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## Update on scrofuloderma

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### ABSTRACT

Tuberculosis is one of the most significant diseases which causes death worldwide. TB infection is assumed to infect the lungs only from a general perspective. In fact, TB infection also causes lesions on the skin. Scrofuloderma, as one of the most common types of cutaneous tuberculosis, often misdiagnosed and managed

improperly due to its similarity with abscess. In addition, there were still no national and international guidelines for scrofuloderma. This review to give insights and review about an update in the basic principle of scrofuloderma and management.

**Keywords:** Scrofuloderma, cutaneous, tuberculosis, management

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### INTRODUCTION

Tuberculosis (TB) is one of the ten most significant diseases which causes death worldwide.<sup>1</sup> Around 45% out of a total of 10.4 million of tuberculosis infections cases are located in Southeast Asia.<sup>2</sup> Indonesia, along with India, China, Philippines, and Pakistan accounted for the most contributor in these cases (56%).<sup>2</sup> Based on the Ministry of Health's data in 2018, the number of tuberculosis cases had reached 845,000 cases in Indonesia.<sup>2</sup> Even Indonesia ranked as third highest TB burden in 2018.<sup>3</sup>

TB infection is assumed to infect the lungs only from a general perspective. In fact, TB infection also causes lesions on the skin. Although the involvement of skin only occurs in 1-2% of people with tuberculosis, tuberculosis skin infection (cutaneous tuberculosis) was still one of the most notable infection in certain patients, especially immunocompromised patients.<sup>4</sup> Scrofuloderma, as one of the most common types of cutaneous tuberculosis, was found at Cipto Mangunkusumo Hospital (84%)<sup>4</sup> and mostly infected the children.<sup>5</sup>

Due to the similarity of scrofuloderma with cold abscess infection, misdiagnosis, and treatment delay often occurs. These challenges often arise in Indonesia and other developing countries even after several laboratory tests have been developed to aid the diagnosis of latent or suspected TB.<sup>6</sup> Therefore, the condition really needs medical professionals to be more cautious in the management of scrofuloderma. In pulmonary TB cases, national

and international guidelines for handling standards have been established. Meanwhile, there is still no such recommendation in cutaneous tuberculosis cases.<sup>7</sup> Thus, it is essential to review and update the principle of scrofuloderma.

### ETIOPATHOGENESIS

Cutaneous tuberculosis is classified based on morphology, route of spread, and immunity status of patients.<sup>8</sup> This disease has six infection routes:<sup>6,9,10</sup>

- Direct transmission to the skin from organs under the skin
- Direct inoculation of the skin around the genital orifice
- Hematogenous transmission
- Direct transmission of lymphokines mucosa
- Germs that enter the skin directly

Cutaneous tuberculosis also had several clinical forms, such as tuberculosis verrucosa cutis, tuberculous chancre, lupus vulgaris, scrofuloderma, orificial tuberculosis, metastatic tuberculosis abscess, and miliary tuberculosis.<sup>11</sup> Scrofuloderma, or often called colliquative cutis, results from the direct spread of tuberculosis lesions from infected organs.<sup>12</sup> The neck, axilla, groin folds with lymph node involvement are the most common sites for scrofuloderma.<sup>10,13,14</sup> Factors related to disease progression can be assessed in host interactions, infectious agents, and the environment detailed below:<sup>15</sup>

- State of host immunity:

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- Only 5-10% of infected patients will cause tuberculosis infection.<sup>16</sup> This is due to the host's ability to deal with infections. Another proposed mechanism is the variations in the apoptotic ability of infected macrophages when eliminating mycobacterium is no longer possible.<sup>17</sup>
  - Some autoimmune conditions, such as SLE and RA, have a higher risk of infection. Apart from defects in the natural and acquired immune systems, the use of immunosuppressant drugs will also affect the host's immune system.
  - Host unmodifiable risk factors for the occurrence of scrofuloderma, such as immature immunity in children. In adults, immunocompromised factors are still the main cause of cutaneous tuberculosis, in addition to malnutrition, alcoholism, silicosis, diabetes mellitus, gastrectomy, and other immunosuppressive conditions.<sup>15</sup>
- b. Route of infection
- The infection route initiated by having close contact with patients, coupled with a person's immune response will affect clinical symptoms. The type of cutaneous tuberculosis depends greatly on the route of infection described previously. Until now, there has been no further explanation about what causes different types

