

The Clinical Practice of Oral Systemic Medicine in the Absence of Antibiotic
Stewardship Guidelines... and More

Systemic Inflammation from Oral Pathogens Needs a Clear Voice From
Organized Healthcare

Position Paper
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Dental practices that have made a commitment to implement oral systemic medicine are using antibiotics and antimicrobials on a regular basis as specific pathogen species have been identified in concentrations above acceptable known tolerated norms. This group has been practicing in this manor with no real set of standards or guidelines from organized healthcare... because none exist.

Many practitioners have concluded the benefit of oral systemic principles applied to patient care outweigh the risks. Organized or mainstream healthcare has been resistant to publicly embrace what may appear to be a more liberal use of antibiotics, as current evidence may or may not support the practice.

Dentistry and Medicine Finding Common Ground

In the recent decade, a movement within dentistry has responded to a call from components of medicine to become more engaged in patient chronic care outcomes by better understanding and managing periodontal disease. Specifically, the polymicrobial, inflammatory, and genetic nature of periodontal disease [PD] that has been linked to or associated with a number of other chronic inflammatory diseases dragging on the American healthcare system.

Perhaps the Jeffcoat study confirmed more than ever that periodontal disease was relevant and required a higher level of attention from both dentistry and medicine. ¹ A recent Surgeon General is quoted; “periodontal disease is perhaps the most prevalent chronic inflammatory disease in the US population, and it is a key indicator of other systemic disease influences critical to overall health and well being”. ² Leadership from within medical and dental academia has begun to echo the need for looking at dentists as primary care providers. The Dean of Harvard School of Dental Medicine states that “the winds of change are blowing... and Harvard needs to look through a new lens at oral health”. ³ “The dental team’s healthcare responsibilities and expectations need to go beyond diagnosing and treating conditions of the mouth; they need now to extend to those conditions’ impact on the rest of the body.” ⁴

Periodontal disease treatment must be considered a part of the preventive armamentarium for chronic disease management.¹ It seems the stage is set for a wave of newly enthusiastic dentists to join a small group of pioneer peers who have long held this belief and practice.

In addition, a new and small component of medicine is moving forward embracing a changed paradigm also. The new medical focus on cardiovascular disease [diabetes, COPD, others], is working to control or eliminate the inflammatory burden rather than primarily limiting itself to the control of only lipids. It seems both professions find common ground as the inflammatory marker cytokines [CRP], myeloperoxidase [MPO], toll-like receptors [TLR], and Lp-PLA2 levels are not only a systemic medical concern, they are found to be elevated by specific periodontal pathogens.^{5,6,7,8} The collaboration between an oral systemically focused dentist and an anti inflammatory based physician is unanimous; dentistry is able to test for, identify, and treat specific pathogens providing the MD a higher level of confidence that a certain percentage of confounding inflammatory markers will be reduced. In addition, the dentist accomplishes a new level of soft tissue health in many heretofore difficult to manage cases.

The factors that have placed patients at high risk for a number of given systemic diseases are the same ones that place a patient at risk for periodontal disease.⁹ Inflammation is the mutually shared systemic factor that has brought two components of medicine and dentistry together. Inflammation is causal in cardiovascular events [CVE]¹⁰, and although oral pathogens have not been found causal to cardiovascular disease [CVD], they are causal to systemic inflammation.^{11,12,13}

Oral Pathogens and Optimal Periodontal Therapy, Inclusive of Antibiotics

For decades, dentistry has relied on mechanical debridement to mitigate the organisms that perpetuate periodontal disease. In the current decade, the use of antibiotics as an adjunct to scaling and root planning [SRP] has been gaining a louder voice. It has been determined in a number of studies that SRP does not alter the pathogenesis of the high risk [red complex, late colonizers] oral pathogens [Aa, Pg, Tf, Td, perhaps Fn], and many times should not be considered as definitive treatment.^{14,15,16} Many have concluded that it may be necessary to utilize antibiotics and antimicrobials to successfully treat periodontal disease.¹⁷ Many researchers have reported that pathogenic microorganisms remain after conventional mechanical debridement and in 2014 a study concluded the adjunctive use of MTZ and AMOX resulted in a greater reduction of oral pathogens than SRP alone.¹⁸

