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REVIEW

Cutaneous tuberculosis overview and current treatment regimens

Lindi van Zyl, Jeanetta du Plessis*, Joe Viljoen

Centre of Excellence for Pharmaceutical Sciences, North-West University, Private Bag X6001, Potchefstroom, 2520, South Africa

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SUMMARY

Tuberculosis is one of the oldest diseases known to humankind and it is currently a worldwide threat with 8–9 million new active disease being reported every year. Among patients with co-infection of the human immunodeficiency virus (HIV), tuberculosis is ultimately responsible for the most deaths. Cutaneous tuberculosis (CTB) is uncommon, comprising 1–1.5% of all extra-pulmonary tuberculosis manifestations, which manifests only in 8.4–13.7% of all tuberculosis cases.

A more accurate classification of CTB includes inoculation tuberculosis, tuberculosis from an endogenous source and haematogenous tuberculosis. There is furthermore a definite distinction between true CTB caused by *Mycobacterium tuberculosis* and CTB caused by atypical *mycobacterium* species. The lesions caused by *mycobacterium* species vary from small papules (e.g. primary inoculation tuberculosis) and warty lesions (e.g. tuberculosis verrucosa cutis) to massive ulcers (e.g. Buruli ulcer) and plaques (e.g. lupus vulgaris) that can be highly deformative.

Treatment options for CTB are currently limited to conventional oral therapy and occasional surgical intervention in cases that require it. True CTB is treated with a combination of rifampicin, ethambutol, pyrazinamide, isoniazid and streptomycin that is tailored to individual needs. Atypical *mycobacterium* infections are mostly resistant to anti-tuberculous drugs and only respond to certain antibiotics. As in the case of pulmonary TB, various and relatively wide-ranging treatment regimens are available, although patient compliance is poor. The development of multi-drug and extremely drug-resistant strains has also threatened treatment outcomes. To date, no topical therapy for CTB has been identified and although conventional therapy has mostly shown positive results, there is a lack of other treatment regimens.

1. Introduction

Tuberculosis (TB) is one the oldest diseases of humankind. As humanity populated the earth, so did this disease spread as well. Typical tuberculous lesions, containing acid-fast bacilli (AFB), have been identified in Egyptian mummies [1–4]. The prevalence of TB increased dramatically during the seventeenth and eighteenth centuries, after which it declined over the next two-hundred years [5]. Later in the nineteenth century, TB again became a major health concern, although improved hygiene and immunisation caused the disease to wane again [6–8].

TB today continues to pose a significant public health threat. The World Health Organisation (WHO) estimates that approximately 20–40% of the world's population are affected, with 8–9 million new cases of active disease being reported every year [9–16]. TB is ultimately responsible for most deaths among patients infected with the human immunodeficiency virus (HIV) [8,17,18,19,20].

Despite TB being such a widespread disease, especially in developing countries, it manifests only as an extra-pulmonary disease in 8.4–13.7% of cases. The difference in data and the low values may also indicate how uncommon and undefined this disease truly is. This increases with co-infection of HIV. Cutaneous tuberculosis (CTB) is relatively uncommon and not a well defined disease, comprising only 1–1.5% of all extra-pulmonary manifestations [21–25,12,26,8,27–29,20,30]. Théophile Laennec [8], inventor of the stethoscope, described the first example of CTB in 1826. CTB is prevalent among women, mostly young adults. The most common site of CTB infection is the face, although it often appears on the neck and torso as well [31].

CTB has many different manifestations, which complicates diagnosis. The increase in multi-drug resistant TB has also resulted in an increase in the occurrence of CTB. Skin manifestations of infections caused by *Mycobacterium tuberculosis* are known as true CTB, but some of the other species of the *Mycobacterium* genus are also responsible for cutaneous manifestations, as summarised in

* Corresponding author. Tel.: +27 18 299 2274; fax: +27 87 231 5432.
E-mail addresses: 20855125@nwu.ac.za (L. van Zyl), Jeanetta.DuPlessis@nwu.ac.za (J. du Plessis), 11320036@nwu.ac.za (J. Viljoen).

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Table 1. Mycobacteria can be sub-divided into two sub-genera, namely rapid/fast growers and slow growers. Slow growing organisms have a more than 7 days incubation period for mature growth, whereas rapidly growing organisms have a 7 days or less incubation period for mature growth [32,33,8,34,35].

To date, no topical therapy exists for any of the TB infections. Although most of the current treatment regimens have demonstrated positive results, they are not all completely effective, especially with the rise in multi-drug and extremely drug-resistant TB strains. The potential of using topical treatments to aid in treating TB thus need to be evaluated for improving therapeutic regimens.

2. Classification of cutaneous tuberculosis

In the past, the lack of an accurate classification of CTB has accounted for much of the confusion relating to the disease. In recent years, a more accurate classification system has been developed, using three criteria, i.e. pathogenesis, clinical presentation, and histologic evaluation [2,22,37,38,7,39–43,29]. Using these criteria, CTB can be classified as:

- Inoculation tuberculosis from an exogenous source.
- Tuberculosis from an endogenous source.
- Haematogenous tuberculosis.

These criteria and their symptoms are described next.

2.1. Inoculation of tuberculosis from an exogenous source

Primary inoculation TB (Figure 1), also known as tuberculous chancre, results from the entry of mycobacteria into the skin, or mucosa, through broken skin of a person not previously being infected with, or who has no immunity against *Mycobacterium tuberculosis* [36,44,39,41,45]. The access of mycobacteria through the skin barrier can be caused by inadequately sterilised needles, tattooing, circumcision, piercings, operations, wounds and post mouth-to-mouth resuscitation [37,8,35]. The lesions have often been reported as having a sporotrichoid appearance [46]. Inoculation can occur through various methods and persons working in a medical profession are most at risk of being infected. This was in fact how the first case of CTB was described by Théophile Laennec in 1826 [8], when he noted his own “prosector's wart”. Mucocutaneous contribution towards CTB accounts for approximately one-third of the total number of reported cases. These include infection through the oral cavity (after tooth extraction), or of the conjunctiva [37,47,8].