**Table 1. Classification of cutaneous tuberculosis<sup>10</sup>**

No	Types of cutaneous tuberculosis	Infection route	Bacterial count	History of sensitization	Symptoms
1	Verucal tuberculosis cutis	Exogenous inoculation	Paucibacillary	++	Verrucal lesions on: • Dorsal manus or digital, ankle or buttocks
2	Primary tuberculosis	Exogenous inoculation	Multibacillary	-	Nodular lesions at: • Face or upper or lower extremities associated with lymphadenopathy
3	Scrofuloderma	Spread directly	Multibacillary	+	More often on: • Children, youth and the elderly; predilection in the neck region; can be co-infected with pulmonary TB
4	Lupus vulgaris	Hematogenous or direct distribution	Paucibacillary	++	Most commonly: • Women and manifests as burning nodules, annular plaques, or vegetative or hypertrophic lesions; the initial lesion begins with a collection of reddish papules that unite to form plaque with the edge of verrucose or serpiginous with the middle part of atrophy and heal.
5	Tuberculosis orificial cutis	Direct spread	Multibacillary	-	Most often in: • Unhealed ulcers in the mouth, mouth, or skin or anogenital mucosa in patients with TB, lung, digestive or genital infections.
6	Acute miliary tuberculosis	Hematogenous	Multibacillary	-	Often occurs in: • Immunocompromised patients with solitary or multiple subcutaneous nodules that have the potential to become ulcers or sinuses without regional adenopathy.
7	Tuberculosis abscess metastases	Hematogenous	Multibacillary	-	Skin lesions appear on: • Can manifest as umbilication and crusty cellulitis or purplish papules. Usually in people with severe immunosuppression (AIDS, malnutrition)
8	Tuberculids	Hypersensitivity reactions to <i>M. Tuberculosis</i> infection	Negative culture	+++	Indications erythema Bazin (more common in women) and manifests as • Painful granulomatous lobular panniculitis, usually of the lower extremities • Papulonecrotic tuberculids (more often in children and young adults) may look like lupus vulgaris and scrofuloderma, appearing with dark red or purplish papules that become pustules or necrotic tissue. • Fever and constitutional symptoms can occur; • Lichen scrofulosorum (more common in children and young adults) with pulmonary or lymphatic TB (this condition is often associated with BCG vaccination and with intracellular <i>M. avium</i> infection)

