

PROCEEDINGS

The 1st International Basic Science Conference 2016

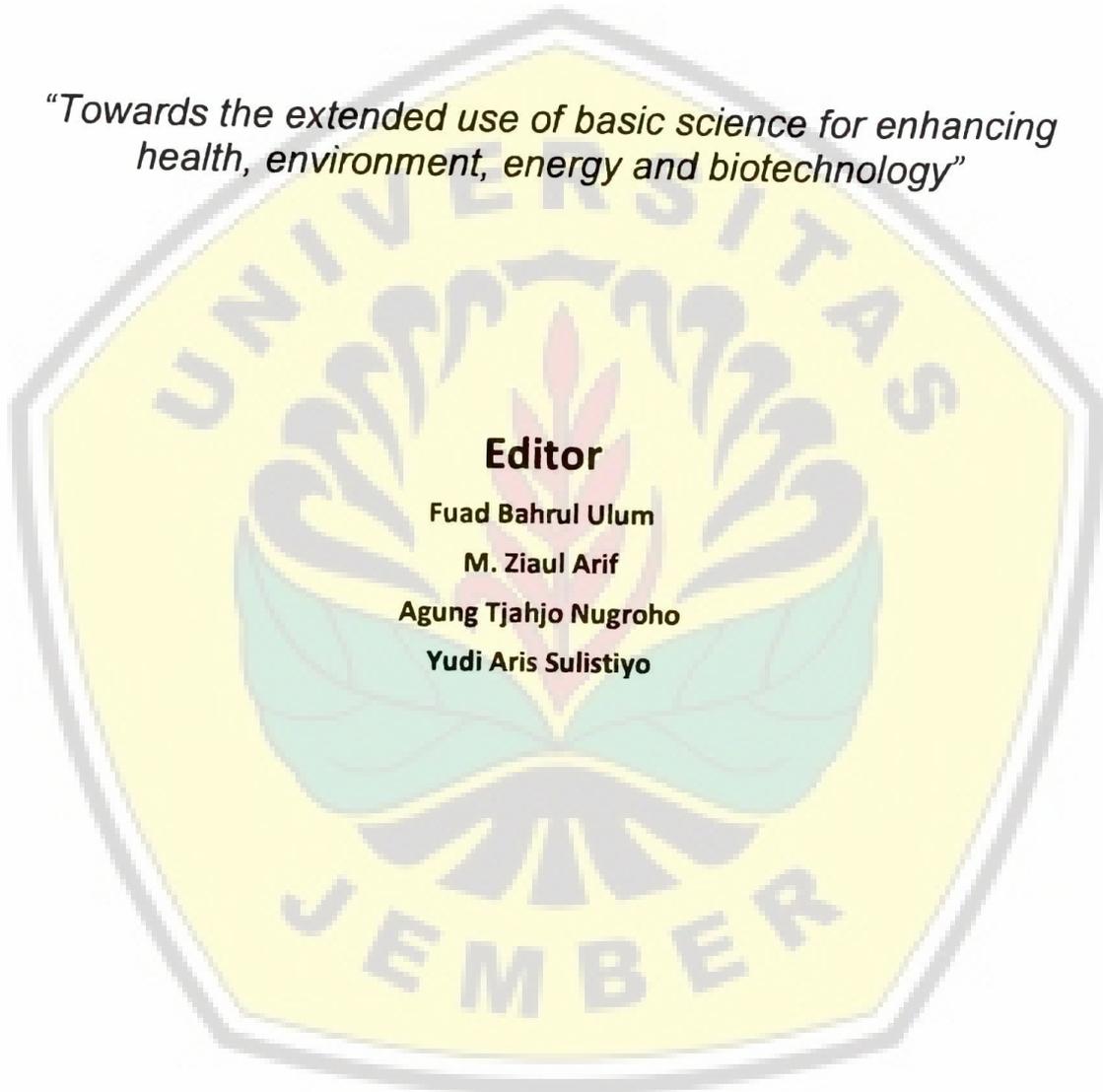
**TOWARDS THE EXTENDED USE OF BASIC SCIENCE
FOR ENHANCING HEALTH, ENVIRONMENT,
ENERGY, AND BIOTECHNOLOGY**

