Update on cutaneous tuberculosis*

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Abstract: Tuberculosis continues to draw special attention from health care professionals and society in general. Cutaneous tuberculosis is an infection caused by M. tuberculosis complex, M. bovis and bacillus Calmette-Guérin. Depending on individual immunity, environmental factors and the type of inoculum, it may present varied clinical and evolutionary aspects. Patients with HIV and those using immunobiological drugs are more prone to infection, which is a great concern in centers where the disease is considered endemic. This paper aims to review the current situation of cutaneous tuberculosis in light of this new scenario, highlighting the emergence of new and more specific methods of diagnosis, and the molecular and cellular mechanisms that regulate the parasite-host interaction.

Keywords: Erythema Induratum; Mycobacterium tuberculosis; Tuberculosis; Tuberculosis, Cutaneous

INTRODUCTION

Tuberculosis (TB) continues to draw special attention from health care professionals and society as a whole. It still meets all the criteria for prioritization of a public health disorder, i.e. large magnitude, vulnerability and transcendence.[1] Cutaneous tuberculosis is an infection caused by *M. tuberculosis* complex, *M. bovis* and bacillus Calmette-Guérin (BCG), which depending on individual immunity, environmental factors and type of inoculum may present varied clinical and evolutionary aspects.[2-4]

Since 2009, the Brazilian Ministry of Health recommends the use of ethambutol as the fourth drug associated with rifampicin, isoniazid and pyrazinamide to treat tuberculosis. It is recommended that cases of cutaneous TB should be discussed within the health unit TB program.[1,5]

The association of TB with HIV infection represents an additional challenge worldwide. An increase in its incidence has been described in several countries in recent years, especially in urban centers and regions with high prevalence of human immunodeficiency virus (HIV) infection.[6] Complications related to immune reconstitution induced by antiretroviral therapy, known as immune reconstitution inflammatory syndrome (IRIS) may occur, including paradoxical worsening of cutaneous tuberculosis and the emergence of subclinical infections. The most common clinical presentations of infection by *Mycobacterium tuberculosis*-associated IRIS are lymphadenitis or lymphadenopathy.[7-9]

Knowledge about TB infection and its clinical management were outside the scope of most dermatological practices. However, the introduction of biologic therapies demanded from dermatologists a deep and up-to-date knowledge of tuberculosis.[10]

This article provides relevant current information on the definition, epidemiology, recognition of clinical presentation, microbiology and immunology of infectious agents, diagnostic methods and treatment of cutaneous tuberculosis.

EPIDEMIOLOGY

According to the World Health Organization (WHO), in 2011, there were about 8.8 million incident cases of TB, 1.1 million deaths from TB among HIV-seronegative persons and an additional 350,000 deaths from HIV-associated TB. In the same year, 84,137 cases of tuberculosis were reported in Brazil, of which, 74,892 were newly diagnosed or retreatment cases and 2,755 were from other causes (unknown his-

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tory). Amongst the new cases, 56% had positive bacilloscopy, 18% had negative smear, 12% were unknown, 14% were cases of extra pulmonary tuberculosis and 1% of unspecified TB. Regarding cases of retreatment, 35% were due to recurrence, 2% to therapy failure, 33% to abandonment of treatment and 29% to other causes (unknown history).[11] Records of TB in Brazil do not specify the cutaneous form, which led to lack of data on its incidence.[1,5]

About 20% of TB cases in children have extrapulmonary presentation. The most common forms are: peripheral lymphadenopathy, pleural, bone and meningoencephalic TB.[12]

According to the Ministry of Health (MH), in 2011, the Brazilian states that reported most cases of TB were Sao Paulo (16,630 cases), Rio de Janeiro (11,651), Bahia (5,257) and Rio Grande do Sul (5,031).[13]

ETIOLOGICAL AGENT

Mycobacterium tuberculosis bacillus, or bacillus Koch (BK) is a transitional form between actinomycetes and eubacteria. It belongs to class *Schizomycetes*, order *Actinomycetales*, family *Mycobacteriaceae* and genus *Mycobacterium*. Robert Koch first described it on March 24th, 1882. This is a non-spore-forming, nonmotile, non-toxin producer, strictly aerobic bacillus and a facultative intracellular species. It has an extended growth period (16 to 20 hours) and doubling time (18 to 48 hours). These bacilli present acid-alcohol-resistant staining properties – i.e., they stain red by fuchsin and will not discolor by the actions of alcohol and acid, hence the name AFB – Acid-Fast Bacilli. Its genome has already been sequenced.[14-17]

Although it may cause illness in men, *M. bovis* is considered a zoonotic disease that usually affects tonsils, lymph nodes and intestine. It may rarely be the cause of the cutaneous form of TB. When causing lung disease, *M. bovis* is not easily transmitted and therefore, there is a tendency for its disappearance.[18,19]

Bacillus Calmette-Guerin (BCG) is a lyophilized vaccine developed in 1908, prepared from a live, attenuated strain of *Mycobacterium bovis*. Adverse events associated with BCG vaccine are uncommon, but local or systemic complications may occur.[20,21] They depend on the strain used and are more common amongst infants than adolescents. Ulceration, subcutaneous abscess and suppurative lymphadenitis occur in 0.4 per 1,000 vaccinations, appearing in the first 6 months after vaccination. Hypertrophic and keloid scarring occur in 4 per million vaccinated. Systemic complications and fatal dissemination are rare (<1.5 per million). Although generally safe, vaccine reactions such as skin complications are well known and can include local hypersensitivity reactions, cutaneous granulomas, fixed drug eruption and cutaneous tuberculosis.[21] The World Health Organization currently recommends that BCG vaccine should be administered to all those living in areas of endemic tuberculosis. In Brazil, the vaccine is part of the national immunization schedule and according to the MH's immunization manual it is indicated right after birth, as early as possible.[22] The interval between vaccination and the development of skin lesions may be of several months or years, with an average duration of 1 year. Factors that may be responsible for the development of BCG reactions include inherent susceptibility of the organism to BCG virulence, to the amount of inoculum and the inoculation technique.[21,23,24]

IMMUNOLOGY IN TUBERCULOSIS

Just as in leprosy and pulmonary tuberculosis, there is a concept of spectrum in cutaneous tuberculosis. Based on bacteriological, histopathological and immunological parameters, Sehgal *et al* proposed a continuous spectrum extending from the greater cellular immunity pole, observed in lupus vulgaris, with active cellular immunity and apparently normal levels of immunoglobulins, to scrofuloderma and cutaneous miliary tuberculosis, which present a relatively less active cellular immunity and high humoral response, as evidenced by elevated immunoglobulin serum levels and low levels of C3.[25,26]