Exogenous inoculation can cause a warty lesion on the fingers, or other extremities, called *tuberculosis verrucosa cutis* (TVC), in patients previously infected with TB and who have moderate to high immunity [2,39,49,50]. TVC (also known as prosector's wart, lupus verricosus and warty tuberculosis) starts as a painful, small papule, surrounded by a purple, inflammatory corona that progresses into an asymptomatic warty lesion, as illustrated in Figure 2 [51,24,44,52,40,53]. TVC may, in 4.4–16% of cases, present in younger patients [41].

Table 1
Atypical *mycobacterium* species responsible for cutaneous infections [36,32].

Common	Uncommon
Slow growing	
M. haemophilum	*M. avium complex*
M. leprae	*M. kanasii*
M. marinum	*M. malmoense*
M. ulcerans	*M. scrofulaceum*
Fast growing	
M. chelonae	*M. abscessus*
M. fortuitum	–

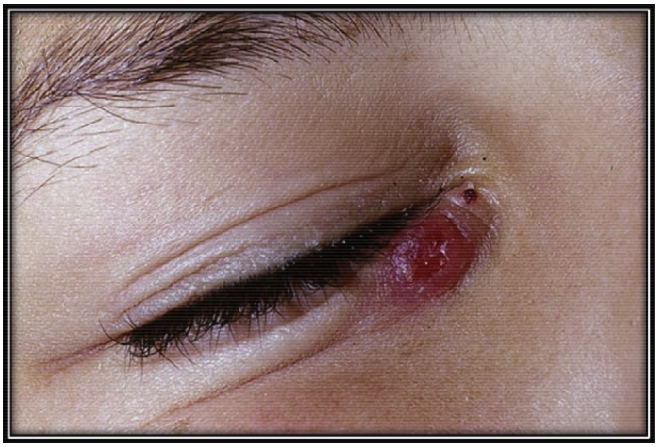

Figure 1. Inoculation tuberculosis in a child [48].

2.2. Tuberculosis from an endogenous source

CTB may also result from the involvement and breakdown of the skin covering a subcutaneous focus, usually a lymph gland (tuberculous lymphadenitis), or TB of the bones and joints, previously described as scrofuloderma (Figures 3 and 4). The lesions start as a subcutaneous, mobile nodule, which soon after attaches to the overlying skin. A discharge then starts and eventually a cutaneous abscess forms. These abscesses may heal spontaneously, although it takes years to completely cure [2,36,54,37,49,53,35]. Scrofuloderma is the most common form of CTB among children younger than ten years of age, with a prevalence of 36–48% [41]. Scrofuloderma suggests that the patient may have a systemic TB infection, particularly pulmonary TB, in 35% of cases. These lesions are more often seen in the axillae, neck, groin and chest [55,8,56].

Orifacial TB (Figure 5) is a rare form of CTB and results from the auto-inoculation of the mucous membrane that occurs when viable organisms are either expectorated, or spread in patients with low immunity. Tissue, normally resistant to infection, is invaded, usually in the nose, oral cavity, perineal and/or perirectal areas. Such

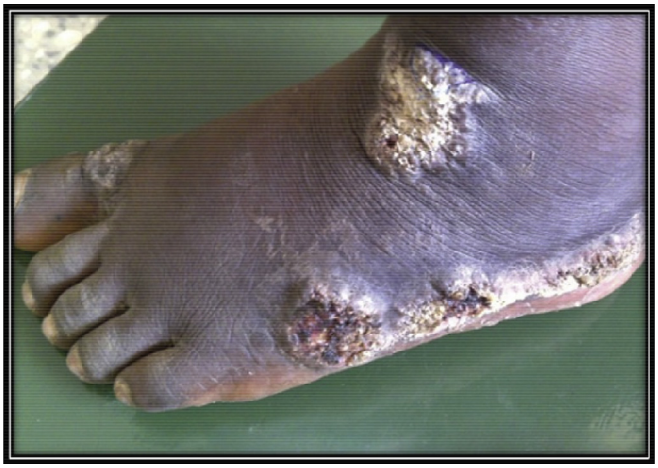

Figure 2. Tuberculosis verrucosa cutis [52].

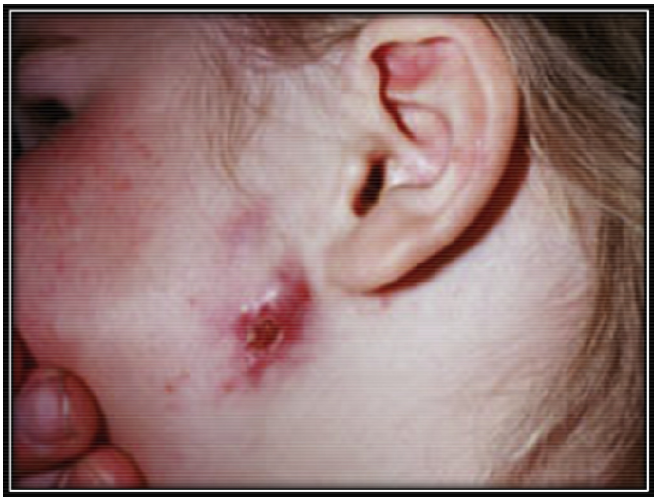

Figure 3. Scrofuloderma [48].

lesions are painful and ulcerative and do not heal naturally. Patients with these infections are likely to have progressive pulmonary, genital, urinary or intestinal TB. In some cases in China, caseation necrosis, visible in orifacial TB and scrofuloderma, has been reported [37,58,49,40,41,59,60].

2.2.1. Haematogenous tuberculosis

Haematogenous spread or lymphatic seeding, accounts for the majority of CTB cases. Haematogenous TB occurs when the AFB spread from a primary site of infection to the rest of the body. Also, it involves chronic CTB in a previously sensitised patient with a high level of TB sensitivity. The most common form of this infection is lupus vulgaris, which also has the highest potential for disfigurement [21,62,25,63,43].

