Mycobacterial infections

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Introduction

The genus *mycobacterium* contains more than 80 species, most of which are harmless environmental saprophytes. The most important obligate human pathogens are *M. tuberculosis* and *M. leprae*, but others such as *M. avium* and *M. ulcerans* are also significant. Diseases-causing mycobacteria other than *M. tuberculosis*, have been variously known as atypical or non-tuberculous mycobacteria.
**Tuberculosis (TB):**

*Mycobacterium TB* are slender, non-motile, aerobic, non-spore forming, rods, with a waxy coating, that makes them resistant to most stains, *once stained*, however, they are not easily decolorized (acid-fast, due to long chin fatty acid attached peptidoglycan). The genus can be subdivided into two subgenera, known as the fast (rapid) growers and the slow growers (include most of the pathogens).

**Immunology of TB:**

*Three* factors in the immunology of TB remain poorly explained: *the latent state*, *balance between protection and immunopathology after previous exposure*, and *failure to eliminate persistent mycobacteria*. **Latent state** - following infection, only 5-10% of individuals develops progressive disease, but some bacteria remain viable in the tissue of the subclinically infected individuals, and can be detected by PCR.
Immunopathological reaction – about 5-10% of exposed individuals manifest disease, and usually develops a powerful necrotizing skin test responsiveness to the antigens of M. TB, as well as it acts as microbicidal mechanism against the M.TB bacilli.

The failure of the immune response to eliminate persistent bacteria (biologically distinct from latent bacteria), this bacteria are not killed by antibiotic therapy (some of bacteria), this is due to the fact that immunopathological response dose note quickly revert to the non-necrotic protective mechanism, characteristic of the response in successfully BCG-vaccinated individuals, therefore treatment must continue for at least 6 months, or relapse will occur.

Protective immunity to M.TB – is mediated by Th1 (CD4), that recognize antigens from M. TB, and as a result secret cytokines including interleukin-2 (IL-2) and interferon Gamma (IFN-gamma), these cells activate macrophage and enhance formation cytotoxic cells (CD8), which are effecter systems involved in killing of the mycobacteria (type-4 delayed hypersensitivity response).
Tuberculin test—this test depends upon delayed–type hypersensitivity to mycobacterial antigens, mediated by lymphocytes, following an intradermal injection of purified protein derivative (PPD). a. PPD is stable but not particularly specific, so positive test can be result from: *clinical or subclinical infections, *BCG vaccination, *contact with environmental mycobacteria. b. New tuberculin's (more species specific), are available, prepared by the ultrasonic disruption of other mycobacteria (e.g. burul in from M. ulcerans).

Tuberculin sensitivity (positive) appears within a few weeks of the onset of an infection with M. TB and is usually life long. Misleading false negative reactions occurs in: *anergic patients (e.g. military TB), *whose with reduced delayed hypersensitivity (e.g. acute viral infections, sarcoidosis, malnutrition, malignancy), *use of immunosuppressive drugs (including corticosteroids and calciferol therapy).

The techniques of tuberculin test are: Mantoux test—in which PPD is injected intradermally into volare aspect of the forearm using a 27-gauge needle, 5 or 10 tuberculin units (TU) may be used initially, unless active TB is suspected (in which dose as low as 1TU may be selected), serial testing, might start with 1TU, than 10TU, followed by 100TU if the test is negative. The test is read at 48-72 hours, by the diameter of the area of induration (in mm), not the area of erythema, if the induration is more than 10mm (using 5TU), it is strongly suggestive of a past or present TB infection.
**Heaf test** – is performed with a spring – loaded instrument, which causes six short needles to penetrate through a solution of PPD or old tuberculin to a depth of 1.2mm (equivalent of 100TU): grade-1 reaction = 4-6 papules, grade-2 = continuous circle of induration, grade-3 = a plaque of 12mm, grade-4 = grade 3 + vesiculation or ulceration. Grade 3 or 4 reactions suggest past or present TB, grades 1 and 2 may be due to other mycobacteria or BCG.
TB. Of the skin:

M. TB. And M. bovis are pathogenic to humans, M. bovis being found in only 1-1.5%. Transmission of infection is mainly by: *inhalation of air born droplet nuclei particles containing M.TB. complex*, resulting in pulmonary TB., *M. bovis may also penetrate the GIT mucosa and lymphatic tissue of the oropharynx* when ingested in milk (from these two site the skin may be secondary infected), *direct inoculation of the skin by M.TB. complex also occurs*. Transmission of infection required close and prolonged contact, M.TB. survival is usually less than an hour outside the patients.

