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Red Complex Bacteria in Periodontitis- An Insight

Nanditha Chandran[1]*, Anil Melath[2], Hemalatha DM[3], Safa[4] and Puvishaa R[5]

[1]Associate Professor, Department of Periodontics and Implantology Mahe Institute of Dental Sciences and Hospital Pondicherry UT, India

[2]Professor and HOD Department of Periodontics and Implantology Mahe Institute of Dental Sciences and Hospital Pondicherry UT, India

[3]Associate Professor Department of Periodontics and Implantology Mahe Institute of Dental Sciences and Hospital Pondicherry UT, India

[4]Fourth Year BDS Mahe Institute of Dental Sciences and Hospital Pondicherry UT, India

[5]Fourth Year BDS Mahe Institute of Dental Sciences and Hospital, India

ABSTRACT

Periodontitis is a chronic inflammatory disease affecting the supporting structures of the teeth and is primarily associated with dysbiotic subgingival microbial biofilms. Among the various periodontal pathogens, the red complex bacteria—Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia—are considered the most significant contributors to the initiation and progression of periodontal destruction. These microorganisms exhibit strong associations with deep periodontal pockets, bleeding on probing, clinical attachment loss, and alveolar bone resorption. The present review discusses the role of microorganisms in the pathogenesis of periodontitis, Socransky's microbial complexes, and the biological characteristics of red complex bacteria. It further highlights the virulence factors of these pathogens, including proteolytic enzymes, fimbriae, endotoxins, outer membrane proteins, and immune-evasive mechanisms that facilitate tissue destruction and chronic inflammation. The synergistic interactions among red complex species and their relationship with other periodontal microorganisms contribute significantly to biofilm maturation and disease severity. Advances in microbiological and molecular diagnostic techniques have improved the understanding of their pathogenic potential and clinical relevance. Knowledge regarding the role of red complex bacteria is essential for accurate diagnosis, risk assessment, and the development of targeted periodontal therapies. Effective control of these pathogens through early diagnosis, proper oral hygiene, and evidence-based treatment remains fundamental in preventing disease progression and maintaining periodontal health.

***Corresponding author**

Nanditha Chandran, 1Associate Professor, Department of Periodontics and Implantology Mahe Institute of Dental Sciences and Hospital Pondicherry UT, India.

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Introduction

Periodontitis is a prevalent dental condition that results in the deterioration of the tissues and structures supporting the teeth. The term "periodontitis" is derived from two components: "periodont-" referring to the structures surrounding the teeth, and "-itis," meaning inflammation. Periodontitis initially develops in the gingival tissue and, if left untreated, the inflammation can extend into the deeper supporting tissues. This progression disrupts bone homeostasis and can ultimately lead to tooth loss.

Periodontal disease develops from multiple contributing factors. While bacterial biofilm on tooth surfaces is the main cause of periodontitis, disease progression largely depends on the host's immune response. Other influences include local irritants like plaque and calculus, genetic predisposition, environmental conditions, overall health, lifestyle, and broader social factors. Additionally, periodontopathogenic bacteria can impact systemic health. These diseases involve complex bacterial communities interacting with host tissues, triggering inflammatory mediators that contribute to the destruction of periodontal structures such as the supporting tissues, alveolar bone, and periodontal ligament.

Bacteria linked to periodontal disease activate inflammatory responses in immune cells, which, in the advanced stages of the condition, lead to the destruction of both soft and hard tissues that support the teeth. To date, only a limited number of bacterial species have been identified as key infectious agents in periodontal disease [1].

Role of Microorganisms in Pathogenesis of Periodontitis

The microbial etiology of periodontal disease has been extensively studied over the years. Approximately 400 microbial species have been identified within the gingival sulcus, with certain organisms—such as *Porphyromonas* gingivalis and *Tannerella forsythia*—widely recognized as key periodontal pathogens due to their strong association with disease and their ability to fulfill established criteria for pathogenicity [2].

Socransky's Postulates

Socransky proposed a modified series of criteria to establish the microbial causation of periodontitis, refining Koch's postulates

to better suit the complex polymicrobial nature of periodontal infections. These criteria include the following:

- **Association with disease:** The microorganism must be found in higher numbers and at greater prevalence in disease sites compared to healthy sites.
- **Elimination or reduction upon treatment:** Successful treatment of periodontitis should result in a decrease or elimination of the organism from the affected sites.
- **Host response:** The microorganism should elicit a host immune response, indicating its recognition by the immune system as a potential pathogen.
- **Virulence factors:** The organism must possess virulence mechanisms that can contribute to tissue destruction, immune evasion, or colonization of the periodontal environment.
- **Animal studies:** The ability of the microorganism to induce similar disease characteristics in animal models strengthens its role as a pathogen.