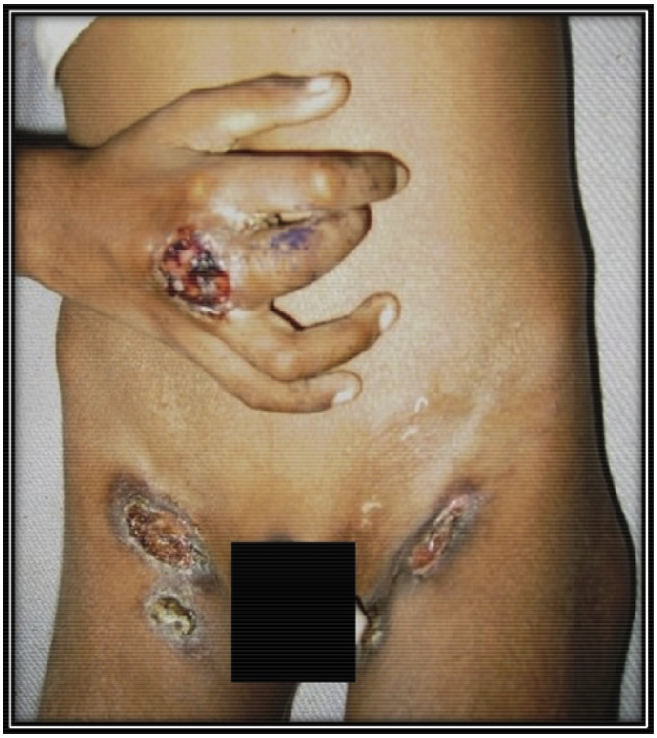

Figure 4. Scrofuloderma in a male patient showing lymph gland involvement [57].

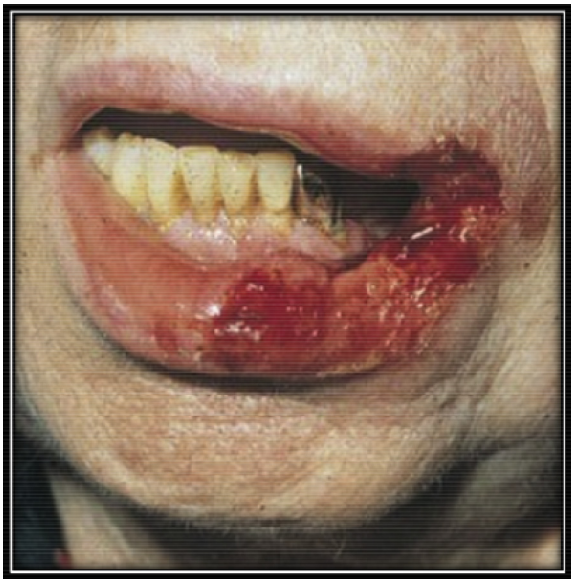

Figure 5. Orifacial tuberculosis [61].

Tuberculous gamma (Figure 6) is a rare form of haematogenous tuberculosis, with an incidence of only 1–2%. The lesions start as firm nodules, which later break down to form abscesses and ultimately ulcers. Tubercles and widespread caseation necrosis are often identifiable. These ulcers are frequently negative for AFB [64,40,60].

Lupus vulgaris (LV) (Figure 7) may develop after *Bacille Calmette Guérin (BCG)* vaccination, or from primary inoculation TB, or as a result of inoculation [25,65]. LV is also very common among younger children, with a prevalence of 41–68% in affected children and adolescents [41]. LV may present in mainly five general forms, of which the plaque form is the most common, representing approximately 32% of all cases. This form of LV starts as a flat, red-brown papule, which slowly expands into a light skin-coloured

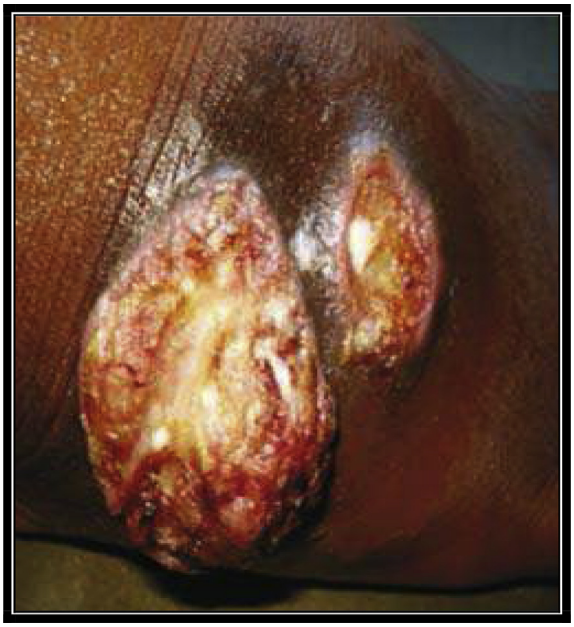

Figure 6. Tuberculous gamma on the dorsum of the right foot of an eight-year old boy [64].

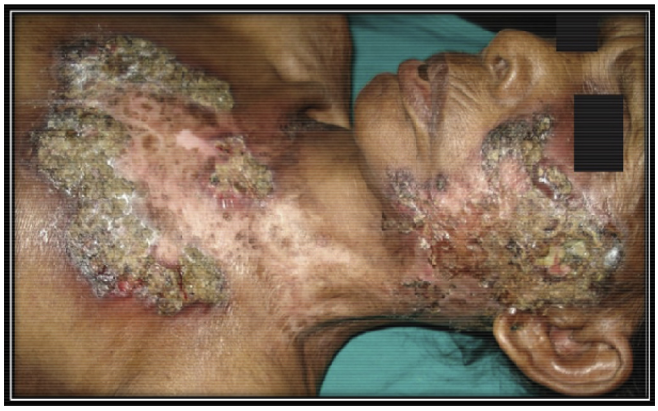

Figure 7. Lupus vulgaris plaque of the face, neck and chest [69].

plaque. It may show irregular areas of scarring and the edge of the plaque is often thickened and hyperkeratotic [66,63,8,53,67,35,68].