The introduction of more specific and sensitive diagnostic methods, as well as a greater understanding of the molecular and cellular mechanisms that regulate the parasite-host interaction may contribute to an efficient fight against tuberculosis. Immunosuppression, either due to a poor state of health, HIV infection or to the use of immunosuppressive drugs, represents the main trigger for active disease development, caused by *M. tuberculosis*.[27]

Tissue macrophages constitute one of the first lines of defense against mycobacteria. After being phagocytized, the bacilli remain within the phagosome. After the phagosome-lysosome fusion, antigens can be processed and subsequently presented to T-helper lymphocytes (CD4 +) through major histocompatibility complex (MHC) class II. CD4 + type 1 cells (Th1) play a major role in the immune response to mycobacteria.[27,28]

In the case of mycobacteria, it was demonstrated that apoptotic vesicles, originated from infected cells and containing bacillary antigens associated to MHC class I, are able to specifically stimulate CD8 + T cells also participating in the immune response to *M. tuberculosis*.[29]

CD4- and CD8- lymphocytes with gamma/delta chain polypeptide-containing receptors

recognize phosphoric components of *M. tuberculosis*, regardless of MHC class I or II, whereas T lymphocyte receptors, restricted only to CD1, can be stimulated by glycolipids derived from the mycobacterial wall. Therefore, the immune system is able to recognize and effectively respond to a broad range of antigenic determinants with different biochemical characteristics. In this recognition process, there is a hierarchy among T cell subpopulations that contribute to the immune response to mycobacteria, with CD4 + and CD8 + lymphocytes being the most important cells in this ranking.[27,30]

Regarding the innate immune response, neutrophils are the first inflammatory cells to settle on the bacillary multiplication site, followed by natural killer cells (NK) and macrophages. The recognition and phagocytosis of bacteria by innate immunity cells (neutrophils, macrophages, and dendritic cells) occur via recognition receptors, such as mannose receptor, antibody Fc portion receptors (FcRs) and complement system activation products receptors, as C3b and C4b (CR1), among others. Activation of pattern recognition receptors, such as Toll-like receptors (Toll-like receptors, TLRs), leads to an important link between the innate and acquired immune responses.[27,31,32]

Cytokines are a central component in the defense against mycobacteria. At all stages of immune response, produced cytokines participate in the regulatory process, and effector functions. Recognition of mycobacteria and subsequent secretion of IL-12 by macrophages are processes initiated prior to the presentation of *M. tuberculosis* antigens to T lymphocytes. IL-12 induces the production of interferon gamma (IFN-γ) in NK cells in the initial phase of immune response and also induces the activation, differentiation, IFN-γ production and antigen-specific Th1 cells expansion. Th1 cells are the major source of IL-2 and IFN-γ during acquired immune response and are necessary to control the chronic phase of infection, because of these cytokines' actions on T cells and macrophages. Produced by macrophages and dendritic cells and acting on T cells, IL-12 forms a link between innate and acquired responses. Individuals with mutations in IL-12 p40 and IL-12R genes show a reduced IFN-γ production by T cells and are more susceptible to disseminated infections by Bacillus Calmette-Guerin vaccine (BCG) and *M. avium*.[27,28,33]

Macrophagic bactericidal activity against *M. tuberculosis* needs to be previously activated and IFN-γ is the main and most potent mediator of this process.[34] IFN-γ is able to increase the expression of several genes in the macrophage, induce an increase in MHC expression (increase in antigen presentation) and in immunoglobulin receptors (FcRs and increased capacity for phagocytosis), recruit T lymphocytes involved in destruction of bacteria and participate in the production of nitric oxide. Although the isolated production of IFN-γ is insufficient to control the bacillus, IFN-γ is one of the crucial components of the protective response against the pathogen. IFN-γ, in synergy with tumor necrosis factor alpha (TNF-α), activates infected macrophages, initiating an important effector mechanism of cell-mediated immunity. While the ability to produce IFN-γ can vary among individuals, some studies suggest that the levels of IFN-γ are decreasing in patients with active TB. These levels are even lower in patients with advanced pulmonary disease. Furthermore, it was demonstrated that *M. tuberculosis* could prevent macrophages from adequately responding to IFN-γ. TNF-α is a proinflammatory cytokine that also plays a central role in the immune response against *M. tuberculosis*, contributing to granuloma formation, which isolates bacilli and prevents their spread. T-helper lymphocytes, from CD4+ lineage, release IFN-γ and TNF-α, which account for the transformation of macrophages and monocytes into specialized histiocytes with bacteriostatic and bactericidal capacity. This immune response is amplified by TNF-α which modulates the synthesis of IL-12 and NF-kB , promoting the expansion of CD4 + Th1 lineage.[35,36]

Th1 cells mediate immunity against TB. However, it was recently reported that, besides the cytokines produced by Th1 cells, there is also IL-4 production in human TB. IL-4 has the ability to downregulate the expression of TLR2 and macrophage activation. Recently, CD4+ and CD25+ regulatory T cells have been identified. These cells produce IL 10 and transforming growth factor-beta, and are able to express TLRs (which can react with myco¬bacteria) and participate in the suppression of protective immunity. Therefore, they constitute a potentially important factor at the onset of the infection, since they can influence the latency or progression of TB.[27]

TUBERCULIN SKIN TEST

Tuberculin skin test (TST) or Mantoux test is the intradermal inoculation of *M. tuberculosis* purified protein derivative (PPD) to measure the cellular immune response to these antigens. It was developed by Florence Siebert in 1939 and remains a reference for all tuberculins. PPD components are mostly proteins with molecular weights of approximately 10,000 d, but there are also polysaccharides and some lipids. The relatively small size of PPD protein constituents is the reason why it does not usually sensitize individuals who have not been previously exposed to mycobacteria. When stored at temperatures between 4 and 8°C, tuberculin remains active for six months. It should not, however, be frozen or exposed to direct sunlight.[1,37]

The tuberculin used in Brazil is PPD RT-23, administered intradermally in the middle third of the left forearm anterior surface, at a dose of 0.1ml, containing 2UT (units of tuberculin), which is biologically equivalent to 5UT of PPD-S used in other countries.[1] The application and reading techniques, and materials used are standardized by WHO.[38-40] Reading should be performed 48 to 72 hours after application and it can be extended to 96 hours if the patient does not attend the scheduled reading date.[41-43]