M. TB. Can induce a spectrum of cutaneous changes dependent on: *rout of infection* and the *immunological stat of the host*. Cutaneous TB. was classified into:-

1. **Inoculation TB. (primary TB)**: which include:-
   a. Tuberculosis chancre 
   b. Warty TB. (verruca cutis) 
   c. Lupus vulgaris (some) 

2. **Secondary TB. (endogenous source)**:
   a. Contiguous spread ----- e.g. scrofuloderma 
   b. Autoinoculation ------- e.g. Orificial TB. 

3. **Haematogenous TB.**:
   a. Acute military TB. 
   b. Lupus valguris (some) 
   c. Tuberculous gamma 

4. **Eruptive TB. (Tuberculides)**:
   a. Micropapular ----------- lichenscrofulosorum 
   b. Papular --------------- papular or papulonecrotic tuberulide 
   c. Nodular --------------- erythema induratum (Bazin)
Histopathology – early, a non-specific inflammatory changes, give rise after 3-6 weeks to a characteristic tubercle, at this stage bacilli are rarely found, although inoculation cultures may be positive. The tubercle consists of a focus of epitheloid cells, containing a variable but usually sparse number of Langhan's giant cells, and a surrounding infiltrate of mononuclear cells, and center may undergoes cassation necrosis and some time calcifies.

1. a. Primary inoculation TB. SYN. TUBERCULOUS CHANCRE.

Definition- it is TB. Of the skin, which is the result of the inoculation of M. TB into the skin of an individual without natural or artificial acquired immunity to this organism.

Pathogenesis – it results from the entry of TB. Bacilli in to the skin through abrasion or minor injuries, usually on the face or limbs, and commonly in children (what ever the source of M. TB.), and may occur any where on body from contact with the source of infection. It's incidence is now a very uncommon primary TB., and a rare form of skin TB.
Histopathology – early changes are non-specific, consisted of acute neutrophilic inflammation, with necrosis, numerous bacilli are present, 3-6-weeks granuloma develop and cassation appears, coinciding with the disappearance of the bacilli.

Clinical features - the earliest lesion may be non-descriptive, brownish papule, nodule, or ragged ulcer, with undermined edge and granular haemorrhagic base, in time the edge becomes firmer, and a thin adherent crust develops. When obvious trauma is absent, the initial lesion is often small with central silvery scale, and show apple-jelly nodules on diascopy, the lesion may be seen on the face, lesions closely simulating paronychia have been described, also regional lymphadenopathy may be accompanied. Mucosal lesions e.g. of conjunctiva causes oedema and irritation, ulceration and oedema of the lids, with preauricular lymphadenitis, oral lesions are uncommon, but painless lesions, often misdiagnosed, may form in a tooth socket or on the gums.

Diagnosis - is by clinical criteria’s, and can be confirmed by microscopy and culture of acid fast bacilli, D.D. is from tularemia, spirotrichosis, actinomycosis, cat-scratch fever and M. marinum infections (swimming pool granuloma), anal and genital lesions, particularly in children are most likely to be overlooked and misdiagnosed.

Course – the chancre will heal slowly taking many months, but rarely may proceed to lupus vulgaris, cold abscesses and sinuses and rarely military TB. develop.
1. b. Warty tuberculosis. SYN. TUBERCULOSIS VERRUCOSA CUTIS.

**Definition** - is an indolent, warty, plaque-like form of TB, occurring as a result of the inoculation of organisms into the skin of a previously infected patient, who usually has a moderate or high degree of immunity, was the predominant type in Chinese and Hong Kong.