These criteria reflect the complex and multifactorial etiology of periodontal diseases, acknowledging that no single microorganism is solely responsible, but rather a consortium of pathogens working synergistically within a dysbiotic biofilm.

Following the application of these modified criteria, three bacterial species have been widely recognized as key etiologic agents in the pathogenesis of periodontitis: *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, and *Bacteroides forsythus* (now reclassified as *Tannerella forsythia*). These organisms consistently demonstrate strong associations with diseased sites, possess numerous virulence factors, elicit host immune responses, and are reduced following successful periodontal therapy.

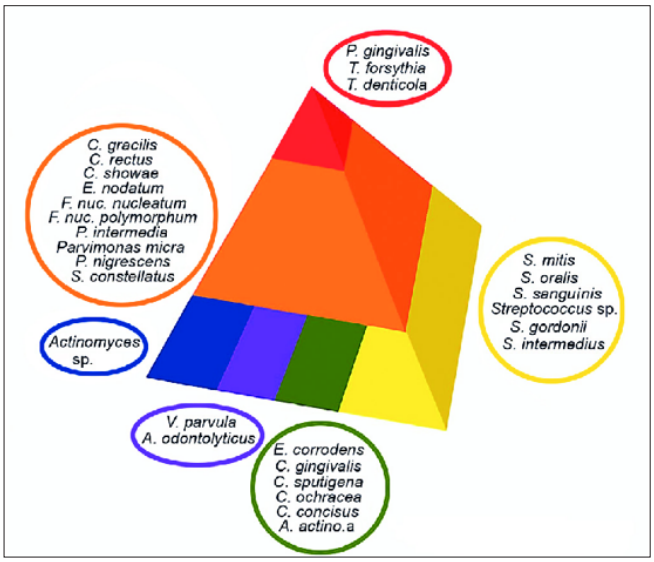
In addition to these primary pathogens, several other bacterial species have been implicated as contributory etiologic agents, though they may not fully meet all of Socransky's criteria. These include *Eubacterium nodatum, Campylobacter rectus*, *Prevotella intermedia* and *Prevotella nigrescens*, *Parvimonas micra* (formerly *Peptostreptococcus micros*), and *Treponema denticola*. While the evidence supporting their role is less definitive, these organisms are frequently associated with periodontal lesions and may participate in the polymicrobial synergy characteristic of periodontitis [2].

A widely accepted classification of subgingival bacteria was proposed by Socransky and colleagues, who categorized these organisms into six color-coded complexes: blue, green, yellow, purple, orange, and red. The red complex, which includes the most virulent pathogens, has the strongest association with clinical signs of periodontal destruction, while the yellow complex consists predominantly of commensal species.

In addition to the red complex bacteria, several other microorganisms have been implicated in periodontal disease, including *Porphyromonas endodontalis*, *Prevotella denticola*, *Filifactor alocis*, *Cryptobacterium curtum*, *Eubacterium saphenum*, *Mogibacterium timidum*, *Prevotella corporis*, *Prevotella disiens*, *Peptostreptococcus magnus*, *Slackia exigua*, *Treponema maltophilum*, *Treponema* sp. Smibert-3, *Treponema lecithinolyticum*, *Treponema putidum*, *Enterococcus faecalis*, Escherichia coli, and Bartonella species. However, the pathogenic significance of many of these organisms remains controversial and continues to be investigated.

Beyond bacteria, the oral mucosa is host to a diverse array of other microorganisms, including viruses, fungi, and archaea, which may contribute to periodontal pathogenesis. Among viruses, members of the Herpesviridae family—such as herpes simplex virus type 1 (HSV-1), Epstein–Barr Virus (EBV), and Cytomegalovirus (CMV)—are believed to play a role in both the initiation and progression of periodontal disease, particularly when co-infecting with subgingival bacteria.

Candida albicans is the most prevalent fungal species detected in both healthy and diseased oral environments. It has been shown to facilitate the invasion of P. gingivalis into gingival epithelial and fibroblast cells in vitro, suggesting a synergistic effect in disease progression. Archaea, though representing a minor component of the subgingival microbiome, are primarily methanogenic anaerobes and may contribute to the metabolic interactions within the biofilm community [3].



Different Types of Complex Bacteria

Periodontitis is considered a dysbiotic condition characterized by a shift in the subgingival microbiota from predominantly gram-positive to gram-negative bacterial species.