People with specific antituberculosis cellular immunity develop limited erythema and induration at the site of the tubercle protein intradermal injection, usually peaking within 48 to 72 hours after exposure. This delayed-type hypersensitivity is a result of the influx of lymphocytes that are sensitized to the injected antigen and lymphokines released from these T cells, resulting in vasodilation, local edema and recruitment of other inflammatory cells to the area.[44,45]

Reaction to tuberculin skin test should be measured by the Sokal ballpoint pen technique and the reading recorded in mm of induration.[46] The largest transverse diameter of palpable induration area should be measured with a transparent millimetered ruler and the result recorded in millimeters. The isolated classification of TT (Tuberculin Test) in nonreactor, weak reactor and strong reactor is no longer recommended, as the interpretation of the test and its cutoff values may vary according to the population and the disease risk. Individuals with documented TT with results equal to or greater than 10 mm should not be retested. It is necessary to emphasize that the size of reaction in the patient, can guide important therapeutic decisions.[1]

The tuberculin test can be interpreted as suggestive of *M. tuberculosis* infection when equal to or greater than 5mm in children not vaccinated with BCG, children vaccinated more than two years before the test was performed or those with any immunosuppressive condition. In children vaccinated less than two years before the test, TT is considered suggestive of infection when equal to or exceeding 10mm.[47,48]

Cellular immunity induced by nontuberculous mycobacteria such as *M. scrofulaceum* and *M. avium* complex can cause a cross-reaction induration, usually around 5-10 mm. The aforementioned classification is valid only for patients with negative serologic HIV testing. Individuals infected with HIV are considered infected with TB bacillus when presenting tuberculin test with induration equal to or greater than 5 mm. Another important detail is that tuberculin test may lose its value in individuals vaccinated with BCG in the three years preceding the test date.[49,50]

False-positive reactions may occur in individuals infected with other mycobacteria or vaccinated with BCG, especially if vaccinated (or revaccinated) after the first year of life, when BCG induces stronger and long-lasting reactions. However, the reaction tends to diminish over time and if TT is performed ten years or more after the last vaccination, the effect of BCG on it may be minimal.[1,43,51-54] False negative reactions (individuals with latent infection by *M. tuberculosis* - LTBI and negative tuberculin test) may occur in the circumstances depicted on chart 1.[53,54]

The loss of skin test reactivity occurs in cases of malignancy, syphilis, severe systemic viral infection, sarcoidosis, malnutrition and concomitant HIV infection. In all these conditions, cellular immunity is depressed and, thus the absence of skin test reactivity correlates with increased susceptibility to infection by *M. tuberculosis*.[2,6,16,40]

Chart 1: Circumstances associated to TT false-negative results

Technical circumstances	Biological circumstances
Poorly conserved tuberculin, exposed to sunlight; contamination by fungi; wrong dilution; maintenance in inadequate vials and denaturation; deep injection or insufficient quantity; use of inadequate needles or syringes; delay administration in relation to preparation time; inexperienced or skewed reader.	Severe or disseminate tuberculosis; other acute viral, bacterial or fungal infectious diseases; severe immunodepression (AIDS, use of corticosteroids or other immunosuppressors or chemotherapy); vaccination with live virus; neoplasms, especially of the head-and-neck and lymphoproliferative diseases; malnutrition, diabetes mellitus, renal insufficiency and other metabolic conditions; pregnancy, infants under 3 months of age; elderly (> 65 years old); ultraviolet light; fever during TT and in subsequent hours; benign or malignant lymphogranulomatosis; severe dehydration; sarcoidosis, hypothyroidism (false negative reaction), post chemoprophylaxis with isoniazid and in 5% of cases idiopathic.

In many individuals, sensitivity to PPD skin test persists throughout life. However, if all mycobacterial organisms and their antigens are eliminated, the number of PPD-specific T cells will decrease with time and in some individuals the response to tuberculin skin test may be negative. If PPD is administered to these individuals, whose skin tests have become attenuated, a stress response may occur in repeated tests. This is called the *booster effect* and can be misinterpreted as a shift in the skin test result. This is very important nowadays, with the use of biological drugs and the possible repetition of PPD during treatment. Originally negative PPD can become positive without any active infection. The Center for Disease Control (CDC) recommends that when a periodic test is performed, as the annual monitoring on hospital personnel, individuals who responded negatively to the initial skin test must repeat it a week after the original test. If the second test is positive, the *booster effect* occurred. If it is negative, the subsequent change of PPD skin test result can be accurately interpreted as infection.[55-58]

CLINICAL FORMS

The cutaneous tuberculosis (TBC) classification covers a wide variety of clinical presentations. Infection can occur through exogenous routes, i.e., cutaneous inoculation takes place directly on the skin (tuberculous chancre, tuberculosis verrucosa cutis and some cases of lupus vulgaris) or endogenous ones, with cutaneous involvement occurring secondarily, through hematogenous route from a distant tuberculosis focus or by contiguity from an already established focus (most cases of lupus vulgaris, scrofuloderma, miliary tuberculosis and orificial tuberculosis).[2,3,5,6,59-61]

It is also possible to discriminate according to the bacterial load of the lesions. Cases with many acid-fast bacilli (AFB) seen on direct examination or microscopically are classified as multibacillary otherwise they are called paucibacillary.[61,62]

TUBERCULOUS CHANCRE OR PRIMARY TUBERCULOUS COMPLEX

It is characterized by the appearance at the first site of inoculation, 2 to 4 weeks post contact, of a shallow, painless ulcer, with granular base with microabscesses or thick crust, undermined borders, accompanied by painful regional lymphadenopathy that may evolve with fistulae and, less often, erythema nodosum. Spontaneous regression with scarring and regional lymph node calcification may occur or the patient may develop lupus vulgaris lesions and tuberculosis verrucosa.[2,5,16]

It is rare, but more frequent in children who were not vaccinated and have contact with patients with pulmonary tuberculosis.[60,63,64] It has also been reported in surgical wounds, tattoos and piercing sites.[61,65] There is often dissemination to regional lymph nodes and lymphatic vessels; the combination of the latter with tuberculous chancre is analogous to the Ghon complex in the lungs.[2]

PPD is initially negative, but becomes positive during the course of the disease (usually after 15 days).[16]

Histopathology initially shows an acute neutrophilic inflammatory reaction, prolific in AFB and necrotic areas. After 3 to 6 weeks, the lesion acquires a granulomatous appearance with enlarged giant cells and decreased number of bacilli.[5,61]

