**ReviewArticle**

# Aggregatibacter Actinomycetemcomitans: A Detrimental Microbial Pathogen: A Review

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**Abstract:**

Periodontal disease is a complex multifactorial inflammatory disease in which some specific microbial pathogens have been implicated in its pathophysiology namely *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia* and *Porphyromonasgingivalis.* This review focuses on *A. Actinomycetemcomitans*, a gram negative micro-oraganisms and its role as one of the causative microorganisms of periodontitis, its interaction with the host, other oral micro-flora and drugs including its association with extraoral diseases.

**Keywords:***Aggregatibacter actinomycetemcomitans,* Antibiotics, Microbiological Test, Periodontal Vaccine, Virulence Factors.

**Introduction:**

In order to understand its pathophysiology, the complex microbial community fostered in dental biofilms of damaged teeth and intra-bony pockets accompanied by the clinical complexity of periodontal disease have necessitated the classification of particular microbials linked to the disease.[1]

Many studies have related periodontal disease to specific bacteria in the subgingival plaque in the 1960s and 70s that activate the immune and inflammatory responses of the host that cause tissue and bone loss. These particular bacteria have virulence factors that help them penetrate and avoid disease-causing host defence mechanisms. Bacterial infection cannot be isolated from host reaction because much of the damage to the tissue occurs from the host that reacts to the infection site, and often the reaction is too extreme for tissues to tear down, causing resistant bacteria to proliferate.[2]

In the World Periodontics Workshop, 1996, the etiological agents of periodontitis were formally assigned as *Aggregatibacteractinomycetemcomitans*, *Tannerella forsythia* and *Porphyromonasgingivalis*. Research has also focused on associating all three species with periodontal disorder since then.[2]Klinger was the first to write on *A. actinomycetemcomitans* in conjunction with actinomycotic lesions in 1912. Jorgen Slots then identified *A. actinomycetemcomitans* role in the pathogenesis of periodontal disease and considered it as one of the most frequently active pathogens.[3]

In the present review, the main focus will be on *A. actinomycetemcomitans,* an unknown gram-negative microorganism and its taxonomy, morphology, virulence factors, role in periodontal disease and interaction with host as well as their interaction with other microorganisms, drugs and their association to disease distant from the oral cavity.

**Taxonomy of *A. Actinomycetemcomitans:***

Topley and Wilson gave the name *Actinobacillusactinomycetemcomitans*and belongs to the genus *Actinobacillus*of the family *Pasteurellaceae* which was mainly introduced for accommodation of numerous types of bacteria, namely fermentative, gram-negative

chemoorganotrophic, facultative anaerobic belonging to the genera *Pasteurella*, *Actinobacillus*and *Haemophilus*, and many more classes of species with diverse phenotypic and genotypic which are part of the above genera. In Bergey's bacteriology manual, the genus *Actinobacillus* contained 11 species.[4,5]

**Structure of *A. Actinomycetemcomitans:***

*A. Actinomycetemcomitans* is roughly 0.4±0.1 to 1.0±0.4μm in size as a gram-negative capnophilic facultative anaerobe. Tiny colonies resembling crossed cigar or star shaped occur between 0.5-1.0 mm in diameter and form the cultures of this organism and some isolates are rough-surfaced in the agar. The only organism in this genus that cannot be grown on MacConkey's agar is this organism. It is a non-hemolytic, nonsporing, immobile, oxidase and catalase positive.[6]

Surface ultrastructure such as vesicles, fimbriae, and extracellular amorphous material is the very reason that makes *A. actinomycetemcomitans* unique and aid the bacteria to thrive in the oral environment but the expressions of these ultra-structures depend on the role of the strains and cultural environment**.**

**Table 1: Virulence factors of *Aggregatibacter***

| **Factors that encourage oral cavity colonisation and persistence** | **Factors causing interference to the host defences** | **Factors that wreak havoc on the host's tissues** |
|---|---|---|
| **Adhesins** | **Leukotoxin** | **Cytotoxins** |
| **Invasins** | **LPS** | **HSPs** |
| **Bacteriocins** | **Chemotactic inhibitor** | **Collagenase** |
| **Antibiotic resistance** | **CDT** | **Bone resorption agents** |
| | **Immunosuppressive factors** | |
| | **Fc binding proteins** | |