- of cutaneous tuberculosis.<sup>14</sup>
- c. Virulence, survival, and mycobacteria resistance
    - Macrophage produces NO and RNI, which are potent bactericidal compounds against mycobacterium. However, the mycobacterium, through series of enzymatic processes, such as peroxiredoxin alkyl hydroperoxide reductase C subunit (AhpC), dihydrolipoamide dehydrogenase (Lpd) dihydrolipoamide succinyltransferase (SucB), or thioredoxin-like AhpD forming a complex compound called nicotinamide-adenotoxidase reductase which acts antioxidant defenses against RNI.<sup>18,19</sup>
    - The ability of mycobacteria to inhibit MHC class II process and presentation also enables the bacteria's survival. All this contributes to the defense of mycobacteria in macrophages.<sup>19</sup>
    - Bacilli resistance is also one of the most critical factors for the emergence of drug-resistant Mycobacteria. Initially, due to environmental factors, bacteria would reduce metabolism rate, replication rate, and at the same time, tolerate small doses of antibiotics. This tolerance is reversible in the initial phase if the treatment is delivered in appropriate periods and doses. However, when the presence of inadequate doses persists and the ability of bacteria to replicate decreases in poor conditions causing spontaneous mutations and resistance to a type of drug.<sup>20</sup> This continued until bacteria emerged with resistance to several types of drugs, called multidrug-resistant (MDR) and extensively drug-resistant (XDR).<sup>21</sup>
  - d. Environmental factor
    - Weather and geographic location determine differences in the prevalence of cutaneous tuberculosis. This is supported by epidemiological data where locations such as scrofuloderma are commonly found in Brazil, and lupus vulgaris is more frequent in Asia and Europe.<sup>22</sup>
- plaque verrucose, or other types of lesions.<sup>23</sup> Scrofuloderma can also resemble bacterial abscesses or malignancies.<sup>24</sup>
- Initial scrofuloderma lesion will appear as a dense, brownish-red, and painless subcutaneous nodule.<sup>10</sup> This nodule then splits into ulcers and sinuses, which secrete purulent fluid. These lesions would be encountered with epidermal hyperplasia, and solid infiltrates in the dermis composed of neutrophils, lymphocytes, and plasma cells.<sup>10,25</sup> Over time, inflammatory cells and granulomatous inflammation will replace neutrophils with caseous necrosis, which varies in degree. Basil can be found in the initial lesion, but it will be difficult to find after granulomas have formed.<sup>23</sup>
  - Scrofuloderma can heal spontaneously into keloids, retractions, and atrophy.<sup>25</sup> A proper diagnosis of scrofuloderma is often delayed because cutaneous tuberculosis is not routinely considered in the differential diagnosis due to varied clinical manifestations.<sup>4</sup> Whereas in the case of pulmonary TB, national and international guidelines for treatment have been made, but there are no specific recommendations that are similar for cases of cutaneous tuberculosis. Therefore, it is essential to consider the type of examination based on evidence.<sup>7</sup>
  - Finding bacilli in cutaneous TB lesions is still a challenge. Overall, all diagnostic methods have lower sensitivity and specificity for cutaneous TB compared to pulmonary TB. This is worsened by uncommon rash and histopathological, which may not have a clear result. Clinicians should use every possible test. Hence, the supporting results can sum up to establish the diagnosis. This is also indeed an effort to reduce empirical treatment.<sup>7</sup>

## DIAGNOSIS

Several data should be obtained from history and physical examination, such as:

- Symptoms caused by scrofuloderma vary greatly. A patient can become infected with pulmonary TB with cutaneous TB, which may have constitutional symptoms of pulmonary TB. Symptoms caused depend on the infected organ. From the patient's history, there may be signs of other causes of immunodeficiency.<sup>23</sup>
- On physical examination, various types of skin lesions can be found in cutaneous tuberculosis, ranging from papules, nodules, pustules, ulcers,

## LABORATORY EXAMINATION

- Tuberculin test (TST)  
Tuberculin tests are used to identify individuals who have been sensitized by Mtb bacteria and will be positive within 2 to 10 weeks after infection. False-negative results can occur in children under two months, pregnant women, diabetes, kidney failure, or disorders of cellular immunity. The history of recent vaccines, children over one year, and atypical mycobacteria co-infection can cause false positives.<sup>7</sup> The tuberculin test has a sensitivity of 33-95% and a specificity of 62.5% when using a cutoff value of 10 mm. In unvaccinated populations, the sensitivity of the tuberculin test is higher.<sup>26,27</sup> In miliary tuberculosis cases, original TB, it

