

UPDATE ON DIAGNOSIS AND TREATMENT OF TUBERCULOSIS CUTANEOUS: A REVISION OF THE LITERATURE RECENT

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ABSTRACT

This review article focuses on cutaneous tuberculosis, a rare form of tuberculosis that affects the skin and subcutaneous tissues. The article discusses the most recent clinical, diagnostic, and therapeutic aspects of cutaneous tuberculosis, including the most common clinical forms, diagnostic tools, and treatment options. Emphasis is placed on the importance of timely diagnosis and treatment of this disease due to its potential for dissemination. The article concludes with the need for more research to develop new treatments and strategies for managing cutaneous tuberculosis and improving the quality of life of affected patients.

Keyword tuberculosis, skin, Zeilen Neelsen, tuberculosis treatment.

1. INTRODUCTION

Cutaneous tuberculosis is a form of extrapulmonary tuberculosis that affects the skin and fabrics soft. Although the tuberculosis cutaneous is a shape strange of tuberculosis, his incidence ha gone in increase in the last years, especially in patients immunocompromised. The presentation clinic of the tuberculosis cutaneous can vary from a injury only to multiple injuries that they can get confused with others diseases of the fur. Go on being a challenge clinical, of agreement to Dodiuk -Gad et to the. (2019) 1 they provided a updated review of cutaneous tuberculosis, highlighting that this condition is a major imitator of other skin diseases, due to the high sensitivity and specificity of existing diagnostic tests. Singh et al. (2017) 2 highlights the importance of the exam physical complete and a high clinical suspicion for the diagnosis of cutaneous tuberculosis.

The World Health Organization's global report on tuberculosis in 2019 (World Health Organization , 2019) 3 provided updated data on the incidence and global burden of tuberculosis, including cutaneous tuberculosis. This report highlights the need for early diagnosis and treatment to improve outcomes in patients with cutaneous tuberculosis. Chaitra et al. (2019) 4 provided a retrospective analysis of the clinical presentation and Histopathological characteristics of cutaneous tuberculosis in Indian patients. In his studio, It was observed that the

clinical presentation of cutaneous tuberculosis varied widely, which makes diagnosis challenging. Furthermore, the importance of an evaluation was highlighted histopathological careful for the definitive diagnosis of the cutaneous tuberculosis. Kumarasinghe et al. (2019) 5 presented a report of case practical of the tuberculosis cutaneous and provided a review of the literature on the condition. In his review, provided a detailed description of the different clinical forms of tuberculosis cutaneous and HE they argued the different approaches therapeutic available, including the standard therapy with antituberculosis drugs and new therapies, such as combination therapy with rifampicin and clarithromycin.

Cutaneous tuberculosis is a rare form of tuberculosis that can present in various ways. forms, which makes its diagnosis a challenge. However, with a physical examination careful and a assessment histopathological precise, HE can carry out a diagnosis definitive. Early treatment is important to improve patient outcomes. with tuberculosis cutaneous. In this article of revision, HE will examine the last progress in the investigation, including new therapeutic and diagnostic approaches.

2.EPIDEMIOLOGY.

Cutaneous tuberculosis is a rare form of tuberculosis that affects the skin and tissues underlying soft. According to a systematic review and meta-analysis published in the journal PLOS ONE in 2018, the global prevalence of cutaneous tuberculosis is 1.5% among all tuberculosis cases around the world. However, the incidence varies by region. geographical. In high-income countries, such as the United States and Europe, tuberculosis skin represents about 1% of all tuberculosis cases, while in countries of low income, as the India and Africa, the prevalence can be so high as of the 3% at 5%. 6

It represented 0.08% of all tuberculosis cases and that the majority of cases were they presented in patients youths and Adults of median age. Besides, the most of the cases were of the lupus vulgaris or verrucosa type and occurred in exposed areas of the skin, as the upper extremities and face. 7

3.PATHOPHYSIOLOGY.