Among the differential diagnoses are those diseases that may present sporotrichoid patterns: sporotrichosis, leishmaniasis, atypical mycobacteriosis, syphilis, cat scratch disease and tularemia.[2,60]

TUBERCULOSIS VERRUCOSA CUTIS

It appears as painless, isolated or multiple verrucous and tuberous papules, of slow evolution and spontaneous involution, without adenopathy, usually located on the extremities. Its most frequent location is on the hands and it results from exogenous inoculation (Figure 1A). It can be considered an occupational disease, due to self-inoculation possibilities, such as

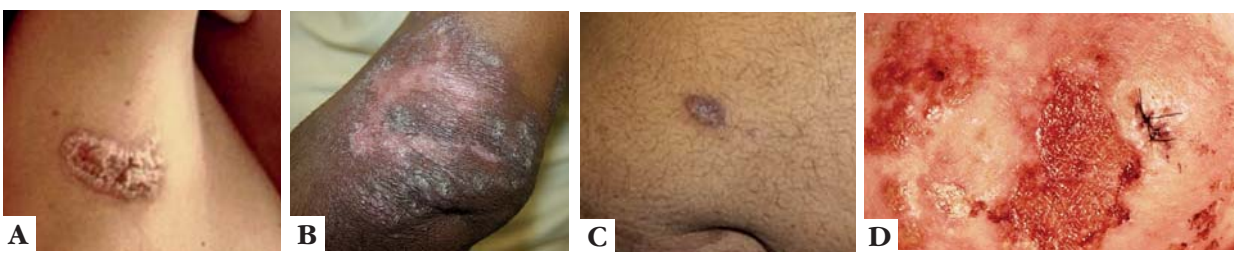


Figure 1: **A.** Tuberculosis verrucosa – verrucous plaque with scaling located on the right axilla; **B.** Lupus vulgaris (Courtesy from Dr. Marcelo Lyra - Fiocruz); **C.** Lupus vulgaris (Courtesy from Dr. Marcelo Lyra - Fiocruz); **D.** Lupus vulgaris – erythematous infiltrating plaque with crusts located on the buttocks

may occur to a dentist treating the mouth of a patient with pulmonary TB or to a butcher handling contaminated meat (in the latter case it is usually due to infection by *M. bovis*). PPD test is strongly positive.[2,16,60,66,67]

Histopathology shows pseudoepitheliomatous hyperplasia and hyperkeratosis, tuberculoid granulomas with or without necrosis and rarely with bacilli. Visualization of mycobacteria and/or their isolation in culture are exceptions and not the rule.[5,60,62]

As differential diagnosis, diseases with verrucous lesions should be considered, such as: paracoccidioidomycosis, leishmaniasis, sporotrichosis, tuberculosis verrucosa and chromomycosis. Lobomycosis, atypical mycobacteriosis, hypertrophic lichen planus, verrucous carcinoma, iododerma, bromoderma, verruca vulgaris, keratoacanthoma centrifugum and pyoderma vegetans should also be considered.[2,5,6,66]

LUPUS VULGARIS OR TUBERCULOSIS LUPUS

It is a form of cutaneous TB that occurs in previously sensitized individuals, with delayed hypersensitivity reaction strongly positive to tuberculin. It may also develop secondarily to TB verrucosa cutis, scrofuloderma or BCG inoculation. Infection occurs endogenously, through a lymphohematogenous route or by continuity, and rarely via exogenous routes.[2,16]

The most characteristic clinical feature is a papulo-tuberous lesion of slow evolution, which can coalesce into a plaque, located on the face, and may invade mucosae. At diascopy, the classic appearance is described as " *apple jelly nodules*." Lesions may also be flat (serpiginous or polycyclic), hypertrophic (keratotic or tumoral), ulcerated (necrosis and ulceration of the plaque, with cicatricial deformities and mutilations) and vegetative (necrosis and ulceration without scarring). Lesions affecting the earlobe may resemble a pseudotumor. Multiple lesions may appear simultaneously, after a temporary immunosuppression (Figures 1B, 1C and 1D).[2,5,59,68,69,70]

The usefulness of dermatoscopy in the diagnosis of lupus vulgaris has been recently suggested, since it revealed peculiar characteristics consisting of linear telangiectasias on a yellow to golden background and whitish reticular streaks. Although none of the observed characteristics are specific enough alone, their combination may increase the diagnostic sensitivity.[71]

Histopathology will show pseudoepitheliomatous hyperplasia and multiple, well developed tuberculoid granulomas, with scarce caseous necrosis, and nonspecific inflammatory infiltrate without visible bacilli. Mycobacterial culture is often negative. PPD result, however, is usually positive.[5,16,72]

SCROFULODERMA OR COLLIQUATIVE TUBERCULOSIS

It is the most common form in our midst, occurring in children and young people. The infection route is always endogenous, usually secondary to bone or lymph node TB. Clinical lesions appear as nodules, gumma and ulcerations due to fistulae. There are reports of involvement of cervical and inguinocrural regions, as well as lesions in epididymis, conjunctiva and mouth. Patients may have active pulmonary or pleural disease with systemic symptoms (Figure 2).[2,5,73,74,75]

Histopathology shows tuberculoid granuloma with wedge-shaped caseous necrosis. AFB are easily seen in biopsy material and / or on exudate direct examination. PPD is strongly positive.[5,16,74,75]

Differential diagnoses include gummous and fistulous diseases, such as tertiary syphilis, paracoccidioidomycosis, actinomycoses, hidradenitis suppurativa, and lymphogranuloma venereum.[6,74,76]