**Pathogenesis** – lesions arises in 3 ways: *by accidental super infection from extraneous sources*, Physicians, pathologists, and post mortem attendants (thus anatomist's warts, prosecutor's warts), *by autoinoculation with sputum* in patient with active TB, *children and young adults, already infected*, become infected from sputum by sitting or playing where organism is present.

**Histopathology** – there is striking pseudoepitheliomatous hyperplasia with superficial abscess formation, bacilli are seen only occasionally.

**Clinical features** - lesions occurs on those areas exposed to trauma and to infected sputum or other TB material, most likely hands, knees, ankles, and buttocks. The lesion starts as a small symptomless, indurated, warty papule, with slight inflammatory areola, by gradual extension, a verrucose plaque is formed. Irregular extension at the edges leads to serpiginous outline with fingerlike projections, the center may evolute, leaving a white atrophic scar, or the whole lesion may form a massive, infiltrated papillomatous excrescence. The colour is purplish, red or brown, with firm consistency, pus may sometimes be expressed from areas of relative softening or from fissures. At time the lesion may resemble lupus vulgaris, psoriasiform or keloidal. TB lymphadenitis rarely occurs, but lymphadenitis may be due to secondary pyococcal infections.
Anomalous form – is deeply destructive papillomatous and sclerotic forms may cause deformity of the limbs. Generalized form, associated with papilonecrotic and lupoid lesions, occurs in patients with active TB.

Differentiation – subungual and digital lesions must be differentiated from warts, and those on the hands from keratosis, Blastomycosis, Actinomycosis, Leishmaniasis, tertiary syphilis, hypertrophy lichen planus, lichenification atypical mycobacterial lesions, and pyoderma due to other organisms.

Course – without treatment, extension of the lesions is usually extremely low and lesions may remain virtually inactive for months or years, spontaneous remission may occur with atrophic scars, the disease responded to anti-TB therapy.

2. Secondary TB.:
2.a. Scrofuloderma:

Definition and pathogenesis – it results from the involvement and break down of the skin overlying a contiguous TB. focus, usually a lymph gland, an infected bone or joint, a lachrymal gland or duct, the face and neck are the most frequently affected sites. It is the commonest form of Cutaneous TB. in childhood in India and in adult from the UK.

Histopathology – there is usually an ulcerated dermal abscess with ill-defined histiocytic infiltrate with marked cassation, TB. bacilli can usually be easily isolated from the pus.

Clinical features – a bluish-red nodule overlying the infected gland or joint breaks down to form undermined ulcer with granulation tissue at the base, numerous fistulae may intercommunicate beneath the bluish skin. Progression and scarring produce irregular adherent masses, densely fibrous in places and fluctuant or discharging in others, excessive granulation tissue may give rise to fungating tumours, after healing characteristic puckered scarring marks the site of the infection.

Diagnosis – from other non-TB. mycobacteria infections and ulcerated SSC.

Course – spontaneous healing can occur, but course is very protected and leaves typical cord-like scars.
2.b. **Orificial TB.** (TB. cutis orificialis, acute tuberculous ulcer).  

**Definition and pathogenesis** - it is TB infection of the mucosa or the skin adjoining orifices in a patient with advanced internal TB. It is now very rare, it occurs particularly in those with pulmonary, intestinal or anogenital disease, mostly in males. It is a form of autoinoculation TB, although extraneous sources are occasionally responsible, in which shaded mycobacteria inoculated into the mucous membranes of orifices.

**Histopathology** – is variable and is often of non-specific inflammation, but tubercle bacilli are usually present.

**Clinical features** - usually the patient is a severely ill, adult with advanced visceral TB, lesions occurs most commonly in the mouth, other sites includes, genitalia, around the anus and other orifices draining an active TB. The lesions are small oedematous red nodules, rapidly breakdown to form painful shallow ulcers, with undermined edges, the ulcer seldom exceed 2 cm in diameter and show no tendency to heal spontaneously.

