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Indonesian Guidelines for Cutaneous Tuberculosis

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Abstract

Tuberculosis (TB) is one of the oldest diseases known to humankind and a common disease worldwide. Cutaneous tuberculosis (CTB) describes dermatological manifestations of TB involving the skin. The clinical manifestations are variable. Sclofuloderma, tuberculosis cutis verucosa and lupus vulgaris are the most common form CTB in Indonesia. The management is similar to other tuberculosis infection. Chemotherapy still remains the treatment of choice for CTB.

Keywords: cutaneous tuberculosis, treatment.

Introduction

Tuberculosis is a common disease in developing countries. Tuberculosis infection can spread to the organs outside the lungs such as skin. Tuberculosis infection of the skin is called tuberculosis cutis or CTB. Cutaneous tuberculosis is one of the less common clinical forms of TB accounting for approximately 1-2% of total extra-pulmonary cases but contributes to significant morbidity. The clinical manifestations are variable and depend on the interaction of several factors including environmental factors, inoculation mechanism and host's immunity.[1-5]

With the improvement of hygiene habits in the general population, the improvement of living standards, the use of the BCG vaccine, and the introduction of effective chemotherapy, there was a significant decrease in the number of cases.[6] However, in the mid-twentieth century onwards, new challenges such as the persistent adverse social conditions, high rates of migration of infected people from areas of relatively high prevalence to low endemic areas, the co-existent *human immunodeficiency virus* (HIV) epidemic, the growing number of patients receiving immunosuppressive treatments and the appearance of extensively drug-resistant tuberculosis have all contributed to worsen the pandemic and offset the efforts made in the last years.[4,6] The increase in multi-drug resistant TB has also resulted in an increase in the occurrence of CTB.[4] So this article provides relevant current information on the CTB and recommendation treatment of CTB.

Reviews

Cutaneous tuberculosis is an infection caused by *Mycobacterium tuberculosis*, *Mycobacterium bovis* and bacillus *Calmette-Guérin* in the skin.[2,7,8] Globally in 2016 there were an estimated 10.4 million incident cases of tuberculosis (TB) (8.8 million to 12.2 million). The five countries that stood out as having the largest number of incident cases in 2016 were India, Indonesia, China, the Philippines and Pakistan, which together accounted for 56% of the global total. In 2016, there were an estimated 211 cases per 100.000 population in India. While in Brazil, 42 cases per 100.000 population had been estimated in 2016.[9] In Dr. Cipto Mangunkusumo hospital, scrofuloderma is the most common (84%), followed by tuberculosis cutis verrucosa and lupus vulgaris (13%) and the other types are rarely found.[10] In Padang, a total of 17 patients with CTB were identified during the 2014 until 2017, which represents 0.48% of the total 3508 cases of tuberculosis. The most common was scrofuloderma seen in 76.48% patient, followed by tuberculosis verrucosa cutis and lupus vulgaris in 11.76% patient.[11]

There are several classifications of CTB. Based on the route of infection, CTB can be classified into; exogenous, endogenous, lymphogen, and hematogen tuberculosis. Based on the number of acid-fast bacillus found, CTB can be divided into multibacillary and paucibacillary forms. Furthermore, there are classification based on host immune status and clinical disease. [2,4,6,8]

Table 1. Classification of cutaneous tuberculosis

Bacillary Form	Method of Inoculation	Host Immune Status	Clinical Disease
Multibacillary Form	Direct exogenous source:		
	Primary inoculation	Naïve	Tuberculosis chancre
	Endogenous source:		
	Contiguous spread	Low	Scrofuloderma
	Autoinoculation	Low	Tuberculosis cutis orificialis
	Hematogenous spread	Low	Acute military tuberculosis, tuberculosis gumma
Paucibacillary Forms	Direct post-primary inoculation	Immune	Tuberculosis verrucosa cutis, lupus vulgaris
	Hematogenous spread	High	Lupus vulgaris, tuberculids

(References: Cutaneous Tuberculosis, Mycobaterial Skin Infections, Italy, 2017)