**Virulence factors of *A. actinomycetemcomitans:***

*A. Actinomycetemcomitans* have a variety of virulence factors helping them to survive in the mouth and allowing them to escape the host's defence mechanisms. The pathogenesis of periodontitis can be implicated in many of these virulence factors. They have the capacity to adhere to extracellular matrix proteins and cells of the epithelium; antibiotic resistance; a bacteriocin; endotoxin or surface-associated material resulting in bone resorption; a chemotactic inhibitor; a collagenase; a cytotoxin; Fc-binding proteins; a leukotoxin; immunosuppressive factors; and capacity to target epithelial cells and tissues.[7]

For a long time, leukotoxin has been the "crown jewel" of this bacterium's virulence factors but a cytolethal distending toxin (CDT) has also been described, however, rendering this species the only oral microbiome member to generate these two protein exotoxins, or either of the two. Virulence factors can be broadly categorized into three groups:[7,8]

***Actinomycetemcomitans***

**Microbiological tests for *A. ACTINOMYCETEMCOMITANS:***

Clinicians are more fascinated with microbial diagnosis for (i) evaluation of active periodontal disease, (ii) to aid in selection of a practical treatment method and (iii) predicting the subsequent periodontal disease status.[9]

The various methods used for microbial analysis include culture methods, immunodiagnostic methods, nucleic acid probe and polymerase chain reaction (PCR).

Of all the microbiological studies, the PCR assay has the ability to be an optimal method of periodontal microorganism identification. It is relatively easy to do and, under optimum conditions, exhibits excellent detection limits and very little cross-reactivity. Most current PCR assays, however, give only qualitative findings and can identify quantities of pathogens that are too poor to be clinically significant. However, the culture methods still remain the most conventional, convenient and economical method.

### *A. ACTINOMYCETEMCOMITANS* in the pathophysiology of periodontitis:

#### 1. Toxins formed by bacteria in the pathogenesis of *A. actinomycetemcomitans*

Major virulence factors of this bacterium include the leukotoxin which has the potential to cause destruction of the host immune tissues. Serotype b leukotoxin can cause greater periodontal attachment loss and in this b serotype, there is the possibility of having more than one highly leukotoxic genotype. *A. actinomycetemcomitans* can lead to alveolar bone loss by increasing the activation and formation pf osteoclasts locally and their differentiation is due to proinflammatory cytokines such as IL-1. The upregulation of IL-1 in periodontal disease is usually in association with progression of the disease.[10-13]

Mechanisms of *A. actinomycetemcomitans's* leukotoxinin the progress of periodontitis. 1) When this bacterium leukotoxin binds to the LFA-1 receptor, it stimulates an inflammasome and the release of ATP into extracellular space 2) binding to P2X7 receptor 3) inducing a potassium efflux.4) Inflammasome initiates caspase 1 5) activating IL-1β 6) causing mass production of IL-1β extracellularly which is a proinflammatory cytokine that controls tissue homeostasis and its disparity can lead to tissue degeneration diseases like periodontitis.[14]

Another major virulence factor of the bacterium is cytolethal distending toxin (CDT) and it is responsible for the preservation of infection by modulation of the immune response. Link between this toxin and periodontal infection is still unclear but CDT is related to the interactivity between the host immunologic response and long-term infection of *A. actinomycetemcomitans*. CDT have the capability to activate interferon γ(IFNγ), interleukin-1β(IL-1β), as well as IL-6 and IL-8 expression by monocytes. CDT other function involves interfering the function of macrophage by stopping phagocytic action and changing the balance of cytokines. This toxin also brings about the apoptosis of non-proliferating and proliferating macrophages. CDT apoptosis mechanisms include the apoptosis-induced factor (AIF), a phosphatase-independent mechanism but for non-proliferating macrophages, it is caspase-independent mechanism.[15-17]