**Diagnosis** - pain is the cardinal feature, with evidence of TB. elsewhere.

**Course** - depended on underlying internal TB.
3. Haematogenous TB:
 3.a. Miliary TB:

**Definition and pathogenesis** - military TB of the skin occurs in association with generalized military TB, due to haematogenous spread of mycobacteria into the skin. It is rare and usually affects young children or immunospressed patients, such as those with HIV infection, or following viral infections such as measles.

**Clinical features** – the skin lesions are often deceptive – profuse crops of minute bluish papules, vesicles, pustules or haemorrhagic lesions, in patient who is obviously ill. The vesicles may become necrotic to form small ulcers, erythematous nodules have been described, lesions showing acid-fast bacilli, and search should be made for evidence of internal TB.

**Diagnosis** - by clinical features of the disease in ill patient, confirmed by biopsy and identification of TB bacilli.

**Course** - the prognosis is poor, but response to treatment is possible.

3.b. Lupus vulgaris:
3.b. Lupus vulgaris:

**Definition and pathogenesis** – it is a chronic progressive, post-primary form of cutaneous TB occurring in persons with a moderate or high degree of immunity. The characteristic lesion is a plaque, composed of soft, reddish-brown papules, said by some on diascopy to resemble apple jelly, it is the most common form of cutaneous TB. in adults in India, South Africa, and second after scrofuloderma in UK, it is more common in women. Lupus vulgaris originates from: *underlying focus (2ry)* of TB, typically in bone, joint, or lymph node, and arise by either contiguous extension, or by haematogenous or lymphatic spread, *exogenous inoculation (1ry)* or as a complication of BCG vaccination.

**Histopathology** - is variable, normally, tubercles with scanty or absent central caseation are present in the superficial dermis, peripheral lymphocytes are often prominent, tubercle bacilli are hard to demonstrate.

**Clinical features** - L.v. commonly appears in normal skin as a solitary lesion. In Europe, 80% of lesions are on the head and neck, particularly around the nose, next in frequency are the arms and legs, but involvement of the trunk is uncommon. In India, the buttocks and trunk are the more frequently affected than the face.

**The initial lesion** is a small, reddish-brown, flat plaque of soft, almost gelatinous, consistency, on diascopy, the diagnostic apple-jelly nodules may be demonstrated. The lesion gradually becomes elevated, infiltrated and brown, and grows by slow peripheral extension to become gyrate or discoid in shape with areas of atrophy, usually as a single focus, except in disseminated forms, which usually occurs in association with active pulmonary TB. Sporotrichoid-like spread has also been reported.
Clinically **L.V. fall in to five** general patterns, depending on local tissue response to the infection, but a typical forms are becoming more common.

**A- Plaque form** – as flat plaques with irregular or sepiginous edge, the surface of the lesion may be smooth or covered by psoriasiform scale. Large plaques may show irregular areas of scaring with islands of active lupus tissue, the edge often becomes thickened and hyperkeratotic.

**B- Ulcerative and mutilating forms** – ulceration and scaring are predominant, crusts form over areas of necrosis, the deep tissues and cartilage are invaded and contractures and deformities occurs. In milder forms, keratotic plugs overlying pinpoint ulcer are associated with slow scar formation.

**C- Vegetative form** – is characterized by marked infiltration, ulceration and necrosis with minimal scaring, mucous membranes are invaded and cartilage is slowly destroyed, when the nasal and auricular cartilage is involved, extensive destruction and disfigurement ensue.

**D- Tumour-like forms** - the hypertrophic form present either as soft tumour-like nodules or as epithelial hyperplasia with the production of hyperkeratotic masses. In the myxomatous form, huge soft tumours occurs predominantly on the ear lobes, which become grossly enlarged, lymphoedema and vascular dilation are some times marked.