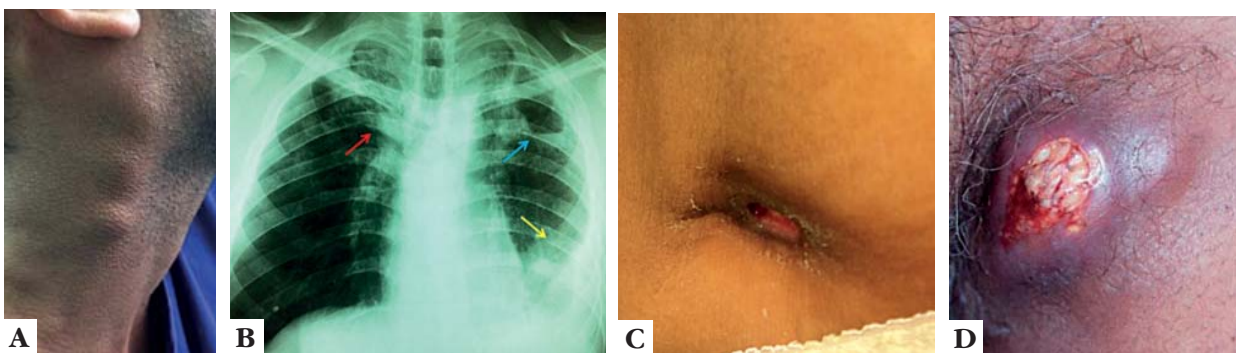


Figure 2: **A.** Scrofuloderma (Courtesy from Dr. Vitor Paulo Perez - Fiocruz); B. Chest X-ray in posterioranterior (PA) position showing a right infraclavicular opacity (red arrow), images of thick-walled cavities, acinar lesions permeating the left superior lobe (blue arrow) and pleural effusion on the left (yellow arrow). Pulmonary tuberculosis – Chest X-ray from the same patient on Figure 3 (Courtesy from Dr. Vitor Paulo Perez - Fiocruz); C. Scrofuloderma (Courtesy from Dra. Julia Ocampo Lyra da Silva – Bonsucesso Federal Hospital); D. Scrofuloderma. Ulcerated nodular lesion on the left inguinal region of an HIV positive patient

ORIFICIAL TUBERCULOSIS

It results from the propagation of tuberculosis infection at the mucocutaneous junction of natural orifices (mouth, anus, vulva, urethra and palate), due to self-inoculation from an active focus on deep tissues, in patients with severe TB on the corresponding area (intestine, urogenital tract). This form of cutaneous tuberculosis is rare and usually affects immunocompromised patients.[2,77]

The most common lesion is a painless ulcer, with fibrinous and pseudomembranous basis. Occasionally, there is no ulcer, however the remnants of a lupus vulgaris hypertrophic tissue or plaque can be observed. Lesions may be localized in any part of the oral and perineal mucosa.[77-81]

Histopathologically, it is characterized by the presence of tuberculoid granulomas with necrosis and ulceration, with abundant AFB. Culture is generally positive, even with a negative tuberculin response (PPD).[5,16]

ACUTE CUTANEOUS MILIARY TUBERCULOSIS

Considered as a form of systemic miliary tuberculosis, it occurs in immunocompromised patients and anergic children, with negative PPD.[5]

It is characterized by numerous erithematous-papulovesicular lesions, occasionally ulceronecrotizing, and sometimes with exanthematous rash. When papules heal, they leave residual hypochromic scars. Cutaneous lesions are the result of bacteremia and the primary focus is often located in the lungs.[82,83,84]

Histopathologically, it is characterized by the presence of tuberculoid granulomas with necrosis and ulceration, with numerous AFB.[5,16,84]

TUBERCULIDS

These are acute or chronic skin conditions, punctuated by acute bouts, with a tendency to spontaneous involution of the hyperergic expression following *M. tuberculosis* infection, active TB or episodic bacteremia. They may occur in the presence of cutaneous tuberculosis or even after BCG vaccination. It is more common amongst children and young adults. Clinical forms usually have a symmetrical distribution, absence of AFB in the lesions (low positivity to PCR), positive PPD and good therapeutic response with favorable outcomes.[2,3,5,6,16,40]

Currently only three entities are considered true tuberculids: papulonecrotic form, erythema induratum of Bazin and lichen *scrofulosorum* (LS).[60,61,62]

PAPULONECROTIC TUBERCULID

It appears as painless, symmetrical erythematous or violaceous papulonodular lesions, which evolve in bouts, leaving depressed scars (varioliform or punched-out), located particularly on the extensor surfaces of legs and forearms, dorsal areas of hands and buttocks of children and young adults. PCR positivity and response to specific treatment are observed (Figure 3A).[2,60,62,85,86]

Histopathology reveals marked leukocytoclastic vasculitis in early lesions and tuberculoid granuloma in older lesions, suggesting that it is initially an Arthus phenomenon (type III reaction) and subsequently a delayed hypersensitivity reaction (type IV). Other findings are dermis-based wedge-shaped necrosis, associated with prominent perivascular mononuclear cells infiltration, without AFB.[5,16]

Differential diagnosis should be made with: *pityriasis lichenoides et varioliformis acuta* (PLEVA), leukocytoclastic necrotizing vasculitis, pruritus and secondary syphilis.[2,5]

LICHENOID TUBERCULID OR *LICHEN SCROFULOSORUM*

This is a rare form in our midst. It is characterized by small, shiny, usually perifollicular erythematous-brownish papules, cover by a crust or by hyperkeratosis; asymptomatic, they appear mostly grouped and in a nummular distribution, located preferably on the trunk, most often in children. Patients show a strong positive reaction to PPD, measuring 18 mm or more. History of BCG vaccination is present in approximately 70% of patients.[4] *Lichen scrofulosorum* was recently described after BCG vaccination and *M. avium* infection.[3,5,16,87,88]

Histopathology shows superficial granulomas with little or no caseous necrosis in follicles and sudoriparous glands or in their midst. The presence of bacilli is rare, although PCR tests have found *M. tuberculosis* DNA in these lesions.[5,16]

Differential diagnosis: lichen planus and lichen nitidus, syphilid lichenoides, eczematid, keratosis pilaris, pityriasis rubra pilaris (PRP) and micropapular sarcoidosis.[2,3,5,16]

ERYTHEMA INDURATUM OF BAZIN

At Saint-Louis Hospital in Paris (1861), Bazin described a nodular eruption that occurred on the lower limbs of young women suffering from tuberculosis, under the name of "érythème induré des scrofuleux".[89] It is clinically characterized by painless, chronic and recurrent erythematous-violaceous nodules and plaques, with a tendency to ulcerate centrally, which occurs in 30% of cases; lesions are located preferably in women's calves (Figures 3B and 3C).[90,91] The ulcers are shallow, with violaceous loose borders, granular red basis with yellow dotting.[89,92] As the lesions evolve, some patients report pain during pressure. Lesions are often symmetric and in the course of evolution, provoke the adhesion of the overlying epidermis thus becoming hardened. The skin has a red-

