HANG TUAH UNIVERSITY

FACULTY OF DENTISTRY PRESENT

INTERNATIONAL SCIENTIFIC MEETING

SEMINAR BOOK

Dentisphere 3

Dentistry Update & Scientific Atmosphere

26th-27th, August 2016

Shangri-La Hotel

Surabaya-Indonesia

Current Concepts and Technology in Improving Dental and Oral Health Care

GREETINGS FROM THE CHAIRMAN

Hello Dentists!
Welcome to the International Seminar 3rd Dentisphere. It's an honor for us, Dentistry Faculty of Hang Tuah University to host the International Seminar 3rd Dentisphere. We are welcoming all of our sponsors, speakers and participants from both inside and outside Indonesia who contribute to this International event. Welcome to Surabaya everyone!

The theme of this time seminar is "Current Concepts and Technology in Improving Dental and Oral Health Care", as the committee we offers a place to learn and exchange dental knowledge with national and international facilitators. International Seminar 3rd Dentisphere will also provide a unique opportunity for participants to develop the knowledge, skills and professionalism with the interaction with other participants. Do not miss the opportunity to interact directly and do hands on with the speakers and experts which are amazingly competent in the field of dentistry from different countries (Indonesia, Japan, Korea, Singapore, and Malaysia).

After all, we apologize if if there are less pleasing for the organization of this seminar. Enjoy the beauty of Surabaya while you also explore the dental sciences.

Chairman,
Dwi Hariyanto, drg., M.Kes

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SHORT LECTURE SCHEDULE

FRIDAY, AUGUST 26th 2016
PELANGI ROOM 2

TIME	PELANGI 2
13.00 - 13.15	**1. Poetry Oktanauli[1], Radinda Myrna Andiani[2]** Faculty of Dentistry, Prof. DR. Moestopo (B) University Jakarta [1]Department of Oral Biology, [2]Post Graduated Student, *"Effect of Piper betle L. Leaves Extract In The Formation of Dental Plaque"*
13.15 - 13.30	**2. Erna Fakhriyana[1], Harry Laksono[2]** Faculty of Dentistry, Airlangga University [1]Resident of Prosthodontics, [2]Department of Prostodontic Surabaya *"Treatment of Temporomandibular Disorder Using Full Occlusal Splint"*
13.30 – 13.45	**3.Atik Kurniawati** Faculty of Dentistry, Jember University, Jember Department of Dental Basic Science *"Immunophatogenesis of Oral Tuberculosis "*
13.45 – 14.00	DISCUSSION
14.00 – 14.15	**4. Elin Hertiana** Faculty of Dentistry, Prof. DR. Moestopo (Beragama) University, Jakarta Department of Prosthodontic *"Impression Technique Using Split Impression Tray in Scleroderma's Patient (Case Report)"*
14.15 - 14.30	**5.Putri Welda Utami Ritonga[1], Vincent[1]** Faculty of Dentistry, Sumatera Utara University Department of Prosthodontics *"Effect of Denture Disinfection with Microwave to Dimensional Change and Water Sorption"*
14.30 – 14.45	**6. Mirna Febriani** Faculty of Dentistry, Prof.DR.Moestopo(B) UniversityJakarta Department of Dental Material *"The Effect Of Chlorhexidine To Colour Of Resin Composite Restoration"*
14.45 – 15.00	DISCUSSION

SHORT LECTURER 3

Immunophatogenesis of Oral Tuberculosis

Atik Kurniawati*
*Department of Dental Basic Science, Faculty of Dentistry, Jember University, Jember

ABSTRACT

Background: *Tuberculosis (TB) is the most important bacterial infectious disease in the world. Infection occurs when a person inhales droplet nuclei containing tubercle bacilli that reach the alveoli of the lungs. The development of TB disease depend on host immune response. Immune mediator such as interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) activate macrophages and promote bacterial killing. IFN-γ is mainly secreted by natural killer (NK) cells and T cells upon instruction by interleukin 12 (IL-12) and interleukin 18 (IL-18). This cytokines are primarily produced by dendritic cells and macrophages in response to Toll-like receptor (TLR) signaling interaction with tubercle bacilli. These signals also induce pro inflammatory cytokines (including TNF-α, IFN-γ) to recruits innate effector cells such as macrophages, polimorphonuclear neutrophils (PMN) and NK cells to the lungs as the infectious foci. If the immune cells settle to form granuloma that prevents tubercle bacilli dissemination, unless becomes Extra Pulmonary TB. Extra pulmonary TB disease occurs in places other than the lungs. It can occur in the lymph nodes, meninges, kidneys, bone, skin and even oral cavity that we called oral tuberculosis. The oral tuberculosis may manifest in various form such as ulcer, gingivitis, nodules, granulomatous, tuberculoma and osteomyelitis. The purpose of this paper to explain how the imunophatogenesis of extra pulmonary TB can manifest in oral cavity.*