University of Jember, September 26 - 27, 2016



(The 1st IBSC 2016)

“Towards the extended use of basic science for enhancing health, environment, energy and biotechnology”



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Preface

A Conference on the extended use of Basic Science was hosted by the Faculty of Mathematics and Natural Science (FMIPA), at CDAST building, Universitas Jember in 26-27th day of September 2016. This conference is intended to promote further developments of basic science for their tangible applications, especially health, environment, energy and biotechnology.

The conference posed the question "what biological, chemical, physical, geological, mathematical, statistical, medical, agricultural and other basic science field changes must be made in order to ensure better live quality in term of health, environment, energy and biotechnology. FMIPA was fortunate to welcome researchers, educators and engineers from various backgrounds representing a variety ways to extend the application of basic science in which safety, environmental friendly and energy efficiency were being pursued. More than two hundred contributors from fifty five different institutions presented the theory, methodology and application of the field and thus the 1st IBSC 2016 was very rich as the proceeding in this volume.

The major theme that emerged from the conference which was conducted by Faculty of Mathematics and Natural Science, Universitas Jember, and The Ministry of Technology and Higher Education (KEMENRISTEKDIKTI), Republic of Indonesia, was that basic science must extend in very fundamental way if high live quality is to become a stable standard of health, environment, energy and biotechnology. Ramkrishna Ramaswamy in his very inspiring talk, present the complexity and simplicity in biological systems; while Agus Salim discussed the big data of biostatistics with stressing on the quantity does not equal quality; Manabu Abe report the design and synthesis of a new Cromophore, and Bambang Sugiharto address the regularisation of sucrose-phosphate synthesis from sugarcane, and many more expert discus the application of basic science for improving live quality.

Having introduced the 1st IBSC 2016, we will introduce the 2nd Conference of basic science (The 2nd IBSC) in near future. This collaboration and link will be maintain. Hand in hand researcher, expert, educator and other professional in basic science is needed to improve live quality.

Jember January 26, 2017

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The Chairman of The 1st IBSC