#### 2. Lipopolysaccharide and pathogenesis

*A. actinomycetemcomitans*'s LPS activates matrix metalloprotease-2 (MMP-2) and this activation is caused by LPS activated serine protease-dependent pathway in cells of periodontal ligament. MMP-2 is implicated in the pathophysiology of periodontal disease patients and found to be greatly elevated in cells of human fibroblast. In osteoblasts and marrow stromal cells, LPS instigates the expression of RANKL. Some studies have reported that elevation in RANKL may play a role in alveolar bone resorption and also has a crucial role in the pathophysiology of periodontitis. The action of LPS can be stop by aprotinin, a serine protease inhibitor by activating MMP-2 and this serine protease inhibitor also have a role in stopping the enhanced expression and concentration of RANKL caused by the lipopolysaccharide of *A. actinomycetemcomitans*.[18]

Mechanisms of A. actinomycetemcomitans LPS-induced chemokine expression and subsequent bone resorption. When this bacterium LPS binds to TLR4, it activates a MyD88-

dependent signalling cascade that leads to the expression of AP-1 and NF-κB and this occurrence also stimulates IP-10 expression via a MyD88-independent pathway. Overall, AP-1, NF-κB, and IP-10 expression secrete proinflammatory cytokines, which induce inflammatory cell infiltration and, as a result, tissue damage and bone resorption.[19]

**3. Biofilm formation and pathogenesis**

*A. actinomycetemcomitans's* biofilm formation is induced by auto-inducer-2 (AI-2) quorum sensing, which further influences the expression of virulence factors and uptake of iron as this bacterium' planktonic development is affected by iron deficiency.[20]

**4. *A. actinomycetemcomitans* and the immune system**

Host immune cells and *A. actinomycetemcomitans* interacts with each other by various virulence factors secretion. When comparing generalised aggressive and chronic cases of periodontal disease, researchers discovered an anomaly in the host immune response: the levels of interleukin-10 and IgG are decreased, while periodontopathogens such as *P. gingivalis* and *A. actinomycetemcomitans* seems to be elevated in aggressive periodontal disease.[21]

**5. *A. actinomycetemcomitans*and innate immune response**

When periodontitis sets in, the change in the environment causes A. actinomycetemcomitans to synthesized heat shock protein (HSPs). Heat stress causes the enhanced increased in GroEL (chaperonin 60; HSP60), DnaK (HSP80), and HtpG (HSP90) which action was to prevent lethal effects on A. actinomycetemcomitans cells. Those A. actinomycetemcomitans that are predisposed to heat stress were shown to improve the synthesis of a GroEL-family (64-kDa protein). As a result, GroEL has been shown to support *A. actinomycetemcomitans* growth in the pocket of periodontium while also causing cytotoxicity against cells of the epithelium. Therefore, when *A. actinomycetemcomitans* is present in various sites of periodontal pocket, it results in increased cell death which can be considered as an outcome of GroEL protein and can regulate cells of immune for influencing host immune response.[22]

Innate host immune response initial cell lines against pathogenic microorganism in periodontal infection are PMNs producing reactive oxygen species and three kinds of cytoplasmic granules, namely gelatinase granules, azurophilic granules and specific granules. Both methods are used to eliminate actinomycetemcomitans. Extracellular release of such elements, on the other hand, destroys chronic and aggressive periodontal tissue. The host's underlying factors, such as diabetes, significantly enhance action of PMNs and bone degradation during periodontal disease due to *A. actinomycetemcomitans*, and the increased connective tissue apoptosis and cells of gingival epithelium is due to a caspase-3-dependent pathway. The main or central cytokines secretion seen in periodontal disease as the inflammatory host response are IL-1β and IL-18. Human gingival epithelial cells exposed to this bacterium produce IL-1 and IL-8 but not IL-6, possibly plays a controlling role in the development of the inflammatory response as well as the elevation of localized immune responses. Microbial challenge increases the appearance of IL-1 and IL-18. CDT and leukotoxin have no influence over the following changes.[10,23]

