which would be transferable to the new classification. AgP would now be stage three or four generalised periodontitis and grade C which is rapid progression.

Summary

Recent evidence concluded a statistical significance in favour of adjunctive antibiotics in the treatment of CP and AgP and showed that antibiotics were more effective for deeper sites and for more aggressive disease which is now referred to as rapid progression periodontitis.[32] However, it is not clear how the statistical significance relates to clinical significance and if the result is maintained. Limitations within recent literature is evident and the studies included within the SR's appraised contained a lot of heterogenicity including: sample size; periodontal condition; type of antibiotic and antibiotic regime; time scale taken to perform mechanical debridement; and the time point at which antibiotics were administered. Also, confounding factors are important and may have influenced

the outcomes. Due to antibiotic resistance within the oral biofilm the use of antibiotics should not be a routine treatment for all and should be used on a case-by-case basis.

Conclusion

The aim of this paper was to critically evaluate the scientific evidence related to systemic antibiotics as an adjunct to mechanical debridement and to provide a conclusion relating to clinical implications. After critically appraising some of the most recent SR's it can be concluded that adjunctive systemic antibiotics may have a role in the treatment of periodontitis and may provide greater results in disease of rapid progression and deeper sites. If systemic antibiotics are recommended, they should be used as an adjunct to mechanical debridement and not used as a monotherapy.[16] Due to heterogenicity among the included literature no definitive guidelines can be recommended with regards to type of antibiotic, dosage and time point of administration. Therefore, large scale, well-designed RCT's are needed to confirm the effects of adjunctive systemic antibiotics in the treatment of periodontitis to define the most optimal conditions including antibiotic regime and at which point adjunctive antibiotics are administered paying attention to initial treatment or retreatment. Also, further research is needed around azithromycin due to the safer nature of the antibiotic.

Author: Sarah is Principal Lecturer in Dentistry/Course Lead in Dental Therapy at UCLan and is a keen advocate for the utilisation of dental hygienists and dental therapists in general practice within an integrated dental team.