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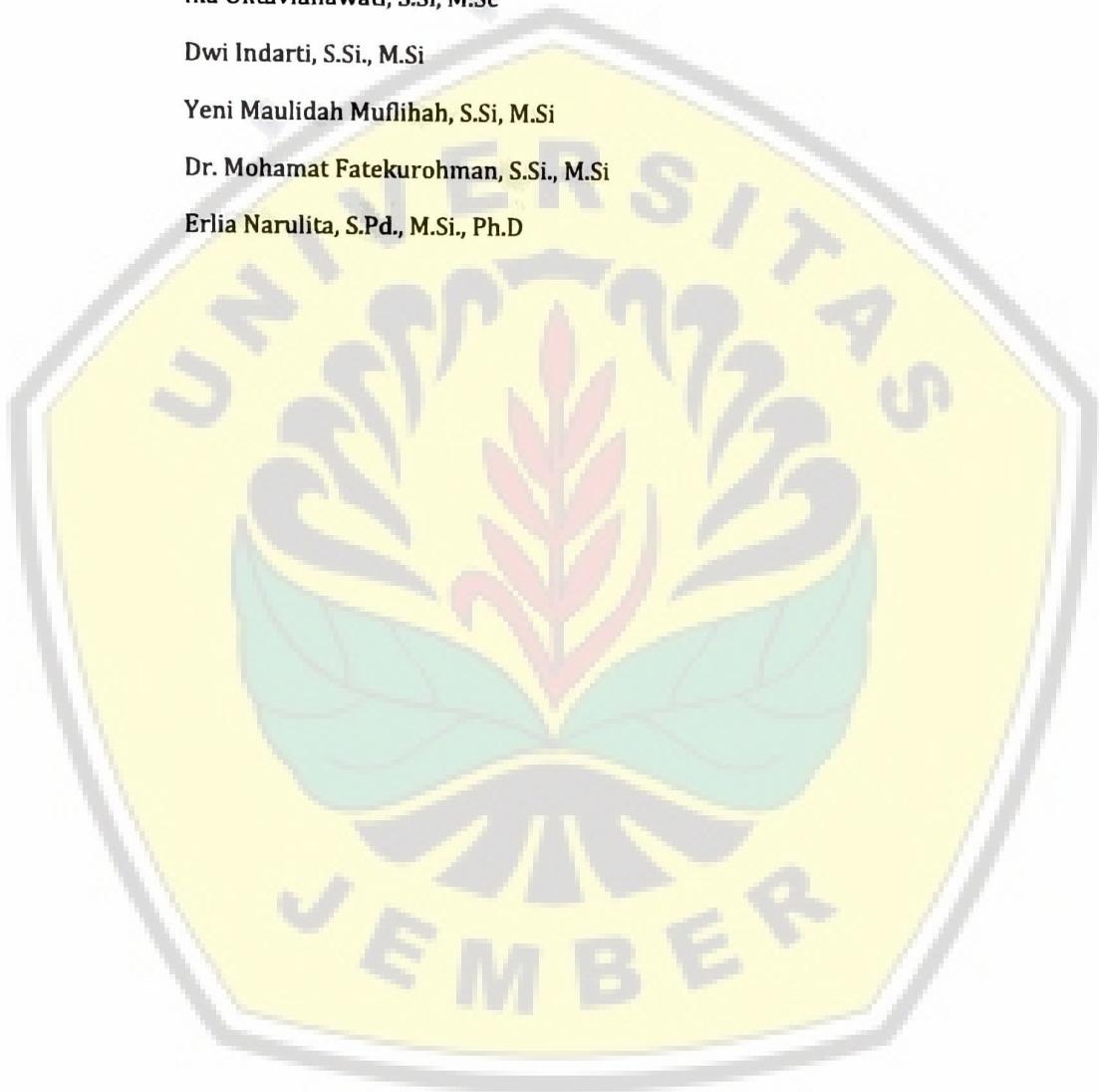


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Clinical Manifestation of Oral Tuberculosis

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Abstract— Tuberculosis (TB) is chronic infectious disease caused by *Mycobacterium tuberculosis*. According to WHO report, it infected almost one third people and Indonesia has been 5th position in the world. Tuberculosis is classified clinically as Pulmonary and Extra Pulmonary. Extra pulmonary tuberculosis 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 : ulcer, gingivitis, nodules, granulomatous, tuberculoma and osteomyelitis. The purpose of this paper to explain the clinical manifestation of oral tuberculosis.

Keywords - manifestation, oral, tuberculosis

INTRODUCTION

Tuberculosis (TB) has afflicted mankind from the time immemorial. Evidence of spinal disease has been found in Egyptian mummies of several thousand years BC and references to TB are found in ancient Babylonian and Chinese writings[1]. Despite more than 100 years of research. Tuberculosis is still the most important bacterial infection worldwide. Tuberculosis (TB) is a chronic granulomatous infection which is caused by *Mycobacterium tuberculosis* that infects numerous people annually and ranked among the highest death causing contagious diseases[2]. World health organization (WHO) estimated there are twenty million active tuberculosis cases worldwide with 80% of them happened in developing countries. Highest incidences occurred in India, Southeast Asia, and Africa. According to WHO, Indonesia soared on 5th place worldwide with 660.000 cases of tuberculosis in 2010. Back in 2008, as many as 14.158 pulmonary tuberculosis incidences were recorded in the province of East Java with mortality rate of 264. Seventy percent of those infected were aged 17-54, which is their productive age. An individual whose has active acid-fast bacteria is able spread the infection up to 10-15 person every year, increasing the number of pulmonary tuberculosis infection[3,4].

