THE UNIVERSITY OF MELBOURNE

What happens in the mouth … doesn't always stay in the mouth

Our current understanding of the interactions between oral and systemic health

Adj Clin A/Prof Mathew Lim

North Western Melbourne PHN Webinar

Wednesday 9 August 2023

theAlfred

The Royal Melbourne Hospital

MONASH University

Webinar overview

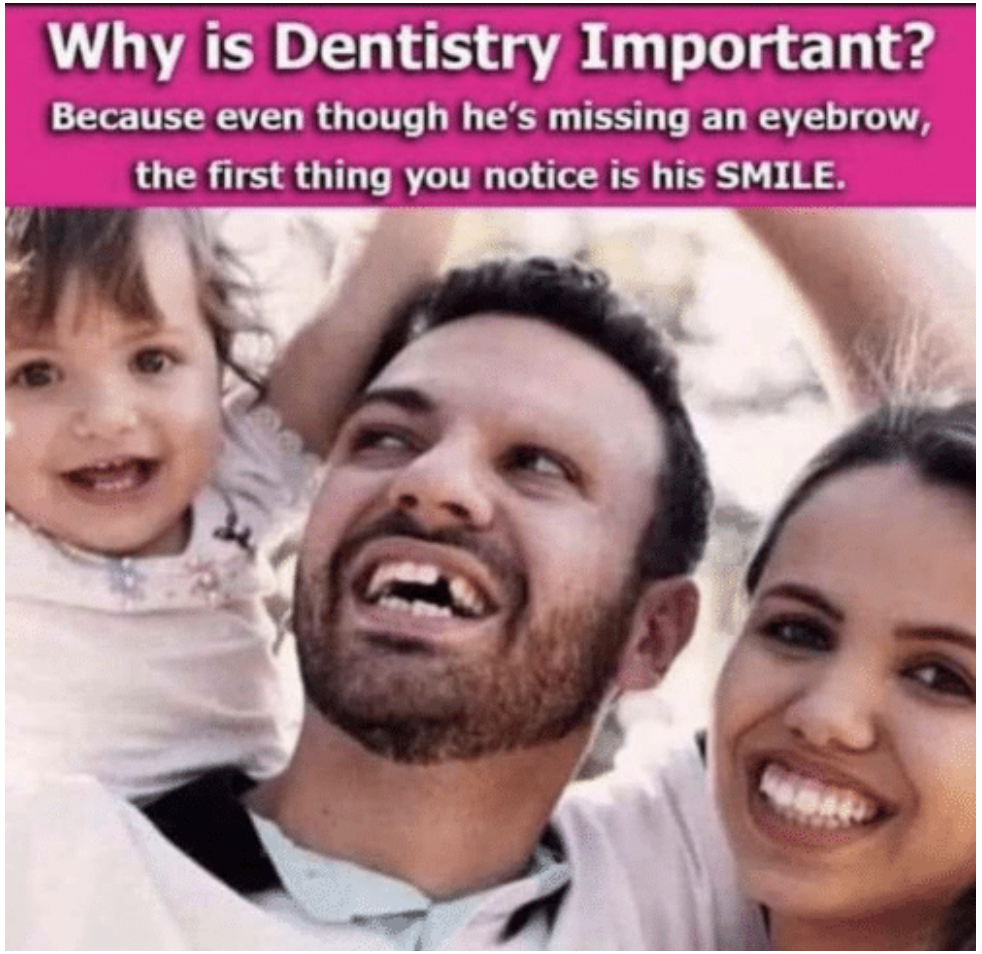
How can we benefit patients by integrating oral health into our daily practice?

Presentation 1: Importance of the oral and general health interface

Presentation 2: Tips and tricks of managing dental presentations in general practice

<u>Learning Outcomes</u>

- Describe the relationship between oral and general health
- Identify and advise at-risk patients and implement relevant referral pathways
- Utilise resources to guide you through a dental presentation of a patient in your clinic



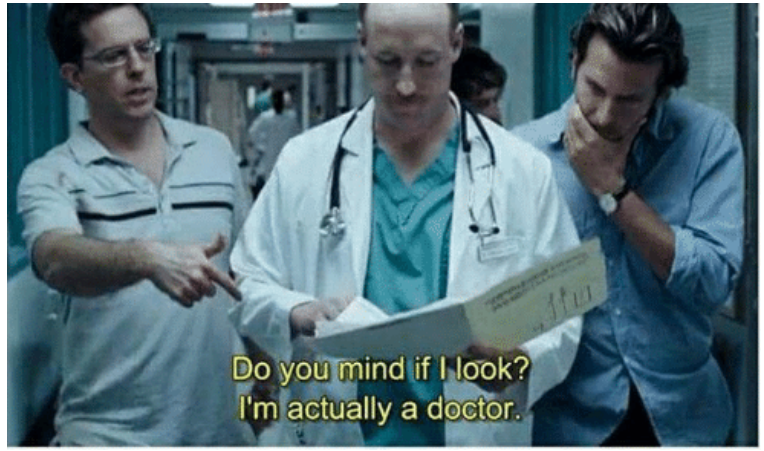
Why does this all matter?

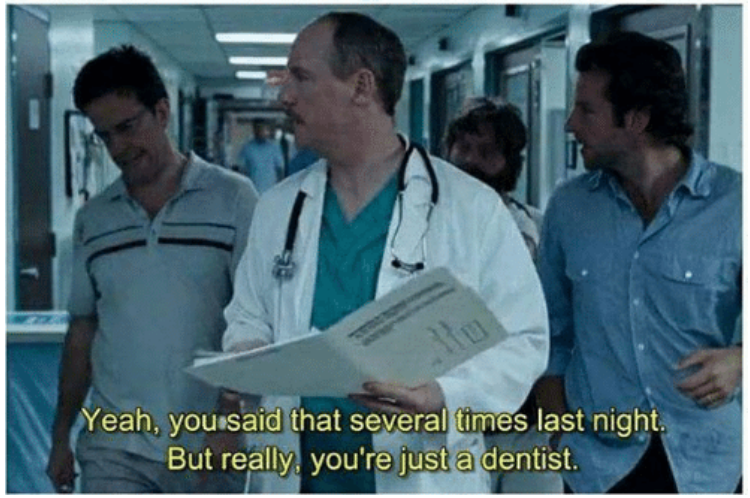
GPs as a primary coordinator of their health care (Samaei et al 2015)

Initial presentations for dental problems are to general medical practices and emergency departments

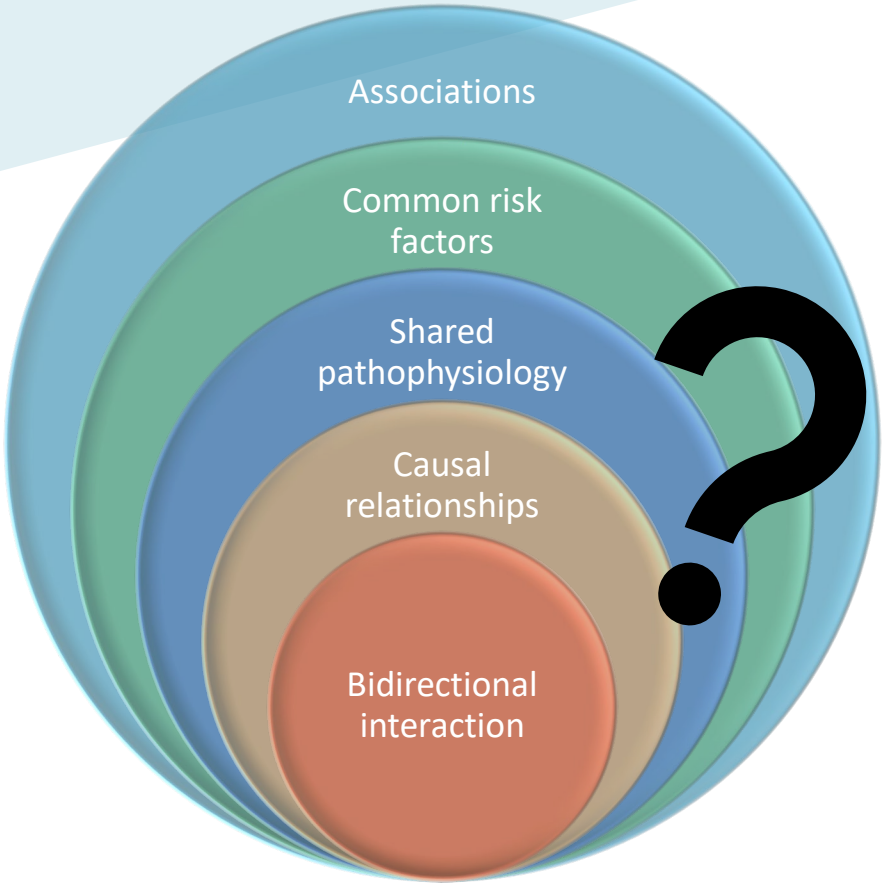
- Interpretation of symptoms
- Perceptions of scope of practice of primary care practitioners
- Comparative ease of navigating medical and dental care symptoms
- Previous experiences of dental care, including anxiety and dissatisfaction with prior treatment
- Financial considerations(Cope et al 2018)

National Oral Health Plan 2015-2024 – medical professionals have significant educational role in oral health literacy and encouraging regular dental check-ups






Stroke
Dementia
Respiratory and lung disease
Heart Disease
End-stage kidney disease
Diabetes
Low birth weight
Autoimmune conditions


Associations
Common risk factors
Shared pathophysiology
Causal relationships
Bidirectional interaction
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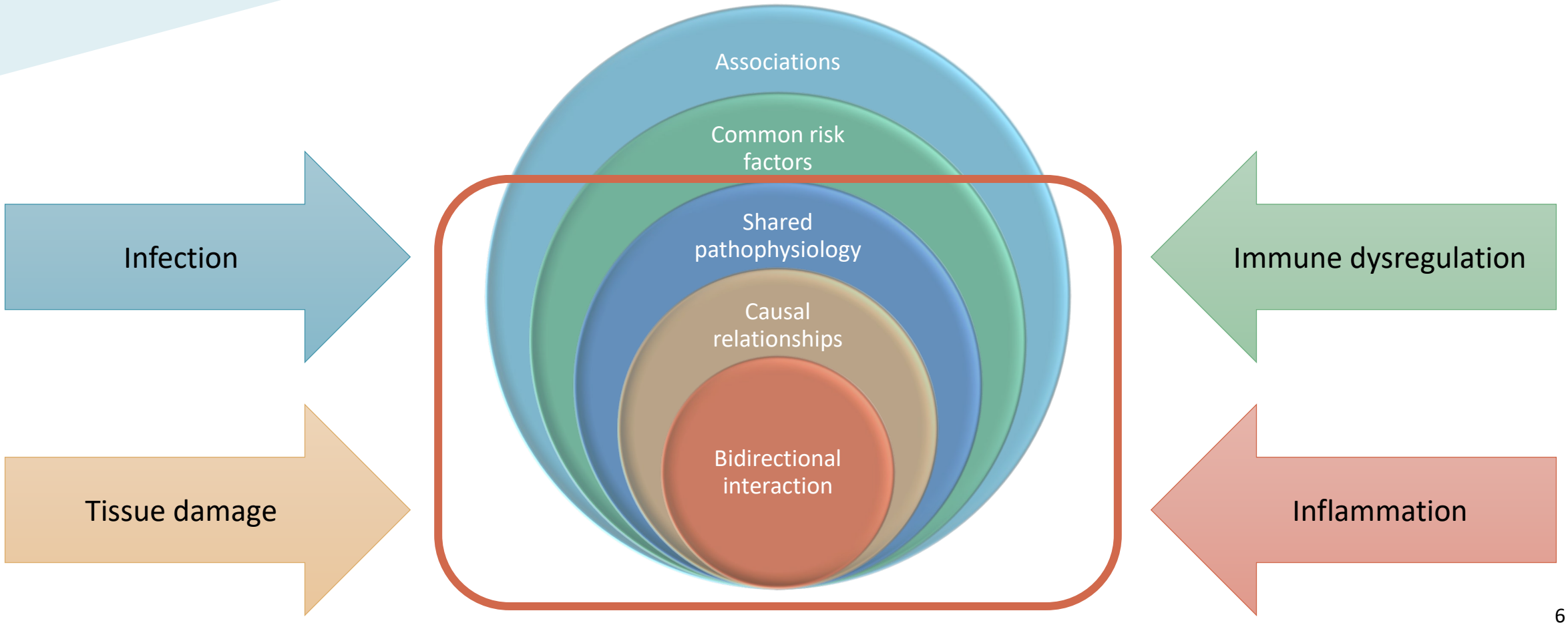
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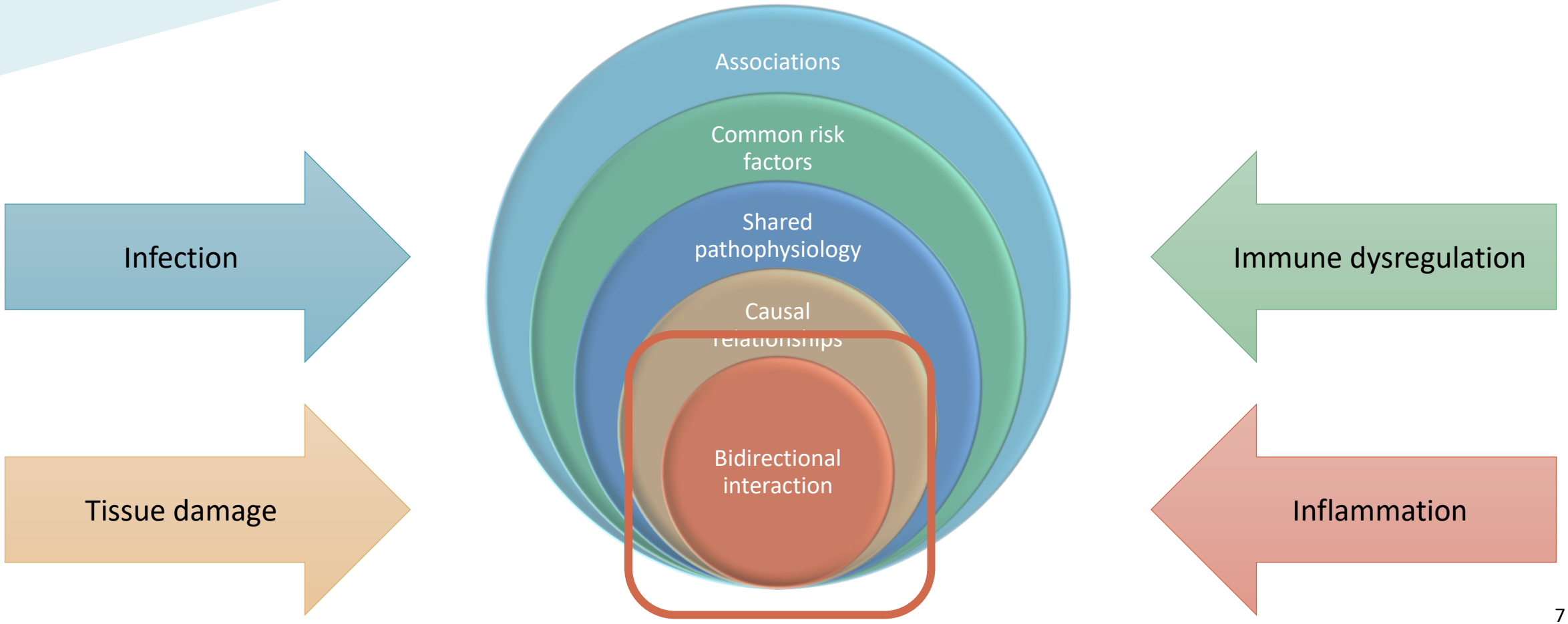
Tissue damage
Immune dysregulation
Inflammation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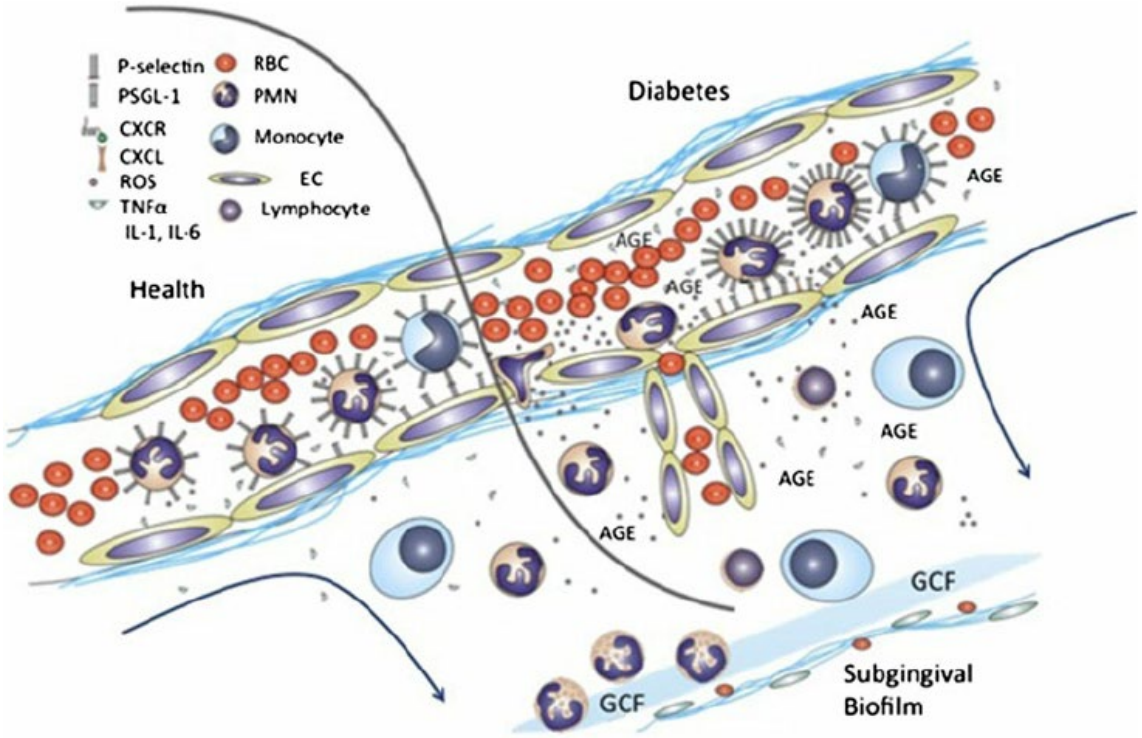
Diabetes mellitus and periodontal disease