Scrofuloderma is the most common form of CTB in children.[3,4,8] Scrofuloderma is caused due to the spread of infection in the structure under the skin such as lymph nodes, joints, bones, and epididymis. The predilection is primarily in areas that contain many superficial lymph nodes, such as neck, armpit, groin.[4]

Tuberculosis verrucosa Cutis (warty tuberculosis), the most common form of exogenous tuberculosis, occurs due to a reinfection by exogenous tubercle bacilli in subjects who have developed a moderate-high grade of immunity to *M. tuberculosis*.[1,6] Lesions are usually solitary, painless and predominate in anatomical locations that are prone to traumas, such as fingers and toes.[6,12]

Lupus vulgaris is an extremely chronic, progressive form of CTB occurring in individuals with moderate immunity and a high degree of tuberculin sensitivity. Females appear to be affected two to three times as often as males; all age groups are affected equally.[4,6,12] The initial lesion is a brownish-red, soft or friable macule or papule with a smooth or hyperkeratotic surface. On diascopy, the infiltrate exhibits a typical apple jelly color.[12]

In addition to the type of clinical feature of CTB above, there are other types; tuberculosis chancre, tuberculosis cutis orificialis, tuberculosis gumma, acute military tuberculosis, and tuberculids. Unlike true CTB, tuberculids were considered a hypersensitivity reaction to *M. tuberculosis* or its products in a subject with a significant immune status.[1,4]

Diagnosis and Treatment

Diagnosis is based on clinical manifestations, histopathologic analysis, demonstration of the relevant *Mycobacteria* in tissue or in culture and host reaction to *M. tuberculosis*. Mycobacterial cultures are still the gold standard to determine *Mycobacteria*, but have a low yield rate and take several weeks. Sample skin cultures are especially necessary for diagnosis in patients with AIDS or immunocompromised because skin manifestations and histopathologic lesions are usually not typical. Cultures are only positive in 6% of cases of lupus vulgaris. Traditional solid-culture media such as Lowenstein-Jensen take 4 to 8 weeks to produce results. Liquid media can accelerate growth and can detect growth in 3 to 7 days. Biopsy specimens can be cultured if stored in a saline solution and ideally taken before the drugs is given.[12-14]

Standard therapy 2RHZE/4RH (pyrazinamide, rifampicin, ethambutol, and isoniazid) of tuberculosis is given to CTB for 6 months. This regimen is given for adult patients. Combinations with surgery may be considered in lupus vulgaris, tuberculosis verrucosa cutis and scrofuloderma to prevent recurrence and resistance. And for CTB in children, can be given 2RHZ/4HR or 2RHZE(S)/4-10HR.[13]

Table 2. First-Line Treatment Guideline for Cutaneous Tuberculosis

Scheme	Drugs	Recommendation Doses				Duration (months)
		Daily		Three times Weekly		
		Doses (mg/kg)	Maximum (mg)	Doses (mg/kg)	Maximum (mg)	
2RHZE Intensive Phase	Isoniazid	5 (4-6)	300	10 (8-12)	900	2
	Rifampicin	10 (8-12)	600	10 (8-12)	600	
	Pyrazinamide	25 (20-30)	-	35 (30-40)	-	
	Ethambutol	15 (15-20)	-	30 (25-35)	-	
4RH Maintenance Phase	Isoniazid	5 (4-6)	300	10 (8-12)	900	4
	Rifampicin	10 (8-12)	600	10 (8-12)	600	

(References modified from : Pedoman Nasional Pelayanan Kedokteran Tatalaksana Tuberkulosis, Kementerian Kesehatan Republik Indonesia, 2016)

For cases of CTB with previous medical history (had taken anti-TB drugs before), called relapse cases, can be given another regimen within first line therapy, which is 2RHZES/1RHZE/5RHE (pyrazinamide, rifampicin, ethambutol, isoniazid, and streptomycin). This regimen is also given to cases of failed treatment, which are cases that have received previous treatment and are declared failed at the end of treatment. Also for cases with drug-resistance can be given second line regimen, which is 6 months intensive phase with pyrazinamide, ethambutol, kanamycin, levofloxacin, etionamide, cycloserine and continued 18 months of maintenance phase with pyrazinamide, ethambutol, levoloxacin, ethionamide, cycloserine (6Z- (E) -Kn-Lfx-Eto- Cs / 18Z- (E) -Lfx-Eto-Cs).[13-14]