Generally, tuberculosis can be classified into two types, i.e: primary and secondary tuberculosis or post-primary tuberculosis. Primary tuberculosis is the first stage when the infected individual first contacted with *Mycobacterium tuberculosis*, the secondary tuberculosis or post-primary tuberculosis occurred after several months or years after primary infection that usually caused by compromised host immunity induced by HIV infection and poor nutrition. The risk of developing disease is greatly increased by acquired immunodeficiency syndrome (AIDS), young children less than 5 years old, malnutrition (Vitamin D deficiency), respiratory viral infection, aging, Diabetes Mellitus, alcoholism, renal failure, malignancy, immunosuppressant : corticosteroid, TNF- α inhibitor, chemotherapy, etc., and other immune-compromising condition[3,4].

Most of tuberculosis bacteria targeting the lungs, occasionally they can also affects the other organs as well, such as brain membrane (meninges), skin, bone, lymph nodes, and oral cavity[2,5] Oral mucosa is the frequent site of tuberculosis infection, especially secondary infection. Oral manifestation of tuberculosis infection that often found including superficial ulcers, patches, indurated soft tissue or bone lesions on the jaw region known as *tuberculous osteomyelitis*[2] According to Farber et al, less than 0,1% of people with tuberculosis have lesions in their oral cavity. Meanwhile

as stated by Katz et al, approximately 20% from 141 patients have oral lesion in sublingual region[6]

Increasing occurrence of tuberculosis and the possibility to manifest in the oral cavity as oral tuberculosis demanded a special consideration for dental clinicians. Dentists are in a risk of cross infection. Therefore dentists are advised to recognize tuberculosis lesion in oral cavity, provide a proper treatment, early detection based on the symptoms and signs, write a medical referral, and also contribute to tuberculosis eradication efforts in Indonesia[7]

a. TRANSMISSION of *Mycobacterium tuberculosis* INFECTION

Tuberculosis is a communicable disease and patients with pulmonary TB are the most important source of infection. Infection is initiated by inhalation of droplet nuclei, which are particles 1-5 μ m in diameter containing *Mycobacterium tuberculosis*, expectorated by patients with active pulmonary TB (open TB), typically when patient coughs. The droplets nuclei, due to their small size, can remain suspended in the air for several minutes to hours. The risk of infection is dependent on several factors such as the infectiousness of the source case, the closeness of contact, the bacillary load inhaled, and their immune status of the potential host[8].

The primary route of infection involves the lungs. Inhaled droplet nuclei avoid the defenses of the bronchi due to their small size and penetrated in to the terminal alveoli where they are engulfed by phagocytic immune cell (macrophages and dendritic cells)[5,8]. In the early phase of infection, *Mycobacterium tuberculosis* internalized by phagocytic immune cells, replicates intracellularly and the bacterial immune cells may cross the alveolar barrier to cause systemic dissemination[8].

Transmission of TB is by inhalation of airborne infectious droplets from persons with active pulmonary TB when they cough, sneeze or speak. Extr pulmonary active TB, affects parts of the body such as the mouth, from which *Mycobacterium tuberculosis* can be transmitted by direct contact. Oral TB usually results from secondary inoculation of oral mucosa breached by any type of ulceration or by minor masticatory trauma, by infected sputum, or by haematogenous dissemination from other infected site[5].

b. ETIOLOGY & PATHOGENESIS of ORAL TUBERCULOSIS

Tuberculosis is caused by acid-fast bacteria *Mycobacterium tuberculosis*. Rod-shaped bacteria, aerobic, thin, non-encapsulated, non spore forming bacteria, with length of 2-5 μ m and 0.2-0.5 μ m width, which was first discovered by Robert Koch in 1882[4,7]. The acid and alcohol resistant bacillus of *Mycobacterium tuberculosis* and alcohol are transmitted via droplet nuclei

through the air and multiplies in the pulmonary alveoli. Bacterial replication occurs in alveolar macrophages and spread through the regional lymph nodes. In most cases, T-helper cells (CD4) activates macrophages through secretion of cytokines and interferon gamma in which the infection permanently suppressed or so-called primary infection, or they can remain latent to reactivate in months or years later. If the host immune response is inadequate and unable to prevent the replication of the bacteria, the disease becomes active again. Roughly 5-10% of patients who are exposed will develop an active TB on a point in their lifetime[8]. Dormant bacterias in primary tuberculosis will re-emerge even many years later as an endogenous infection and then becomes secondary tuberculosis. In contrast with primary tuberculosis, the lesions of secondary infection is generally chronic and less likely to be spontaneously recovered[5,9].