Mycobacterium tuberculosis infects the fur and the fabrics underlying. The bacteria can enter through small lesions in the skin or through the hematogenous spread from a primary infection elsewhere in the body. According to one review published in the journal Clinics in Dermatology in 2019, once the bacteria infects the skin, a local inflammatory response occurs that leads to the formation of granulomas and inflammatory nodules. The presence of the bacteria inside the granulomas causes a T cell-specific adaptive immune response that can lead to the destruction of the fabrics. The interaction of the bacterium with the immune system also can result in the formation of skin ulcers. 8

The interaction between Mycobacterium tuberculosis and the cells immune in the fur triggers a complex waterfall of signaling molecular that includes cytokines proinflammatory, such as tumor necrosis factor alpha and interleukin-1, and chemokines that attract cells immune to the place of the infection. Besides, the bacterium also can alter the function of immune cells, such as macrophages and dendritic cells, to prevent the elimination. The immune response in cutaneous tuberculosis is complex and can influence in the clinical course of the disease. 9

4.CLINICAL MANIFESTATIONS

Cutaneous tuberculosis is a rare form of extrapulmonary tuberculosis that represents approximately the 1-2% of all the cases of tuberculosis. exist different shapes clinics of tuberculosis skin, each a with a morphology and sites of condition characteristic. The five most common forms of tuberculosis will be described below. cutaneous and the references used to obtain this information . 10 Tuberculosis cutaneous luposa vulgar: Is the shape further common of tuberculosis cutaneous and represents 60-80% of all cases. It is characterized by the presence of nodules and plaques erythematous or yellowish, which are often covered by a meliceric crust . Are injuries they can be unique either multiple and HE locate Commonly in the expensive, neck and Superior limbs. Lupus vulgaris cutaneous tuberculosis may be associated with tuberculosis pulmonary in up 80% of the cases. eleven Orifical tuberculosis :

It is characterized by the appearance of ulcerative lesions in the orifices, natural parts of the body, such as the mouth, nose, anus and genitals.

The injuries are usually painless and HE present as ulcers superficial either deep. The tuberculosis official can be associated with tuberculosis pulmonary either gastrointestinal and It represents approximately 15-20% of all cases of cutaneous tuberculosis 12 Verrucous tuberculosis: Also known as vegetative or papulonecrotic tuberculosis, it is a rare form of cutaneous tuberculosis that accounts for 12.5% of all cases. HE characterized by the appearance of nodules and warty plaques with areas of central necrosis and purulent discharge. Lesions commonly occur on the face and neck and can be unique either multiple. The tuberculosis warty can be associated with tuberculosis pulmonary in up to 75% of cases. 13 Scrofuloderma: Is a shape of tuberculosis cutaneous that HE produces due to the lymphatic dissemination of pulmonary or lymph node tuberculosis. It is characterized by the appearance of nodules and abscesses that HE ulcerate and form scars. The injuries HE present commonly in the neck and armpits and may be associated with suppurative lymphadenopathy. He scrofuloderma It represents approximately he 4.7% of all the cases of tuberculosis cutaneous. 14 Miliary tuberculosis is the least common form of cutaneous tuberculosis and presents as multiple papules and nodules. The injury can appear in any part of the body and generally HE presents in patients with tuberculosis scattered. The nodules are small and dark red in color and can be found on the skin, mucous membranes and organs internal.

Diagnosis is made by biopsy of the lesion and tissue culture affected. fifteen Cutaneous tuberculosis is a rare but important disease that can occur in different clinical forms, each with a characteristic morphology and specific sites of affectation. It is important to take these aspects into account for diagnosis and treatment. suitable of the illness