Contact: SDuerden1@uclan.ac.uk

References

1. Tonetti MS, Eickholz P, Loos BG, Papapanou P, Van Der Velden U, Armitage G et al. „ Principles in prevention of periodontal diseases: consensus report of group 1 of the 11th European Workshop on Periodontology on effective prevention of periodontal and peri-implant diseases. *J Clin Periodontol.* 2015;**42**:S5-11. European Federation of Periodontology. (2012) Perio and General Health. URL: http://perioworkshop.efp.org/wp-content/uploads/2013/04/MANIFESTO_FULL_VERSION.pdf [accessed 01/02/2019]
2. Cekici A, Kantarci A, Hasturk H, Van Dyke TE. Inflammatory and immune pathways of periodontal disease. *Periodontol* 2000. 2014;**64**(1):57-80.
3. Do T, Devine D, Marsh PD. Oral biofilms: molecular analysis, challenges and future prospects in dental diagnostics. *Clin Cosmet Invest Dent*. 2013;**5**:11-19.
4. Socransky SS, Haffejee AD, Cugini MA, Smith C, Kent RL. Microbial complexes in subgingival plaque. *J Clin Periodontol.* 1998;**25**:134-144.
5. Walters J, Lai C. Should antibiotics be prescribed to treat chronic periodontitis? *Dent Clin North Am*. 2015;**59(4)**:919-933.
6. Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. *Nat Rev Microbiol.* 2012;**10(10)**:717–725.
7. West N, Chapple I, Claydon N, D'Aiuto F, Donos N, Ide M, Needleman I, Kebschull M; British Society of Periodontology and Implant Dentistry Guideline Group Participants. BSP implementation of European S3 - level evidence-based treatment guidelines for stage I-III periodontitis in UK clinical practice. *J Dent*. 2021;**106**:103562. doi: 10.1016/j.jdent.2020.103562. Epub 2021 Feb 8. PMID: 33573801.
8. British Society of Periodontology. BSP UK Clinical Practice Guidelines for the Treatment of Periodontitis | BSP (bsperio.org.uk) https://www.bsperio.org.uk/professionals/bsp-uk-clinical-practice-guidelines-for-the-treatment-of-periodontitis.
9. Zandbergen D, Slot DE, Niederman R, Van Der Weijden FA. The concomitant administration of systemic amoxicillin and metronidazole compared to scaling and root planning alone in treating periodontitis: a systematic review. *BMC Oral Health*. 2016;**16**:1-11.
10. Haffejee AD, Socransky SS, Gunsolley JC. Systematic anti-infective periodontal therapy. A systematic review. *Annals Periodontol.* 2003;**8(1)**:115-181.
11. Ahuja A, Baiju CS, Ahuja V. Role of antibiotics in generalised aggressive periodontitis: A review of clinical trials in humans. *J Ind Soc Periodontol.* 2012;**16(3)**:317-323.
12. Kappoor A, Malhotra R, Grover V, Grover D. Systemic antibiotic therapy in periodontics. *Dent Res J.* 2012;**9(5)**:505-515.
13. Goodson JM. Antimicrobial strategies for treatment of periodontal diseases. *Periodontol* 2000. 1994;**5(1)**:142-168.
14. Akobeng AK. Principles of evidence based medicine. *Arch Dis Child.* 2005;**90(8)**:837-840.
15. Herrara D, Alonso B, Leon R, Roldan S, Sanz M. Antimicrobial therapy in periodontitis: the use of systemic antimicrobials against the subgingival biofilm. *J Clin Periodontol*. 2008;**35(8)**:45-66.
16. American Academy of Periodontology. Position paper: Systemic antibiotics in periodontics. *J Periodontol.* 2004;**75(11)**:1553-1565.
17. Keestra JAJ, Grosjean I, Coucke W, Quirynen M, Teughals W. Non-surgical periodontal therapy with systemic antibiotics in patients with untreated aggressive periodontitis: a systematic review with meta-analysis. *J Perio Res.* 2015;**50(6)**:689-706.
18. Keestra JAJ, Grosjean I, Coucke W, Quirynen M, Teughals W. Non-surgical periodontal therapy with systemic antibiotics in patients with untreated chronic periodontitis: a systematic review and meta-analysis. *J Perio Res.* 2015;**50(3)**:294-314.
19. Bowling A. Research Methods in Health. Berkshire: Open University Press (2002).
20. Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement' *British Medical Journal (2009)* Online URL: https://www.bmj.com/content/bmj/339/bmj.b2700.full.pdf [accessed: 09/02/2019].
21. Hedeghan C. & Badenoch D. *Evidence-based Medicine Toolkit.* Oxford: Blackwell Publishing BMJ Books (2006).
22. Charrois TL. Systematic Reviews: What do you need to know to get started?' *Canad J Hosp Pharma.* 2015;**68(2)**:144-148.
23. Cohrane collaboration. (2011). *Cochrane handbook for systematic reviews of Intervention*. URL: https://handbook-5-1.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm [accessed 08/02/2019].
24. Zhang Z, ZhengY, Bian X. Clinical effect of azithromycin as an adjunct to non-surgical treatment of chronic periodontitis: a meta-analysis of randomised controlled clinical trials. *J Perio Res.* 2016;**51(3)**:275-283.
25. Herrera D, Sanz M, Jepsen S, Needleman I, Roldan S. A systematic review on the effect of systemic antimicrobials as an adjunct to scaling and root planning in periodontitis patients. *J Clin Periodontol.* 2002;**29(3)**:136-159.
26. Griffiths GS, Ayob R, Guerrero A, Nibali L, Suvan J, Moles DR, Tonetti MS. Amoxicillin and metronidazole as adjunctive treatment in generalized aggressive periodontitis at initial therapy or re-treatment: a randomized control trial. *J Clin Periodontol.* 2011; **38(1)**:43-49.
27. Larsen T. Susceptibility of porphyromonas gingivalis in biofilms to amoxicillin, doxycycline and metronidazole. *Oral Microbiol Immunol.* 2002;**17(5)**:267-271.
28. Hirsch RD, Deng H, Loahachai MN. Azithromycin in periodontal treatment: more than an antibiotic. *J Perio Res.* 2012;**47(2)**:137-148.
29. Eaton K. & Ower P. Practical Periodontics. London: Elsevier (2015).
30. Serino G, Ramberg P, Helstrom MK, Socransky SS, Linde J. The effect of systemic antibiotics in the treatment of patients with recurrent periodontitis. *J Clin Perio.* 2001;**28(5)**:411-418.
31. Mani A, Dalvi A, Mani S. To prescribe or not to: Systemic antibiotics in treatment of periodontal infections. *Int J Sci Res.* 2013;**4(9)**:1902-1904.
32. Dietrich T, Ower P, Tank M, West NX, Walter C, Needleman I et al. Periodontal diagnosis in the context of the 2017 classification system of periodontal diseases and conditions – implementation in clinical practice. *Brit Dent J.* 2019; **226(1)**:16 – 22.

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