Human oral cavity produces saliva that serves as the cleansing and protecting agent with its anti-bacterial properties so the tuberculosis bacillus cannot get through the epithelium walls. However, clinical founding revealed that epithelium trauma causes tuberculosis bacillus to infect the connective tissue below. The occurrence of infection depends on systemic factors including poor host immunity and the increased virulence of microorganisms. Local predisposing factors in the mouth that can lead to oral tuberculosis include: local trauma, poor oral hygiene, the presence of previous lesions such as leukoplakia, peri apical granuloma, cysts, abscesses, fractures of the jaw, and periodontitis[2,8,9]

c. IMMUNE RESPONSE of THE HOST to M.tuberculosis

Infection with *Mycobacterium tuberculosis* starts with phagocytosis of the bacilli by phagocytic antigen-presenting cells in the lung including alveolar macrophage and dendritic cells. The recognition of pathogen-associated molecular patterns (PAMP) by specific pathogen recognition receptors (PRRs) is central to initiation and coordination of the host innate immune response[10].

The *Mycobacterium tuberculosis* or *Mycobacterium tuberculosis* component (ligands) are recognized by host receptors that include Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD) like receptors (NLRs), and C-type lectins. The interaction of *Mycobacterium tuberculosis* with TLRs initiates an intracellular signaling cascade that culminates in a proinflammatory response. The TLR engagement, particularly TLR2 and TLR4 with *Mycobacterium tuberculosis*, induce the activation of innate immune response[5,7].

The *Mycobacterium tuberculosis* cell envelope is composed of cell wall that is covered with a thick waxy mixture of lipids and polysaccharides and is characterized by high content of mycolic acids. The most important *Mycobacterium tuberculosis* cell wall surface ligands that interact with TLR is lipoarabinomannan (LAM). The interaction LAM with TLR results in activation of nuclear transcription factor (NFkB) and production of proinflammatory cytokines such as TNF- α , IFN- γ , interleukin, chemokine and nitric oxide that serve as a signal for infection. The monocytes, neutrophils and lymphocytes migrate to the focal site of infection, but they are unable to kill the bacteria efficiently. During this time, the bacilli resist the bacterial mechanism of the macrophage (phagolysosome) by preventing phagosome-lysosome fusion, multiply in the phagosome and cause macrophage necrosis[7,10]. The released bacilli multiply extracellularly, are phagocytosed by another macrophage that also fails to control the growth of *Mycobacterium tuberculosis*, and likewise are destroyed. In the

meantime, dendritic cells with engulfed bacilli mature, migrate to the regional lymph node, and prime T cells (both CD4 and CD8) against mycobacterial antigens. The specific immune response produces primed T cells (CMI) which migrate back to the focus of infection, guided by the chemokines produced by the infected cells. The accumulation of macrophage, T cells and other host cells (dendritic cells, fibroblast, endothelial cells and stromal cells leads to formation of granuloma[8,11,12].

The granuloma formation walls off tubercle bacilli from the rest of the lung tissue, limits bacterial spread and provides microenvironment for interaction among macrophages and other cells of the immune system and the cytokines produced by these cells. The CD4, T cells producing IFN- γ recognize infected macrophage presenting antigens from *Mycobacterium tuberculosis* and kill them. Within the resulting granuloma, there is a balance between mycobacterial killing and survival. The survival of some bacilli leads to latent TB infection (LTBI), which is contained by the granulomatous process. Following acute *Mycobacterium tuberculosis* infection, this process is adequate to control the infection in 95% of subjects, while the remainder progress to primary TB disease[5,8].