Patients who are declared cured were TB patients with positive bacteriologic examination at the beginning of treatment whose bacteriologic examination at the end of treatment became negative and on one of the previous examinations.[13-14]

Treatment of CTB in Certain Condition

- Cutaneous Tuberculosis in HIV Patients
  The principle of treatment CTB in HIV patients is prioritizing tuberculosis treatment. Antiretroviral treatment (ARV) is started as soon as possible after being tolerated in 2-8weeks of early phase treatment. Regimen of choice for CTB in HIV patients is as same as normal cases, which is 2RHZE/4RH. But is should be noted that anti-TB drugs often interacted with ARV treatment, for example their interaction could increase the risk of side effect.[13-14]

- Cutaneous Tuberculosis in Pregnancy and Lactation

  Maternal tuberculosis is associated with an increased risk of spontaneous abortion, perinatal mortality, small for gestational age and low birth weight. [13-14]

  Isoniazid (Category Pregnancy A) is recommended for TB in pregnancy despite an increased risk of hepatotoxicity in pregnant women. Symptoms should be monitored with liver function tests recommended every 2 weeks in the first 2 months and every month of the following month. Pyridoxine 50mg / day is recommended for every pregnant woman consuming isoniazid because deficiency is common in pregnant women compared to the general population.[13-14]

  Rifampicin (Category Pregnancy C) can cause bleeding associated with hypoprotrominemia in infants when taken in the third trimester of pregnancy. The use of rifampicin is recommended in pregnant women with tuberculosis and vitamin K should be given to the mother (10mg / day) and the infant after delivery if rifampicin is used in the third trimester of pregnancy before the childbirth.[13-14]

  Ethambutol (Category A Pregnancy) is recommended for TB in pregnancy. Until now there have been no reports of side effects of Pyrazinamide on the management of TB patients. If pyrazinamide is not used in the regimen, then a 9-month regimen of isoniazid, rifampicin and ethambutol is recommended.[13-14]

  In breast-feeding TB patients, anti-TB drugs and breast milk still can be administered, although some anti-TB drugs may enter breast milk, but the concentrations are small and do not cause toxicity in infants. Rapid and appropriate anti-TB drugs is the best way to prevent mother-to-child transmission.[13-14]

- Cutaneous Tuberculosis in Diabetic Patients

  Diabetic patients with CTB infections have more severe infection, larger mycobacterium colonization, higher treatment failure rate, and longer conversion time. After one year, diabetic patient with CTB infection tend to be more likely having drug resistant than CTB patient without diabetes mellitus. Guideline of CTB treatment for diabetic patient is same with no-diabetic patient, can be given standard therapy 2RHZE/4RH. If the blood sugar level is uncontrolled, the duration of treatment can be continued for up to 9 months. Be careful with the use of ethambutol, because of the side effects of ethambutol; whereas diabetic patients often experience complications of abnormalities in the eye. And please note the use of rifampicin because it will reduce the effectiveness of oral antidiabetic drugs (sulfonyl urea) so that the dose needs to be increased.[13]

- Cutaneous Tuberculosis in Chronic Renal Failure

  Patient of CTB with history of chronic renal failure can be given standard therapy, which is 2RHZE/4RH. But there are several precautions that should be noted. During receiving isoniazid, patients with renal impairment as well as renal failure should be given together with pyridoxine to prevent peripheral neuropathy. Excretion of ethambutol and pyrazinamide metabolites occurs in the kidneys so that dose adjustment is required for both drugs. Ethambutol is given 15 mg/kg and pyrazinamide 25 mg/kg as much as 3 times a week. Isoniazid and rifampicin are eliminated through biliary excretion so dose adjustment is not necessary.[2,13]