**6. Acquired immune response in *A. actinomycetemcomitans***

In periodontal disease, *A. actinomycetemcomitans* may cause an acute immune response and suppressing T-helper 1 and 17 cells induces loss of bone and damage to the connective tissue. In dendritic cells, *A. actinomycetemcomitans* induces toll-like receptor 2 and 4, but toll-like receptor 2 production is higher than toll-like receptor 4 level. Toll-like receptor 2 reacts to the O-polysaccharide in LPS, whereas toll-like

receptor 4 reacts to the lipid A in LPS. In periodontitis, toll-like receptor 2 help in developing immune mediated inflammation causing damage to connective tissue and subsequent resorption of alveolar bone. In periodontal infection, toll-like receptor 2 and 4 signalling in DCs stimulates the synthesis of cytokines like tumour necrosis factor-α, β and interleukins1β, 12, 23 as well as production of CC-chemokine receptors 5 and 6. The inflammation of *A. actinomycetemcomitans* is influenced by tumour necrosis factor-α and interleukins 1β, 7, 17. In animal models of periodontal disease, RANKL-OPG mechanisms and interleukins 7,17 are linked to bone loss.[10,24]

Macrophage migration inhibitory factor and interleukins 19,21,24 have all been implicated in the development of rheumatoid arthritis as well as the escalation of periodontal infection linked to *A. actinomycetemcomitans* in various trials. *A. actinomycetemcomitans*-induced periodontitis are determined by the factors namely APRIL and BAFF (B-cell-activating factor; TNFSF13B) and these are overexpressed among kids with atopic dermatitis. An inflammatory cytokine having chemotactic activity associated with teeth erupting process as well as bone resorption in rat periodontal disease models is EMAP-II (endothelial monocytes-activating poly peptide-II; SCYE1).[10,25]

According to these findings, *A. actinomycetemcomitans* periodontitis causes inflammatory cytokines that are linked to inflammation as well as bone resorption. Furthermore, these cytokines are being linked to chronic diseases such as cancer, diabetes and autoimmune diseases. The result observed a clear association among systemic disorders and onset and progression of periodontitis.[10]

**Spread of *A. ACTINOMYCETEMCOMITANS* between individuals and oral ecosystem:**

In periodontal disease, as in other infectious diseases, knowing the origins of the pathogens and the risk of transmission becomes critical when planning preventative steps. Periodontal pathogens are known to form clusters in families. This indicates that bacteria are passed down through the generations or that family members are vulnerable to bacterial colonisation. Family studies are currently the only source of information on *A. actinomycetemcomitans* transmission between people. Although the dissemination of *A. actinomycetemcomitans* continues to be uncommon among cohabiting individuals, there isa probability that periodontally stable offspring of *A. actinomycetemcomitans*-positive parents may get infected. Offspring and parents can have similar factors that encourage *A. actinomycetemcomitans* oral colonisation, or the window of opportunity is during childhood. In order to prevent *A. actinomycetemcomitans* spread from parent to new born, bacterium-positive parents of young children are suitable candidates for better knowledge and treatment. Periodontitis can be prevented in certain populations by screening for unique clones of *A. actinomycetemcomitans*. Future research aimed at determining what causes changes in oral homeostasis that enable *A. actinomycetemcomitans* to develop could lead to novel prevention strategies for *A. actinomycetemcomitans*-associated periodontal disease.[26]

**Role of *A. ACTINOMYCETEMCOMITANS* in non-oral infection:**

The most common nonoral *A. actinomycetemcomitans* infection is endocarditis. *A. actinomycetemcomitans* endocarditis has been published in over 80 medical and dental journals since it was first identified in 1964. *A. actinomycetemcomitans* endocarditis has been reported in patients with prosthetic heart valves in at least 20 studies.[27]

Infections caused by facultative and stringent anaerobic bacteria, both gram-positive and gram-negative are widespread in nonoral diseases involving *A. actinomycetemcomitans*. As a result, single antibiotic therapies could not be successful. Furthermore, owing to the presence of

antibiotic-resistant *A. actinomycetemcomitans*, prophylactic antibiotic regimens for moderate and high-risk patients with endocarditis can have problems.

Penicillins are commonly used as first-line antibiotics, but penicillin-resistant *A. actinomycetemcomitans* still exist. Amoxicillin, cephalosporins, and ciprofloxacin are typically effective against *A. actinomycetemcomitans*, but clindamycin is not. Nonoral manifestations of periodontal infections warrant special consideration, particularly in light of recent findings linking periodontal disease to preterm birth, coronary heart disease, and cerebral infarction. Individuals who are usually well are unlikely to become sick as a result of dental focal infections.