d. SIGNS AND GENERAL SYMPTOMS

The main symptoms of tuberculosis including productive cough for three weeks or more and sometimes coughing up blood. Patients who experienced reactivation of tuberculosis are typical symptoms are fatigue, weight loss, anorexia, mild fever and night sweats. Pulmonary symptoms include cough, which is dry at first but then a productive form of purulent sputum and often accompanied by blood[4]

e. ORAL TUBERCULOSIS LESIONS

Tuberculosis lesions in the oral cavity are rarely found, however some researchers reported that 0.1-0.5% of patients with pulmonary tuberculosis have oral lesions of secondary tuberculosis, the highest occurrence were on the palate followed by tongue, lips, buccal mucosa, gingiva, and alveolar bone.^{2, 9} secondary tuberculosis in the oral cavity are found in almost 97% of tuberculosis cases in the form of ulcers and 50% of them occurred on the tongue. Those lesions characterized as a shallow, oval shaped, indolent, sick, yellow-gray with a clear edge. Ulcers on the tongue can be found on the tongue tip, the lateral edges, dorsum, midline, and on the base of the tongue[2].

Lesions of the oral mucosa can emerge from the opalescent vesicles or nodules that can burst and turn into ulcers as a result of necrosis induced by caseation of mycobacterium bacteria in infected tissue. Ulcers on the oral mucosa are generally single, irregular shaped, indurated, rough, with a yellowish base, erythemic edge, and painless. Oral lesions of tuberculosis on the palate are mostly secondary tuberculosis in the form of small and painless ulcers. They're often found on the hard palate more frequent than the soft palate. While the lesions in the gingival are mainly primary tuberculosis lesions. Gingival lesions contain a lot of granulated lesion and can also be manifested as erosion with marginal periodontitis. Gingival enlargement in patients with tuberculosis are painless, extends progressively and going through the gingival margin toward the vestibule and might be accompanied by enlarged lymph nodes. This refers to the protective effect of gingival squamous epithelial cells that provide a direct resistance to the bacillus mycobacterium resulting in increased thickness of the epithelium and growing larger and thicker gingiva.

Lesions on the lips are usually present themselves as small, granular ulcers[2,9,10].

Tuberculosis can also affects maxilla and mandible, causing osteomyelitis. The mandible is more frequently affected than maxilla. The symptoms including trismus, paresthesia of the lower lip, and the enlargement of the regional lymph nodes. The involvement of the maxillary and mandibular presumably through the expansion of the gingival infection and also after teeth extraction that affected by tuberculous granulomas and metastasis of lung tuberculosis that spread both hematogenous and limphatically[11].

Periapical tissue involvement and post extraction socket with tuberculosis infection have been reported. Basil tuberculosis can enter through the exposed pulp down to the periapical tissue, thus causing periapical granuloma tuberculosis or tuberculoma. Lesions in the periapical region can lead to tooth loss and the post extraction sockets can be filled with large mass of granulated tissue[2,9].



Figure 1. Ulceration on the lateral of the tongue[15]

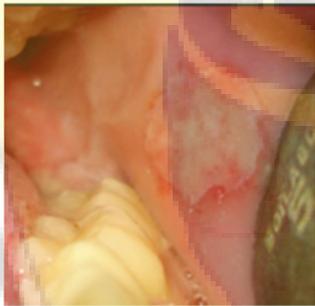


Figure 2. Ulceration on the buccal mucosa[2]

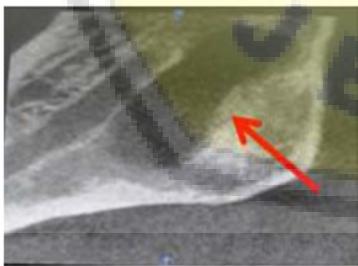


Figure 3. Mandible osteomyelitis Radiograph[11]



Figure 4. Tuberculoma radiograph[12]

f. DIAGNOSTIC & DIFFERENTIAL DIAGNOSTIC

Diagnosis of TB can be conducted through anamnesis to obtain patient's medical history, physical examination, tuberculin skin test, radiological examination of the lungs, and the Mantoux test. In children, tuberculin test is proven to be the most useful way to know whether they're being or have been infected with *Mycobacterium tuberculosis* and is often used in "TB Screening" [7,10].