"Sixth complication of diabetes" (Loe 1993)

- Prevalence / severity (Khader et al 2006)

- Advanced glycation end products (AGE)
- Microvasculature in periodontal tissues
- Impaired macrophage and neutrophil function
- Inflammatory cytokines (IL-1, IL-6, TNF-α) influence glycaemic control (Preshaw et al 2000)
- Dysregulation of immune response exacerbates periodontal disease
- RAS / Oxidative stress and tissue damage



Sima et al 2013

Bidirectional relationship

Periodontitis contributes to poor metabolic control in diabetes (Taylor & Borgnakke 2008)

Diabetes → Periodontal disease

- 2-3x greater risk of periodontal disease
- Risk increases exponentially with glycaemic control (HbA1c > 7%)
- Higher risk of infections

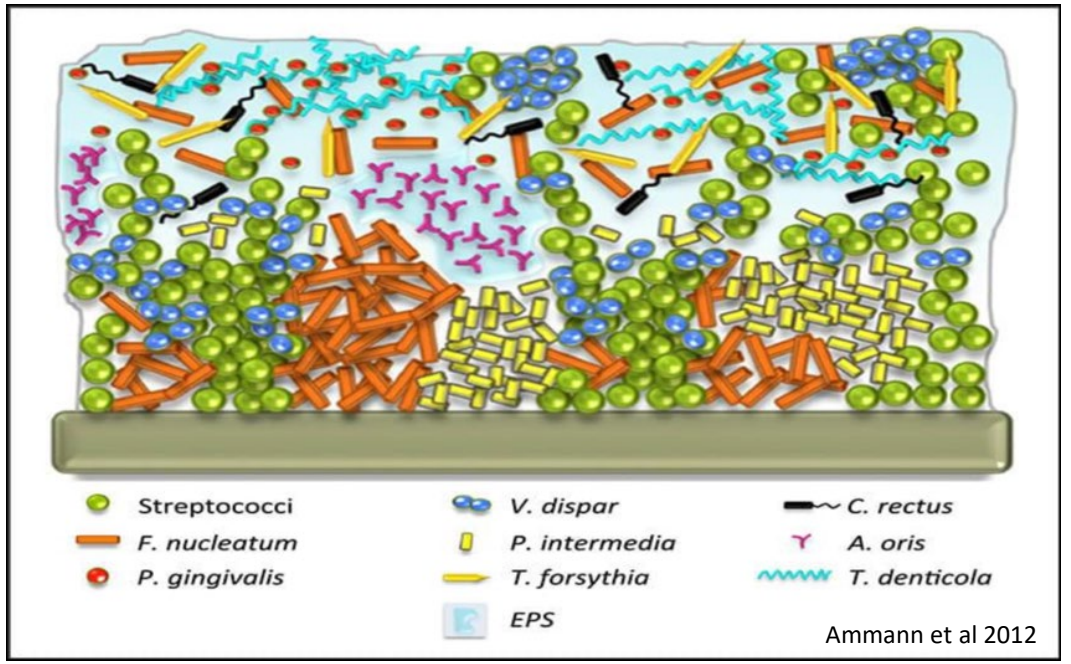
Pathophysiology of diabetes exacerbates progression of periodontal disease

Periodontal disease → Diabetes

- Severe periodontitis associated with increased risk of poor glycaemic control
- Increased diabetic complications – cardiovascular, retinopathy, neuropathy, proteinurea, ESRD
- 3.2 increased risk of cardiorenal mortality
- Peri ontal treatment can reduce HbA1c 0.4%

"INFECTION" = PATHOGEN + SUSCEPTIBLE HOST

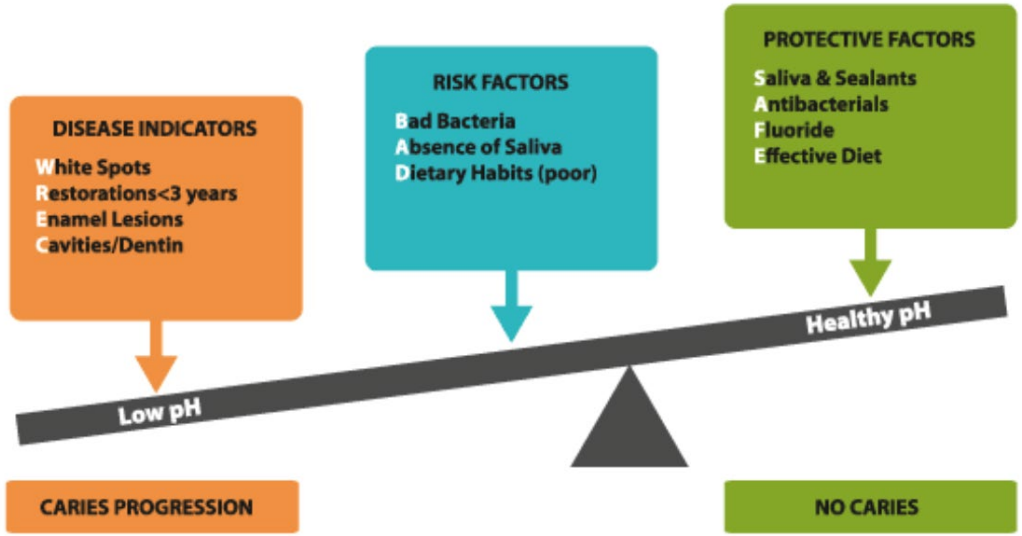
PLAQUE / BIOFILM

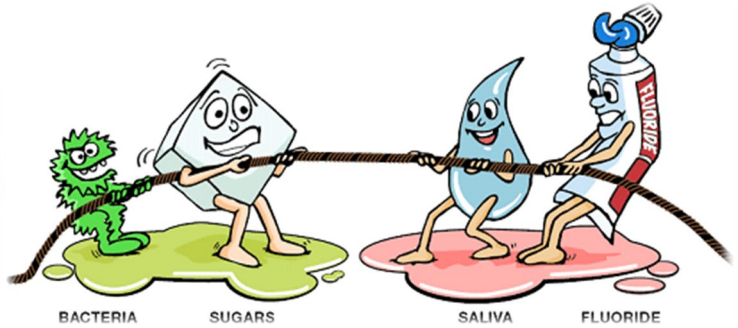


Ammann et al 2012

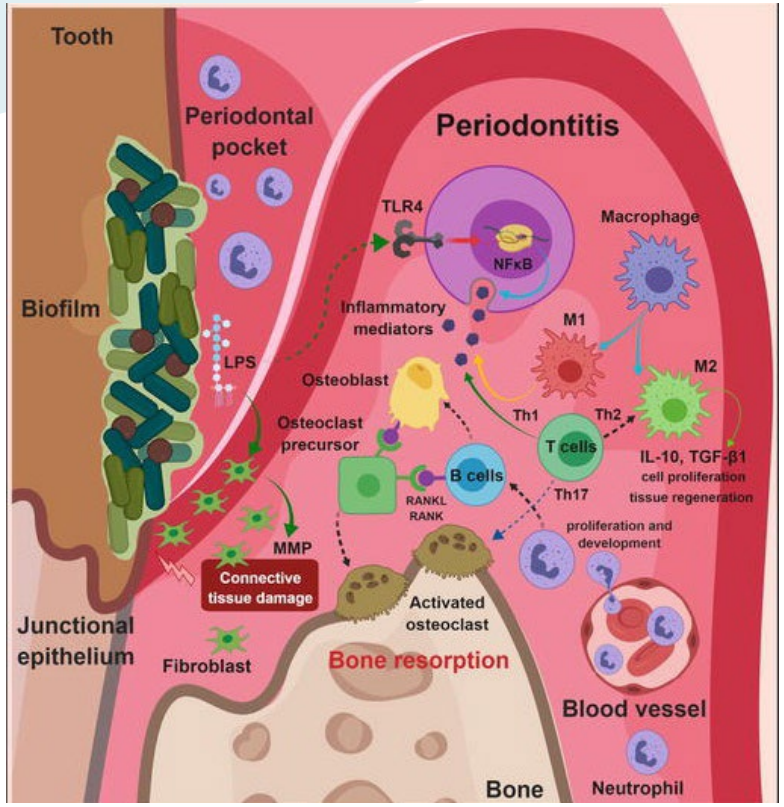
"INFECTION" = PATHOGEN + SUSCEPTIBLE HOST

Dental caries (decay)