5. DIAGNOSIS.

The diagnosis of cutaneous tuberculosis is made by taking samples of the skin lesions. Samples can be of different types, including scraping of the injury, skin biopsy and pus aspiration. Culture media: For the cultivation of Mycobacterium tuberculosis in the samples, specific culture media such as Lowenstein-Jensen medium or Middlebrook medium 7H10/7H11. He crop HE makes to a temperature of 37°C during 4 to 6 weeks, the take of sample for crop HE take by half of the puncture of the injury with a needle sterile and HE collect he material purulent in a tube sterile. The sensitivity of the crop for the cutaneous tuberculosis varies from 20% to 80%, depending on the technique used, experience of the technical and incubation time. Crop specificity is close to 100%. Special stains: Ziehl-Neelsen staining can be performed directly on the samples of scraped off of the injury for detect the presence of bacilli acid-alcohol resistant, indicating the presence of M. tuberculosis. Additionally, you can use other stains specialties such as Kinyoun stain and auramine-rhodamine stain. Immunohistochemistry: The immunohistochemistry is a method of diagnosis that HE uses for the detection of specific antigens of M. tuberculosis in tissue samples cutaneous. Molecular biology: The polymerase chain reaction (PCR) technique can be Use for the detection of M. tuberculosis DNA in skin tissue samples. This method It has high sensitivity and specificity. Dermatoscopy: Dermatoscopy is a non-invasive technique that allows the observation of the skin with magnifications of up to 10 times. Dermatoscopy is useful in diagnosis of the cutaneous tuberculosis, since it can reveal characteristic findings such as the presence of granulomas and Favre-Keratos bodies 17 Confocal microscope: The confocal microscope is an imaging technique that is used for the detection of skin lesions. This technique has been shown to be useful for detection of cutaneous tuberculosis.

Microscopic characteristics: The structures observed under the light microscope are bacilli acid-alcohol resistant (AFB) with Ziehl-Neelsen stain. Molecular biology: The polymerase chain reaction (PCR) technique can be use to detect he DNA of M. tuberculosis in lesions. Bacilluscopy: Bacilluscopy is a technique that allows direct observation of bacilli. acid-alcohol resistant (BAAR) in samples clinics of injuries cutaneous. The sensitivity of smear microscopy varies widely depending on the type of sample, the number of bacilli present in the lesion, the skill of the technician and the quality of the microscope used. In Generally, the sensitivity of smear microscopy is around 50% to 60% in lesions skin, while the specificity is close to 100% Histopathology: Histopathological examination is useful for the diagnosis of cutaneous tuberculosis. and can reveal findings characteristic as the presence of granulomas and cells epitheloids. Special stains such as Ziehl-Neelsen stain and Grocott stain - Gomori they can help to identify the bacilli in the fabrics. The sensitivity of the histopathology in the diagnosis of cutaneous tuberculosis is 50% to 60%, while specificity is located around 90% Molecular biology: Polymerase chain reaction (PCR) is a biology technique molecular that allows the detection of genetic material of Mycobacterium tuberculosis

in samples clinics. The PCR is a tool useful in the diagnosis of the tuberculosis skin, especially in lesions that do not produce enough bacilli for detection by culture or bacilloscopy. The sensitivity of PCR in the diagnosis of cutaneous tuberculosis it varies from 50% to 90%, while the specificity is close to 100%

6. DIFFERENTIAL DIAGNOSIS

Includes other diseases granulomatous as the leprosy, the sarcoidosis and the mycosis fungoid. Also can get confused with infections bacterial and fungal, neoplasms cutaneous and diseases autoimmune. The assessment clinic, the microbiology, the histopathology and the evidence serological and immunological are tools for differentiate the tuberculosis cutaneous of other diseases. The biopsy of the injury is essential for establish a definitive diagnosis and should be examined by a pathologist experienced in dermatopathology. 18 The injuries of tuberculosis cutaneous to slight are Chronicles and they can simulate other diseases as psoriasis, eczema, lichen flat and leprosy. The detection of acid mycobacterium in smear of the lesion, culture of Mycobacterium tuberculosis and the test of the tuberculin They are also useful in differential diagnosis. 19 Skin lesions may be atypical and may not respond to standard treatments. The diagnosis differential includes infections fungal, bacterial and viral, So as neoplasms cutaneous and diseases autoimmune. The histopathology and the microbiology are useful in differential diagnosis. 20

Table -1 Differential Diagnosis

Differential Diagnosis	Clinical Features	Histological Features
Cutaneous leishmaniasis	Nodular lesions, ulcers, and plaques on skin, mucous membranes, and cartilage	Presence of plasma cells, lymphocytes, histiocytes, and Langhans-type giant cells
Atypical mycobacteriosis	Erythematous lesions, papules, nodules, and plaques with elevated and poorly defined edges	Presence of histiocytic cells and non-caseating granulomas
Cutaneous lymphoma	Nodular lesions, plaques, and tumorous masses on skin	Presence of lymphoid cells and tumor cells in the tissue
Cutaneous sarcoidosis	Papular lesions, plaques, and nodules with symmetrical distribution	Presence of non-caseating granulomas with epithelioid cells and multinucleated giant cells
Cutaneous Crohn's disease	Erythematous lesions, nodules, and plaques with asymmetrical distribution	Presence of non-caseating granulomas and multinucleated giant cells
Leprosy	Lesions on skin, peripheral nerves, and mucous membranes with sensitivity impairment, scaly skin patches, non-healing skin lesions, lesions on the nose, fingers, toes, and eyes. There may be loss of sensation in the affected areas	Presence of acid-fast bacilli and granulomas with epithelioid cells, cellular infiltrates in the dermis and epidermis, with Schwann cells and epithelial granulomas. Acid-fast bacilli can be observed in the lesion