The ulcerative and mutilating form (Figure 8) of LV is the most destructive and deforming of all LV lesions. Underlying tissue is invaded and becomes ulcerative and necrotic, leaving an atrophic, crust-like scar [39,70,8,35]. The vegetative form of LV is also characterised by ulcers and necrosis, but with minimal scarring. Vegetative and ulcerative forms are especially destructive when the nasal, or auricular cartilage are involved [8,35].

Miliary, or disseminated TB (Figure 9), also known as *tuberculosis cutis miliaris disseminata*, is a life-threatening form of TB, resulting from the dissemination of tubercles, usually from a pulmonary source [44,42,43]. This disease primarily occurs in children and infants, following an infection such as measles or scarlet fever that reduces their immune response. This is a very rare form of TB, but re-emerges in patients infected with HIV and having a CD4 count lower than 100 cells/μL [44,39,40,35]. The lesions are initially papules (bluish to brownish-red in colour), which may be covered by small vesicles that eventually rupture, or dry with a crust that later develops into an ulcer. The lesions are often closely packed and are teeming with AFB [37,8,41,43].

2.2.1.1. Tuberculids. Tuberculids are not true CTB lesions, but rather arise as the result of hypersensitivity reactions to the TB organism, or its products present in the body of a patient with high immunity. All of the tuberculids show a positive response to anti-tuberculous

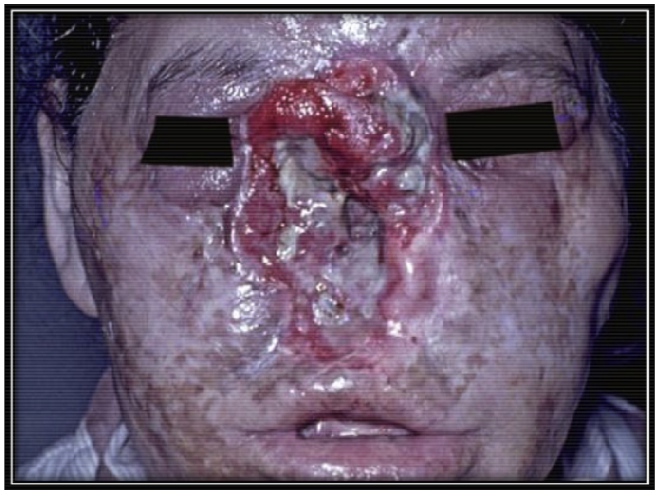

Figure 8. Deforming, ulcerative lupus vulgaris in a caucasian male [71].

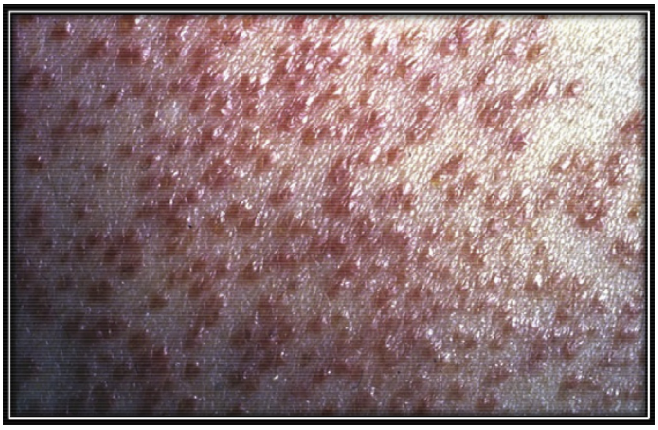

Figure 9. Cutaneous miliary TB before rupture of papules and crust formation [48].

therapy, though they are characterised by negative smears for AFB. Tuberculids may also occur as a result of BCG vaccination, and consequently the vaccination is now only recommended for certain high risk groups [21,72,73,37,25,74,8,35]. True tuberculids can be classified as follows:

- Micropapular: lichen scrofulosorum.
- Papular: papulonecrotic tuberculid.
- Nodular: erythema induratum of Bazin and nodular tuberculid [36,44,41,35].

Lichen scrofulosorum (LS) is a rare, asymptomatic skin eruption that primarily affects children and adolescents with high immunity. The lesions are closely grouped, lichenoid papules that are usually light skin-coloured, although they can also be yellowish or reddish-brown (Figure 10). The lesions are generally found on the chest, abdomen and back areas and are often reported after BCG vaccination. These lesions are also very common in children, with a prevalence among them in 23–33% of cases. The lesions have previously been misdiagnosed as psoriasis due to their inflammatory and scaly appearance [25,75,44,41,35].

Papulonecrotic tuberculids (Figure 11) present as an eruption of dusky-red, necrotising papules, with central crust that mainly affect the extremities of young adults, although it is also observed in infants and children (4% prevalence). The lesions are small and symmetrical and usually appear in clusters. The necrotic lesions leave behind a hyperpigmented atrophic scar and are essentially

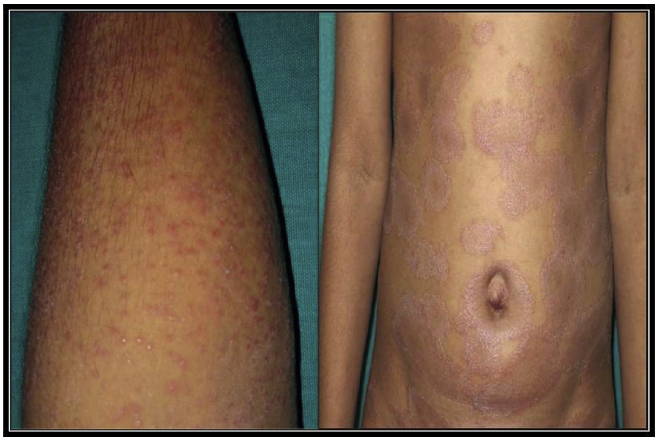

Figure 10. Lichen scrofulosorum of the forearm and abdomen [76,77].