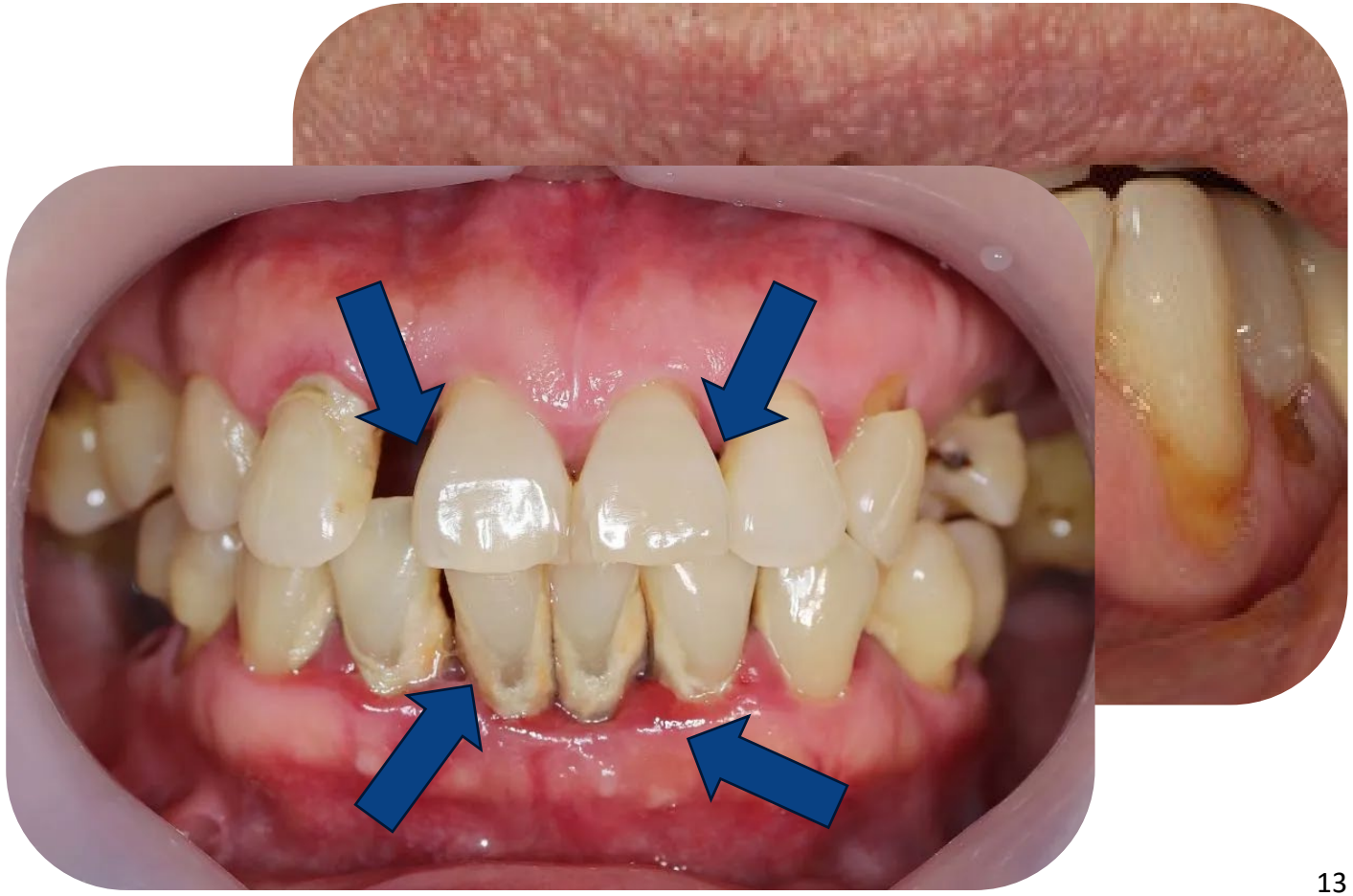


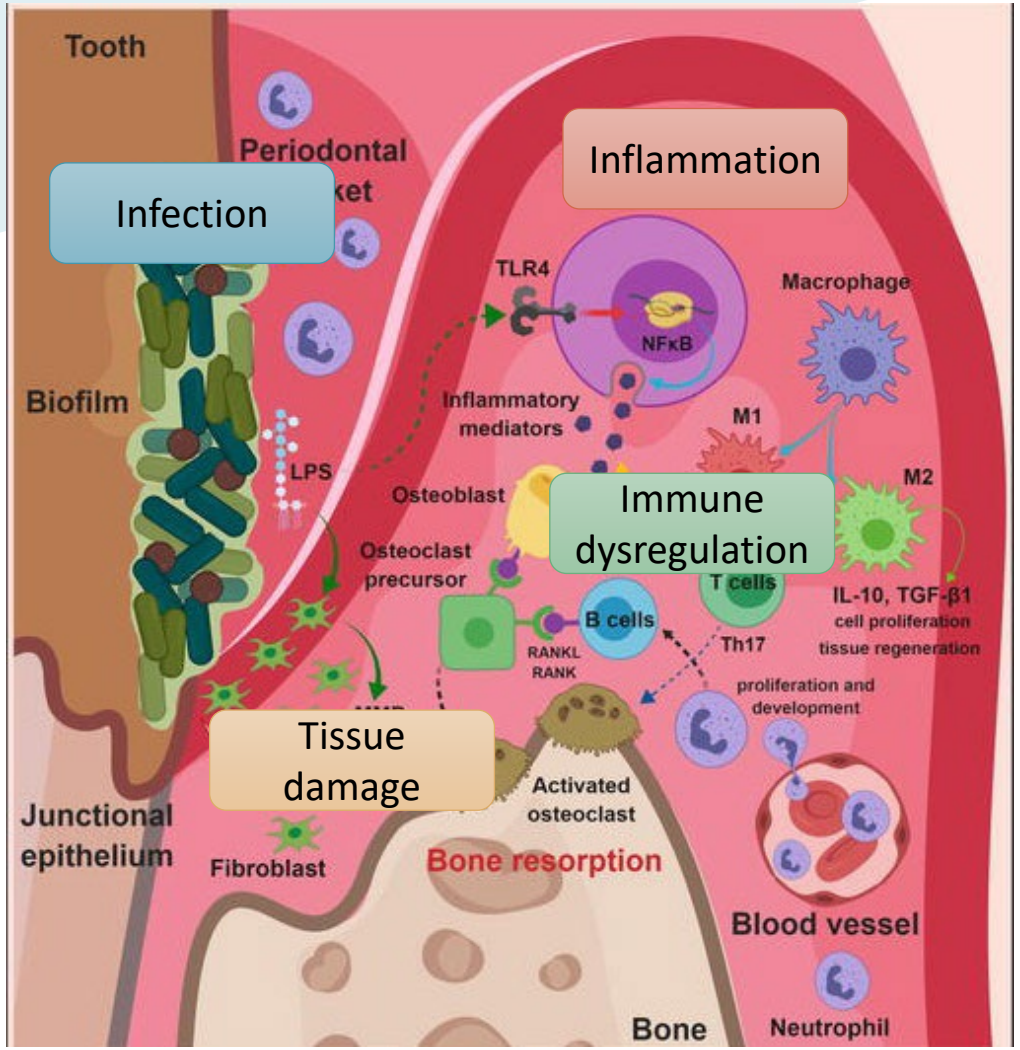


Periodontal (gum) disease



(Muñoz-Carrillo et al 2019)





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(Muñoz-Carrillo et al 2019)


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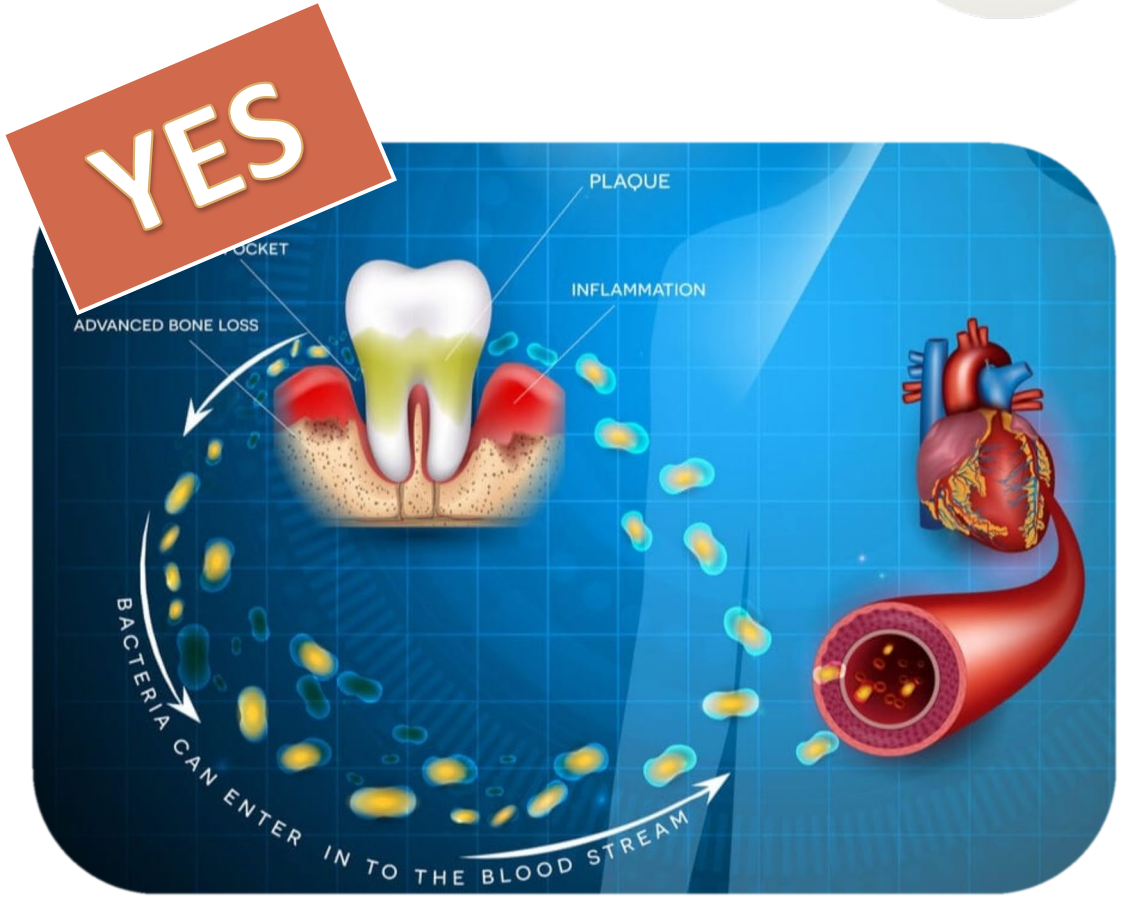
Can oral bacteria cause distant infections?

"Focal infection theory"

- Haematogenous metastatic spread of oral bacteria to other areas of body to cause infection



Getty Images

<u>Examples:</u>

Endocarditis:

- 14-20% Group A streptococci (Carmona et al 2002)
- 1-3% HACEK (Revest et al 2003)

Peri-prosthetic joint infections 6-13% (Zimmerli et al 2004)

Distant abscesses

- Brain - 30% streptococci (Yang 1981)
- Spinal epidural – 7% streptococci (Shweikeh et al 2014)

Is bacteraemia caused by dental pathology?

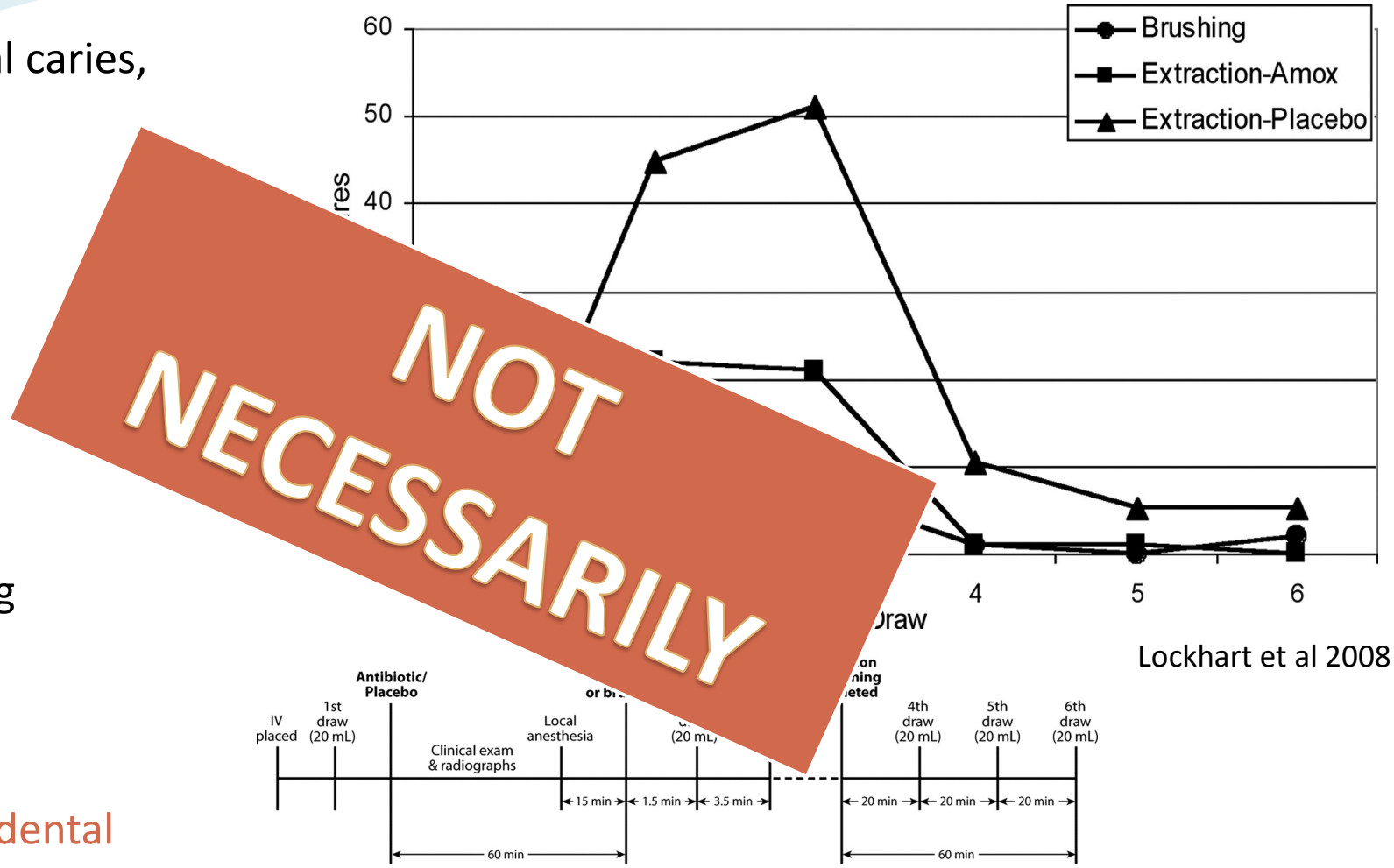
Streptococcal species may cause dental caries, but also part of normal oral flora

Positive culture ≠ 'Dental infection'

Bacteraemias are associated with:

- Dental procedures
- Oral hygiene – brushing and flossing
- Chewing

Evidence for antibiotic prophylaxis for dental procedures for only high-risk populations



