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Atrial fibrillation and cardiac arrhythmia associated with acute dental infection: a systematic literature review and case report

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Key Words: Cardiovascular disease, atrial fibrillation, dental infection, oral diseases, periapical periodontitis, cardiac arrhythmia

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Review criteria: how did you gather, select and analyse the information you considered in your review?

- We undertook electronic searching of literature using MEDLINE and SCOPUS based on keywords and MeSH terms, between 01 Jan 1970 and 30 June 2020, and undertook backwards and forwards citation chasing.
- Observational studies that included cardiac arrhythmia and atrial fibrillation as outcomes of acute dental infections were included and scored using the Newcastle-Ottawa tool.

Message for the clinic: what is the 'take-home' message for the clinician?

- There are few high-quality studies on acute dental infections and cardiac arrhythmias, (including atrial fibrillation), despite literature suggesting that poor oral health is linked to cardiovascular disease outcomes.
- Screening and follow-up of patients with acute dental infections may lead to early intervention and prevention of cardiovascular complications.

Abstract (250 words)

Objectives: This paper outlines how oral diseases such as periodontitis and periapical periodontitis may be linked to cardiovascular disease, atrial fibrillation and cardiac arrhythmia. We undertake a systematic review of the literature focused on acute dental infection and types of cardiac arrhythmia and also describe an illustrative case where an acute dental infection diagnosed as periapical periodontitis was associated with occurrence of atrial fibrillation.

Methods: An electronic search was undertaken using MEDLINE and SCOPUS from 01 Jan 1970 until 30 June 2020. We also undertook manual searches using forward and backward citation chasing. Inclusion criteria were any primary research studies investigating any acute dental infection, with outcomes of cardiac arrhythmia or atrial fibrillation.

Results Over the last fifty years, only two low quality studies have been investigated this area. Our illustrative case involved a 58-year-old who was diagnosed with an acute dental infection from an upper canine tooth who then developed atrial fibrillation.

Conclusions: Based on the biological plausibility of a link between acute dental infection and types of cardiac arrhythmia such as atrial fibrillation, together with the case report presented, it is evident that further study in this area is needed. If there are possible cardiovascular consequences for patients suffering with acute dental infection, then this has implications for healthcare staff since they can integrate professional advice related to oral health with cardiovascular disease and atrial fibrillation. Screening programmes situated in dental settings can facilitate early intervention and prevention producing benefits for patients and savings to the health system.

Introduction

There are several conditions which cause abnormal heart beats, of which atrial fibrillation (AF) is the most common. Atrial fibrillation, a subtype of cardiovascular disease (CVD), represents a significant burden of disease worldwide: around 33.5 million people are affected worldwide and between 2.7-6.1 million in the US.[1,2] However, this is set to rise as the population ages, since 70% of AF sufferers are aged 65-85 and for people over 80, there is a 9% chance of having AF.[3] Sufferers of AF are five more times likely to develop stroke and have a greater risk of heart failure and death.[4,5] Sepsis, along with other risk factors such as obesity, diabetes, hypertension, age, gender and smoking are among the many AF risk factors which have been identified.[6-9] Table 1 summarises the incidence, classification, examples of risk factors and complications associated with having AF.

Although underlying mechanisms differ depending on the type of CVD, inflammation is thought to be an important underpinning aetiological mechanism common to many. In the case of AF, studies show that elevated levels of biomarkers such as Interleukin-6 (IL-6) and C-reactive protein (CRP) increase during acute infections, which drives systemic inflammation and the development of new-onset AF.[10-12] These inflammatory markers are thought to have a direct effect on cellular function and an electrophysiological remodelling of the heart,[13] although further work needs to be done to understand the mechanisms involved.[14] Inflammation arising from oral diseases are also increasingly becoming recognised as being a causative factor in a range of conditions such as diabetes, cancer, HPV and CVD.[15-17] While research to date on oral diseases and CVD has mainly focused on exploring links between chronic low-grade oral inflammation and bacteraemia associated with poor oral hygiene resulting in the slow progression of atherosclerosis, the potential relationship between more acute dental infections and an increased risk of cardiac arrhythmia mediated by an acute inflammatory response has received little attention.[18-20]

We therefore undertook a systematic review specifically focused on this area, with a research question: 'Are patients with a history of acute dental infection more at risk of developing cardiac arrhythmias and AF?' We then describe an illustrative case where an acute oral infection was associated with occurrence of new onset AF and outlined possible biological mechanisms thought to link oral diseases with adverse CVD outcomes.