Keyword : *immunopathogenesis, oral tuberculosis*

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IMUNOPATHOGENESIS OF ORAL TUBERCULOSIS

INTRODUCTION

Tuberculosis (TB) is a respiratory disease due to chronic infection caused by Mycobacterium tuberculosis, which mainly affects lung tissue and can attack other organs, including the oral cavity, known as extra pulmonary tuberculosis (EPTB). Not only in humans but animals can also get tuberculosis. Mycobacterium tuberculosis is special, which is resistant to acid in Ziehl Neelsen (ZN) staining so it is called Acid Resistant Bacteria (BTA). Bacterial resistance to acids is due to the presence of wax in the cell wall, this is what causes Mycobacterium tuberculosis to have a stronger resistance in nature than other bacteria. With sunlight or heat, the bacteria will die within minutes, but can survive several hours in a dark and damp place (Jawetz, 2007). In body tissues, Mycobacterium tuberculosis has the ability to change the macrophage immune response because of its ability to live and multiply within macrophages, thereby avoiding phagocytosis. Macrophages are the main key in the elimination process of bacteria. If there is a disturbance of the body's immune response, the bacteria will avoid the elimination mechanism so that the immune response plays a fundamental role in the outcome of tuberculosis infection (Scluger et al., 2001; Flyn, 2001; Abbas et al., 2010).

MECHANISM OF ORAL TUBERCULOSIS

The pathogenesis of tuberculosis begins with the inhalation of Mycobacterium tuberculosis bacilli into the alveoli of the lungs, then an inflammatory response occurs, neutrophils and macrophages accumulate. These bacilli can then migrate to regional lymph nodes and form primary complexes (Dormans, 2005). Bacilli in lung tissue lesions or lymph nodes can be engulfed by macrophages and multiply within macrophages. The primary lesion heals, resorption of the inflammatory exudate and destruction of the bacilli occurs. If the bacilli survive, they can reach the lymphatic ductus thoracicus and the bloodstream and expand to other organs in the body (Dormans, 2005). After the initial infection (3 to 13 weeks), an immune response can be detected. Lesions in the lungs or elsewhere are not visible, 90-95% of infected individuals are asymptomatic, although there is a hypersensitivity reaction. In these hidden lesions, bacilli can survive which can later experience activation (Abbas, 2009).

Five to ten percent of infected individuals may experience a pathological response, proliferation of bacilli takes place and a positive tuberculosis clinical examination. The bacilli persist and multiply at the site of infection, followed by an increase in mononuclear cells, tissue macrophages and other cells (Brook, 2001). Macrophages and epithelioid cells form elongated and densely form tubercle. Some of these cells combine to form giant cells. The tubercle appears as a granular nodule (granuloma), this is a host mechanism to inhibit multiplication. Within the tubercle, bacilli are produced. Neutrophils in the lesion release lysosomal enzymes which can destroy not only the bacilli but also the tubercle. This tissue damage results in a semi-solid clumping mass of host cells and bacilli, which is called caseous necrosis. These lesions heal by calcification, while the bacilli within them can survive for several years. This calcification allows radiographic visualization (Barera, 2007).

If the infection is not controlled. Caseous lesions may ooze. This liquid material can escape and form cavities in the lungs. Bacilli that escape from the lesion can spread via pulmonary or systemic vessels. Live bacilli can be brought into the bronchi, then aspirated to the lower part of the lungs or out through sputum (Barera, 2007). When the disease appears to be over, reinfection can occur by activation of bacilli that survived the primary infection, or inhalation of new bacilli from the environment. This condition is called reactivation tuberculosis, occurs mainly in the elderly or the presence of factors of malnutrition, diabetes mellitus, long-term corticosteroid therapy (Abbas, 2009).