Lockhart et al 2008

Other pathways for oral bacterial infections

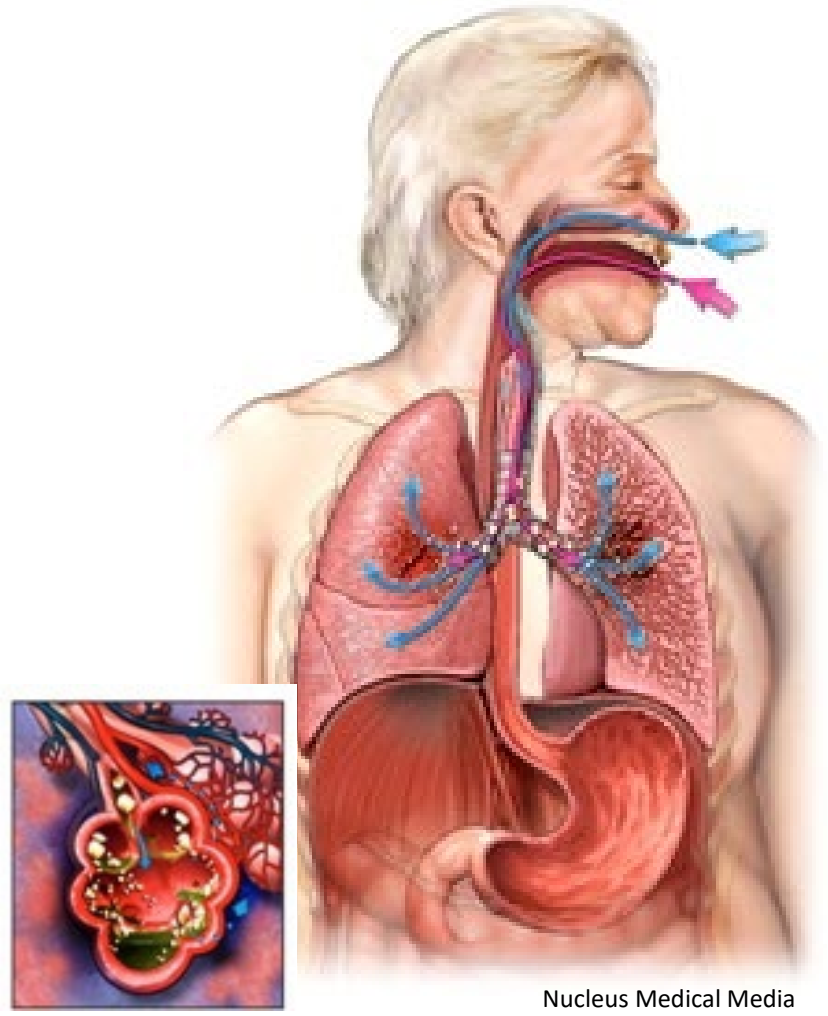
Aspiration and ventilator-acquired pneumonia

- Aspiration of oral flora (Scannapieco et al 2003, Azarpazhooh & Leake 2006)
- Confirmation with bronchoalveolar lavages (Imsand et al 2002)

Simple oral hygiene interventions can reduce 40% (Raghavendran et al 2000)

- Decrease mortality by 10% (Sjogren et al 2008)

Mechanical cleansing found to be most effective (van der Maarel-Wierink et al 2013)



Nucleus Medical Media

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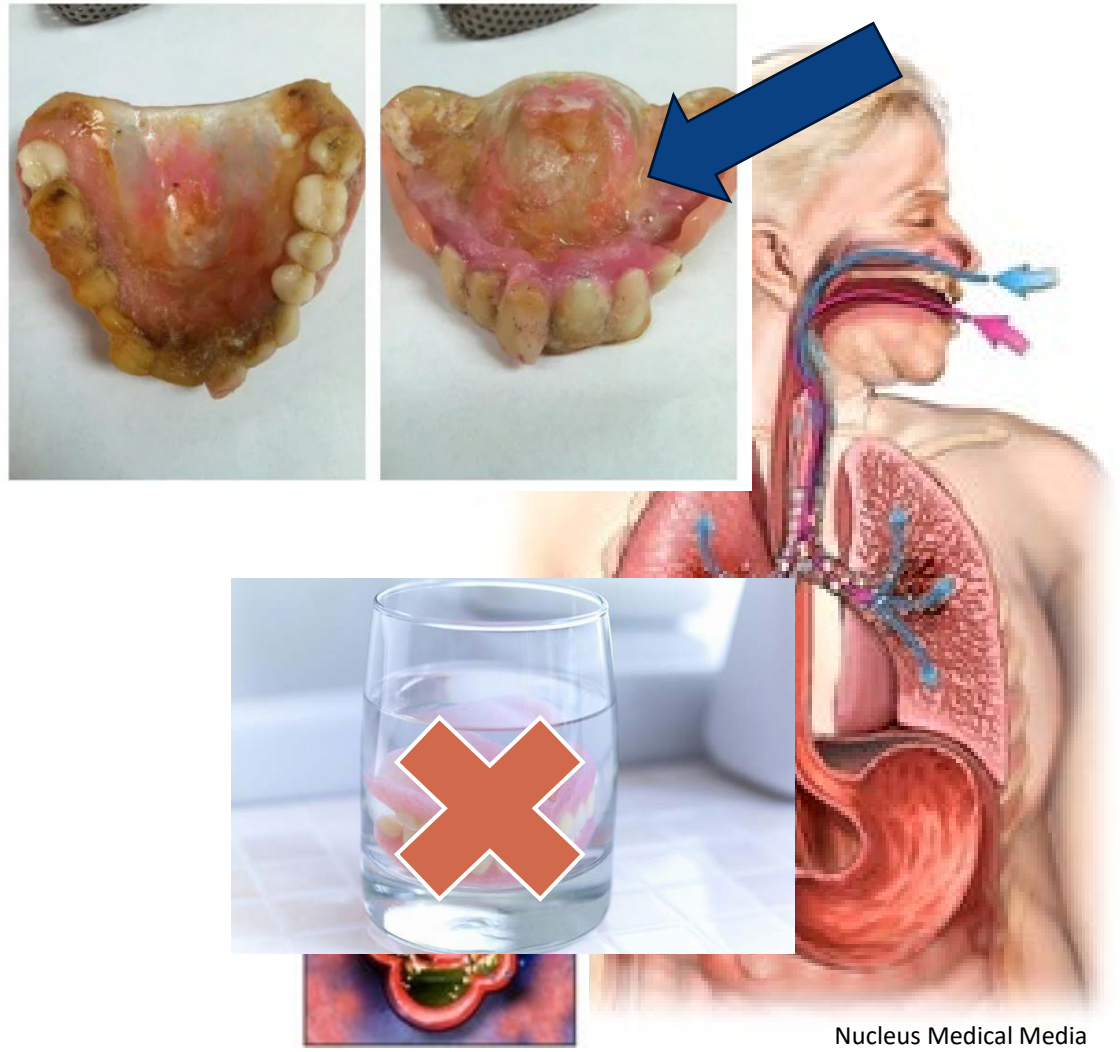
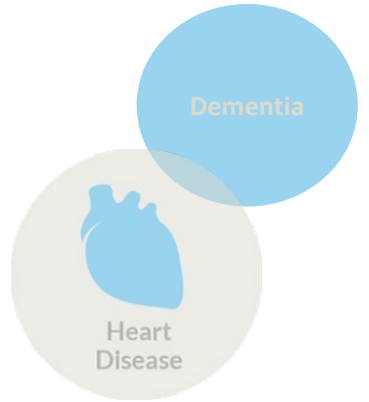
Nocturnal denture wearing doubles risk (Iinuma et al 2014)



Nucleus Medical Media

Oral bacteria and non-infective changes



Carotid atherosclerotic plaques

- P gingivalis 100% (Ford et al 2005)
- F nucleatum <80% (Ford et al 2005)
- T denticola (Haraszthy et al 2000, Okuda et al 2001)

AAA

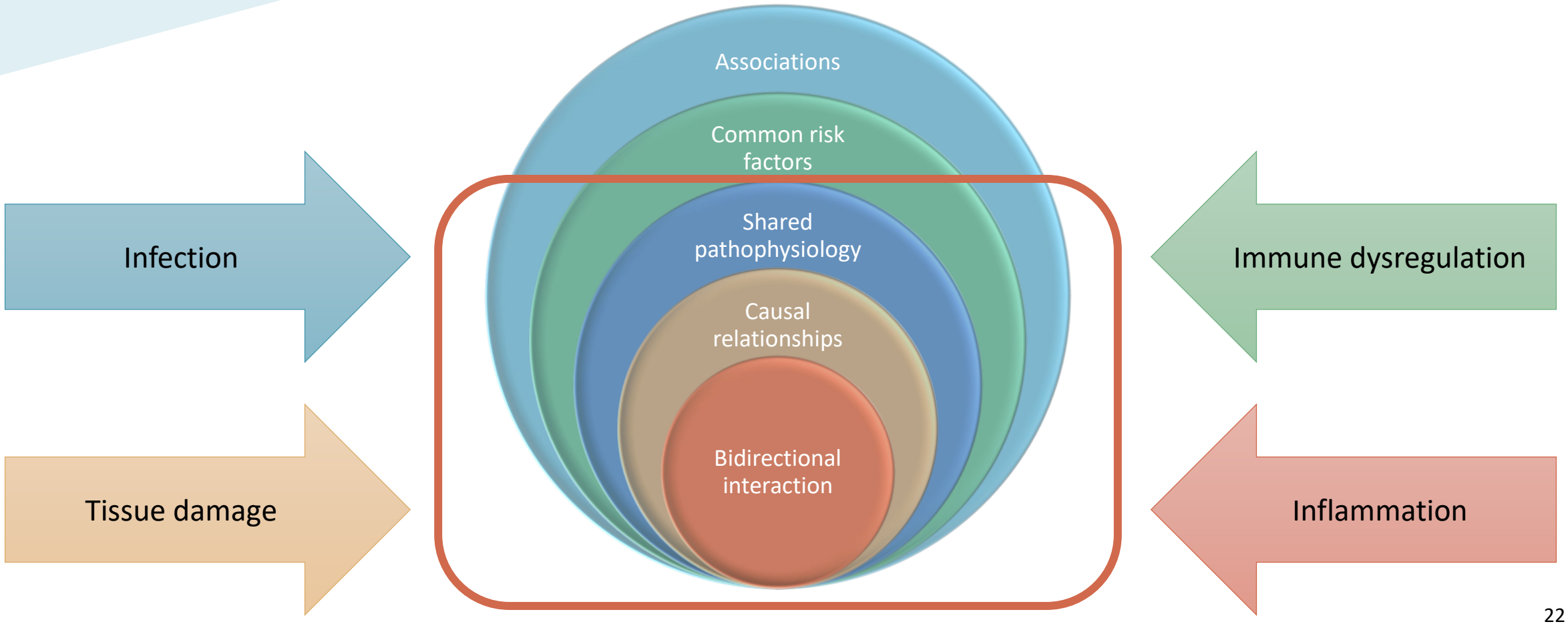
- P gingivalis 85% (Kurihara et al 2004)

Alzheimer's disease

- Brain: P gingivalis LPS / DNA / gingipain proteases (Poole et al 2013, Dominy et al 2019)
- CSF: P gingivalis DNA (Dominy et al 2019)
- Linked with Tau and ubiquitin pathology, amyloid beta (Ryder 2020)

Initiating or modulating pathogenesis?

Secondary colonisation?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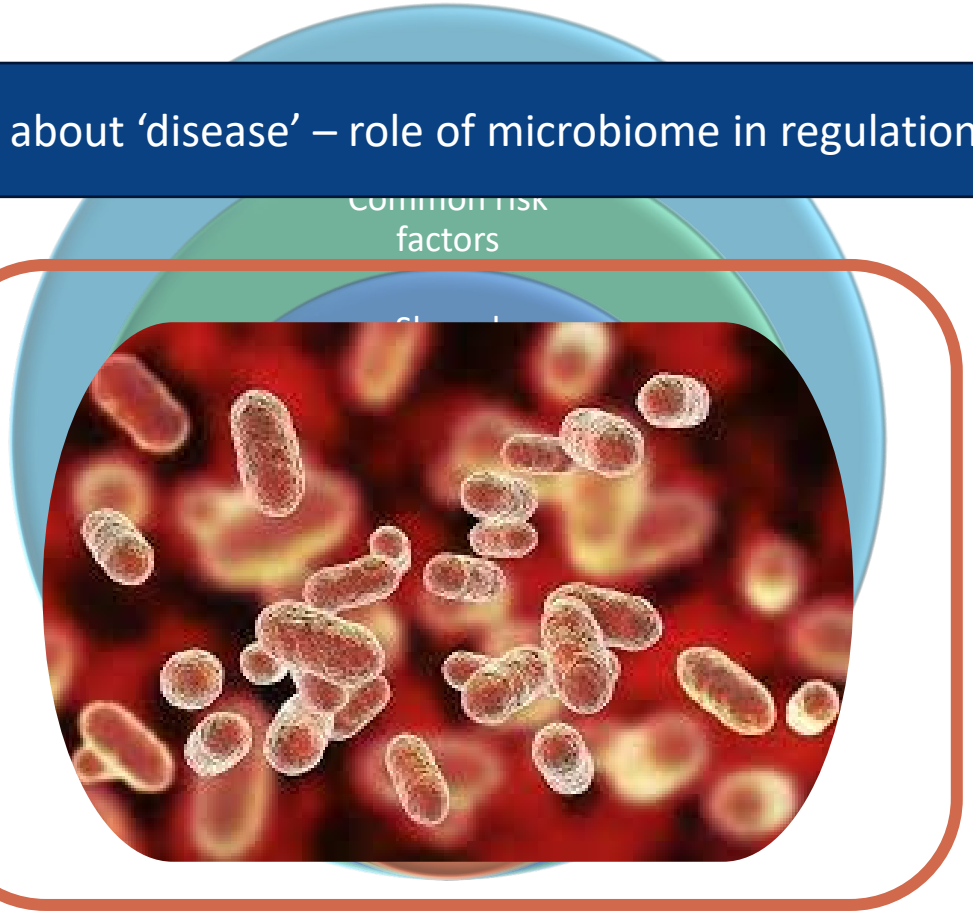
No necessarily about ‘disease’ – role of microbiome in regulation of immunity