**Table 2. Differential diagnoses of cutaneous tuberculosis<sup>4</sup>**

Classification Cutaneous TB		Comparative Diagnosis
Exogenous Cutaneous TB	Tuberculosis chancre	Sporotrichosis, atypical mycobacteriosis, syphilis, cat scratch disease, tularemia
	Tuberculosis verrucosa cutis	Paracoccidioidomycosis, leishmaniasis, sporotrichosis, verrucose tuberculosis and chromomycosis, lobomycosis, atypical mycobacteriosis, hypertrophic lichen planus, verrucose carcinoma, vulgaris verrucose, pyoderma vegetans
Endogenous Cutaneous TB	Scrofuloderma	Tertiary syphilis, Paracoccidioidomycosis, actinomycosis, lymphogranuloma venereum, bacterial abscess, metastatic tumor, histiocytosis, and hidradenitis
	Orificial tuberculosis	Bullous disease, trauma, fungal disease, syphilis, sarcoidosis, or squamous cell carcinoma
	Lupus vulgaris	Basal cell carcinoma, sarcoidosis, discoid lupus, leprosy, severe fungal infection
	Tuberculous gumma	Leishmania, sporotrichosis, nocardiosis, mycobacteria apical, pyogenic infection, and fungal infection
	Acute miliary TB	Metastatic carcinoma
Tuberculids	Papulonecrotic tuberkulid	Pityriasis lichenoides et varioliformis acuta (PLEVA), leukocytoclastic necrotizing vasculitis, pruritus, and secondary syphilis
	Lichen scrofulosorum	Lichen planus, lichen nitidus, syphilid lichenoides, eczematid, keratosis pilaris, pityriasis rubra pilaris, and micropapular sarcoidosis
	Erythema induratum of Bazin	Erythema nodosum, cutaneous polyarteritis, pancreatic panniculitis, lupus profundus, subcutaneous sarcoidosis, and cutaneous T-cell lymphoma.

**Table 3. Tuberculosis treatment in adult**

Regiment	Composition	Bodyweight	Dose
Intensive phase (2 months)	(R) Rifampicin – 150 mg	>50 kg	4 tablets
	(H) Isoniazid – 75 mg	36 – 50 kg	3 tablets
	(Z) Pyrazinamide – 400 mg	20 – 35 kg	2 tablets
	(E) Ethambutol – 275 mg		
	Available combination (tablet): R(150 mg) + H(75 mg) + Z(400mg) + E(275 mg)		
Maintenance phase (4 months)	(R) Rifampicin – 300 or 150 mg	>50 kg	2 tablets or capsule A
	(H) Isoniazid – 200 or 100 mg	36 – 50 kg	1 tablet or capsule A or 1 tablet or capsule B
	Available combination (capsule or tablet): A: R(300 mg) + H(200 mg) B: R(150 mg) + H(100 mg)	20 – 35 kg	1 tablet or capsule A

will also give a negative result. However, results can be positive on scrofuloderma and lupus vulgaris and vary depending on types of other cutaneous tuberculosis, especially the type of paucibacillary. In addition to TST and chest X-ray on all patients, it is very important to do a histopathological examination, detection of acid-resistant bacillus through culture, and amplification of *Mycobacterium tuberculosis* (Mtb) DNA with (PCR) both in tissue samples and in blood.<sup>7</sup>

- **Acid-fast bacilli (AFB) staining**  
The microscopic examination with the Ziehl-Neelsen (ZN) staining method is still an effective diagnostic tool for early detection of TB. The ZN is a common, inexpensive, and high specificity technique for detecting AFB in sputum. However, studies reported quite low sensitivity (20-60%).<sup>7</sup>
- **Culture**  
Culture is the standard diagnostic method for TB. In addition to a confirmative or definitive diagnosis, it also plays an important role in *Mycobacterium tuberculosis*'s sensitivity test to the anti-tuberculosis drug. Culture also could be used in monitoring and detecting cases of MDR.<sup>7,28</sup> The principle of culture is multiplying and growing bacteria in order to overcome the challenge in diagnosing HIV co-infection with TB cases, which are often found with smear-negative. With slow bacterial growth, it takes more than three weeks to have the results. At this time, more accurate and sensitive culture methods have been developed, both liquid and solid culture media, called the BACTEC system and *Mycobacteria* Growth Indicator Tube (MGIT). An accurate and straightforward method is still being developed at a low cost.<sup>29</sup> Liquid media in the form of blood are expected to be similar to in vivo conditions in lung parenchymal tissue, which are also rich in iron and albumin and other nutrients. Therefore, by using the biphasic media blood jelly, it can promote the growth of *Mycobacterium tuberculosis* optimally so it will be easily identified. Establishing a TB diagnosis helps to determine the proper treatment, thereby accelerating the recovery of TB, in results, stopping the chain of transmission.<sup>29,30</sup>
- **PCR**  
Detection of *Mycobacterium tuberculosis* in sputum can be done by Polymerase Chain Reaction (PCR) technique, microscopic examination, and bacterial culture. Microscopic examination of *Mycobacterium tuberculosis* requires a certain number of germs (about