The pathogenesis of tuberculosis starts from the entry of bacteria until the appearance of several clinical symptoms can be described as follows (Kaufmann, 2002):

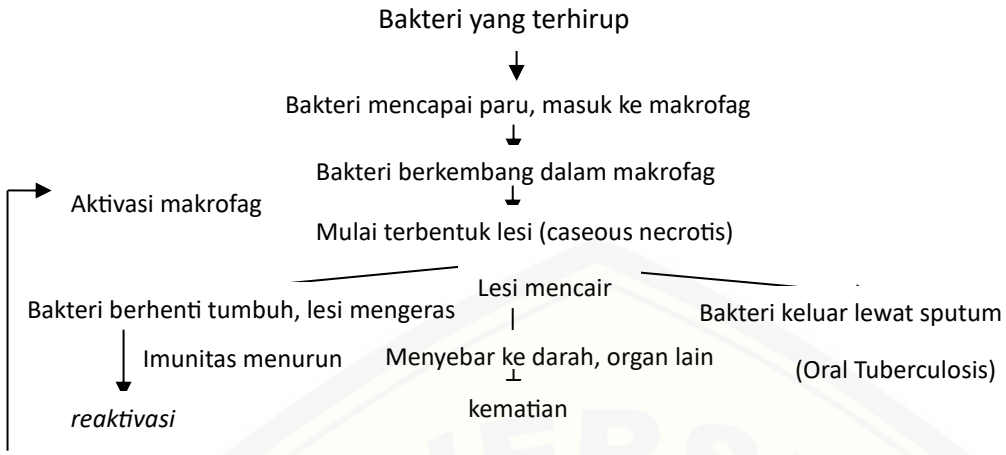


Figure 1. Schematic of tuberculosis pathogenesis (Handayani, 2012)

The first response that appears after infection is the accumulation of mononuclear cells, both macrophages, lymphocytes, plasma cells and neutrophils. According to Dorman et al., (2004) the parameters used were peribronchiolitis, perivasculitis, alveolitis and granuloma. The results in this study, peribronchiolitis occurred in all treatment groups namely K(+), P1, P2 and P3 where peribronchiolitis occurred. This is due to the way mice were infected with the intratracheal method. This means that the bacteria will pass through the bronchi first before invading the lung tissue. The presence of Mycobacterium tuberculosis in the bronchi causes the body to provide a defense response by mobilizing inflammatory or inflammatory cells. This inflammatory reaction aims to prevent Mycobacterium tuberculosis from invading the lung tissue. This inflammatory process causes damage to the bronchioles, resulting in peribronchiolitis.

The response to Mycobacterium tuberculosis then develops until acquired immunity develops with the formation of granulomas. There are 2 types of immunity acquired in tuberculosis, namely cell mediated immunity (CMI) and delayed type hypersensitivity (DTH). CMI shows a process that causes the accumulation of a number of activated macrophages that are microbicidal, while DTH shows a cytotoxic immune process that kills immature and unactivated macrophages causing multiplication of Mycobacterium tuberculosis (Saunders et al., 2007).

Granuloma formation begins with the introduction of CD4+ Th1 cells that recognize the peptide fragment antigen formed via the major histocompatibity (MHC) II receptor. Peptide fragment antigens are formed by proteolytic digestive enzymes generated by antigen presenting cells such as macrophages and dendritic cells. Several cytokines are formed by CD4+ Th1 cells, namely IFN-γ, GMCSF to macrophages infected with Mycobacterium tuberculosis to increase effector function in these macrophages. Another cytokine, namely IL-2, is also produced by CD4+ Th1 cells to stimulate CD8+ cytotoxic T cells, which are then activated to surround the infected lesion by releasing chemotactic cytokines, including IFN-γ, monocyte chemoatrantant protein 1 (MCP 1) and IL-8. After aggregation occurs in the lesion, monocytes move from the circulation to the lesion. A number of monocytes become alveolar macrophages, which then become palisade or epithelial histiocytes. Several cells fuse to form Langhans giant cells which are characteristic of granulomas (Saunders et al., 2007).