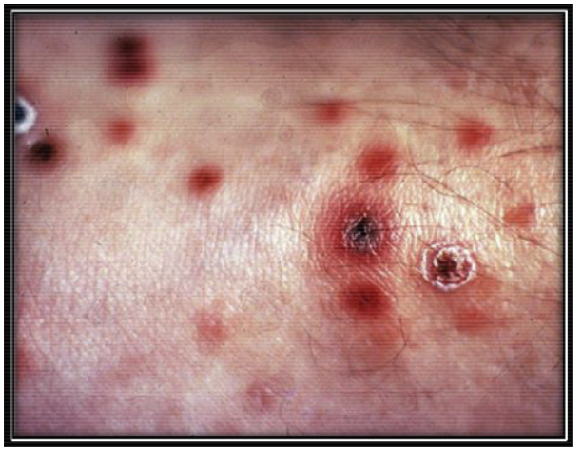

Figure 11. Papulonecrotic tuberculid [79].

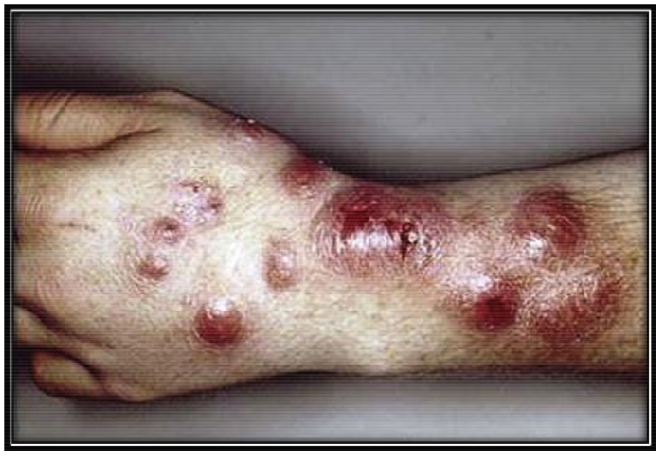

Figure 13. Infection with *Mycobacterium marinum* in the upper extremities [86].

found on the elbows, knees, legs, feet and hands [78,72,74,49,40,8,41,35].

Nodular tuberculids present as dusky-red, non-tender nodules of the lower extremities. The nodules progress into purple-red masses that have a tendency to ulcerate into asymmetrical, superficial ulcers that heal with an atrophic scar [49,40,41]. Erythema induratum of Bazin (EIB) (Figure 12) is accepted as the true nodular tuberculid in which the main pathology is located in the subcutaneous fat. Another pattern has also been identified where the pathology lies in the junction between the subcutaneous fat and the dermis, hence the term nodular tuberculid [44,8,35].

3. Atypical *mycobacterium* infections of the skin

More than 135 species of atypical *Mycobacterium* [or more recently known as non-tuberculous mycobacteria (NTM)] have been described [32,80,81,34], but only a few show cutaneous manifestations, as summarised in Table 1, of which only the most common ones are discussed in this article, namely:

- *Mycobacterium marinum.*
- *Mycobacterium ulcerans*, or Buruli ulcer.
- *Mycobacterium haemophilum.*
- *Mycobacterium fortuitum.*
- *Mycobacterium chelonae.*
- *Mycobacterium abscessus.*
- *Mycobacterium leprae*, or Hansen's disease [32].

NTM can be found in soil, water, flora and some fauna, almost anywhere in the world. The mode of transmission is not completely understood, but human-to-human transmission does not seem to occur. Infection predominantly occurs in immuno-compromised patients, or after skin trauma in immuno-competent patients. Some cases of cutaneous *Mycobacterium* infections have been reported to occur after individuals receive tattoos, subcutaneous insulin therapy, foot baths at nail salons and even acupuncture [82,80,81,49,83].

M. marinum infections are primarily localised at the site of inoculation, typically in the upper extremities [32,80]. These infections are also known as “swimming pool granulomas” or “fish tank granulomas”, since *M. marinum* is widespread in both fresh and marine water [84,85,32,33]. In 2008, an outbreak of *M. marinum* infections occurred on a fish farm in China that workers had contracted from abrasions, or trauma to the skin that had became infected. These infections are characterised by papular lesions (Figure 13) and cellulitis, also often as warty nodules, or plaques that may sometimes present with a sporotrichoid pattern. The nodules may contain a purulent fluid that is positive for AFB and that can ulcerate and become necrotic [85,32,33,86,35].

Mycobacterium ulcerans infections, also known as the Buruli ulcer, are prevalent in warmer climates in riverine areas, such as

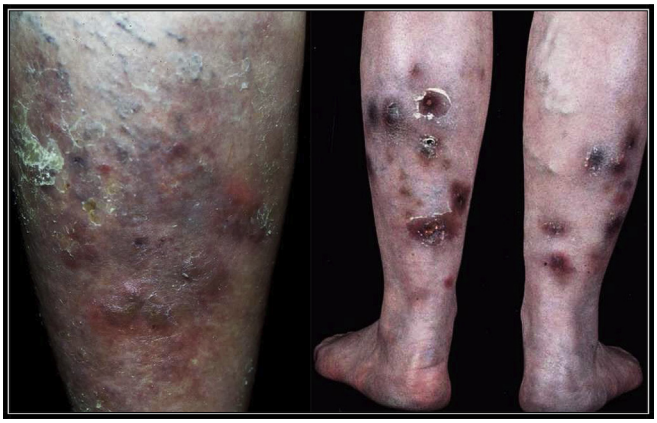

Figure 12. Erythema induratum of Bazin showing prevalence in the lower extremities [79].