Review methods

We reviewed the MEDLINE and SCOPUS database (1970-2020) using electronic Medical Subject Headings (MeSH) search terms and keywords as follows: Pulpitis/ OR Pericoronitis/ OR ((periapical or periodontal or dent* or tooth or endodontic or pulpal or apical or periradicular or radicular adj2 abscess).ti,ab. OR acute dental infection.tw. OR ((periapical or acute or symptomatic or periradicular or radicular or apical) adj2 periodontitis).ti,ab. AND Cardiovascular Diseases/ OR Atrial Fibrillation/ OR Arrhythmia. We included CVD in the search in case AF was included as a subtype in the study, in which case these would be identified during paper screening. Forward and backwards citation of key papers was also undertaken. Two reviewers independently assessed studies for inclusion. Data from included papers were independently extracted by two reviewers (AH, RH). To rate the quality of cohort, case control and cross-sectional studies we reviewed the articles using the Newcastle-Ottawa tool (NOS), but did not contact study authors.[21]

Criteria for inclusion of studies in the review were as follows: Acute dental infection was defined as a symptomatic condition related to the teeth and supporting structures or a dental condition necessitating emergency attendance to dental or wider health services, or presence of one or more periapical abscess diagnosed clinically. Outcome measures reported incidence for any type of temporary or permanent cardiac arrhythmia, or atrial fibrillation identified through medical records, electrocardiogram (ECG) or electronic databases.[22] A subtype of arrhythmia was required since tachycardia alone is defined as a heart rate of more than 100 beats per minute,[23] but including tachycardia without a subtype would have incorporated articles where patients experienced an increased heart rate due to sepsis, anxiety or local anaesthetic being administered. Inclusion criteria were limited to English language articles because of limited resources. Included studies were any types of human studies (observational or interventional, including secondary analysis of datasets), studies on either adults or children; and any type of setting (primary, secondary or tertiary care). Systematic and narrative reviews were excluded.

Results

Electronic searching identified 109 article titles and abstracts with a further 21 articles added following manual searching and forwards and backwards citation chasing of key papers. De-duplication involving 17 articles left 113 studies involved in title and abstract screening, of which 50 were deemed suitable for full paper screening (see PRISMA diagram, Figure 1). Only 2 of these papers met inclusion criteria. Table 2 provides more detail of the two included studies – one of which was a single case report,[24] and was therefore judged as very low quality (although the Newcastle-Ottawa toolkit is designed for cohort, case-control and often adapted for cross sectional studies, case studies would be viewed as a weaker study design).[25,26] The other article, a cohort study, involved only thirty participants,[27] was graded one out of four (low quality) using the Newcastle-Ottawa tool. Since meta-analysis was not appropriate, the two studies are described in detail.

The case study from Poland reported a diagnosis of AF alongside clinical findings of periapical periodontitis and dental abscesses.[24] The patient had a pre-existing condition of hard-to-treat chronic spontaneous urticaria (CSU) and was diagnosed as having an "acute-phase response" (APR) which is a local and systemic coordinated reaction following inflammatory states associated

with changes in levels of circulating proteins such as C-reactive protein (CRP) and cytokines IL-6.[46, 47] Observation of an irregular pulse led to an ECG and diagnosis of longstanding AF. Following dental treatment, serum CRP and CSU symptoms were markedly reduced, leading authors to suggest that dental infection had provided an inflammatory foci, and while the urticarial inflammation did not seem to be explicitly related to AF, oral inflammatory processes may have contributed and/or triggered a systemic inflammatory response associated with activation of APR proteins which influenced the initiation and progression of several systemic disease processes, including AF.[47]

The second article involved a prospective analysis of participants where the presence or absence of a range of observations were recorded for twenty-four hours using an ECG, blood pressure (BP) and pulse monitor. Thirty patients with a history of symptomatic versus non-symptomatic apical dental infection were compared.[27] Authors found a significantly increased mean systolic and diastolic pressure for patients with symptomatic apical dental infections, compared to those with non-symptomatic infections (*P*-value= 0.05), Table 2. All 30 patients had normal sinus rhythm. Five out of 10 participants with symptomatic pulp necrosis and acute dental infection had episodes of atrial or ventricular arrhythmia, compared to 1 out of 10 participants with asymptomatic infection who were identified as having episodes of arrhythmia. These randomly disturbed episodes did not resolve during the 24-hour ECG recordings, even following dental treatment. Two participants had reported a history of hypertension but were not excluded, and participants were selected without regard to age, sex, or medical history. Although most participants did not report a history of CVD, no baseline ECG/BP recordings were available prior to the occurrence of dental infection. The authors suggested that since the arrhythmia did not change following dental treatment, this may have been coincidental findings and not related to the episode of acute infection.