Anamnesis or medical interview includes some questions about the data or identity of the patient, the main symptoms, history of systemic disease, history of oral disease in the past, medical history, family history, social history and patient's occupation. There are certain groups that on a high risk of tuberculosis infection according to the American Lung Association: 1. A person who has the signs and symptoms of active TB, 2. People who interact with people with TB, 3. Persons who have low economic status and poor health, 4. People who do not have a permanent place to live, 5. People who recently returned from countries with high TB incidence rate, 6. Those who volunteered to take care of TB patients, 7. Alcoholics and intravenous drug users, 8. People who suffer from HIV / AIDS or other immunosuppressing conditions, 9. Inmates, 10. People who work within a community that have a high-risk of tuberculosis infection[7,8,10].

On physical examination of the patient's general condition we can often found pale conjunctiva of the eyes and or pale skin due to anemia, a high body temperature (fever), chronic productive cough that lasts more than 2 weeks, night sweats, and weight loss. In primary tuberculosis, physical examination the patient often resulting in no abnormality[4]. However, on the extra-oral examination we can found enlargement of the lymph nodes[4,5,12].

g. TREATMENT AND PROGNOSIS

Tuberculosis treatment regimen including medications for 6-9 months. If the patient fails to comply with the initial treatment, the patient will become resistant to a number of medicines. If this occurs the patient must consume at least three medicines for two years. Nevertheless, nearly 60% of patients who are resistant to multiple TB drugs died from the disease. Direct observation found that the treatment regimen of TB medicines have been successfully treating tuberculosis and prevents development of drug resistance if the use of medicine according to indications. So is the case with oral lesions both in primary and secondary tuberculosis lesions in the oral cavity will experience full recovery with tuberculosis drug therapy regimen[3,4,8,9].

Table 1. Tuberculosis Infection Treatment

Time	Medicines
1 st and 2 nd months	INH, RIF, PZA, EMB
4 th to 7 th months	INH, RIF

based the patient's condition
 Note: INH = Isoniazid, RIF = Rifampin (rifabutin can be used as substitute to rifampin), PZA = Pyrazinamide, EMB = Ethambutol

There are some prevention programs that can decrease TB incidence like six to twelve months long isoniazid therapy for those who belonged in the high risk group of TB as a preventive action. The health center should provides facilities such as ultraviolet light, sufficient lighting, special filtration, good air circulation, and the use of masks to prevent the spread of TB through air droplets. Those with active TB should be isolated in a room with ventilation control until they recovered. Bacilli- vaccine Calmette-Guerin (BCG) in children effectively prevent TB infection at 60-80% rate[8].

DISCUSSION

Mycobacterium tuberculosis is usually transmitted via aerosols and establishes infection in the lung. The first cells to encounter the bacilli are alveolar macrophage and dendritic cells. *Mycobacterium tuberculosis* survives and proliferates within macrophage and, to some extent in dendritic cells. Immune mediators such as interferon gamma (IFN- γ) activate macrophage and promote bacterial killing. (IFN- γ) is predominantly secreted by natural killer (NK) and T cells upon instruction by interleukin 12 (IL-12) and interleukin 18 (IL-18) produce by dendritic cells (DC) and macrophage. Upon infection in the lung, DC become activated through Toll-like receptor (TLR) signal and migrate to the draining lung lymph node to initiate an immune response, i.e. activation of T cells. Mycobacterial ligands for TLRs promote inflammation which is characterized by the release of chemokines and pro-inflammatory cytokines, expression of adhesion molecules and attraction of macrophage. DC and polymorphonuclear neutrophils (PMN). IL-12 in synergy with IL-18 induces NK cell activity and biases the immune response toward a T helper 1 cells (Th1) profile characterised by interferon- γ (IFN- γ) production. IFN- γ activates macrophage to become efficient effector cells that express microbicidal substances and cytokines, of which tumour necrosis factor alpha (TNF- α) contributes to control of mycobacterial infection and granuloma formation [5,8,14].