7.TREATMENT

It recommended for the tuberculosis cutaneous is a combination of drugs anti-tuberculosis, the duration HE extends during a period total of 9 to 12 months. He treatment has to be administered low the supervision of a doctor and monitored regularly to detect side effects and ensure the adherence to treatment. twenty-one In occasions can be difficult due to his low frequency and to the lack of studies controlled and randomized studies that compare different therapeutic schemes. The authors point out that the Most studies use a combination of isoniazid, rifampicin and pyrazinamide for 6 to 12 months, although some studies suggest that the duration of treatment can be further short. The authors also emphasize the importance of a follow-up dragged on after of the treatment for detect recurrences and assess the effectiveness of the treatment. 22 The basic treatment consists of a combination of four drugs: rifampicin, isoniazid, pyrazinamide and ethambutol, which is administered over a period of 6 to 9 months. However, In cases of drug-resistant cutaneous tuberculosis, a treatment dragged on with medicines of second line, as aminoglycosides, fluoroquinolones, cycloserine and ethionamide . 23

The dose and duration of treatment depend on the clinical form of cutaneous tuberculosis. For example, for orifical cutaneous tuberculosis , a treatment of 6 to 9 days is recommended. months, while miliary cutaneous tuberculosis requires prolonged treatment of until 12 months or more. 24 It is important to mention that the treatment of cutaneous tuberculosis can lead to a complete healing, but it can be a slow and prolonged process. Regular monitoring by a specialist doctor is essential to evaluate the response to treatment and adjust the dose as may be necessary. Regarding the response rate of each treatment, several studies have shown that the therapy antituberculous standard (Rifampicin, isoniazid, pyrazinamide and ethambutol) is highly effective in most cases of cutaneous tuberculosis. The response rate to Treatment varies depending on the clinical form of the disease and the duration of treatment. By For example, in cutaneous lupus tuberculosis , the cure rate varies between 60% and 90% after a treatment of 6 to 12 months. On the other hand, the response rate in miliary cutaneous tuberculosis may be less due to its greater severity and the need for a more treatment dragged on. 25 There are some clinical forms of cutaneous tuberculosis that may require a period of more treatment dragged on. Lupus or vulgaris cutaneous tuberculosis : The recommended treatment for this clinical form of cutaneous tuberculosis is the standard anti-tuberculosis therapy with a combination of four medicines: isoniazid, rifampin, pyrazinamide and ethambutol. In the phase initial of the treatment, these four drugs should be administered for two months, followed by a phase of maintenance of isoniazid and rifampicin during four months additional. The duration total of the treatment is of six months. The rate of success of the treatment in the tuberculosis cutaneous luposa or vulgaris is high, with a cure rate of 85% to 100 % 26 Tuberculosis cutaneous official : He treatment recommended for this shape clinic of cutaneous tuberculosis is the standard anti-tuberculosis therapy with a combination of four medicines: isoniazid, rifampin, pyrazinamide and ethambutol. In the phase initial of the treatment, these four drugs should be administered for two months, followed by a phase of maintenance of isoniazid and rifampicin during four months additional. The duration total of the treatment is of six months. The rate of success of the treatment in the tuberculosis original skin is high, with a cure rate of 84% to 100% 27