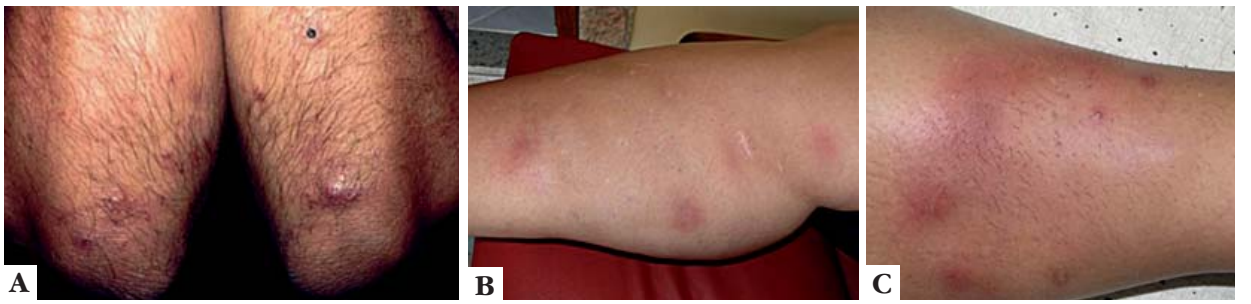


Figure 3: **A.** Papulonecrotic tuberculid – erythematous papules with central crust; **B** and **C:** Erythema induratum of Bazin

dish-brown or purplish coloration.[2,3,5,90] It may be precipitated by cold weather or venous stasis and association with erythrocyanosis and follicular keratosis is often seen.[89,90,91] It may also be associated with varicose veins, livedo, and cold edema. The identical clinical presentation that is not associated with tuberculosis is called nodular vasculitis of Montgomery.[2]

The skin surface tends to flake when the nodes are well established, forming a collarette around the lesions or crusts covering the ulcers.[2,91] Some lesions spread forming subcutaneous plaques.[89] Most lesions disappear spontaneously within a few months, leaving post-inflammatory hyperpigmentation, and occasionally atrophic pigmented scars.[91,92]

Epidemiological studies allow us to establish solid knowledge: higher predisposition rates for females, adolescents and young adults, predisposition in Caucasians, high incidence in lower temperature countries (colder months) and an apparent association with circulatory disorders of lower limbs and obesity.[6,16,91] The disease has a chronic course and ulcerations and new lesions may appear during treatment.[90,91]

Clinically, erythema induratum of Bazin can mimic a variety of conditions that present as chronic nodules on the lower extremities, including erythema nodosum, cutaneous polyarteritis, pancreatic panniculitis, lupus profundus, subcutaneous sarcoidosis and cutaneous T-cell lymphoma.[91]

Histopathology consists of tuberculoid granulomatous infiltrate, vascular alterations and areas of caseous necrosis. The process is primarily located in the hypodermis, the center stage for reactions in which venules and small to medium caliber arteries are affected.[5,6] Vascular walls may show several changes: thickening, edema, hyalinization, necrosis and invasion by cell infiltrate. The altered vascular endothelium may present a simple swelling or partial / complete proliferation with obliteration of the lumen leading to thrombosis and necrosis.[15,16] Cellular infiltrate is form by lymphocytes, histiocytes, epithelioid and giant cells. It is interposed between adipose cells that are progressively replaced - proliferative atrophy ("wucheratrophie").[15,91,93-96]

It is the opinion of the authors that, when qualified laboratory techniques are not available for the molecular diagnosis of a likely tuberculosis infection and proof of the infectious agent, one should proceed with a therapeutic test and observation of outcome. We highlight that in these cases the patient should be informed of the decision and of the possibility that the lesions will not resolve, however, according to the authors' experience, most cases respond to treatment.

BIOLOGIC DRUGS AND TUBERCULOSIS

Latent tuberculosis infection (LTBI), defined as positive PPD, negative bacteriological analysis and lack of clinical or radiological evidence of active tuberculosis, should be considered in patients treated with immunobiological therapies because of the high risk of developing active TB. Performing the diagnostic tests capable of excluding LTBI is an essential step before initiating treatment. All biologic drugs, especially anti-TNF-α antibodies, can lead to reactivation of *M. tuberculosis* infection, and a detailed patient history of previous disease or contact with tuberculosis is mandatory, in addition to thoracic radiography (x-ray) and PPD.[97,98]

In asymptomatic patients, tuberculin skin test is initially recommended and, if the induration is equal to or larger than 5 mm (PPD reactor), chest X-rays should be performed. If chest X-rays are normal, chemoprophylaxis is recommended (treatment of latent TB) with isoniazid at 5 to 10 mg/kg to a maximum dose of 300 mg/day. It must be maintained for a minimum of six months. There is evidence, however, that continuing treatment for nine months offers more protection than keeping it for only six months, especially in patients with HIV/AIDS.[1,99-103] Operational feasibility and patient compliance should be considered when choosing between six and nine months of treatment. If chest X-rays are altered (suspect image or tuberculosis sequelae), specific treatment should be implemented. The recommendation is that biological therapy should begin after 1-2 months of starting prophylaxis or after the clinical treatment of active disease, following clinical evaluation.[97,98]

DIAGNOSIS

Currently the diagnosis of tuberculosis may already include detection, identification of species / complex and determination of the etiologic agent's drug sensitivity. Besides a suggestive clinical presentation, probability criteria include: histopathology with tuberculoid granuloma with caseous necrosis; granuloma without necrosis, but with positive tuberculin skin test or TB confirmed in another organ and a successful therapeutic test after a week. Culture and species identification (Lowenstein, Bactec, PCR) are used to confirm the diagnosis.[5,6]

Culture is a method of high specificity and sensitivity in diagnosing TB. Classical methods of mycobacteria culture use sample seeding in solid media: Lowenstein-Jensen and Ogawa-Kudoh. The time to detect bacterial growth ranges from 14 to 30 days and may extend up to eight weeks. Streptomycin, isoniazid, rifampicin, ethambutol and pyrazinamide are the antimycobacterial drugs usually tested.[15,16]

Species identification is made by biochemical and phenotypic methods or using molecular techniques analyses. Culture for mycobacteria is indicated if there is a suspicion of cutaneous tuberculosis and atypical mycobacteriosis.[1,5]

Culture with identification and susceptibility testing are indicated in the following cases: patients with history of previous treatments, regardless of the time elapsed; immunocompromised patients, especially patients with HIV; anti-TB treatment failure; investigation of populations at higher risk of harboring resistant strains of *M. tuberculosis* (health care professionals, homeless, prisoners, patients admitted to long-term facilities or hospitals that do not adopt biosecurity measures) or which are difficult to approach for follow-up (indigenous).[1,5,6,15,16]

The authors suggest an algorithm for the management of patients with lesions that are suspected to be cutaneous tuberculosis (Figure 4).