Illustrative case presentation

A 58-year-old male patient attended the Accident and Emergency department complaining of a left sided swelling, vomiting, numbness, and headache. The patient's history of complaint was that he had seen the dentist two days beforehand, regarding the pain, and been prescribed 400mg of Metronidazole and 500mg of Amoxicillin, to be taken orally three times a day, for five days. His

medications included Ramipril, Aspirin, Atenolol and Atorvastatin. He had not been previously diagnosed with atrial fibrillation.

Initial assessment was carried out by the emergency unit with the following observations:

- Blood Pressure 153/96 mm HG
- Respiratory Rate 16/min
- Oxygen saturation 95%
- Temp 38.3 °C
- Heart Rate 102 bpm

A panoramic radiograph (OPG) (see Figure 2) revealed a radiolucency near to the upper left canine root apex; the radiolucency near the tip of the crown on the OPG was clinically diagnosed as tooth decay and the shadowing of the bone near the root apex was a result of infected pulp that had spread to the surrounding apical tissues. Clinical diagnosis revealed an acute dental infection and associated canine space swelling caused from symptomatic periapical periodontitis of the upper left canine tooth.

A full Blood Count was taken which had abnormal and elevated levels of:

- Total White Cell Count (WCC) at 11.3, (reference range) 4.0 - 11.0 x10^9/l (x10^9/l)
- Serum C Reactive Protein (CRP) level at 92, (reference range) 0 - 10 mg/L (mg/L).

The patient was accepted for hospital admission and given Benzylpenicillin 1.2g and Metronidazole 500mg intravenously (IV). One hour later the patient developed acute epigastric pain which was dull, not radiating and tender. An ECG showed slight elevation of ECG reading anterior ST segment and he was then assessed according to Airway, Breathing, Circulation, Disability, Exposure (ABCDE), deemed unfit for transfer and moved to the resuscitation department in the hospital. The patient then developed tachycardia (150/min), Hypotension, GCS 15/15, Temp 38.3^{o}C and atrial fibrillation.

The patient was given 2.5mg Bisoprolol, 5mg IV morphine, 15 litres of oxygen, IV Hartman's solution 500ml IV. Blood cultures were also taken but this showed no anaerobic or aerobic growth.

Despite no blood culture growth, the patient was diagnosed with an acute periapical periodontitis and secondary diagnosis of sepsis. The patient was deemed high-risk classification for sepsis according to NICE guidelines, with an increased heart rate of more than 130 beats per minute.[28] The following morning, symptoms had improved and returned to normal rhythm. A dentist performed an extraction of the tooth as required and monitored the patient closely over the next few days for any signs of deterioration. A Holter ECG was requested by the cardiology department following discharge but there were no abnormal findings from the tests.

Discussion

Our illustrative case adds to two other small and low-quality studies suggesting that acute dental infection may potentially trigger cardiac arrhythmia and AF. On the other hand, our presented case may have had an elevated risk of developing AF regardless of the dental sepsis, due to his pre-existing cardiovascular history. Although this is a possibility, the individual had not been identified as having AF previously, but was diagnosed with AF in the emergency dental setting alongside an acute dental infection, which was then reversed with a single use medication. Further investigations and a referral to a cardiology department did not reveal further arrhythmia or a diagnosis related to persistent AF. Another potential explanation may be that the exacerbation of his cardiac condition was purely coincidental. Given the dearth of studies in this area, with only a couple of other studies in this area identified in our literature review, as well as some biological plausibility, more research in this area is indicated, particularly given the prevalence for the occurrence of acute dental infections and the potential seriousness of cardiovascular complications which may follow.

Acute dental infection and CVD

Acute dental infections are a common reason to seek emergency health care: 0.7% of all patients visiting emergency services in England are because of dental problems.[29] Approximately 2.5% of US emergency department visits are related to non-traumatic dental problems making this the second most common reason for attendance for adults aged 20-39.[30] If left untreated dental infections can lead to severe pain, abscesses, or if severe enough, spread to nearby spaces in the face and neck that require surgical intervention and management of sepsis, including incision and drainage under general anaesthetic.[31] In some instances this can lead to morbidity and mortality.[31] In 2004-2005, approximately 1500 patients had emergency incision and drainage under general anaesthetic due to dental infections in England.[31] The number of actual admissions for dental

infection is expected to be higher since patients can be managed without the need for surgical intervention and treated with intravenous antibiotics alone. Since routine dental care has been disrupted from the COVID-19 pandemic and routine dentistry suspended in many parts of the world because techniques used involve aerosol generated procedures,[32] the prevalence of acute dental infections among the population is set to rise. This study indicates that follow-up for development of new-onset AF, cardiac arrhythmia and CVD of patients experiencing acute dental infections is warranted, as is further study in this area.