As discussed, it cannot yet be stated that periodontal pathogens cause a specific cardiovascular event, except in infective endocarditis [IE]. The professions do have more than adequate evidence to declare a close

association or direct link between oral pathogens and cardiovascular events. Genco has concluded there is significantly greater risk of heart disease in the presence of periodontal disease, ¹⁹ while others have identified specific strains of pathogens at endothelial sites of penetration, endothelial breakdown, or endothelial foam cell aggregation. ^{20,21,22}

The American Dental Association [ADA] has been reserved in its endorsement for the regular use of antibiotics to treat periodontal disease, or to prophylactically protect certain [yet to be professionally defined] high-risk patients before invasive therapy. The ADA guidelines do recognize that the practitioner may feel patients who present with immune compromising conditions may benefit from prophylactic antibiotic protection. A number of medical conditions are described which would potentially qualify a patient to be a candidate for such. Absent from the educational public and professional dialogue is the concept of an accumulating systemic burden of inflammation, in or out of context with genetic predispositions as being a factor or factors for all parties to consider.²³

A similar voice is heard from the American Heart Association [AHA]. The rationale for the conservative endorsement, conservative guidelines, and conservative patient education comes from two perspectives; [1] the link between cardiovascular events and periodontal pathogens has not been found to be causal, and [2] the ongoing antibiotic stewardship movement. ²⁴

With a sincere respect for each of those organizations, and an understanding for the time and scrutiny required to sort through a myriad of purported evidence based data, we can appreciate the careful manor in which they articulate information. On the flip side, a plethora of data supports inflammation is causal to CVD, and oral pathogens do induce an inflammatory response that is in fact adding to an already burdened immune system.

Perhaps there is an underlying fear that a wave of antibiotics would be thrown at the most prevalent infectious inflammatory disease in America, and the efforts in behalf of antibiotic stewardship could be set back.

The Pathogenic Nature of Specific Bacterial Strains

Not all oral pathogens exhibit the same capacity to inflict insult to systemic or oral tissues. Over the past decade a number of researchers have identified the complexes of organisms that make up the human biofilm and have some relative agreement on their level of virulence. Purple [Aa] and red [Td, Pg, Tf] complex are

designated high risk and late colonizers, while orange [En, Fn, Pi, Cr, Pm, Ec] complex organisms have been found to be moderate risk and mid-level colonizers.^{25,26} Each organism [and others] can be linked or associated with systemic insult and most already mentioned as causative to an inflammatory response.

***Bacteremia from Invasive Dental Procedures-
Setting the Stage for Antibiotic Stewardship Using the Infective Endocarditis [IE] Model***

A bacteremia of oral microorganisms can be measured less than one minute after a dental procedure, and in that time will have reached the heart, lungs, and peripheral capillary system.²⁷ This dissemination of oral pathogens is observed in 100% of extraction cases, 70% of SRP therapy, and 20% of endodontic treatments.²⁸ From 2010 ADA statistics on patient appointments by a hygienist, knowing 30% of them would be dedicated to periodontal maintenance, it could be roughly calculated there are 41 to 45 million bacteremias from SRP procedures created annually.

Infective endocarditis has garnered more extensive research than any other pathogen initiated condition affecting the heart. It has been accepted that oral strains of strep and staff are responsible for a majority of IE cases. The incident ratio for IE in this country, that seems to be most quoted currently is 15/100,000.²⁹ Statistics from a 2010 study by Mayo Clinic place about 43% of IE cases from community; out patient clinics, including dental offices.³⁰ That puts the IE incidence ratio from the dental practices at about 6.45/100,000.