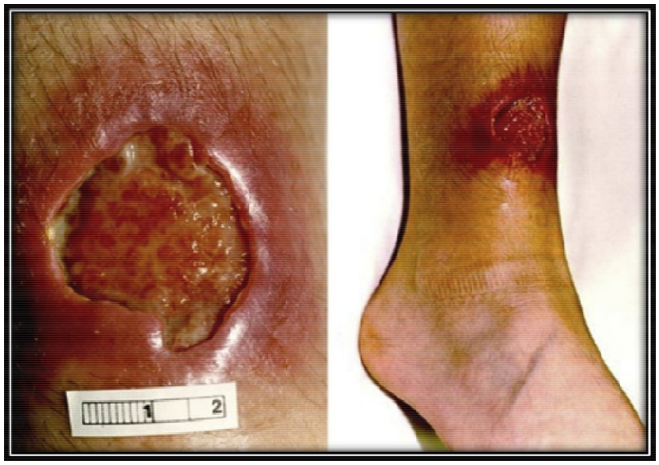

Figure 14. Buruli ulcer in an eleven-year old boy from Australia [90].

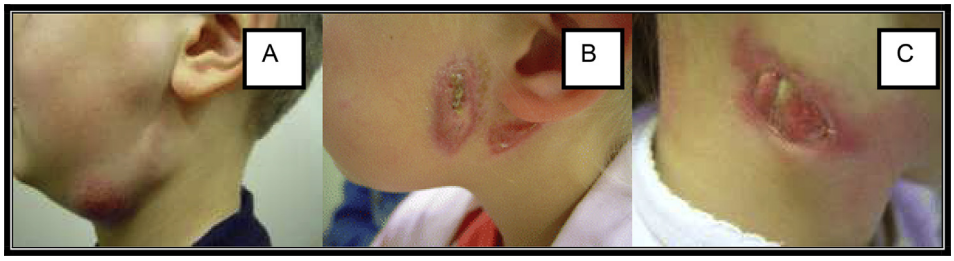

Figure 15. Cervicofacial *Mycobacterium haemophilum* lymphadenitis in a child, A: presenting as a red swelling of the skin, B: after skin breakdown, and C: ulcerating open wound [92]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

lakes and swamps. The exact mode of transmission is unknown. Children under the age of fifteen are more prone to these infections. Because these ulcers are painless and the patients often live in remote areas, most patients receive treatment too late, when the damage is already extensive. The lesions start as small, subcutaneous nodules, which may be pruritic. Later, the nodules break and form a shallow necrotic ulcer (Figure 14) that may grow over massive areas of extremities and the body [87,88,33,89,35].

Mycobacterium haemophilum infections are commonly recognised in immuno-compromised patients, although the habitat of this organism and its means of acquisition are unknown [32,35]. Infections have been observed among patients who underwent organ transplants, who received long-term immuno-suppressive therapy and in immuno-competent children with lymphadenitis. *M. haemophilum* causes tender, nodular skin lesions, which may develop into ulcers, or abscesses, seeping a purulent exudate (Figure 15). These lesions may also present as annular plaques, or panniculitis, which typically occur on the extremities and are often located across joints [91,88,33,80,35].

Mycobacterium fortuitum infections also cause nodular skin lesions in immuno-compromised patients, like *Mycobacterium haemophilum* [33]. This organism can grow at a temperature of 45 °C [35]. The lesions are present as ulcers, abscesses, nodules, cellulitis and sinuses. Lesions may form a purulent discharge and may prompt extensive subcutaneous necrosis and pus formation [80].

Mycobacterium chelonae (Figure 16) and *Mycobacterium abscessus* (Figure 17) infections present as disseminated cutaneous diseases in immuno-compromised patients. Such infections present as multiple, nodular lesions in no particular pattern. Patients over than forty-five years of age are more often affected. *M. chelonae* infections are associated with corticosteroid therapy and often occur after direct inoculation. This organism causes community-acquired disease, for example after skin or soft-tissue infections and as sporadic, nosocomial infections (after surgery, injections, transplants and catheter use). *M. abscessus* more often than not causes abscesses at injection sites. This organism represents the most pathogenic and drug resistant mycobacteria of the fast growing group [83,35].

Mycobacterium leprae causes leprosy that mostly affects the skin, testes, upper respiratory passages, the superficial segment of peripheral nerves and anterior segments of the eyes. Leprosy, also known as Hansen's disease, has been widely discussed in the literature [95,96]. The disease starts as a few lesions that multiply and attack the peripheral nerves in susceptible patients. Transmission of *M. leprae* may be respiratorial, or via direct skin contact with the organism (e.g. through BCG vaccination) [73,32]. Early manifestation may present as a visible skin lesion, or an area of numbness on the skin. The most common initial lesions are that of indeterminate leprosy, which consist of one or more faintly hypopigmented, or erythematous macules, with poorly defined borders. Established leprosy (Figure 18) can be divided into tuberculoid leprosy, lepromatous leprosy and borderline leprosy, as summarised in Table 2 [95].

4. Current treatment regimens of cutaneous tuberculosis

Most cutaneous tuberculosis forms are sensitive to anti-tuberculous therapy taken orally [54,25,99,55,44,40,34,60]. *Mycobacterium tuberculosis* has the ability to create drug resistance and to avoid this, several anti-tuberculous drugs are administered

Figure 16. A fresh tattoo infected with *Mycobacterium chelonae* [93].