Chronic oral inflammation and CVD

Two chronic oral diseases have been studied in this context: periodontitis which is an inflammatory disease of the supporting tissues of the teeth, [33,34] and periapical periodontitis which involve tissues within the tooth's pulp chamber and root canals.[35]

There is emerging evidence linking periodontitis with subclinical CVD and Peripheral Artery Disease (PAD).[36,37] A systematic review involving data from twelve cohorts identified six observational studies reporting increased coronary artery disease and three reporting an increased risk of stroke in periodontitis sufferers.[38] There are a few systematic reviews linking CVD with periodontitis,[34,39,40] but none which have specifically investigated AF as a possible outcome of periodontal disease, although there is a retrospective cohort study using data from a large Taiwanese database that has reported a positive association between periodontitis and AF.[19] The suggested biological mechanism involved is an interplay between periodontal pathogens, vascular endothelial damage, and atherogenesis from systemic inflammation, as indicated by chronically elevated inflammatory markers IL-6 and CRP found during the periodontal disease process.[10,11,33] Occurrence of atrial dilation and AF physiopathology involves fibrosis and deposition of connective tissue, alongside platelet and coagulation activation, suggesting the inflammatory pathway may lead to the development of AF and thrombolytic events such as stroke.[41]

While previous work on poor oral health and systemic conditions have predominantly focused on inflammatory pathways with chronic periodontal disease, an association with chronic periapical periodontitis with cardiovascular disease and AF have also been acknowledged, although evidence is relatively scarce in this area.[25] A systematic review of the literature found significant positive associations in thirteen out of nineteen studies between CVD and periapical periodontitis which

was defined as chronic, asymptomatic inflammation and destruction of the periapical periodontal tissues following bacterial invasion of the pulp, although most of the articles were of low quality.[25] None of the included studies considered the impact of acute episodes of dental infection or hospitalisation with CVD and did not include AF or cardiac arrhythmia as an outcome under investigation. Again, common inflammatory pathways and biomarkers related to CVD and AF (CRP and IL-6) have been found to elevated during chronic apical periodontitis infections, suggesting that a localised inflammatory response to the bacterial infection can lead to the release of cytokines into systemic circulation, with subsequent harmful vascular effects.[42]

Chronic oral bacteraemia and CVD

Bacteria entering the bloodstream is thought to precipitate an inflammatory and auto-immune response, with interleukin-1 (IL-1) and interleukin-8 (IL-8) being released following the invasion of bacteria into the bloodstream.[43,44] IL-1 is also thought to be linked with the body's response to acute infections and the development of sepsis.[45] Lack of toothbrushing and dental treatment have been frequently associated with causing bacteraemia and some studies have shown evidence of cardiovascular complications, including development of atherosclerotic plaques and AF.[18,20,46,47] A previous study has also shown a lower risk of infective endocarditis for patients receiving dental scaling.[48] The presence of oral bacteria, particularly *Porphyromonas Gingivalis* in the bloodstream can result in induction of systemic inflammation, release of bacterial toxins and sepsis, a common life threatening complication when the body's immune system responds to infection and injures its own tissues and organs.[49-51] The inflammatory pathways can impact the contractility of the heart though structural and electrical remodelling, with cardiovascular complications consequent on severe infection, as depicted in Figure 3.[52]

Conclusions

This review and illustrative case are to our knowledge is the first to highlight potential avenues for research in acute dental infections with cardiac arrhythmia and AF. Here, we highlight the implications that acute dental infections might have for an increased risk of developing AF.

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Table 1: A table summarising the classification and complications of atrial fibrillation[6-9,53]

Classification of atrial fibrillation	Features	Pattern
Initial	First detected, symptomatic or asymptomatic (unkown)	Can recur
Paroxysmal (temporary)	Under 7 days	Recurring
Persistant	Greater than 7 days but treated successfully	Recurring
Permanent	Accepted	Established

Incidence of atrial fibrillation	Examples of risk factors for atrial fibrillation	Factors influencing pathophysiology for atrial fibrillation
Incidence in primary care: 2.4%	Age	Inflammatory mediators
Acute medical admissions: 3-6%	Hypertension	Bacteraemia
Hospital admissions: 4.7%	Diabetes	Acute oral diseases: periodontitis and periapical periodontitis?
	Ischaemic heart disease	
	Obesity	
	Gender	
	Smoking	
	Sepsis	
	Acute dental infection?	