The AHA has recommended limiting the use of antibiotics prior to invasive dental therapy to prevent IE to a published list of high risk conditions [adopted by the ADA]. This action is aimed at decreasing antibiotic resistant organisms by engaging professionals in antibiotic stewardship. In addition, recent studies have shown that tooth brushing and flossing can create a bacteremia on a similar scale as an extraction.³¹ As a result, many conclude that poor hygiene is a risk factor for IE,³² and organizational [AHA, ADA] comments stating oral invasive procedures may not an important cause of IE, therefore prophylactic use of antibiotics may be of no value in most cases.

In 2008, the United Kingdom abandoned all criteria for the prophylactic use of antibiotics before invasive dental procedures to prevent IE. Patients, who were previously deemed at risk, were no longer given prophylactic antibiotics. By 2015 it was reported that cases of IE had increased significantly, and were back to or beyond those levels before high-risk guidelines were in place.³³ There is no official organizational

response to the British scenario in place, and in the end, this may be an acceptable risk in light of a greater risk factor observed from the antibiotic resistance potential.

The current U.S. AHA/ADA stewardship position, related to the use of antibiotics to deter the onset of IE after invasive dentistry, could be restated as follows: In the face of a national incidence of 15/100,000, it is recommended to use antibiotics prior to invasive dental procedures for four described high risk scenarios. In addition, there is a serious ongoing discussion relative to how important this really may be.

***Bacterial Resistance- the Incidence of Clostridium difficile [Cdif]
Setting the Stage for Antibiotic Stewardship for Patients at Risk from an Accumulated Inflammatory Burden***

Evidence of effective antibiotic stewardship continues to be the incidence of Cdif, and in recent years there has been some reduction [2.5%] in the overall rate measured.³⁴ On the other hand the incidence of community acquired Cdif has increased and some are reporting this as an increasing public health threat.³⁵ The incidence of Cdif in community [versus institutional] is about 52/100,000 [some smaller studies have the incident ratio at 33/100,000] with 82% of community incidents potentially coming from outpatient or dental clinics.³⁶

The calculated incidence of Cdif potentially coming from dentistry [outpatient clinics] is about 43/100,000 and could be as low as 27/100,000.

The IE model based on an incident ratio of 15/100,000 would encourage the calculated use of antibiotics, while the established ratio for Cdif at 43/100,000 would not have created a favorable risk benefit ratio. There seems to be credible evidence for the United Kingdom to have abandoned all risk factors for antibiotic premedication, and the U.S. considering the long term value of same.

***Heart Attack Incident Ratios and Invasive Dental Procedures-
Setting the stage for Antibiotic Stewardship for Patients at Risk from an Accumulated Inflammatory Burden***

The current available cardiovascular and stroke statistics that record the impact of these diseases on humanity are mindboggling. The numbers are so large they could seemingly be written off as surreal.

The prevalence of CVD [heart attack and stroke] begins to significantly express it self at about age 50, thirty eight percent of this population has some level of CVD. In the next decade of their life, 68 percent of the population is affected, and the following 10 years bring the prevalence rate to eighty five percent.³⁷

Of the 720,000 to 785,000 patients who have a first time heart attack annually in the United States^{37,38}, there is a death about every 60 seconds. Recurrent events occur in 470,000 to 500,000 patients annually. Recent statistics show the total incidence of new and recurrent heart attacks annually from 1.2 to 1.5million. ³⁷ Most all the same reports indicate the number of annual strokes is about 795,000.