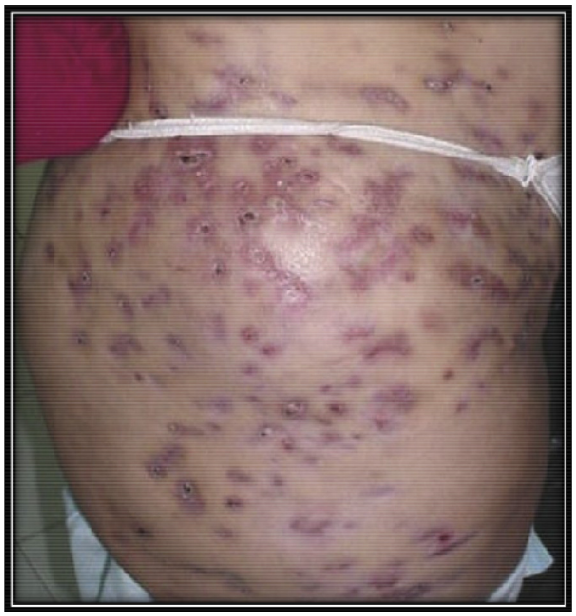

Figure 17. Lesions caused by *Mycobacterium* abscessus [94].

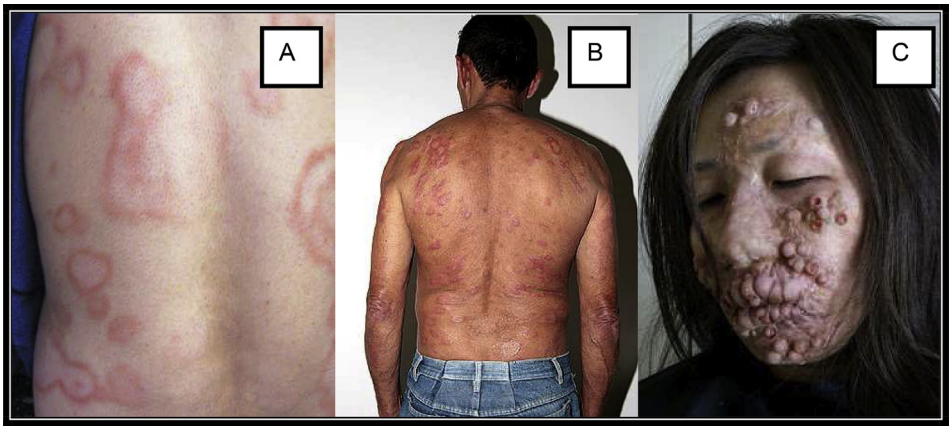

Figure 18. Established leprosy in order from A: tuberculoid leprosy, B: borderline leprosy, to C: lepromatous leprosy [97,98,79].

simultaneously. Frequent treatment is required (daily or every 3 days, according to individual need) in a combination of drugs and for a sufficiently long duration to ensure that the lesions are completely free of infection. Anti-tuberculous therapy usually stretches over a few months, which makes patient compliance difficult [100,20]. In 1993, the WHO launched the so called, directly observed treatment, short-term (DOTS) strategy, to improve patient compliance. Since 1995 to 2008, 83.7% of cases treated under DOT were cured and case fatalities had decreased from 8 to 4% [101,102,28].

The DOTS program, however, has not demonstrated adequate impact to eliminate TB by the targeted year 2050. The main setback in reaching this target has been the lack of resources to implement the Global Plan to Stop TB project, as launched in 2006 [103].

Table 2
The classification of established leprosy [95,49,96].

Types of leprosy	Clinical features
Tuberculoid leprosy (TT)	• Number of lesions is 1–10. • Nerve involvement is marked with anaesthesia localised to lesions. • Borders are well defined. • Lesion is typically a plaque that is erythematous, copper-coloured or purple and hypopigmented in the centre. • The surface is dry, hairless, insensitive and sometimes scaly.
Borderline leprosy (BB)	• More lesions are present, compared to TT. • Nerve involvement is common. • Borders are less defined than TT. • Lesions may take the form of macules, plaques, bizarre-shaped bands, or annular lesions. • BB is the most common type of leprosy and is unstable. It could down-grade to LL or upgrade to TT.
Lepromatous leprosy (LL)	• Multiple lesions are present. • Nerve involvement is common, with anaesthesia on dorsal areas of hands and feet. Blindness can result if corneal nerves are affected. • Borders may be vague. • Lesions can be a combination of macules, papules, nodules, or infiltration. Distribution is symmetrical and can also cause ulceration and bleeding in the nasal mucosa. • Nails become thin and brittle. Fingers may become crooked or short. Skin thickens and lines become deeper on the forehead. The voice becomes hoarse and teeth may become loose, or fall out.

Resistant TB has become a major public health challenge worldwide, since progress in TB treatment has declined, due to increasingly fewer patients being fully cured by pharmacotherapy [104,38,50,27,105]. This overall has led to increased research into the development of TB vaccines, and as a result promising vaccines are in the pipeline [106].

4.1. True cutaneous tuberculosis and tuberculids

The WHO recommends a drug regimen for the treatment of tuberculosis and thus also for true CTB. The regimen consists of two phases, i.e. firstly the intensive phase for 8 weeks, and secondly, the maintenance phase for 16 weeks. In HIV positive patients, phase two is administered for 28 weeks, instead of 16 [10,37,25,44]. The most useful first-line drugs for CTB treatment include isoniazid (INH), rifampicin (RIF), ethambutol (EMB), pyrazinamide (PZA) and streptomycin (STR). Phase one treatment consists of INH, RIF, EMB and PZA for 2 months, followed by 4 months' treatment with INH and RIF in phase two. If INH resistance is suspected, EMB can also be given in phase two [22,6,47,38,13,14,29,65,56,34,20,35,30].

In cases where CTB is located around natural openings, additional treatment with 2% of lactic acid and with local anaesthetics is applied. Surgical excision of lesions and the correction of deformities can also be performed [66,25,44,107,20]. Since tuberculids are an allergic reaction to *M. tuberculosis*, present in the patient's system, anti-tuberculous therapy is also recommended for such lesions [62,74,35].

4.2. Atypical mycobacterium infections

Since non-tuberculous mycobacteria (NTM) is resistant to most anti-tuberculous drugs, the treatment of these organisms is long and difficult [33,81].