Damage to lung tissue in tuberculosis infection is also caused by Mycobacterium tuberculosis, which can induce the expression of matrix metalloproteinase enzymes (MMPs). This enzyme functions to

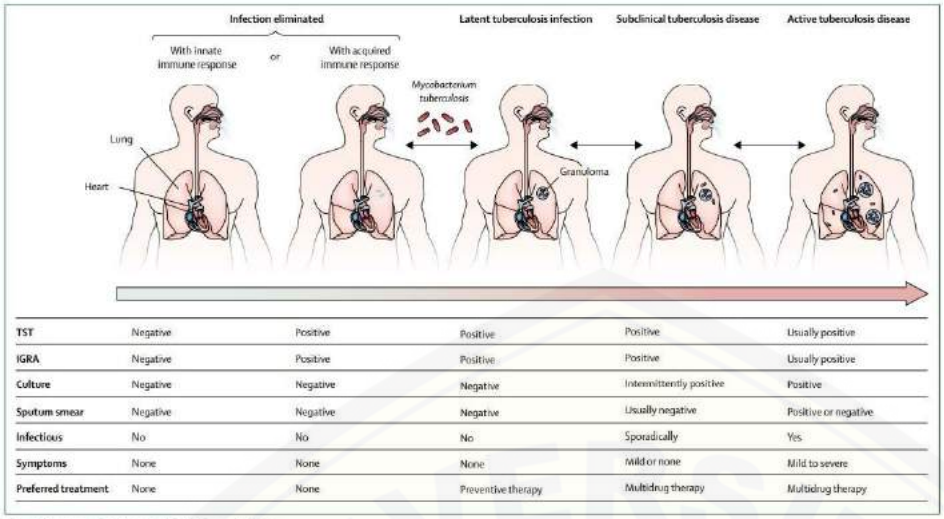
break down matrix and change tissue shape. MMPs are members of the protease family which are capable of degrading cellular matrix components. MMPs activity is regulated at the transcriptional level and their activation is carried out by proteolytic cleavage. MMPs are specifically inhibited by tissue inhibitor of metalloproteinase (TIMPs) enzymes. The excessive increase in the activity of this enzyme causes a broad pathological picture in lung tissue which is characterized by damage to the extracellular matrix (Elkington et al., 2011).

MMP-1 has the ability to degrade type 1 collagen which causes lung tissue damage. Research on tuberculosis patients showed an increase in MMP-1 and a decrease in TIMPs enzymes. This study is in line with studies in experimental animals, namely mice infected with Mycobacterium tuberculosis, showing an increase in the MMP-1 enzyme which correlates strongly with an increase in alveoli tissue damage and a significant increase in collagen breakdown (Elkington et al., 2011).

The course of Mycobacterium tuberculosis infection varies greatly, depending on immune factors, host cell sensitivity and virulence of the bacteria (Dormans, 2004). TB lesions early in the course of the disease are proliferative and exudative. In individuals who have good immunity, the phagocytic reaction will be sufficient for the formation of fibroblastic wall boundaries and scarring. In susceptible individuals, the exudative lesions are extensive, involve many inflammatory cells and have poor localization. Furthermore, the response to germs develops until it grows acquired (adaptive) immunity with the formation of granulomas. There are 2 types of adaptive immunity in TB, namely CMI and DTH. CMI shows a process that causes the accumulation of a number of activated macrophages that are microbicidal, while DTH shows a cytotoxic immune process that kills immature macrophages and is not activated, causing the multiplication of tuberculosis bacilli.

Granuloma formation begins with the introduction of CD4+ TH1 cells that recognize antigen peptide fragments via the MHC II receptor. Peptide fragment antigens are formed by proteolytic digestive enzymes generated by APCs such as macrophages and dendritic cells. Several cytokines are produced by CD4 TH1 cells, namely IFN-γ, GMCSF, TNF-α to enhance the effector function of these macrophages. Another cytokine, namely IL2, stimulates CD8 as a cytotoxic, which then plays a role in destroying infected immature macrophages by apoptosis. Activated macrophages surround lesions infected with Mycbacterium tuberculosis by releasing chemotactic cytokines including IFN-γ, MCP-1, IL-8. Likewise, aggregation occurs in the lesion, monocytes move from the circulation to the lesion. Some of these monocytes become alveolar macrophages, which then turn into palisade histiocytes or epithelial cells. Some of these cells function to form Langhans giant cells which are a characteristic feature of granulomas (Pissens, 2000). Granulomas in mice are different from humans. In mice, it is composed of neutrophils, macrophages and lymphocytes with activated macrophage structures and lymphocytes surrounding a collection of infected macrophages. In this granuloma there is no necrosis and Langhans cells so HPA is different. Although the structure is different, the function is the same, namely controlling and preventing the spread of infection. The absence of necrosis in mice granulomas indicates that the immune response that is generated is stronger so that the degree of spread of infection is lower (Cardona, 2004).