This dysbiosis develops gradually over time, transforming the initially symbiotic relationship between the host and microbial community into a pathogenic one.

Among the microbial complexes, the orange complex—comprising anaerobic gram-negative species such as *Prevotella intermedia*, *Prevotella nigrescens*, *Prevotella micros*, and *Fusobacterium nucleatum*—is the first to be associated with disease onset.

As the condition progresses, there is a transition toward the red complex, which includes highly pathogenic species such as *Tannerella forsythia*, *Treponema Denticola*, and *Porphyromonas gingivalis*.

Among the diverse microbial species forming the biofilm, three are particularly significant in the initiation and progression of periodontal disease: *Actinobacillus Actinomycetemcomitans* (Aa), *Porphyromonas gingivalis* (Pg), and *Tannerella forsythensis* (Tf) [4].

Current Classification System of Bacteria Responsible of Periodontal Disease (Socransky and Haffajee, 2002)

Complex	Bacteria	Role in periodontal disease
Yellow	-*Streptococcus sanguis*	Early colonizers
	-*Streptococcus gordonii*	
	-*Streptococcus intermedius*	
Green	-*Capnocytophaga gingivalis*	Secondary colonizers
	-*Capnocytophaga ochracea*	
	-*Capnocytophaga sputigena*	
	-*Campylobacter concisus*	
Orange	-*Fusobacterium nucleatum*	Secondary colonizers Precede colonization by bacteria of the "Red complex"
	-*Prevotella intermedia*	
	-*Prevotella nigrescens*	
	-*Peptostreptococcus micros*	
	-*Streptococcus constellatus*	
	-*Eubacterium nodatum*	
	-*Campylobacter showae*	
	-*Campylobacter gracilis*	
	-*Campylobacter rectus*	
Purple	-*Veillonella párvula*	Bridge species between "Orange complex" and "Red complex"
	-*Actinomyces odontolyticus*	
Red	-*Tannerella forsythia*	Secondary colonizers Main pathogens, associated with bleeding on probing
	-*Porphyromonas gingivalis*	
	-*Treponema denticola*	

Red Complex Bacteria

Red complex bacteria are frequently found together in plaque samples, particularly near the epithelial lining of deep periodontal pockets. This co-localization is largely driven by interspecies interactions, including co-aggregation and metabolic interdependence among the three key species.

The red complex—comprising *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* (formerly *Bacteroides forsythus* or *Tannerella forsythensis*)—emerges in the later stages of biofilm development and is strongly associated with the pathogenesis of periodontitis. These organisms are considered hallmark periodontal pathogens and represent a significant component of the climax microbial community at sites exhibiting active disease progression.

Notably, red complex species are rarely present without the prior colonization of orange complex bacteria. As colonization by orange complex members increases, a corresponding rise in the presence of red complex bacteria is observed [5].

Species within the red complex show a strong correlation with pocket depth and bleeding on probing. For instance, *Tannerella forsythia* and *Porphyromonas gingivalis* increase in both prevalence and abundance as pocket depth deepens. The "red complex" — composed of *P. gingivalis*, *T. denticola*, and *T. forsythia* — is widely recognized as a key bacterial consortium strongly linked to the clinical progression of chronic periodontitis. These species share common features such as:

- Extracellular proteolytic activity
- Complex anaerobic amino acid fermentation
- Production of toxic metabolites
- Release of outer membrane vesicles

Their cooperative interactions and virulence factors contribute significantly to periodontal tissue destruction and disease advancement [6].

Porphyromonas gingivalis (P. gingivalis)

P. gingivalis is a well-established periodontopathogen critically involved in the progression of periodontal disease, including the destruction of bone and soft tissue. Classified by Darveau et al. as a periodontal pathogen, this small, gram-negative, black-pigmented anaerobe plays a pivotal role in subgingival colonization through interactions with other oral bacteria like *Streptococcus* spp. and *Fusobacterium nucleatum*.

Morphological Characteristics

P. gingivalis is a gram-negative, non-motile, asaccharolytic, obligate anaerobic coccobacillus, measuring approximately 0.5–0.8 to 1.0–3.5 μm in diameter. On blood agar, its colonies transition from white/cream-colored to deep red or black over 4–8 days, reflecting heme concentration.