Studies have shown that rifampicin and rifabutin are the most active drugs against *Mycobacterium marinum* [35]. In immunocompetent patients, therapy consists of single or dual therapy with drugs, such as clarithromycin, minocycline, doxycycline, or trimethoprim-sulfamethoxazole, or combination therapy with EMB and RIF. Therapy should continue for at least 3–6 months. Deeper, more serious infections should primarily be treated with clarithromycin and RIF for at least 7 months [85,32,80,35].

Mycobacterium ulcerans infections are non-responsive to pharmacotherapy and extensive surgical management is the key treatment in virtually all cases. Skin grafting is also an option in some cases. Therapy with RIF and either STR, or amikacin has shown complete healing in 50% of patients after 8 weeks and has thus been adopted by the WHO. If the disease is diagnosed and treated at an

early stage, it may respond to a regimen including clarithromycin, RIF and EMB, although the optimal therapy duration is still unknown [87,32,80,89,35]

The *Mycobacterium haemophilum* organism is typically resistant to INH, EMB and STR. Multi-drug regimens, including rifabutin, RIF, clarithromycin, ciprofloxacin, amikacin, trimethoprim-sulfamethoxazole, levofloxacin, cefoxitin, doxycycline and cotrimoxazole have been found to be successful. Immuno-competent patients must continue with therapy for 6–9 months, whereas immuno-compromised patients have to continue with therapy indefinitely. Surgical excision has also been reported as being beneficial [91,108,32,80,35].

Typical treatments for the *Mycobacterium fortuitum* organism consist of clarithromycin and either doxycycline, trimethoprim-sulfamethoxazole, or ciprofloxacin for 2 months. Recently it has been found that this organism is susceptible to newer macrolides (e.g. roxithromycin, clarithromycin and azithromycin), doxycycline, minocycline, sulphonamides, cefoxitin, amikacin, ciprofloxacin and imipenem. More serious infections involving larger areas, deep tissue and extension into bony structures, are treated with intravenous amikacin, cefoxitin, or imipenem and treatment is recommended for 4–6 months. Surgical debridement is beneficial and the addition of clarithromycin to the treatment regimen has been suggested [32,80,34,35].

Combination therapy of at least two agents must be given to decrease the chances of resistance against *Mycobacterium chelonae*, although therapy with clarithromycin alone has shown effective results. Ciprofloxacin is for this reason combined with clarithromycin, whilst doxycycline has also shown effectiveness against this organism. More serious infections with deep tissue involvement can be treated with a combination of imipenem, amikacin, tobramycin, linezolid and macrolides for at least 6–12 months. *M. chelonae* usually shows resistance to cefoxitin [109,32,80,83,34].

Therapy for a mild infection of *Mycobacterium abscessus* may include clarithromycin/azythromycin, clofazimine and linezolid for 3–6 months. For a more serious infection, clarithromycin/azithromycin (oral) and either cefoxitin, imipenem, or amikacin (intravenously) may be given for a minimum of 6 months. The same course of treatment as for *M. fortuitum* may be followed, although the prognosis may be worse than for *M. fortuitum* infections [32,80,34,35].

Regimens recommended by the WHO for *Mycobacterium leprae* have been classified into three categories for simplicity:

- For few or singular lesions some clinicians prescribe RIF, ofloxacin and minocycline in combination or individually, depending on patient needs. Due to insufficient follow-up data, however, the WHO recommends that these patients can also be treated by the pauci-bacillary regimen.
- The pauci-bacillary regimen consists of rifampicin once a month and dapsone daily for 6 months.
- The multi-bacillary regimen is administered for more serious infections and includes RIF and clofazimine (300 mg) once a month, and dapsone and clofazimine (50 mg) once a day for at least 12 months. Clofazimine may be substituted by prothionamide, ethionamide, or minocycline in cases where communities disapprove of clofazimine, due to its adverse effect of darkening the skin, especially of the lesions [32,95,96].

5. Summary

TB poses a major health challenge worldwide [104,50,41,105]. CTB is an uncommon form of TB, with only a 1–1.5% prevalence among all reported extra-pulmonary TB cases [21,27,29,20,30]. CTB is difficult to diagnose, due to its rare nature and the fact that it may present in various clinical forms [55,110,65]. Such clinical presentations can vary from small papules, warty lesions, ulcers, or papules to highly deformative plaques that are thickened and hyperkeratotic [24,37,49,63,8,53,35]. It is very important to diagnose and treat TB as early as possible to avoid any complications, although it has often been misdiagnosed as tinea corporis and carcinoma, for example [2,70,41,59,65].

True CTB is caused by the *M. tuberculosis* organism and the BCG vaccine. It can be contracted through inoculation from an exogenous source (e.g. tuberculous chancre), from an endogenous source (e.g. scrofuloderma), or through haematogenous spread (e.g. lupus vulgaris). Atypical CTB infections are caused by other *Mycobacterium* species, such as *M. abscessus*, *M. chelonae* and *M. ulcerans* [22,32,38,80,81,43,65,34,45].

True CTB can be treated with the regular anti-tuberculous regimens, including INH, RIF, EMB and PZA. Surgical excision and reconstruction are often required in very serious cases. Atypical *Mycobacterium* infections can be treated with a variety of antibiotics, although treatment is difficult, due to these organisms often being resistant to regular TB medication [25,38,7,13,44,46,14,107,111,56,20].

CTB and other cutaneous mycobacterial infections are mostly unsightly and thus often also significantly impact on the patient's social and mental wellness. To date, no topical therapy has been identified for any of the discussed infections, and although most of the current regimens have demonstrated positive results, they are not all completely effective. There is furthermore a high probability of drug resistance formation, due to low patient compliance and ever evolving organisms.

In addition to the need for improving typical therapeutic regimens currently used, such as reducing the duration and adverse effects of TB treatments, the potential of topical treatments to aid in treating these infections need to be properly explored. No current topical treatment for CTB has been found in the literature. Although topical therapy would not be a substitute for conventional treatments, it may be used concurrently and possibly aid in improving treatment outcomes.

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