Immune dysregulation

Infection

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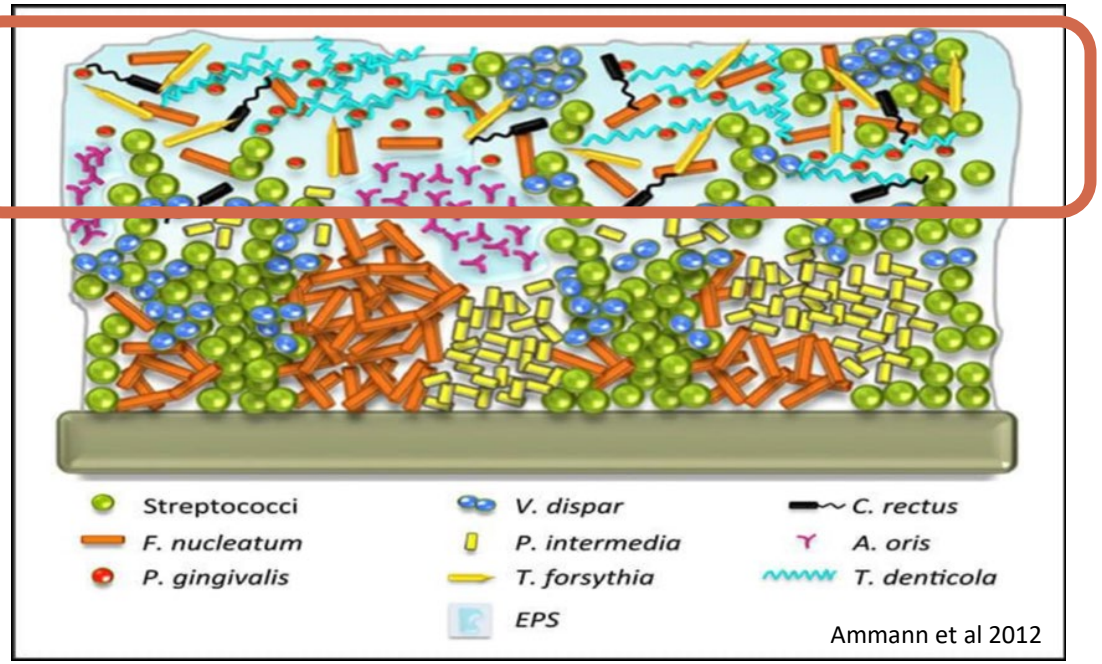
PLAQUE / BIOFILM

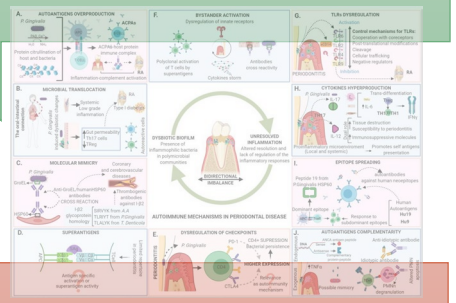


Ammann et al 2012

Commensal microflora is part of health – but keystone pathogens may cause **dysbiosis**

No necessarily about ‘disease’ – role of microbiome in regulation of immunity

Immune dysregulation



Inflammation

Common risk factors

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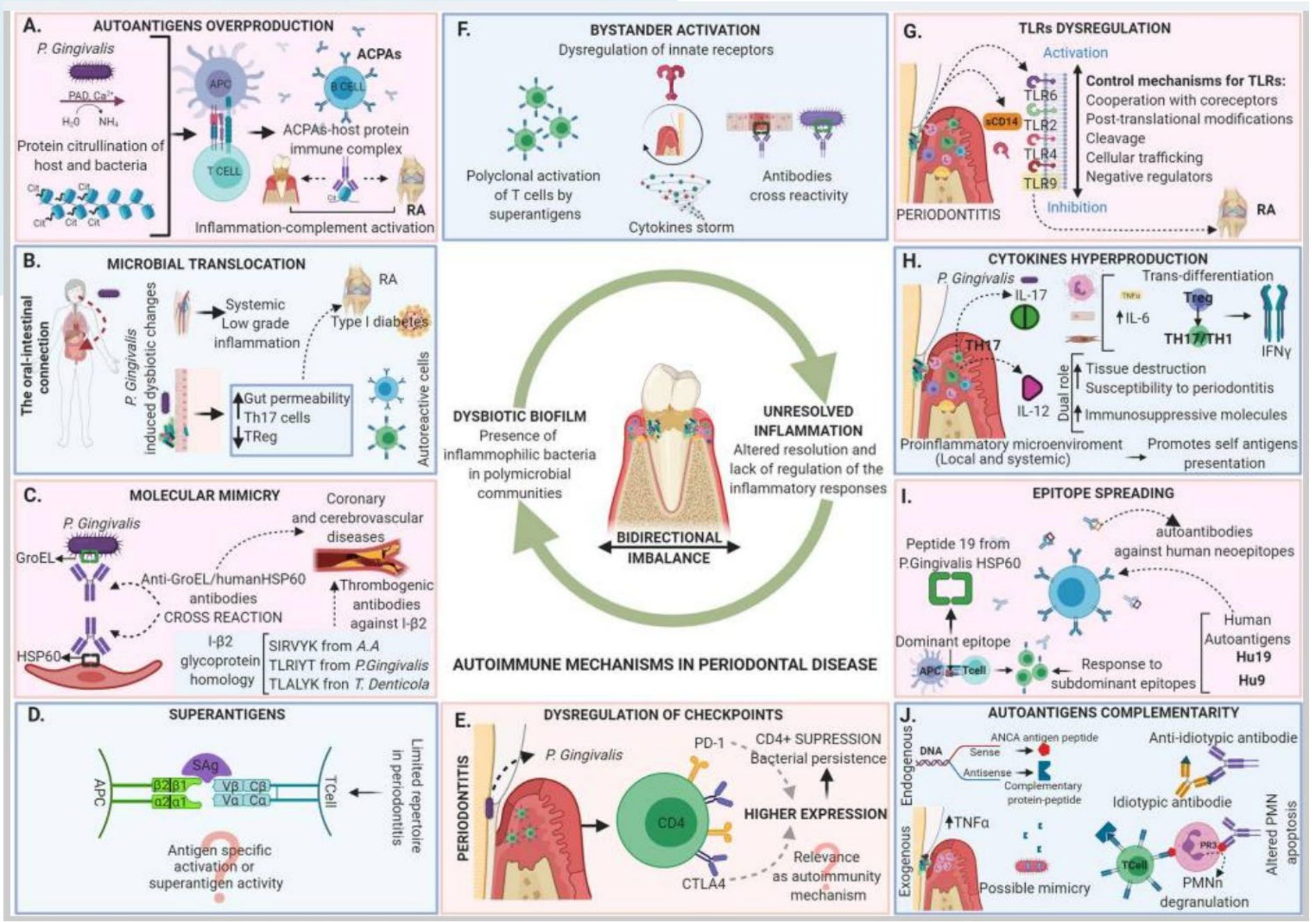
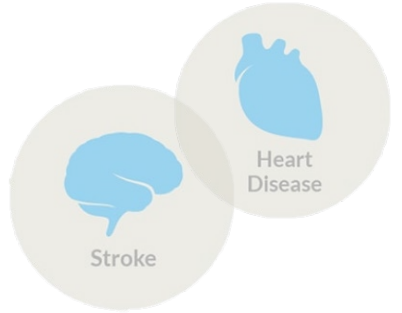
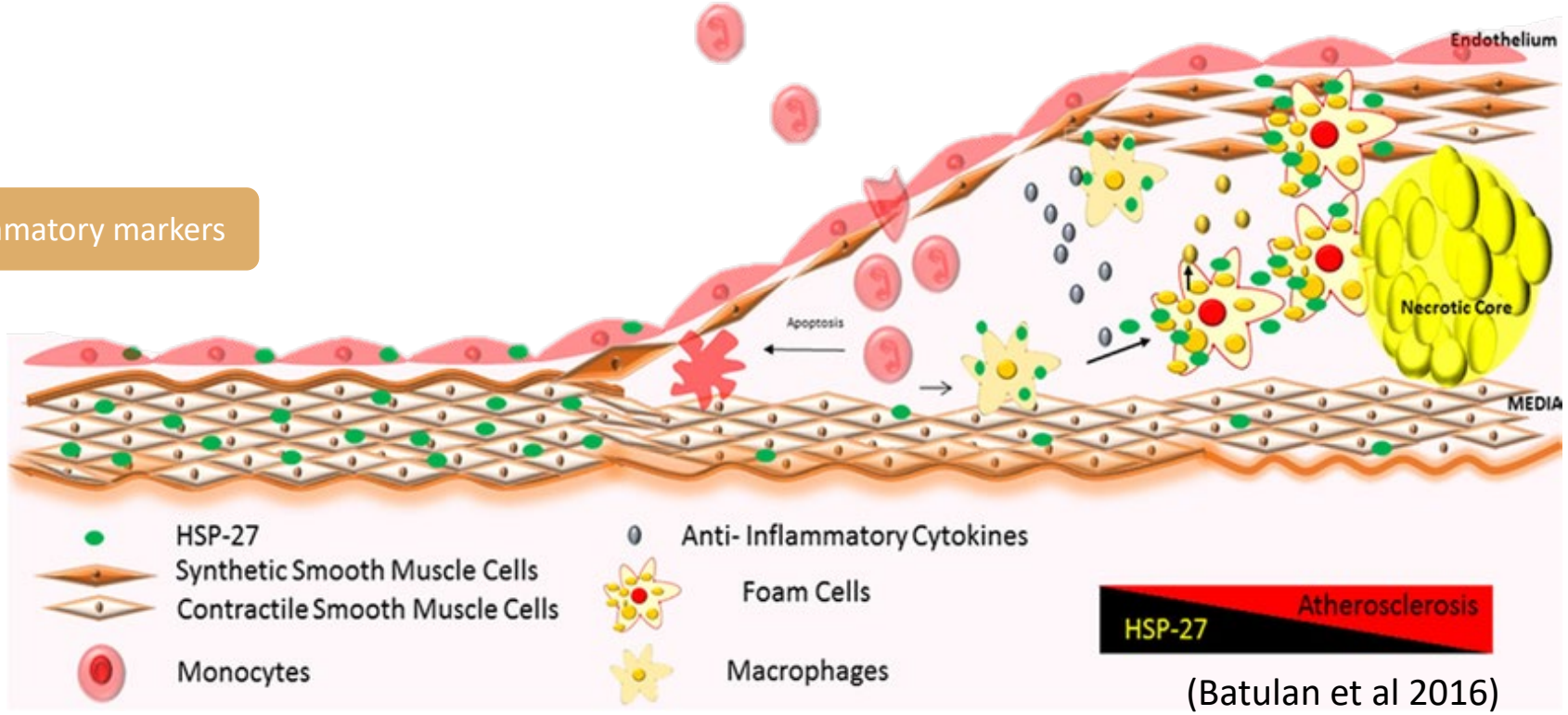


(Suarez et al 2020)

Atherosclerosis and thrombosis



↑ Inflammatory markers



(Batulan et al 2016)

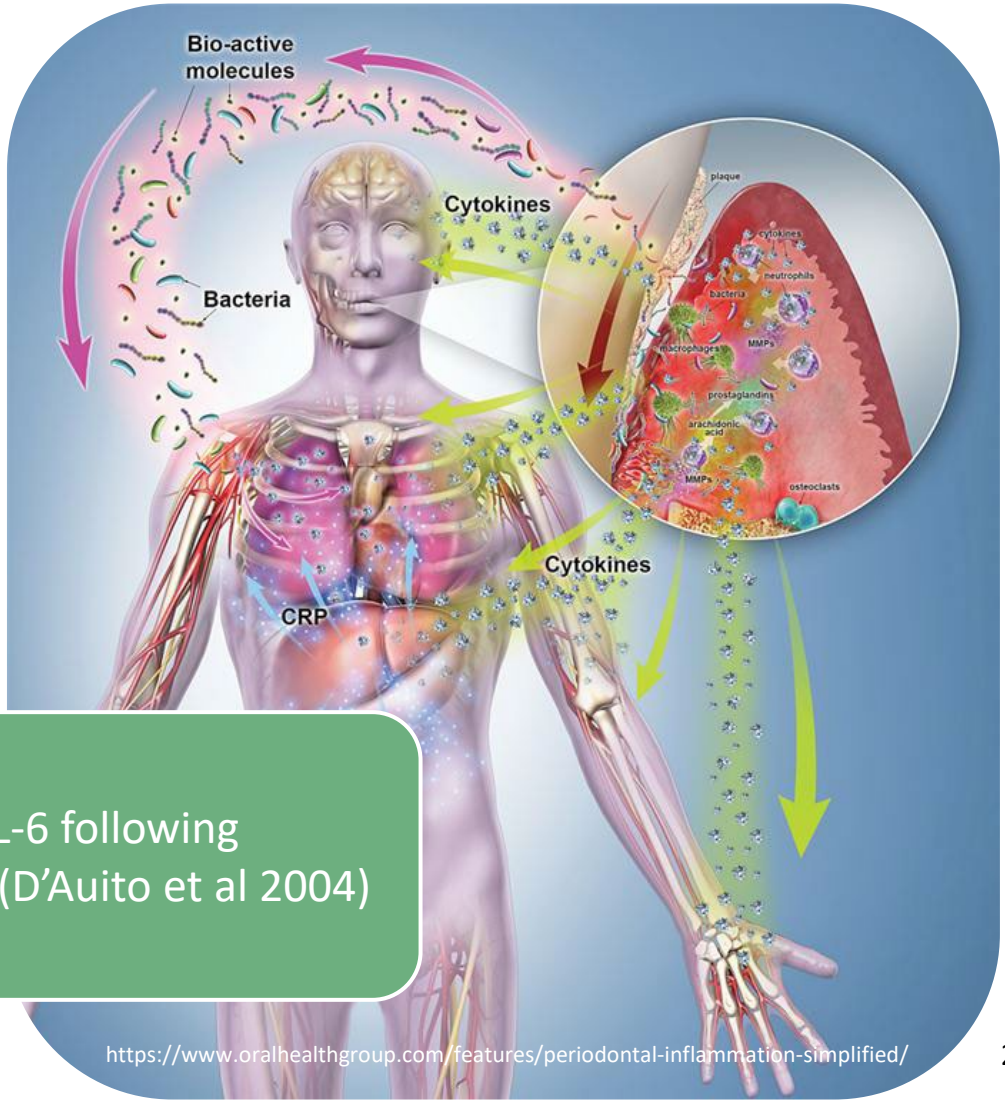
Immune dysregulation and inflammation

In response to P gingivalis and periodontitis:

- ↑ Circulating cytokines (IL-1, IL-6, TNF-α)
- ↑ Inflammatory mediators (C-reactive protein)

Underlying mechanism for:

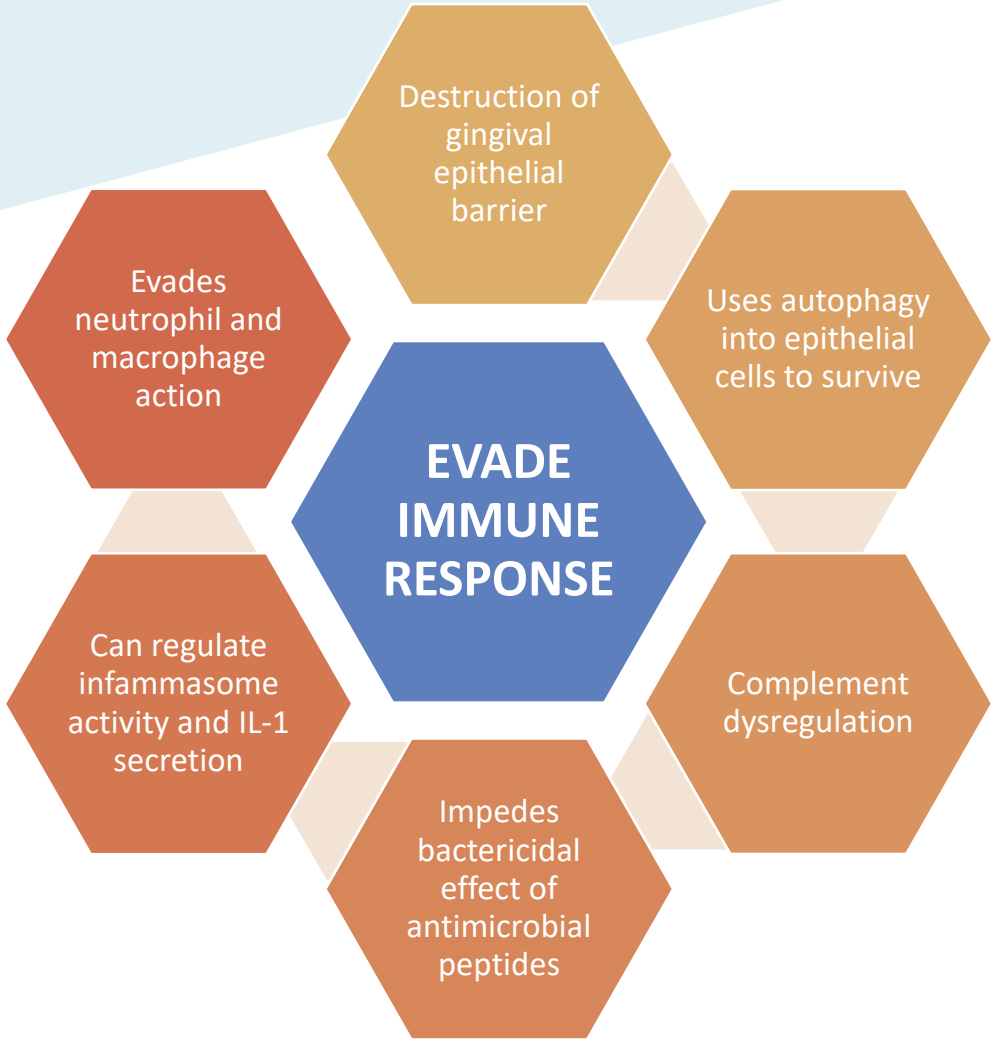
- Stroke – 2x (Fagundes et al 2019)
- Pre-term birth – 4.28x (McGregor et al 1988, Khader & Ta'ani 2005)
- Alzheimer's disease
- Chronic kidney disease

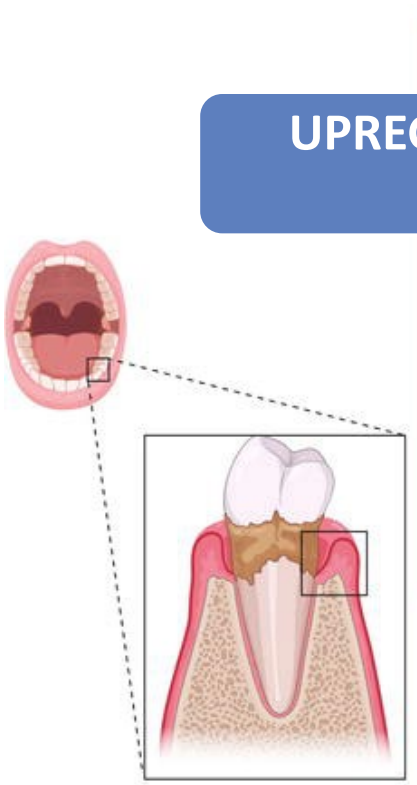


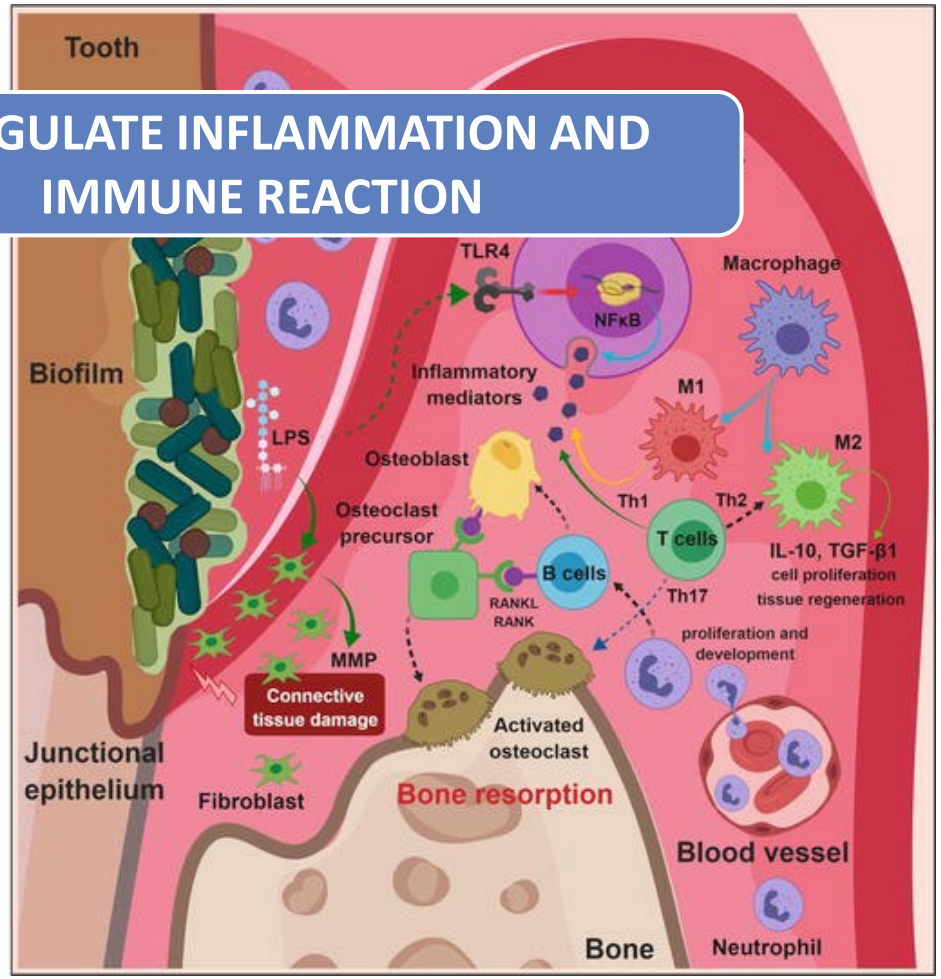
Reduction in CRP and IL-6 following periodontal treatment (D'Auito et al 2004)

https://www.oralhealthgroup.com/features/periodontal-inflammation-simplified/

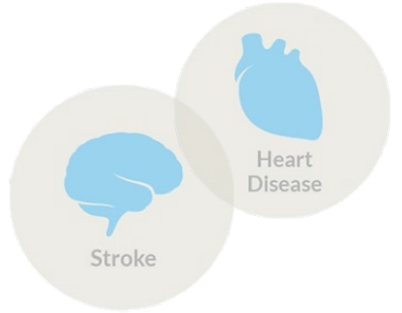
Change and evade the immune response



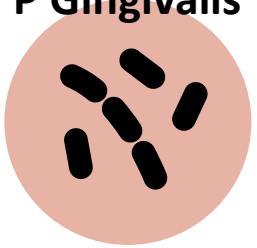




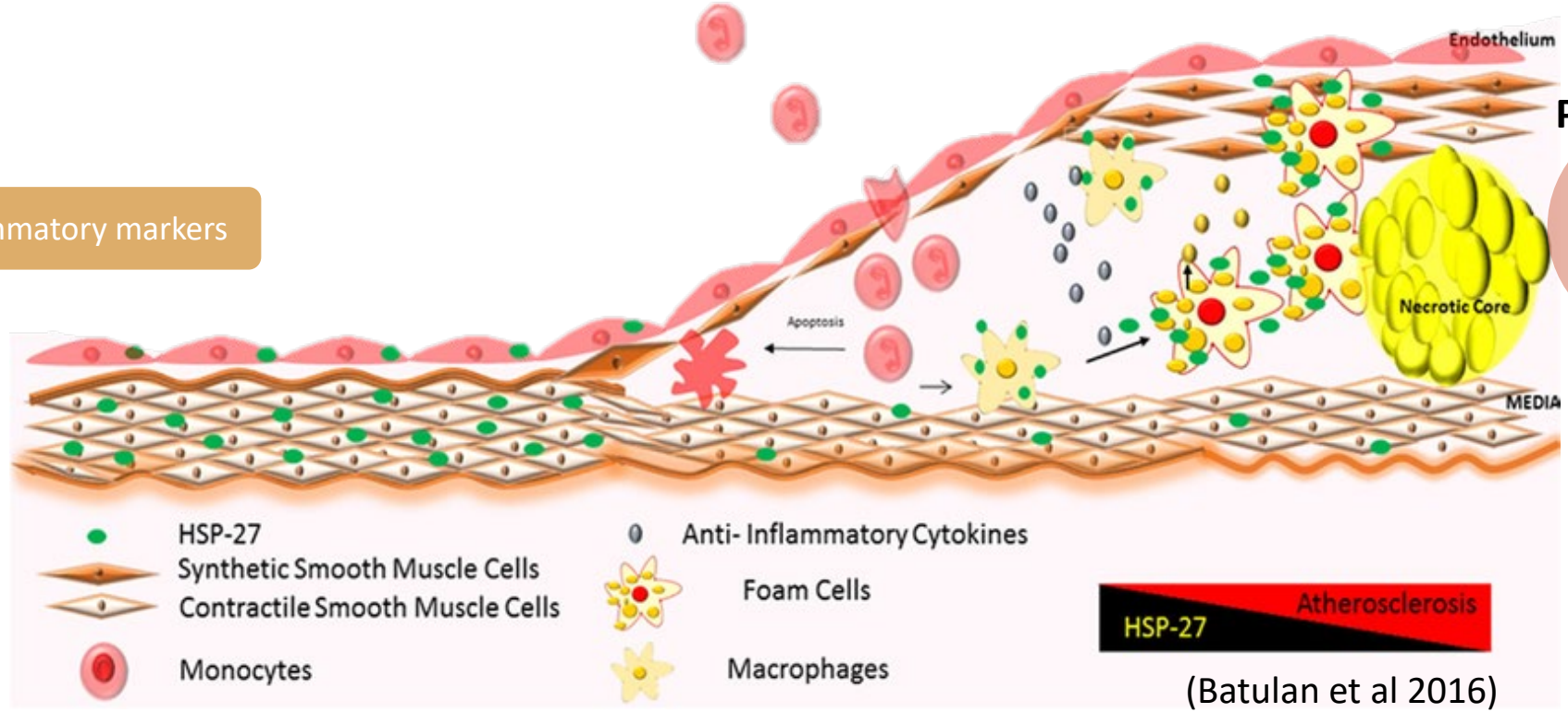
Atherosclerosis and thrombosis



P Gingivalis



↑ Inflammatory markers



P Gingivalis

Inflammation +++

(Batulan et al 2016)

Molecular mimicry: Cross-reactivity

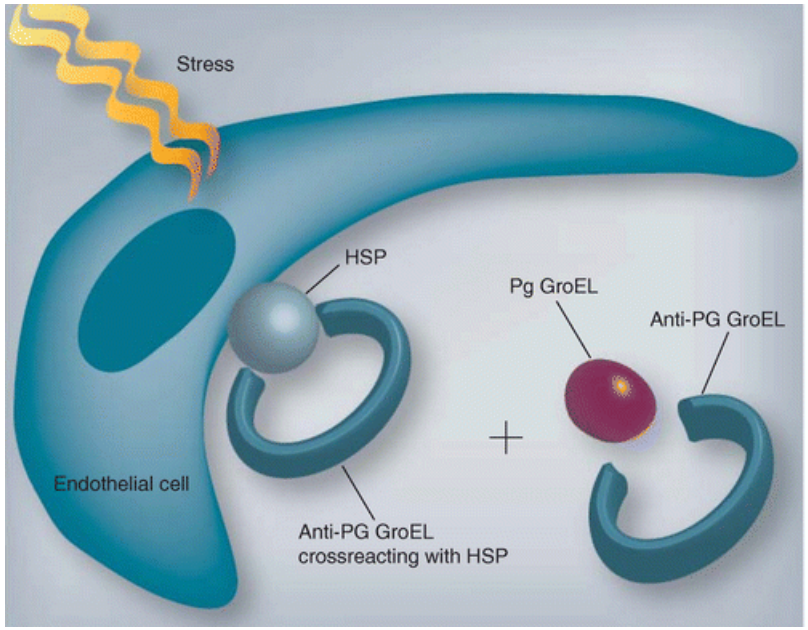
Heat shock proteins (HSP) – strongly immunogenic

- Expressed as protective mechanisms when host cell is stressed
- Higher levels of expression can have 'toxic' effect

GroEL antigen on P gingivalis – 60% of peptides similar to HSP60

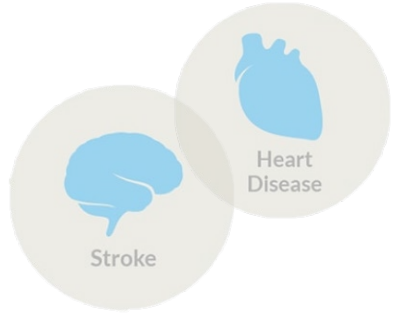
- Antibodies to bacterial/human HSP detected in gingival tissues of periodontitis and healthy patients, (Ford et al 2005, Tabeta et al 2000, Seymour et al 2007)

IgM that recognise gingipains from P gingivalis can also cross-react with oxidised LDL



(Seymour et al 2009)