Tuberculosis is a disease of poverty. Mycobacterium tuberculosis and humans have coexisted for thousands of years. 1-7 billion people globally are estimated to be infected with M. tuberculosis, only a few of these people will go on to develop active tuberculosis. The understanding of the pathophysiology of tuberculosis continues to develop, the complex dynamics of bacteria and hosts results in the pathology of tuberculosis as shown in the following figure.



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Figure 1: **Spectrum of tuberculosis infection and disease**
Reproduced from Pai et al,[14] by permission of Springer Nature. IGRA=interferon-γ release assay. TST=tuberculin skin test.

TB is caused by the acid-alcohol fast bacillus M. tuberculosis. M. tuberculosis is an aerobic bacterium, not encapsulated and does not form spores. The bacterial wall which contains lipids is relatively resistant to many disinfectants and is also a host defense mechanism and this plays an important role in the pathogenesis of TB disease. The organisms are usually airborne and grow in the alveoli of the lungs and macrophages and are accompanied by a local inflammatory response. (Samaranayake et al., 2008). TB bacteria can remain suspended in the air in droplets for hours. Talking or a single cough or sneeze can produce many infectious droplets, and just 10 bacilli can cause infection. If inhaled by a susceptible host, Mycobacterium can persist in the alveoli and can eventually be phagocytosed by alveolar macrophages; if phagocytosis is successful, the patient has latent TB. If macrophages fail to phagocytize, active TB will occur. Only patients with active disease are contagious (Singer-Leshinsky, 2016).

Mucus-secreting goblet cells are the first line of defense against TB infection, followed by alveolar macrophages of the innate immune system. The complement system aids in phagocytosis by producing the protein C3, which binds to the bacterial cell membrane, enhancing recognition and opsonization. Macrophages produce proteolytic enzymes and cytokines that degrade bacteria, and attract T cells that trigger a cell-mediated immune response, releasing IL-12 and IL-18. CD4 T lymphocytes release gamma interferon, causing further phagocytosis. Interferon gamma causes the release of tumor necrosis factor alpha (TNF), granuloma formation, limiting bacterial replication.

The center of the granuloma is a caseous necrotic material characterized by low oxygen levels, low pH, and limited nutrient supply. There the bacteria remain dormant and protected by an adequate immune system until the granuloma undergoes fibrosis and calcification. The initial cell-mediated immune response takes 2 to 12 weeks to develop in patients with normal immune systems, and is identified by a positive tuberculin skin test.

ORAL MANIFESTATIONS OF TUBERCULOSIS

The main etiology of tuberculosis in humans is Mycobacterium tuberculosis, a rod-shaped bacterium that is acid-fast, non-motile and obligate aerobic. Oral tuberculosis is actually rare, and according to research the possibility of occurrence is only 0.1-5%. Oral tuberculosis is usually accompanied by the

appearance of lesions, which can be primary or secondary lesions. Oral lesions present in various forms, such as ulcers, nodules, tuberculomas, and periapical granulomas.

For those with primary lesions, it could be because initially the patient had lesions or mucosal lesions due to chronic inflammation, so from there it could be a route for bacteria, especially M. tuberculosis, through sputum or inhalation from the outside. The primary lesion is also rare, usually occurs in younger patients, and presents as a single, painless ulcer with enlarged regional lymph nodes. But if the secondary lesion is caused by TB bacilli from the lung tissue it can reach the oral mucosa through hematogenous or lymphatic spread. Secondary lesions are common, usually appearing as a single, indurated, irregular, painful ulcer covered by inflammatory exudate in patients of all age groups but are relatively more common in middle-aged and elderly patients.