The oral cavity can serve as a large pool of pathogens in immunocompromised patients. Infection of endodontic origin, periodontal disease and abscesses of odontogenic origin, and all raise the chances of spread of dental microorganisms to nonoral places. New associations between systemic illness and diseases of dental origin, as well as new risk factors for dental focal infection, are expected to be discovered in future research. Periodontal species that cause nonoral infections must be described in terms of their prophylactic and therapeutic implications.[27]

**Interaction of *A. ACTINOMYCETEMCOMITANS* with other bacteria:**

In a study published in 2019, Zhu B et al. discovered that under microaerobic conditions, *Streptococcus sanguinis* suppressed *Porphyromonasgingivalis* development by releasing $H_2O_2$. In *S.sanguinis-P. gingivalis-A. actinomycetemcomitans* tri-species biofilms, *A. actinomycetemcomitans* decreased concentration of $H_2O_2$ thus helping *P. gingivalis* in its survival.

However, these types of experiments were carried out in anaerobic environments. Under these circumstances, $H_2O_2$ production can be reduced. As a result, when opposed to microaerobic conditions, the killing effect of *Streptococcus gordonii* on *P. gingivalis* can be reduced under anaerobic conditions.[28]

**Interaction of *A. ACTINOMYCETEMCOMITANS* with drugs:**

Multidrug resistance is a major concern in dermatologic disorder, especially among the Latin Americans, where it is estimated to occur at a rate of 24.7 percent, compared to 10.8 percent in Europe and North America (3.2 percent). Antimicrobial susceptibilities in Latin America are also the lowest in any region for polymyxin B, aztreonam, gentamicin, cefepime, imipenem, ceftazidime, piperacillin/tazobactam, and ciprofloxacin. Latin America had the lowest imipenem susceptibilities (65.3 percent) compared to Europe (80.7% percent) and North America (88.7 percent). In Latin America, imipenem resistance on multiple occasions had been mostly cause by emergence as well as spread of metallo-β-lactamase enzymes. Furthermore, there has been a rise in the prevalence of penicillin-resistant pneumococci all over the world, and Latin America is no exception.[29]

The most active antibiotics against *A. actinomycetemcomitans* were moxifloxacin and amoxicillin/clavulanic acid, according to different reports, with all isolates susceptible. The less successful being clindamycin, metronidazole, and amoxicillin. Because of regional and temporal variations, it's likely that antibiotic overuse and misuse are affecting the emergence of more highly resistant strains associated with periodontal infections in our population. For improving the local prescription guidelines, longitudinal surveillance studies have been instrumental in tracking and identifying regional antimicrobial resistance patterns as they provide useful information.[29]

Vaccination against this periodontopathogen bacteria have been tried by utilizing its multiple antigens. In a rabbit model, a synthetic oligopeptide based on the amino acid sequence of *A. actinomycetemcomitans* fimbriae was found to be efficient

in inhibiting adhesion and subsequent colonisation. In addition, mice immunised with capsular serotype b-specific polysaccharide antigen (SPA) subcutaneously and intranasally showed positive results. Mice provided with anti-surface associated material from *A. actinomycetemcomitans* produced defensive antibodies that acted as an opsonin.[7]

Owing to the multifactorial and polymicrobial existence of periodontal disease, immunisation of the world population with periodontal vaccine is still a dream that's yet to be achieve. This necessitates a sophisticated vaccine formulation regimen that addresses several pathogenic pathogens, which is currently undergoing extensive research.[7,29]

**Conclusion:**

The understanding of this organism still lags behind that of enteric pathogens, owing to the fact that genetic modification methods have only recently become accessible. However, with the rapid advancement in medical science technologies such as parallel DNA sequencing, proteomics, metabolomics, transcriptomics, and many others, the discovery and exploration of *A. actinomycetemcomitans* molecular genomics is now feasible in order to offer greater information about the evolution of the bacteria's relationship with the host, so as to aid in the prevention and treatment of destructive periodontal disease.

Conflict of Interest: There is no conflict of interest.
Source of funding: Nil.

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**How to cite this article:** Salam E,Mehrotra S, Dhruvkumar D. *Aggregatibacter actinomycetemcomitans*: A detrimental microbial pathogen:A review . *TMU J Dent 2022;9(1):29-37.*