Atherosclerosis and thrombosis



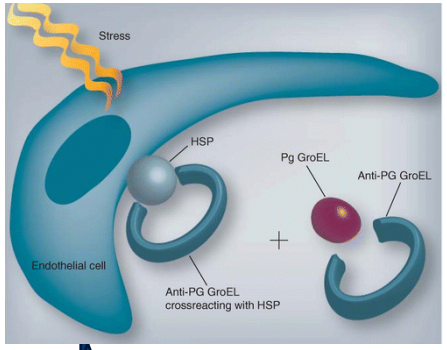
P Gingivalis

Gingipains

FIX

FX

Thrombus formation ++



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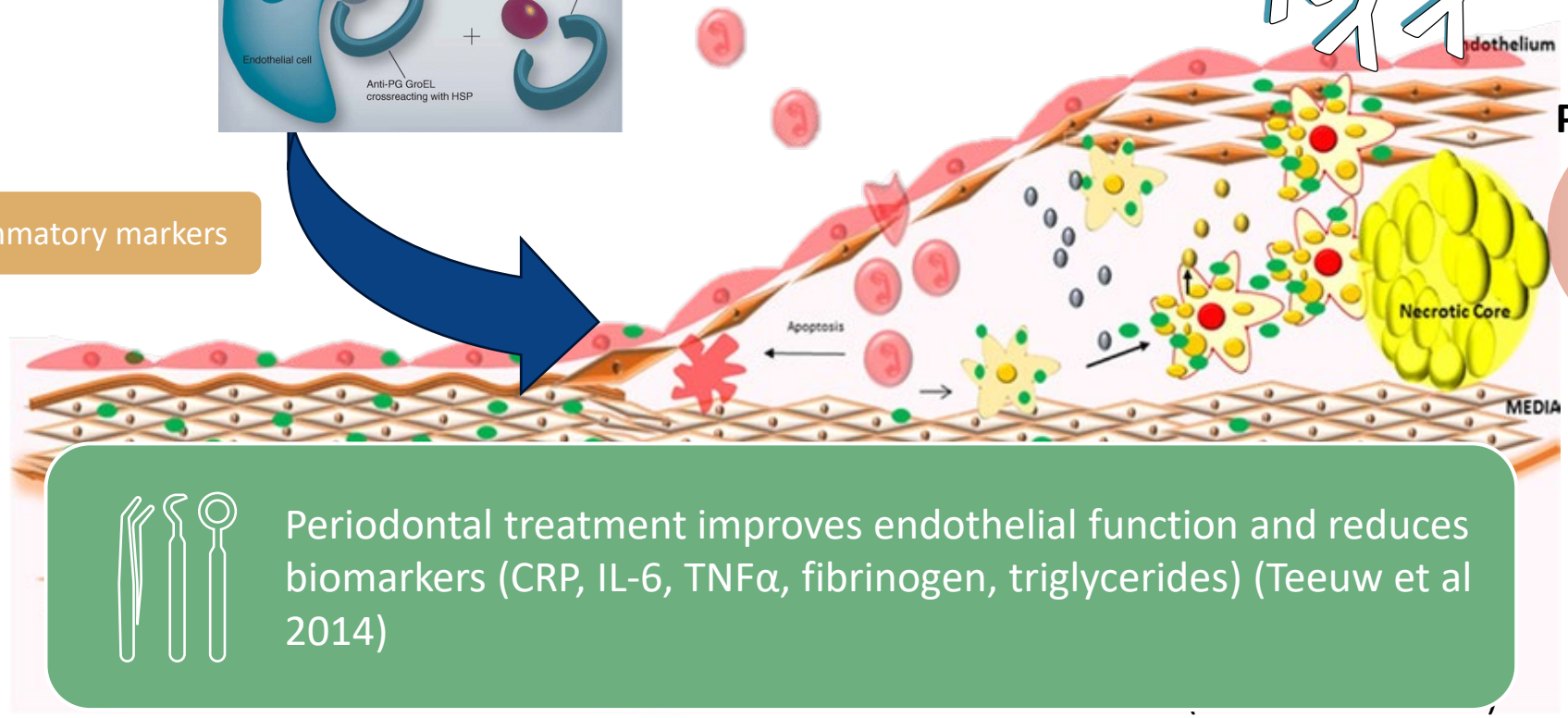
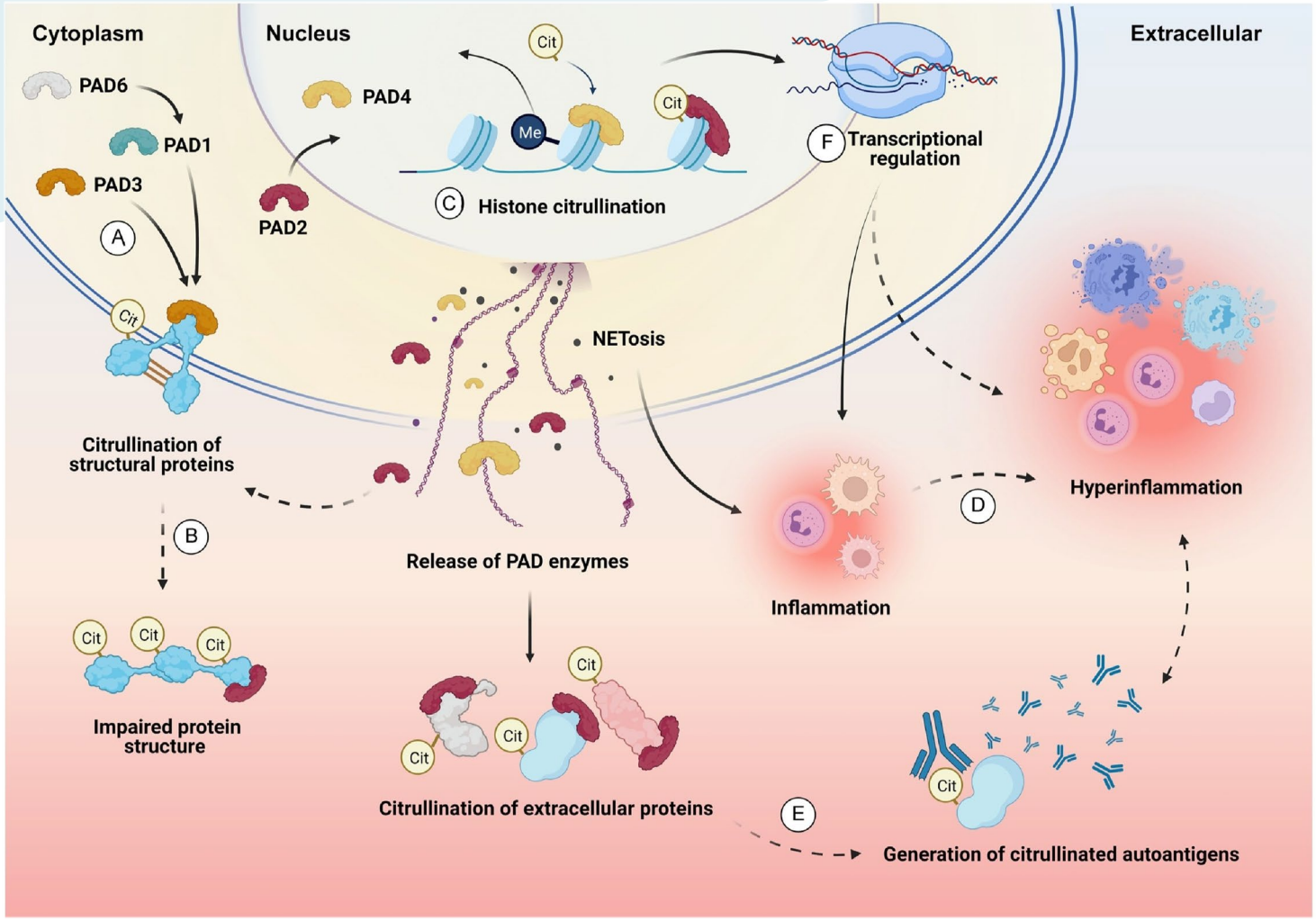


P Gingivalis

Inflammation +++

Periodontal treatment improves endothelial function and reduces biomarkers (CRP, IL-6, TNFα, fibrinogen, triglycerides) (Teeuw et al 2014)

Autoantigen production: Citrullination



(Yu et al 2002)

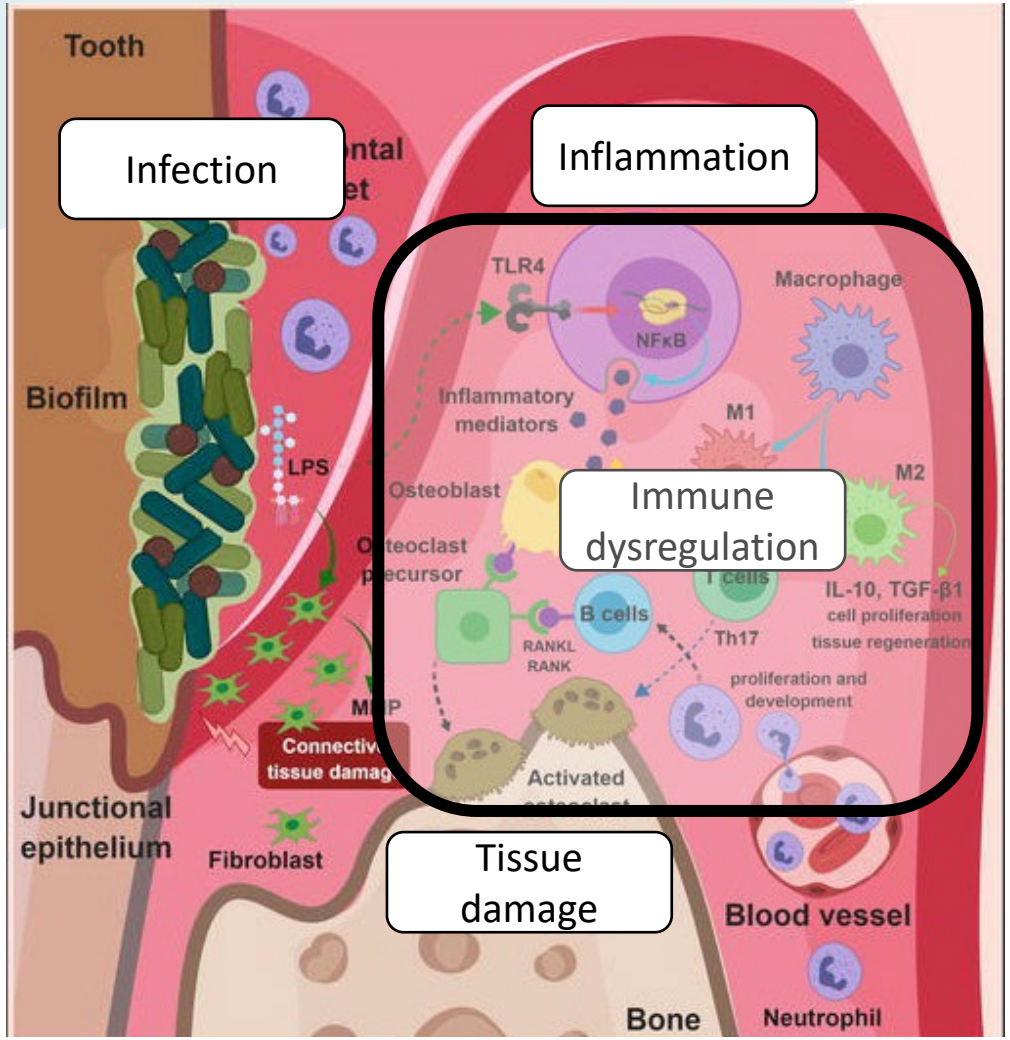
P gingivalis can modify the shape of host proteins to increase their immunogenicity

- P ginigvalis is only known periodontal pathogen to produce Peptidylarginine deiminases (PADs)
- Citrullination of bacterial and host peptides (Wegener et al 2010)

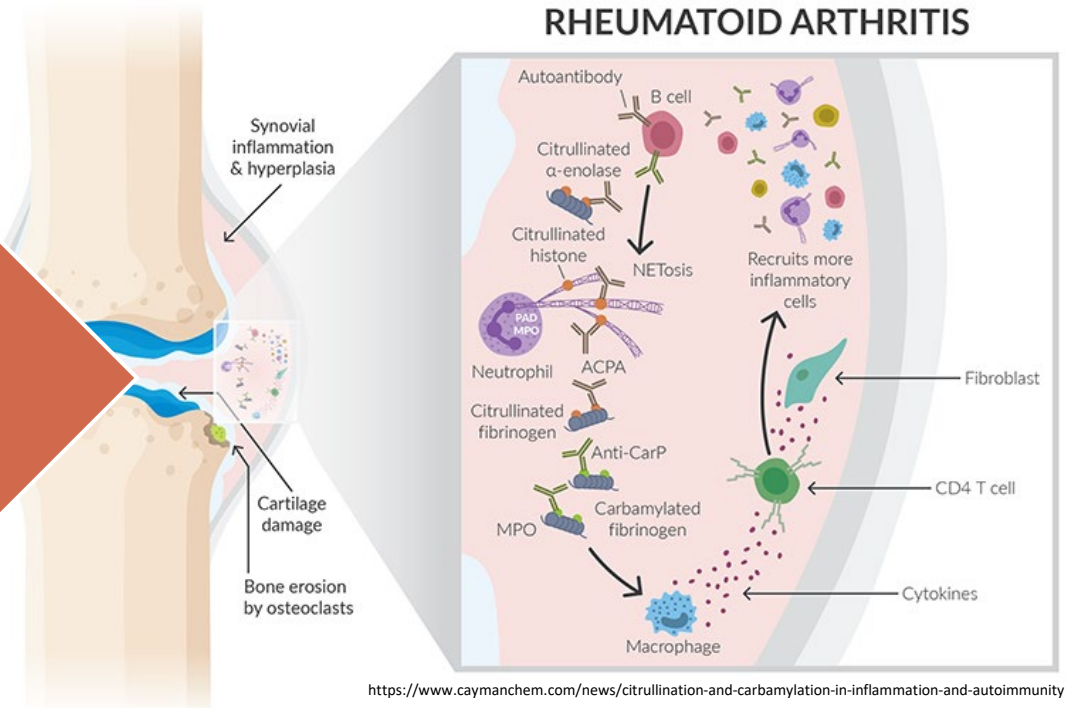
Anti-Citrullinated Protein Antibodies (ACPA) = autoimmune conditions