IMMUNOLOGICAL TESTS – IGRAS- INTERFERON-GAMMA RELEASE ASSAYS

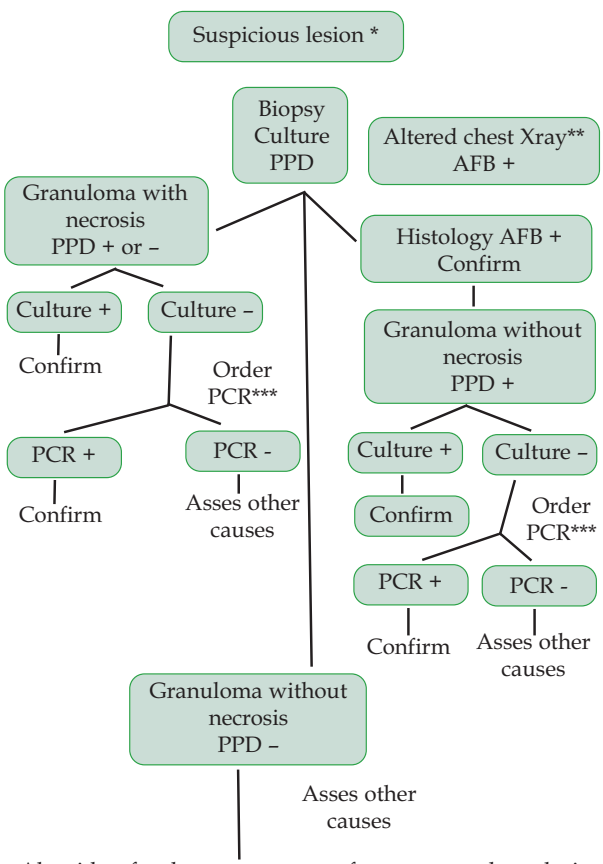
These are immunological tests based on cellular response stimulation through peptides that are absent from BCG and most non-tuberculous mycobacteria. They assess sensitization to *M. tuberculosis* by measuring the amount of INF gamma released by lymphocytes confronted with *M. tuberculosis*-specific antigens, such as ESAT-6 (early secretory antigenic target-6) and CFP-10 (culture filtrate protein 10). ESAT-6 and CFP-10 are present in *M. kansasii*, *M. marinum* and *M. szulgai*, and sensitization to such organisms may contribute to the release of IFN-γ in response to these antigens, leading to false-positive results.[1,104]

Two tests approved by the FDA (Food and Drug Administration) are QuantiFERON-TB Gold In-Tube test (QFT-GIT) and T-SPOT.TB. These tests are still not recommended for use in routine diagnosis of active and / or latent TB in our midst.[104]

MOLECULAR TESTS

Molecular tests for TB diagnosis are based on the amplification and detection of specific nucleic acid sequences of *M. tuberculosis* complex in clinical specimens; known as nucleic acid amplification test (NAAT), they provide results in 24 to 48 hours. Importantly, NAAT was approved in industrialized countries only for use in respiratory samples, i.e., for the investigation of pulmonary TB in adult patients without previous history of anti-TB treatment. It should not be used to monitor treatment, nor replace culture tests for mycobacteria.[1,105]

Tests of mycobacterial sensitivity to antituberculosis drugs can be used to define the therapeutic regimen for an individual or to plan strategies for large-



Algorithm for the management of cutaneous tuberculosis:

Figure 4: Algorithm for the management of cutaneous tuberculosis:

scale treatments. Resistance can be defined as an in vitro decrease of *M. tuberculosis'* susceptibility, for each drug, compared with the wild type strain (which never had contact with the drug). Tests may be classified in 2 types: phenotypic and genotypic.[106,107] The main characteristics of each method are presented in chart 2.[1,106,108-113]

TREATMENT

Tuberculosis is curable in virtually 100% of new cases that are sensitive to anti-TB drugs, as long as the basic principles of drug therapy and the proper treatment operationalization are observed.[1,5]

In 1979, Brazil proposed a TB treatment system comprised of 2RHZ/4RH for new cases of pulmonary and extrapulmonary TB, except the meningeal form.[114] This scheme consists of 2 months of rifampin (R), isoniazid (H) and pyrazinamide (Z) and another four months of only rifampicin and isoniazid. In 2009, ethambutol (E) was added as a fourth drug in the intensive phase of basic scheme treatment (first two months).[1] The pharmacological presentation of this scheme became a fixed-dose tablet with a combination of four drugs (RHZE), in the following dosages: R150mg, M 75mg, Z 400mg and E 275mg (Table 1).

Chart 2: Mycobacterial sensitivity phenotypic and genotypic tests

Phenotypic Methods	
Proportional Method[106]	It consists in detecting the proportion of resistant strains present in a sample of M. tuberculosis tested with a drug concentration that is able to inhibit the growth of susceptible cells, but not of resistant cells. It is a sensible and cost-effective methodology, however, the results are only available after 60 days
BACTEC 460[106,108]	The device detects radioactive CO2 released from the use of C14 palmitic acid, present in the liquid culture medium based on Agar, consumed by mycobacteria. It is a sensitive methodology and provides results within 14 days, however it is costly, and uses radioactive material, which is difficult to discard. It has 95 to 97% agreement rate with the proportional method
BACTEC-MGIT 960[1,106,109,110]	The device does not use radioactive material because the agar-based culture medium is composed of fluorescent material. Microorganism growth is visualized by spectrophotometry. It has similar performance to that of proportional method with an average detection time of seven days. In Brazil, it is considered the gold standard. It is validated and approved by ANVISA for the following drugs: streptomycin, isoniazid, rifampicin and ethambutol.
MODS (Microscopic Observation Broth Drug Susceptibility Assay)[1,106,111]	The MODS technique permits, after eight days, the visualization of the cord factor, formed by growing mycobacteria and seen in an inverted light with darkfield filter microscopy. Because of the trehalose dimycolate glycolipid present in the bacterial cell walls, the growth of M. tuberculosis complex in microscopic serpentine cords, called cord factor or cord growth, in which acid-fast bacilli (AFB) are arranged in parallel chains, can be seen in appropriate conditions in virulent strains of TB bacillus. It has sensitivity and specificity similar to those of traditional methods of culture.
D29-PhaB Assay[106]	It is based on the ability of the mycobacteriophage of infecting the cells when the mycobacterium is drug-resistant. When the phage infects the cells, it can lyse the cell wall thus detecting resistance.
E-Test[1,106,112]	It is a quantitative sensitivity test, and results can be obtained from five to ten days following the growth of M. tuberculosis in culture medium. It has high concordance rates, for the detection of multidrug-resistant strains, when compared with the proportional method. Because it is inexpensive, it can be an option for the rapid diagnosis of mycobacterial resistance in developing countries.
Genotypic Methods	
Sequencing[106]	It analyzes all nucleotide from a specific DNA region chosen on the genome. It allows the identification of mutations in the resistant strain, which may be related to resistance to certain drugs. It is considered the gold standard when it comes to diagnosis by molecular biology techniques.
PCR-SSCP (Single Strand Conformation Polymorphism) [1,106,113]	It uses the analysis of the amplification product obtained from the DNA target region in the mycobacterial genome. It permits the identification of alterations in amplified genomic regions. It is a fast method (24 hours).