Verrucous tuberculosis: The recommended treatment for this clinical form of tuberculosis Skin care is the standard anti-tuberculosis therapy with a combination of four drugs: isoniazid, rifampicin, pyrazinamide and ethambutol. In the initial phase of treatment, manage these four drugs during two months, followed of a phase of maintenance of isoniazid and rifampicin during six months additional. The duration total of the treatment is of eight months. The rate of success of the treatment in the tuberculosis warty is tall, with a cure rate of 85% to 100% 28 Scrofuloderma : The recommended treatment for this clinical form of cutaneous tuberculosis is the therapy antituberculous standard with a combination of four medicines: isoniazid, rifampicin, pyrazinamide and ethambutol. In the initial phase of treatment, manage these four drugs during two months, followed of a phase of maintenance of isoniazid and rifampicin during six months additional. The duration total of treatment is eight months. The success rate of treatment in scrofuloderma is high, with a cure rate of 86% to 100% 29 Miliary tuberculosis, all four drugs should be administered in the initial phase for a minimum of 6 months. After the initial phase, isoniazid and rifampicin are continued for a minimum of 18 months in total. The recommended dose of isoniazid is 5 mg/kg body weight. body weight per day, while the dose of rifampicin is 10 mg/kg body weight per day. Pyrazinamide is administered at a dose of 20-30 mg/kg body weight per day and the dose of ethambutol is 15-20 mg/kg body weight per day . 30 The response rate to antituberculosis treatment for miliary tuberculosis is variable and depends of diverse factors as the gravity of the disease, the presence of comorbidities and adherence to treatment. In a study conducted in China, it was found that the rate of healing for the tuberculosis miliary was of the 66.7% with he treatment standard anti-

tuberculosis treatment, while the cure rate was 90% in patients with a disease less serious and without complications
s 31

In addition to standard anti-tuberculosis therapy, there are other treatments used for cutaneous tuberculosis. One of them is streptomycin therapy, which has been used in combination with others drugs as rifampin, isoniazid and ethambutol in cases of Cutaneous tuberculosis resistant to standard treatments. However, this therapy associated with a greater risk of hearing and kidney toxicity, so it should be used with caution and regular monitoring of hearing and kidney function . 32 Another treatment that has been used in cases of cutaneous tuberculosis resistant to multiple drugs is the therapy with agents of second line as amikacin, capreomycin , cycloserine , ethionamide and kanamycin. However, these drugs have greater toxicity and should be used under the supervision of a tuberculosis specialist . 33 Regarding the duration of treatment, a minimum of 6 months of therapy is recommended standard antituberculous drug for most clinical forms of cutaneous tuberculosis. In cases of original cutaneous tuberculosis , treatment can be prolonged up to 12 months due to the high recurrence rate. In cases of miliary cutaneous tuberculosis, it is recommended a minimum duration 12 months anti-tuberculosis therapy standard . 3. 4 Is important stand out that he treatment of the tuberculosis cutaneous has to be individualized and supervised by a specialist in tuberculosis. Besides, HE has to have in account the need for regular follow-up and monitoring to evaluate response to treatment and detect possible adverse effects. He use of medicines of second line, as amikacin, capreomycin , cycloserine , ethionamide and kanamycin, has been studied in cases of cutaneous tuberculosis resistant to first line medications. In one study, it was found that the use of a regimen of second-line treatment that included amikacin, ethionamide , and cycloserine , had a rate of cure rate of 77.8% in patients with cutaneous tuberculosis resistant to first line. 35 However, the use of second-line medications is associated with increased toxicity and side effects compared to first-line medications. Furthermore, these medicines have a minor effectiveness and a elderly cost in comparison with the first- line medications Therefore, they should only be used in cases of tuberculosis cutaneous resistant to the medicines of first line and low the supervision of a specialist in infectious diseases . 36 The amikacin and the capreomycin are antibiotics aminoglycosides that HE they use in he treatment of the tuberculosis resistant to the medicines of first line. However these medicines they can have effects secondary serious, as nephrotoxicity and ototoxicity. Therefore, careful use of these medications and a monitoring close of side effects during treatment . 37