Other environmental factors e.g. smoking

Breakdown of immune tolerance



INITIATES or UPREGULATES

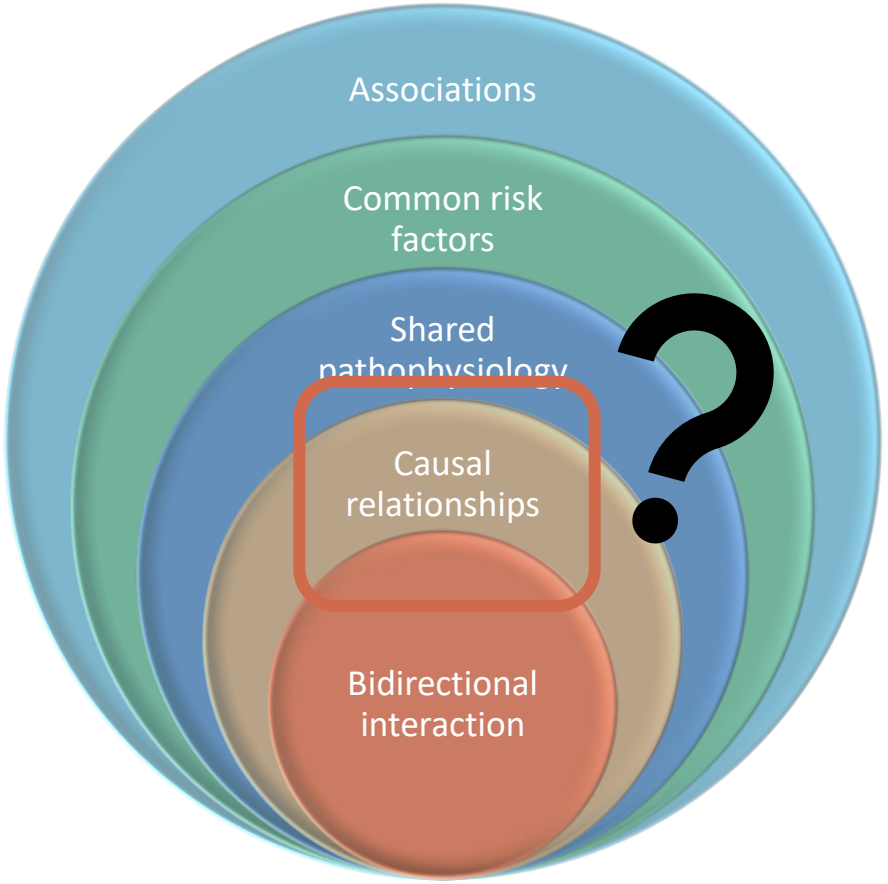


https://www.caymanchem.com/news/citrullination-and-carbamylation-in-inflammation-and-autoimmunity

Basic oral hygiene may prevent or limited upregulation of inflammatory responses in autoimmune conditions

Infection

Tissue damage



Immune dysregulation

Inflammation

P gingivalis … a weapon of mass destruction?

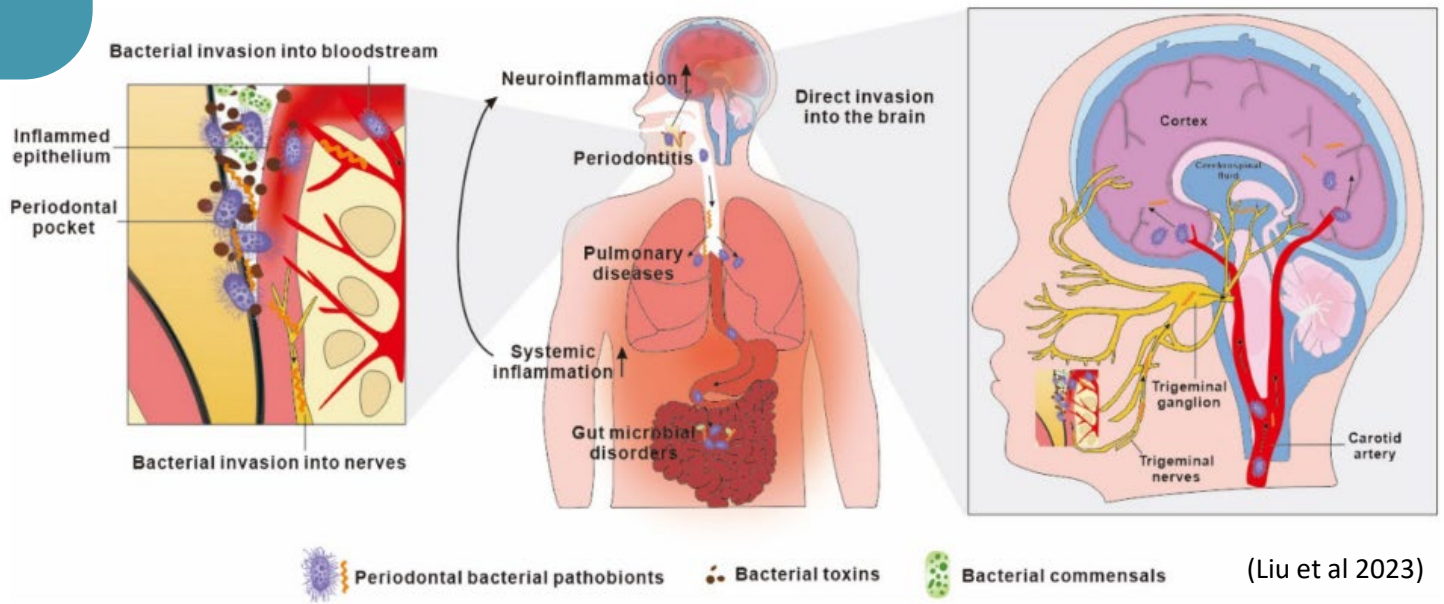
“MASTER OF DISGUISE”

Alter signalling pathways for inflammation and immunity to colonise

Create environment most suited to survival

Alzheimer’s disease (Liu et al 2023)

1. Chronic inflammation → neuroinflammation from microbiota-gut-brain axis
2. Direct infection of brain



(Liu et al 2023)

P gingivalis … a weapon of mass destruction?

"MASTER OF DISGUISE"

Alter signalling pathways for inflammation and immunity to colonise

Create environment most suited to survival

"MASS DESTRUCTION?"

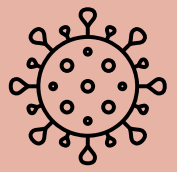
Translate pathog… elsewhere …

Alzheimer's disease (Liu et al 2023)

1. Chronic inflamm… …oinflammation from microbi…
2. D…

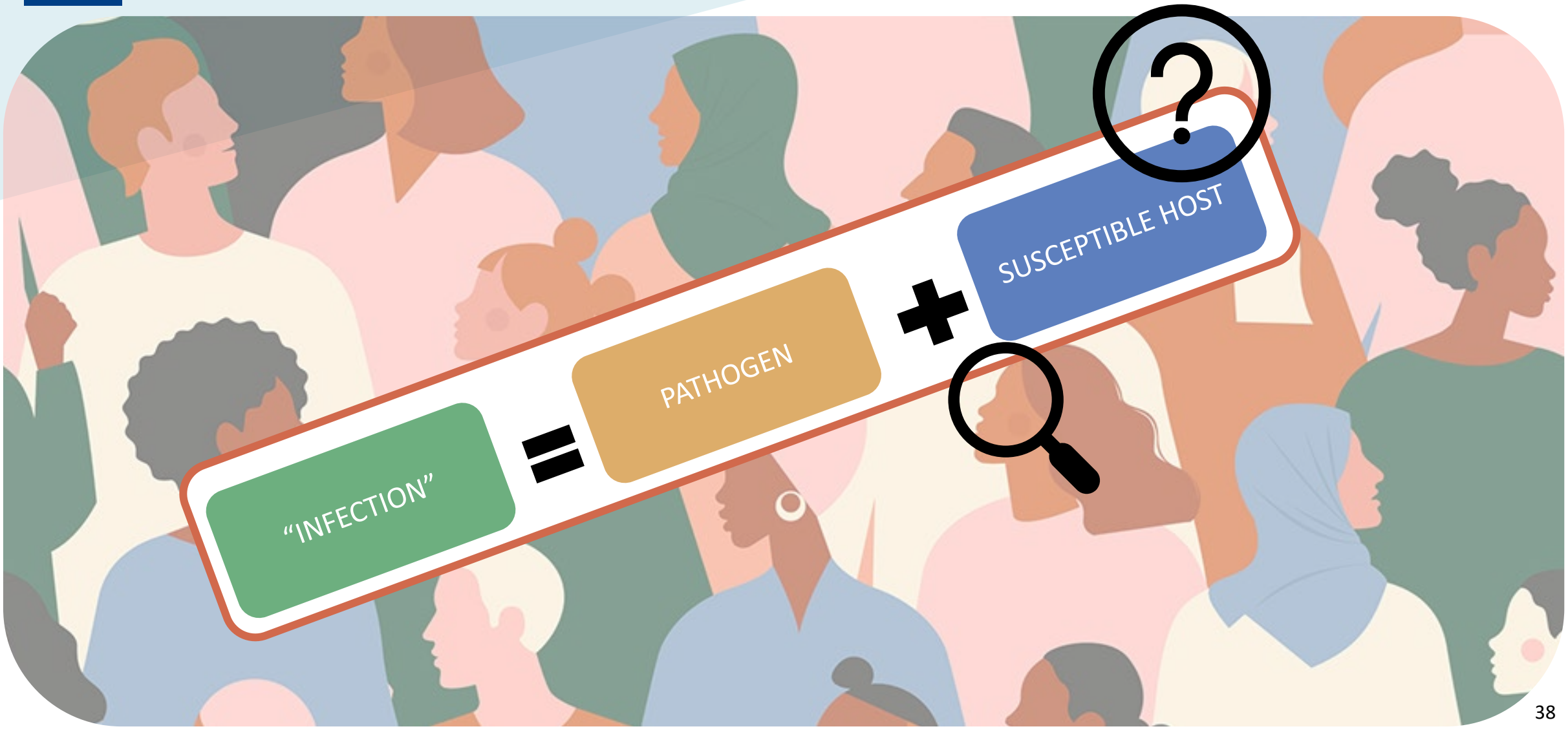
…isk of MI (Rydén et al 2016)

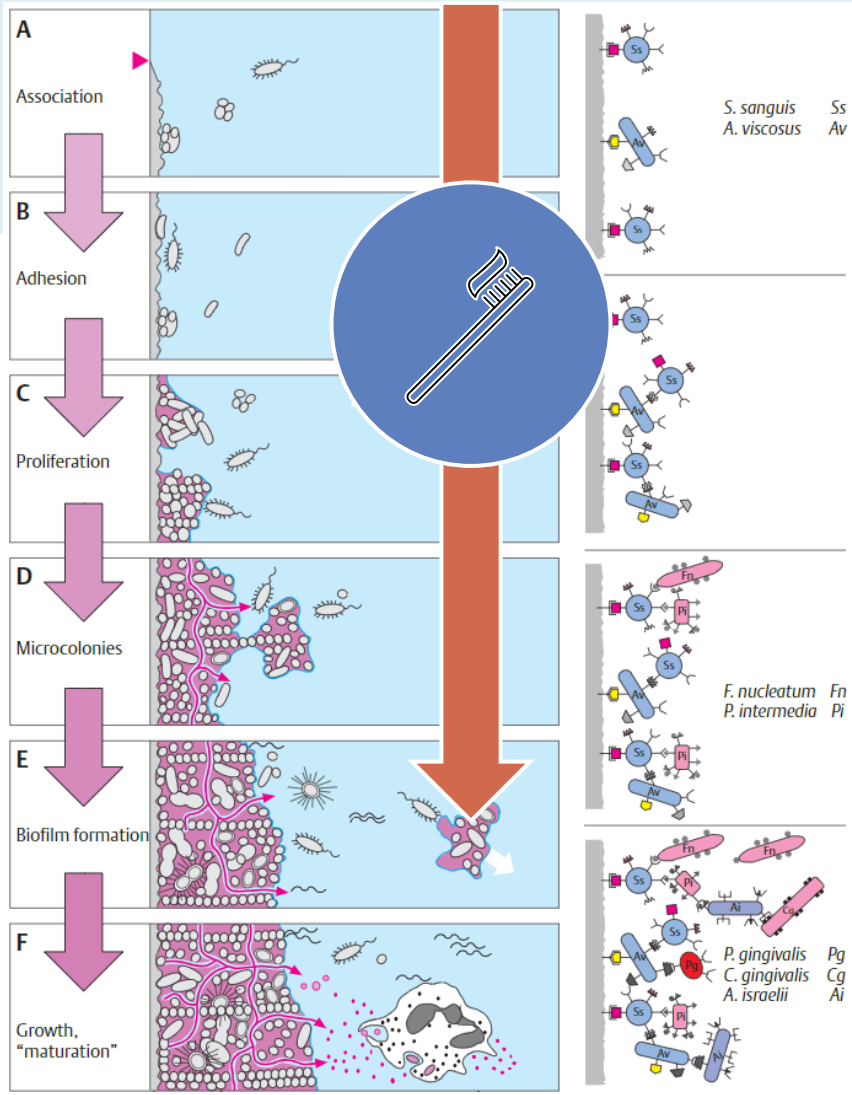
Likely direct action of cardiomyocytes –promotes apotosis by enhancing oxidative stress and exacerbating inflammatory response



Increased risk of oropharyngeal and oesophageal SCC
- Dehydrogenation of ethanol to acetaldehyde (Gao et al 2016)

"INFECTION" = PATHOGEN + SUSCEPTIBLE HOST


"INFECTION"
=
PATHOGEN
+
SUSCEPTIBLE HOST
?



Wolf 2006

Dental caries and periodontal disease are preventable

- Conditions initiated by dental plaque
- Reversible in early stages
- Addressing common risk factors

Plaque / biofilm = Commensal microflora

- Maturation allows for keystone pathogens to thrive
- **Disruption through oral hygiene**

While prevention is ideal, even effective management likely to have positive impact on oral and systemic health

What happens in the mouth … doesn't always stay in the mouth

We have known for a long time …

- Mouth reflects what is happening in body
- Chronic disease – can be indicator on progression

Shared risk factors and pathophysiology

- Interactions initiated and modulated by oral microflora, particularly keystone pathogens in dental conditions

Maintaining oral health through basic oral hygiene and regular dental care

- Preventing initiation of chronic dental disease process
- When established, reducing inflammation and immune dysregulation

Thank you

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