Incidence ratio for heart attacks in the US population, as averaged by increments of 10 years of age, are as follows: [1] age 45-54 is 222/100,000, [2] ages 55-64 is 380/100,000, [3] ages 65-74 is 637/100,000, and [4] age 75-84 is 1000/100,000. The average U.S. incidence of having a heart attack from the AHA data is about 560/100,000.³⁷

Fatal cardiovascular events [heart attack and stroke] increase by 50% for patients with periodontal disease. CVD and PD share the same risk factors and elicit similar inflammatory markers at different levels. The risk of adverse vascular events sharply increases in the four weeks following invasive dental treatment, including SRP. The event risk slowly returns to normal after six months. This study provides some indication that cardiovascular event [heart attacks and strokes] incidence increases by 50% following the dental procedure [incidence ratio 1.50; 95% CI 1.09–2.06] and for heart attacks alone, the incidence rate increased by 56% [1.56 {0.98 – 2.47}].³⁹

Using an average incidence ratio value for the U.S. population, across the 45-84 year old age group of 560/100,000, and submitting a patient in that risk category to an invasive dental procedure, would potentially have the net effect of increasing their ratio by 56%, [313.6 points] to 873.6/100,000.

If IE garners professional guidelines for antibiotic use with patients at risk, with an incident ratio of 15/100,000 compared to a potential Cdif ratio of 43/100,000 what logic would prevent organizational guidelines for antibiotic use for high risk patients in the face of a heart attack incidence ratio of about 873/100,000 as compared to the Cdif incidence ratio of 43/100,000?

The benefit of using an antibiotic for treating certain strains of oral pathogens or for prophylactically preventing a potential CVE before an invasive dental procedure seems to outweigh the risk of threat from a resistant organism.

Should dentistry and medicine agree on what a high risk patient looks like, and publish guidelines to protect

high risk patients who present with high risk pathogens with systemic antibiotics specific to those organisms?

***Determining the Use of Systemic Antibiotics in Oral Systemic Medicine-
A Suggested Criteria Identifying the High Risk Patient***

Patients who are at greatest risk could be described as: [a] having unacceptable levels of high risk pathogens, [b] having predisposing genetics, [c] carrying an inflammatory burden based on ongoing chronic disease, and [d] having reached an age that disease prevalence statistics shift significantly. In the end, that profile represents a compromised the immune system. Guidelines for the responsible systemic use of antibiotics in oral systemic medicine could be stated as follows:

- 1) Any patient over 50 years old, testing positive over acceptable concentrations for any of the

red/orange [high risk] complex pathogens, and testing at a moderate to high level of hsCRP, and testing positive for a genetic predisposition to inflammatory disease, or a pregnant female. The method of using laboratory tests is most accurate, reliable, and available.

[or]

- 2) Any patient over 50 years old, testing positive for any red/orange [high risk] complex pathogens, and

presenting with a medical history depicting ongoing inflammatory disease [diabetes, previous heart attack, HBP, COPD, rheumatoid arthritis, CA, Sleep Apnea, and/or a smoker], and a medical history showing a direct family member who has PD, CVD, or Diabetes, or a pregnant female. The method depending on a medical history review is more subjective but credible.

Summary

Many entities and concerned parties recognize that more well designed studies are needed to definitively provide irrevocable evidence to many of the educated assumptions or conclusions oral systemic medicine makes in a sincere effort to make a difference in caring for the chronic conditions of patients.

This subject is relevant and important to dentistry and medicine. An understanding of oral systemic principles facilitate greater collaboration between professions, and in the end, patients are better served. The profession is best served when accepted organizational guidelines speak to encourage engagement in clinical practices supported by a preponderance of logical evidence. Proposed guidelines should ere on the side of safer clinical practices until proven otherwise. The message that organized healthcare delivers is significant,

they have the capacity to frame a level of importance and urgency that both professional and patient populations respect and will respond to.

The benefits of utilizing systemic antibiotics for managing high-risk oral pathogens in high risk patients outweigh the risk of bacterial resistance as exhibited in the onset of Cdif.

Organized components of dentistry and medicine may find that benefits outweigh risks if the concept of reducing chronic systemic inflammation by better managing oral pathogens was endorsed and promoted to their constituents. It is one thing to recognize that an oral systemic connection is a reality; it is quite another to implement clinical practices that have the potential to change both systemic and oral disease outcomes.

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