The cycloserine is a agent antituberculous that HE ha used in he treatment of the cutaneous tuberculosis resistant to first-line drugs. However, its use is has been associated with a higher incidence of neurological side effects, such as dizziness, drowsiness and convulsions. HE recommends a monitoring careful during he treatment with cycloserine . 38 Ethionamide is an antituberculosis agent used in the treatment of tuberculosis resistant to first-line drugs. However, its use has been associated with a increased incidence of gastrointestinal side effects, such as nausea, vomiting, and pain abdominal HE recommends he use careful of this medicine and a monitoring narrow of side effects during treatment . 39 Kanamycin is an aminoglycoside antibiotic that has been used in the treatment of cutaneous tuberculosis resistant to first-line drugs. However, its use is has been associated with a higher incidence of serious side effects, such as nephrotoxicity and ototoxicity. Careful use of this medication and close monitoring of the effects side effects during treatment . 40 In summary, although second-line medications, such as amikacin, capreomycin , Cycloserine , ethionamide and kanamycin may be effective in the treatment of tuberculosis. resistant to first-line medications, their use is associated with greater toxicity and effects and of the gravity of the tuberculosis cutaneous resistant to multiple drugs.

Overall, hidradenitis suppurativa can have a significant impact on patients' quality of life, underscoring the importance of comprehensive, multidisciplinary care that addresses both the medical and psychological aspects of the disease. With a comprehensive approach and early diagnosis, patients can receive appropriate treatment and have a better quality of life.

Table -2 Treatment

Clinical Form of Cutaneous Tuberculosis	Standard Treatment	Treatment Duration	Cure Rate
Lupus Vulgaris Cutaneous Tuberculosis	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol	6 months	85% to 100%
Orificial Cutaneous Tuberculosis	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol	6 months	84% to 100%
Verrucous Tuberculosis	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol	8 months	85% to 100%
Scrofuloderma	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol	8 months	86% to 100%
Miliary Tuberculosis	Isoniazid, Rifampicin, Pyrazinamide, Ethambutol (followed by Isoniazid and Rifampicin for an additional 18 months)	Minimum 12 months	66.7% (variable depending on severity and adherence)
Drug-Resistant Tuberculosis	Second-Line Treatment	Duration and Notes	Effectiveness and Risks
Resistant to first-line drugs	Amikacin, Capreomycin, Cycloserine, Ethionamide, Kanamycin	Use under medical supervision	Higher toxicity and side effects
Streptomycin Therapy	Combination with Rifampicin, Isoniazid, Ethambutol (in cases of resistance)	Regular monitoring of hearing and kidneys	Risk of auditory and renal toxicity
Use of second-line drugs	Amikacin, Capreomycin, Cycloserine, Ethionamide, Kanamycin	Supervision by a tuberculosis specialist	Reduced effectiveness, higher toxicity and cost

8. FORECAST

It is generally good, with a 90% cure rate with proper treatment. Without However, patients with cutaneous tuberculosis have a higher probability of relapse in comparison with tuberculosis patients pulmonary. 41 Of agreement to Dermatology Clinics in 2021 points out that he forecast of the tuberculosis cutaneous depends of the

degree of extension of the disease, he state immunological of the patient and the presence of concomitant diseases. The authors also emphasize the importance of a diagnosis and treatment oportune for improve he forecast of the disease. 42 The patients with tuberculosis cutaneous extrapulmonary have a rate of relapse significantly higher compared to patients with pulmonary tuberculosis, a Prolonged follow-up after treatment is necessary to detect recurrences and ensure complete cure of the disease. 43

9. CONCLUSIONS

Cutaneous tuberculosis is a rare form of extrapulmonary tuberculosis that can occur as a result of primary or disseminated infection. It comes with a variety of clinical manifestations, including nodules, ulcers and warty lesions on the skin. He diagnosis of the tuberculosis cutaneous can be difficult and requires a assessment clinic carefully, along with laboratory tests and imaging studies. It is important to consider the diagnosis differential with other diseases that can present similar symptoms. He treatment of the tuberculosis cutaneous includes therapy antibiotic with multiple medicines, with a duration that can vary depending of the gravity of the disease and the patient's response to treatment. The prognosis of cutaneous tuberculosis is generally good, but there may be a higher chance of relapse compared with the tuberculosis pulmonary. He follow-up dragged on after of the treatment is important for detect any recurrence and ensure the healing complete of the disease. In summary, cutaneous tuberculosis is a rare but important disease that can introduce challenges in he diagnosis and treatment. A approach interdisciplinary with dermatologists, infectious disease specialists, and other physicians is essential for the successful management of the illness.

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