5,000 germs/ml of sputum). Meanwhile, growing bacteria via culture needs a minimum of 50-100 germs/ml of sputum. TB detection by PCR technique has a very high sensitivity. Mycobacterium tuberculosis in vitro can be used specifically for DNA amplification for the PCR test. This process requires a double-stranded DNA template containing the target DNA, a DNA polymerase enzyme, a nucleotide triphosphate, and a pair of primers.<sup>7,28</sup>

## TREATMENT

Recently the principle of cutaneous tuberculosis treatment is the same as for pulmonary tuberculosis. In addition to TB treatment, at least two bactericidal drugs must be included. The drug of choice should be personalized and consider the economic condition, the severity of the disease, and whether there are any contraindications.<sup>1,3,7,28,32</sup>

In the treatment of tuberculosis, there are two stages, an initial or intensive 2 month-treatment phase followed by a continuation phase.<sup>31</sup> During the initial or intensive phase, which included four types of drugs, there should be a reduction in the number of germs accompanied by clinical improvement. Infected patients become no longer infectious within two weeks. During the continuation phase, fewer drugs are needed, but over a longer period of time. The latter phase is sterilization activities to kill slow-growing germs. The sterilizing effect of these drugs was to clean up germs remnants and prevent a recurrence. In patients with smear-positive sputum, there is a risk of selective resistance. The use of 4 drugs (3 drugs in the child) during the intensive phase and two drugs during the continuation phase will reduce the risk of selective resistance. In patients with negative smear sputum or extrapulmonary TB, there is no

**Table 4. Tuberculosis treatment in the child**

Regiment	Composition	Bodyweight	Dose
Intensive phase (2 months)	(R) Rifampicin – 75 mg	16 – 24	4 tablets
	(H) Isoniazid – 50 mg	12 – 15	3 tablets
	(Z) Pyrazinamide – 150 mg	8 – 11	2 tablets
		4 – 7	1 tablet
	Available combination: R(75 mg) + H(50 mg) + Z(150mg)		
Maintenance phase (4 months)	(R) Rifampicin – 75 mg	16 – 24	4 tablets
	(H) Isoniazid – 50 mg	12 – 15	3 tablets
		8 – 11	2 tablets
		4 – 7	1 tablet
	Available combination A: R(75 mg) + H(50 mg)		

A child with 25kg of body weight or more recommended using an adult dose

**Table 5. Daily dose recommendation in adult and child**

Drug of choice	Adult		Child	
	Dose and range (mg/kg body weight)	Maximum dose (mg)	Dose and range (mg/kg body weight)	Maximum dose (mg)
(R) Rifampicin	10 (8 – 12)	600	15 (10 – 20)	600
(H) Isoniazid	5 (4 – 6)	300	10 (7 – 15)	300
(Z) Pyrazinamide	25 (20 – 30)	-	35 (30 – 40)	-
(E) Ethambutol	15 (12 – 18)	-	20 (15 – 25)	-
(S) Streptomycin	15 (12 – 18)	-	Not recommended as first-line	

**Table 6. The medical approach to major adverse reaction of tuberculosis treatment**

Causative drug(s) probability	Major adverse reaction	Medical consideration
Isoniazid Streptomycin Pyrazinamide Rifampicin	Itchy or non-itchy skin rash	Tuberculosis medication discontinuation. Reintroduce medication with time interval after skin improvement. Recurrent skin rash should consider avoiding causative agent on continuation tuberculosis treatment
Streptomycin	Nystagmus and vertigo	Streptomycin discontinuation. Reinitiate without streptomycin
Rifampicin	Acute kidney failure, purpura, shock	Rifampicin discontinuation. Reinitiate without rifampicin
Streptomycin	Hearing loss	Streptomycin discontinuation. Reinitiate without streptomycin
Ethambutol	Visual problems	Ethambutol discontinuation. Reinitiate without ethambutol
Rifampicin Isoniazid Pyrazinamide	Hepatotoxicity (hepatitis or jaundice)	Tuberculosis medication discontinuation. Reintroduce medication with time interval separately after transaminase improvement
Streptomycin	Low urine production	Streptomycin discontinuation. Reinitiate without streptomycin
Isoniazid	Seizure, coma, psychosis or toxic encephalopathy	Isoniazid discontinuation. Reinitiate without isoniazid