Atrial fibrillation associated complications		
Cardiovascular mortality	Myocardial infarction	Stroke
Congestive heart failure	Sudden cardiac death	Chronic Kidney disease
Peripheral arterial disease	Ischaemic heart disease	All-cause mortality

Table 2: Included studies of acute dental infection and atrial fibrillation/arrhythmia

Study	Quality rating	Setting	Study design	Participant demographics	Co-morbidities	Exposures measured	Outcomes measured and findings
Kasperska-Zajac et al (2015)	Low	Dermatology department, Medical University, Poland	Single case report	36-year-old male	Severe, difficult to treat (with steroids and anti-histamines) chronic urticaria/ angioedema Cardio magnetic resonance imaging showed good left ventricle contractility with no signs of inflammation or other myocardial disease	Dental examination showed 6 decayed teeth and one root. Radiographs revealed at least two periapical abscesses	Irregular pulse rate Diagnosed with Electrocardiography (ECG) as probably longstanding persistent AF.
Steiman HR et al (1982)	Low	Graduate endodontic dental clinic, geographical	Prospective cohort study analysis comparing symptomatic and	Thirty adult participants aged between 18 years to 74 were split	No exclusion criteria were reported and participants had been selected without regard	Non-symptomatic and symptomatic apical infection with dental	Irregular pulse, heart rate and blood pressure

		location not stated	non-symptomatic apical dental infections with a range of CVD related observations including pulse readings, blood pressure and heart rate	into three equal groups according to symptomatic diagnosis of apical infection with pulp death (necrosis), symptomatic apical infection without pulp necrosis and asymptomatic apical infection	to age, race, gender, or medical history	procedures (Endodontic/root canal treatment)	Seven of thirty patients had episodes of premature ventricular or supraventricular complex arrhythmia. There were no significant differences to heart rate and blood pressure for participants when exposed to different dental treatment, although blood pressure was significantly higher in participants with symptomatic dental infection compared to those without symptoms (*P*-

							value=0.05)