This medication should be taken once daily.[1,5]

For children (under 10 years old) the recommendation of RHZ persists (Table 2). In children under 5 years old with difficulty to ingest tablets, the use of drugs in syrup or suspension forms is recommended. Medications should be administered preferably during fast (one hour before or two hours after breakfast), in one take, or in case of digestive intolerance, with a meal. Cutaneous TB treatment should last six months, as well as the treatment of patients co-infected with HIV, regardless of the stage of evolution of viral infection.[1]

If retreatment is necessary, 2RHZE/4RH regimen should be initiated until culture results and susceptibility testing are back. Cases progressing to treatment failure should be carefully evaluated for therapeutic history, adherence to previous treatments and evidence of drug resistance.[1]

The recommended treatment for erythema induratum of Bazin is similar to that for new cases of pulmonary and extrapulmonary TB, with rifampicin, isoniazid, pyrazinamide and ethambutol taken for two months, only rifampicin and isoniazid taken for another four months.[1] The difference however, is that treatment with isoniazid 400 mg / day must be maintained for a longer period of time, up to two years.[6,15,91] Pyridoxine should be added to the treatment to prevent peripheral neuropathy.[1] Tuberculin protein in various dilutions is used for desensitization as an adjuvant, as well as corticosteroids. Potassium iodide, dapsone, gold salts and doxycycline are cited as adjuvant treatments and some studies have reported satisfactory results.[91,92]

Special attention should be given to the treatment of groups considered at high risk for toxicity, consisting of people over 60, in poor health conditions, alcoholics, HIV-infected, those in concomitant use of anticonvulsants and with hepatic disorders.[1]

The RHZE scheme can be administered in usual doses for pregnant women and the use of pyridoxine (50mg/day) during pregnancy is recommended because of the risk of neurological toxicity (due to isoniazid) to the newborn. There are no contraindications to breastfeeding, as long as the mother does not have tuberculous mastitis, however special attention on monitoring of adverse effects is necessary.[1]

Patients with hepatic diseases should be monitored with serial assessment of liver enzymes (Table 3). In nephropathic patients it is necessary to measure the creatinine clearance levels (before starting the

Table 1: 2RHZE/4RH scheme for newly diagnosed cases in adults and adolescents (> 10 years old), for all forms of cutaneous diagnosis, infected by HIV or not

Scheme	Drugs	Weight range	Unit / dose	Months
2 RHZE	RHZE	20kg to 35kg	2 tablets	2
Intensive phase	150/75/400/275 Fixed-dose combined drug tablet	36kg to 50kg	3 tablets	
		> 50kg	4 tablets	
4 RH	RH	20kg to 35kg	1 tablet or capsule 300/200mg or 2 tablets 150/75	4
Maintenance phase	300/200 or 150/100 tablets or capsules or 150/75 tablets	36kg to 50kg	1 tablet or capsule 300/200mg + 1 tablet or capsule 150/100mg or 3 tablets 150/75	
		> 50kg	2 tablets or capsules 300/200mg or 4 tablets 150/75	

Table 2: 2RHZ/4RH scheme for newly diagnosed cases in children (< 10 years old), for all forms of cutaneous diagnosis, infected by HIV or not

Treatment phases	Drugs	Weight range			
		Up to 20kg mg/kg/day	>21kg to 35kg mg/ day	>36kg to 45kg mg/ day	> 45kg mg/ day
2 RHZ	R	10	300	450	600
Attack phase	H	10	200	300	400
	Z	35	1000	1500	2000
4 RH	R	10	300	450	600
Maintenance	H	10	200	300	400

Source - Guide: recommendations for tuberculosis control in Brazil, 2011.

Table 3: Conduct for patients with hepatopathy

With previous hepatic disease	With cirrhosis	AST/ALT > 3 x upper limit of normality (ULN)	2 SRE / 7RE 2 SHE / 10 HE 3 SEO / 9 EO
- Acute viral hepatitis		AST/ALT < 3 x ULN	Basic scheme
- Chronic hepatopathy: viral, autoimmune and cryptogenic			
- Alcoholic hepatopathy: Hepatic steatosis, alcoholic hepatitis	Without cirrhosis	3 SEO / 9 EO	
Without previous hepatic disease (Hepatotoxicity after the start of treatment)	AST/ALT 5 x ULN (or 3 x ULN with symptoms) Jaundice	Re-introduction RE ➢ H ➢ Z	Re-introduction of Basic Scheme or similar
	Persistency of AST/ALT 5 x ULN for 4 weeks or severe cases of TB		3 SEO / 9 EO

Source - Guide: recommendations for tuberculosis control in Brazil, 2011.

Table 4: Creatinine clearance calculation

Creatinine Clearance for men	(140 – age) x weight (in kg) 72 x creatinine (in mg%)
Creatinine Clearance for women	(140 – age) x weight (in kg) x 0.85 72 x creatinine (in mg%)

Source - Guide: recommendations for tuberculosis control in Brazil, 2011.

Table 5: Dose adjustment for patients with nephropathy

Drug	Method	Creatinine clearance		
		> 50 – 90	**10 – 50**	**< 10**
Rifampicin	None	100%	100%	100%
Isoniazid	Dosage	100%	75 – 100%	50%
Pyrazinamide	Time	24h	24h	48 – 72h
Ethambutol	Dosage	100%	50–100%	25 – 50%
Streptomycin	Time	24h	24–72h	72 – 96h

treatment regimen so that dose adjustment may be performed) (Tables 4 and 5).

The association of pyrazinamide to ketoconazole increases the risk of hepatotoxicity. Regarding ethambutol, antacids decrease absorption and dideoxyinosine - DDI - and dideoxycytidine - DDC potentiate peripheral neuritis.[1,115,116,117] ❑

ERRATUM

Dr. Leninha Valério do Nascimento was not co-author of the article "Atualização em tuberculose cutânea/ Update on cutaneous tuberculosis", published in journal 89(6), p.925-38

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