**Table 7.** The medical approach to minor adverse reaction of tuberculosis treatment

Causative drug(s) probability	Minor adverse reaction	Medical consideration
Isoniazid Ethambutol	Neuropathy (burning, tingling, numbness in the feet or hand)	Vitamin B6 prescription (50-75mg) daily
Pyrazinamide	Arthralgia	Analgesic, non-steroidal anti-inflammatory drugs
Rifampicin	Red or orange urine, sweating	Encourage and comfort patient about common side effect and continue medication
Pyrazinamide Isoniazid Ethambutol Rifampicin	Nausea, vomit, stomach ache, anorexia	Symptomatic medication, tuberculosis medication reschedule (with breakfast or two hours after breakfast), transaminase evaluation
Isoniazid	Anxiety, cephalgia, sleep disturbance, euphoria	Encourage and comfort patient about common side effect and continue medication
Isoniazid Rifampicin	Mild rash or itchy	Anti-histamine prescription
Isoniazid Rifampicin	Fever	Encourage and comfort patient about common side effect and continue medication

risk of selective resistance because the number of bacteria in the lesion is relatively small. Initial phase treatment with three drugs and advanced phase with two drugs are usually sufficient.<sup>1,3,7,28,32</sup> First-line drug of choice based on available fixed drug combination (FCD) (**Table 3** and **Table 4**) have been provided.<sup>7,28,32-35</sup> However, the specific guideline for cutaneous tuberculosis is not available yet.

Several conditions should be treated as special considerations such as renal insufficiency, pregnancy, elderly, and hepatic insufficiency. Streptomycin and ethambutol have a teratogenic effect and contraindicated in pregnancy.<sup>7,28,33</sup> In elderly patients, daily dose reduction recommended increasing drug tolerance. The standard dose should be administrated if creatinine clearance more than 30 ml/minute. Drug administration should be adjusted on the condition which creatinine clearance less than 30 ml/minute.<sup>7</sup> Isoniazid, rifampicin, and pyrazinamide increasing liver damage (hepatotoxic) and required special consideration. Elevated up to three times of transaminase upper normal limit can be given with standard treatment. Transaminase elevation more than three times normal upper limit should consider to suspend pyrazinamide, keep using ethambutol, streptomycin, and another drug of choice (ofloxacin, rifampicin, isoniazid) addition. Transaminase should be evaluated every month.<sup>7,28,32-36</sup> Patient management on major adverse event need special medical consideration (**Table 6**). Discontinuation specific medication often needed to achieve the treatment goal. Side effect control without discontinuation anti-TB drug applied on minor adverse reaction (**Table 7**).<sup>7,32-37</sup>

In re-infected patients who have been treated previously, there is a risk of resistance will happen. The re-medication guide consists of 5 drugs for

the initial phase and three drugs for the advanced phase. During the initial phase, at least 2 of the drugs given must be selective. Standard treatment with isoniazid, rifampicin, pyrazinamide, and streptomycin is recommended. First-line re-treatment with 2RHZES/1RHZES/5RHE if a low or medium case of TB MDR (multidrug resistance) reported or data not available in that country.<sup>32-36</sup>

The surgical approach, such as excision, is the treatment of choice in lupus vulgaris, tuberculosis verrucosa, including scrofuloderma. If an ulcer is found, it should be covered with a wet soak and added 1:5000 potassium permanganate to the solution. Patients with cutaneous tuberculosis have improved if the therapy was administered accordingly.<sup>7,28</sup>

## CONCLUSION

Scrofuloderma is the most common type of cutaneous tuberculosis. Misdiagnosed and managed improperly due to its similarity with other skin infection often occurs. National or international guidelines for scrofuloderma was not available. Thus, this review is expected to provide an appropriate description and management of scrofuloderma.

## AUTHORS CONTRIBUTION

All authors contributed to this review.

## CONFLICT OF INTEREST

None.

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