It is generally assumed that formation of granuloma represent a host strategy to contain the infection and limit pathogen dissemination. At the same time, granulomas have the potential for pathological damage through caseous necrosis, by haematogenous or lymphogenous and its become extra pulmonary TB (EPTB). It can occur in the mouth that we called oral tuberculosis. Oral tuberculosis prevalence is rarely. *Mycobacterium tuberculosis* in the oral fluid of people with pulmonary TB is common, but oral tuberculosis is uncommon. This is probably owing to the protection of the intact oral epithelial barrier against *Mycobacterium tuberculosis* penetration, and to the anti bacterial properties and the flushing effects of the saliva. 0,1% - 0,5% people with pulmonary TB will develop secondary oral TB affecting most commonly the tongue, followed by the palate, the lips, the buccal mucous and the gingival. Its usually manifest as non healing ulcers, but may also occur as nodules, granulomata or fissures, or as ulcers are usually single, has an indurated, irregular, undermined margin, and a necrotic base [7,13,14].

CONCLUSION

Human's oral cavity can suffer from localized diseases and also from the manifestation of certain systemic disorders. One of the systemic diseases that have symptoms and signs in the oral cavity is tuberculosis. Although rare, medical workers, including dentists should pay special attention to the oral lesions of tuberculosis because of 5-10% of patients who have been exposed to the mycobacterium tuberculosis will suffer from an active form of TB. An individual with active TB can infects 10-15 people every year so we might found some of them during dental examination. Dentists are expected to be able to identify the oral lesions of tuberculosis and compare them with a variety of other differential diagnoses. Therefore, to provide an accurate diagnosis of tuberculosis it is advised to perform histopathology tissue biopsy in conjunction with the mycobacterium bacillus cultures.

Oral lesions of tuberculosis was found in 3% of all tuberculosis case. Although oral lesions are usually a sign of secondary tuberculosis or oral manifestation of

pulmonary tuberculosis, there are several reported cases of tuberculosis primary manifested as oral lesions. Primary tuberculosis infection in the oral cavity occurs if the bacillus mycobacterium make a direct contact with the damaged epithelium of the oral tissues. Primary infection can occur in gingival socket after tooth extraction and buccal folds. While the secondary infections that are often encountered in the form of ulcers on the tongue and they spreads through blood (hematogenous), lymph nodes, or from autoinoculation of infected sputum in the areas close to the pharynx. Secondary lesions can occur at all places including the tongue, palate, oral mucosa, lips, and jaw bones. By recognizing the oral lesions of both primary and secondary tuberculosis, dentists are expected to provide the accurate diagnosis.

Treatment of tuberculosis requires a long time so a good cooperation between the patient and the physician is needed. The prognosis of oral lesions of tuberculosis are usually good, so does the case with oral lesions primary tuberculosis that responds well with anti-tuberculosis medication regimen.

Therefore, when treating tuberculosis in the oral cavity, the dentist should know the patient's medical history. Dental evaluations targeted at patients with active disease who have been manifested in the oral cavity. The medical history should include questions about family members who are infected with TB as other possibilities that related to this disease. Previous tuberculin skin test should be recorded. Patients known to have TB should be asked about the therapy that has been taken, is it went well or not, and the latest activity status of the disease. Furthermore, dentists should cooperate with doctors whose dealing with patients to determine the status of the patient. In patients with active tuberculosis, dental treatment should be postponed until the infection healed. Any dental treatment should be conducted carefully to reduce infection, whether it is a direct infection to the dentist or cross infection with a standard precaution such as mask usage, gloves, and protective lens when dealing with TB patients due to the spread of infection through aerosol droplets. Gasses are used in sterilization for the instruments such as handpieces that cannot be sterilized by autoclave.

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