Occasionally, the lesion has ulcerated and a caseous granuloma has formed. The formation of these granulomas has indeed become a characteristic if someone has tuberculosis. These granulomas contain a central necrotic core surrounded by a layer composed of macrophages, T and B lymphocytes, neutrophils, epithelioid cells, foamy macrophages, multinucleated Langshan giant cells, and cellular matrix components. In most people who are infected with TB, granulomas do not develop / are static because they are covered by fibrous tissue. However, in a small proportion of people who are infected with TB, their granulomas can develop as a further process of infection for a long time after infection, which can be more than a year and 2 years. So the caseous center that has already formed in the granuloma undergoes liquefaction, the TB bacilli proliferate and produce more antigens at the infected site causing a greater cellular immune response and larger lesions, and finally the necrotic zone ruptures and spreads, caseous fluid flows near the zone. infected, and increasingly colonize there and cause further cellular inflammation.

Tabel 4. 1 Perbedaan Oral TB primer dan Sekunder

Variabel	TB Oral Primer	TB Oral sekunder
Insidensi	Sangat jarang	Lebih sering
Predeleksi	Anak-anak	Setengah baya dan lansia
Ulser	Dangkal, tertutup jaringan granulasi atau lebih besar dan lebih dalam.	Tepi undermine dan irregular dan tertutup jaringan granulasi
Rasa sakit	Tidak sakit	Sakit
Kelenjar limfe	Membesar dan sakit	Bisa membesar/tidak dan biasanya tidak sakit

During the incubation period and before the development of cellular immunity, lymphogenous and hematogenous spread may occur. In hematogenous spread, MT enters the blood vessels and spreads throughout the body, especially in organs that have good vascularization, this is thought to be the pathogenesis of primary TB lesions in the oral cavity. MT can be inoculated directly into the oral cavity in a person who does not have acquired immunity against this disease. Wounds from tooth extraction can be a place for MT to enter the oral cavity. A history of local trauma in the oral cavity such as bites or incisions needs to be considered, because physiologically the stratified squamous epithelium in the oral cavity normally functions to prevent the entry of MT. In addition to the state of the integrity of the oral mucosa, saliva also has a supporting role, especially in mechanical rinsing, salivary pH, and salivary antibodies which function as inhibitors against the entry of MT into the oral cavity.

Tuberculous lesions of the oral cavity do occur but are relatively rare. Oral TB lesions can be either primary or secondary in occurrence. Rare primary lesions seen in younger patients are often associated with enlarged cervical lymph nodes. Secondary oral TB usually coexists with lung disease, can occur in all age groups; However, middle-aged and older people are more likely to be involved. The most likely route of inoculation is introduction of the organism in the sputum and, from there, into the mucosal tissue through small surface breaks. It is possible that organisms may be introduced into the oral tissues by the hematogenous route, to be deposited in the submucosa, and then proliferate and ulcerate the overlying mucosa.

One of the common modes of entry for microorganisms is into the periapical inflammatory area via the bloodstream. It is also possible that these microorganisms may enter the periapical tissues by direct immigration through the pulp chambers and root canals of teeth with open cavities. The resulting lesion is essentially a tuberculous periapical granuloma or tuberculoma; Diffuse involvement of the maxilla or mandible may also occur, usually by hematogenous spread of infection, but occasionally by direct extension or even after tooth extraction. Tuberculous osteomyelitis often occurs in the late stages of the disease and has an unfavorable prognosis.

CONCLUSION

Mycobacterium tuberculosis bacillus which is acid and alcohol resistant is transmitted via droplet nuclei in the air and multiplies in the alveoli of the lungs. Bacterial replication occurs in alveolar macrophages and spread of infection by regional lymph nodes. In most cases, T-helper cells (CD4) activate macrophages and infection via secretion of cytokines and gamma interferon where the infection is suppressed permanently is called primary infection or can remain latent to reactivate months or years later. If the immune response is poor and cannot prevent bacterial replication, the disease becomes active again. 5-10% of exposed patients will develop active TB during their lifetime. Bacteria that are dormant in primary tuberculosis will appear months or even years later as an endogenous infection to become secondary tuberculosis. In contrast to primary tuberculosis, the lesions from secondary infection are generally chronic and have little chance of spontaneous resolution. The occurrence of infection depends on systemic factors including low host immunity and increased virulence of the microorganism. Local predisposing factors in the oral cavity that can trigger the occurrence of oral tuberculosis include: local trauma, poor oral hygiene, the presence of previous lesions such as leukoplakia, periapical granuloma, cysts, abscesses, fractures of the jaws and periodontitis

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