- Cutaneous Tuberculosis in Liver Dysfunction

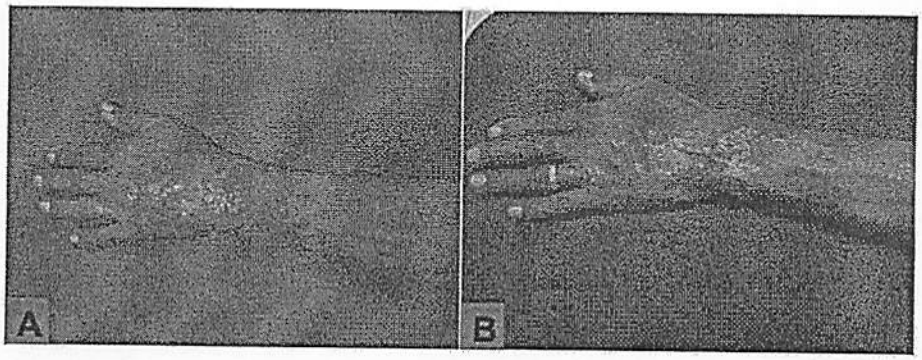
  Patients with hepatitis virus carriers, a history of acute hepatitis and excessive alcohol consumption when there is no evidence of chronic liver disease and normal liver function can consume standard therapy (2RHZE/4RH). If AST levels> 3x normal before therapy is started, then the following guidelines need to be considered;[13]

  - Two hepatotoxic drugs: 9 months isoniazid + rifampicin + ethambutol, or 2 months isoniazid + rifampicin + ethambutol + streptomycin followed by 6 months isoniazid + rifampicin, or 6-9 months rifampicin + pyrazinamide + ethambutol,
  - One hepatotoxic drug: 2 months of isoniazid, ethambutol, streptomycin followed by 10 months of isoniazid + ethambutol,
  - Without hepatotoxic drug: 18-24 months of streptomycin, ethambutol, fluoroquinolone.

  The use of antituberculosis in liver disorders depends on the severity of disease and degree of decompensation. In moderate liver disease (cirrhosis Child B) can be used one or two hepatotoxic drugs while all hepatotoxic drugs should be completely avoided in severe liver disease (cirrhosis Child C). In liver disorders, pyrazinamide should not be given. The recommended regimen (WHO recommendation) is 2RHES/6RH or 2HES/10HE. In acute and/or clinical icteric patient, anti-TB drugs should be delayed until acute hepatitis is healed. In most circumstances, S and E can be given up to 3 months until hepatitis is healed and followed by 6RH.[2,13]

Case Report

A case of 58-year old woman was diagnosed as tuberculosis verrucosa cutis (TVC). Patient had been worked more than 20 years in paddy field and never used gloves or boots while doing her job. The reddish-verrucous patches initialized since 15 years ago and expanded slowly to edge side of patches. Laboratory examination was within normal limit, except there was an increased of erythrocyte sedimentation rate (ESR) which was 30mm/hr. Chest x-ray and sputum examination were within normal limit. From histopathology examination was found pseudoepitheliomatous hyperplasia with marked hyperkeratosis, a dense inflammatory infiltrate, and abscesses in the superficial dermis. Epithelioid cells are found in both upper and middle dermis. This patient also got treated with standard multidrug TB therapy 2RHZE/4RH resulting in lesion decreased after two months.



Figures 1. A. A 58-year-old woman presented with tuberculosis verruoca cutis (before treatment). **B.** The lesion reduced in size and no more verrucous plaque (after four month of treatment).

Conclusion

Tuberculosis is a serious infection that affects many people worldwide, with a recent increasing prevalence especially in high-risk patients, such as those from endemic countries, in an immunocompromised state, with a history of previous tuberculosis infection, and/or with multiple comorbidities. Treatment is similar to other tuberculosis infection. Chemotherapy still remains the treatment of choice. The highest priority in any CTB control program is the proper, accurate, and rapid detection of cases and the availability of chemotherapy to all tuberculosis patients until cure.

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