Virulence Factors

Key virulence factors include:

- **Capsule:** Provides antiphagocytic properties, enhances serum resistance, and reduces chemotaxis of polymorphonuclear leukocytes (PMNs).
- **Fimbriae:** Cellular appendages facilitating adhesion, motility, toxin delivery, and co-aggregation with other bacteria. They also exhibit chemotactic abilities influencing host immune response and tissue destruction.
- **Outer Membrane Proteins:** Around 20 major proteins ranging 20–90 kDa, including outer membrane vesicles capable of stimulating fibroblast activity.
- **Proteinases (Gingipains):** Numerous proteolytic enzymes including trypsin-like Arg- and Lys-specific cysteine proteinases, collagenase, and others that degrade host tissues

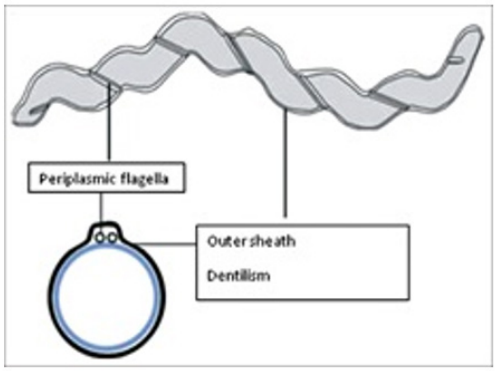
and modulate immune responses.

Treponema denticola (T. denticola)

T. denticola is a gram-negative, spiral-shaped, anaerobic spirochete characterized by its corkscrew motility. Its morphology and motility are observable via darkfield microscopy.

Morphological Characteristics

Treponema denticola is a long, thin, corkscrew-shaped, gram-negative anaerobic spirochete, distinguished by its unique motility and morphology, which are easily observed under darkfield or phase-contrast microscopy. Its spiral cells are enveloped by a fragile outer sheath. Located between the outer sheath and the cytoplasmic membrane are periplasmic flagella, which wrap around the cytoplasmic cylinder. Typically, *T. denticola* possesses four such flagella. The major outer sheath protein (Msp) is the dominant structural protein of the outer sheath



Role in Periodontal Disease

Spirochetes, including *T. denticola*, are strongly associated with deeper periodontal pockets and increased inflammation, bleeding, and tissue destruction. Their presence correlates with clinical markers of disease progression, although they are rarely found in healthy sites.

Bacterial Co-aggregation

T. denticola forms synergistic relationships with *P. gingivalis* and *F. nucleatum*, which facilitates biofilm formation and disease progression. Specific proteins like LrrA mediate adhesion to host cells and other bacterial species.

Virulence Factors

Produces a variety of hydrolytic enzymes, including hyaluronidase, collagenase, proteases, phospholipases, and phosphatases. Other important factors include:

- Major outer sheath protein (Msp)
- FH-like binding protein
- Dentilisin
- Leucine-rich repeat protein A

Tannerella forsythia (t. Forsythia)

Previously known as *Bacteroides forsythus*, *T. forsythia* is an anaerobic gram-negative member of the Cytophaga-Bacteroides family. It is frequently found at higher levels in periodontal disease compared to healthy individuals and is notably associated with increased risk in overweight and obese populations.

Virulence Factors

Identified factors include:

- Trypsin-like and PrtH proteases
- Sialidases (SiaH and NanH)
- Leucine-rich repeat protein (Lrr) and BspA surface proteins
- α-D-glucosidase and N-acetyl-β-glucosaminidase
- Hemagglutinin

Biofilm Formation

T. forsythia forms poor monospecies biofilms in vitro; however, disruption of exopolysaccharide synthesis enhances biofilm formation. It also forms mixed biofilms synergistically with *F. nucleatum*, which acts as a bridging organism facilitating plaque development [6].

Conclusion

the red complex bacteria—*Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*—play a critical role in the pathogenesis and progression of periodontitis. These microorganisms are strongly associated with deep periodontal pockets, clinical attachment loss, and increased disease severity. Their ability to function synergistically, along with their potent virulence factors such as proteolytic enzymes, endotoxins, and immune-modulating mechanisms, enables them to disrupt host tissue integrity and evade immune responses effectively.

Moreover, the presence of red complex bacteria reflects a shift in the subgingival microbial ecosystem toward a more pathogenic biofilm, contributing to chronic inflammation and progressive tissue destruction. Their interactions with other microbial complexes and the host immune system highlight the multifactorial and dynamic nature of periodontal disease.

Understanding the biological behavior and pathogenic potential of these bacteria is essential for improving diagnostic accuracy and developing targeted therapeutic strategies. Advances in molecular techniques and microbiological research continue to provide deeper insights into their role, paving the way for more personalized and effective periodontal treatments.

Ultimately, controlling red complex bacteria remains a cornerstone in the prevention and management of periodontitis, emphasizing the importance of early detection, proper oral hygiene, and evidence-based clinical interventions to maintain periodontal health and prevent disease progression.

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