Figure 1. PRISMA flowchart

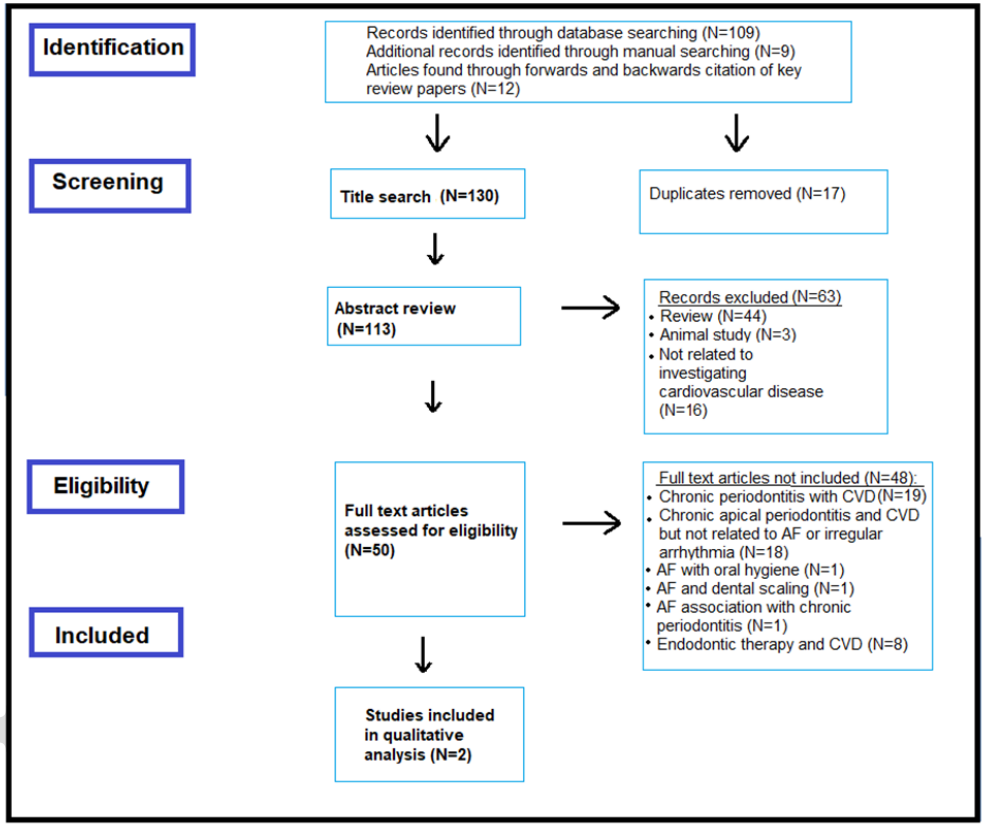

Figure 2. An OPG image of the patient with suspected radiolucency around the upper left canine root apex.

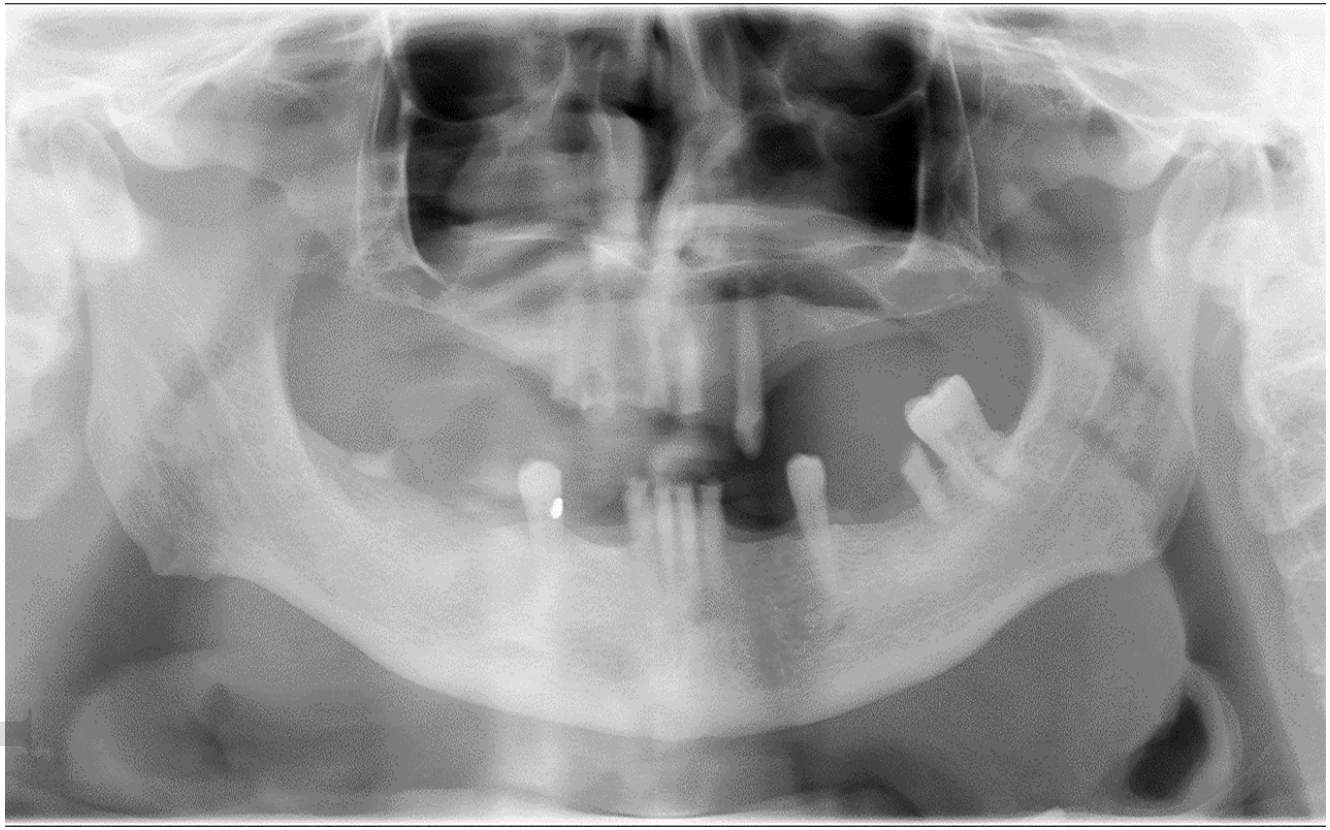

Figure 3. Mechanisms of action relating infection to cardiovascular complications