**E- Papular and nodular form** – multiple lesions occurs in disseminated lupus-(true military lupus).
Mucosal involvement – the nasal, buccal, or conjunctival mucosa may become involved, either primarily by a papule, nodule or ulcer or by spread from contiguous skin lesion. Nasal lesions start as nodules, which bleed easily and then ulcerated, leading sometime to destruction of cartilage, dry rhinitis. Granulating, vegetating or ulcerating lesions of buccal mucosa, palate, gingival or oropharynx may occur.

Prognosis and complications - the natural course of untreated lesion is progressive, scarring, contractures and tissue destruction are prominent features, active lupus vulgaris frequently reappears in scar tissue. Scars may become keloidal, contraction may lead to ectropion or microstomia, squamous cell carcinoma, and less commonly BCC, sarcomas may occur in up to 8% of patients.

Diagnosis - early stage lupus may easily be confused with lymphocytoma, Spitz naevus, DLE, 3ry syphilis, deep mycosis, lupoid leishmaniasis, on the face roacea, port-wine stain, and other mycobacterial infections, on extremity, leprosy and sarcoidosis are the chief causes of diagnostic difficulty, psoriasis, Bowen's disease, lichen simplex chronicus. The diagnosis is made by clinical criteria of the disease and confirmed by histopathological examination, tuberculin test, PCR, and bacteriiological studies.
3.c. Metastatic tuberculous abscess (Tuberculous gamma):

**Definition** - TB. which is the result of haematogenous dissemination from a primary focus of TB. during periods of lowered resistance, resulting in single or multiple lesions, seen particularly in malnourished children or in immunosuppressed patients, and has been noted after local trauma.

**Histopathology** - are those of TB. granulation tissue, necrosis and abscess formation, tubercle bacilli can usually be isolated from the pus.

**Clinical features** - it presented either as a firm subcutaneous nodule or as a fluctuant abscess, most likely on extremities, than the trunk. The overlying skin may break down to form undermined ulcer, often with sinuses, lesions may be multiple.

**Diagnosis** – clinically and confirmed by culture.

4. Eruptive TB (tuberculides):

**Definition** - tuberculides are a hypersensitivity reaction to M. TB., the main features are: *a positive tuberculin test,* evidence of manifest or past TB., *positive response to anti-TB. therapy,* there is virtually always absence of bacilli in skin biopsy specimens and culture, although PCR has detected mycobacterial DNA in some forms.

True tuberculides can be grouped as follows:
- Micropapular – lichen scrofulosorum.
- Papular – papulonecrotic tuberculide.
- Nodular – erythema induratum of Bazin.

**Aetiology** - the pathogenesis of tuberculides is poorly understood, all tuberculides are thought to be due to haematogenous spread of bacilli in a person with moderate or high degree of immunity against M. TB.. However, it is not usually possible to detect the TB. bacilli in tuberculides, either because they are present in a fragmented form or because they have been destroyed at the site of tuberculides by immunological mechanisms. Mycobacterial DNA has been detected in significant numbers of the papular and nodular forms of tuberculides, but not as yet in the micropapular form. It has therefore been suggested that papular and nodular forms of tuberculides should be regarded as forms of true post-primary TB.. Fluctuations in the immunological state of the patient may determine the development and features of the eruption.
4.a. Lichen scrofulosorum:

**Definition** - it is a lichenoid eruption of minute papules occurring in children and adolescents with T.B., it is usually associated with a strongly positive tuberculin reaction.

**Pathogenesis** - previously a common tuberculide, it is now rarely seen in Europe, except among immigrants, it occurs mainly in association with: *TB. lymph nodes*, *foci in bone*, recently, it has been reported with *pulmonary TB.*, *generalized lymphadenopathy*, *in association with M. avium infection*, *after BCG vaccination*, *military TB.*, *meningeal TB.*, where the host's immune response is usually poor, it may coexist with other forms of skin TB.

**Histopathology** – superficial dermal granulomas surround hair follicles and sweat ducts, and may occupy several dermal papillae, no cassation, no M. TB are seen in the sections and can not be cultured from biopsy material, no M.DNA has been detected by PCR.

**Clinical features** - the eruption consists of symptom less, 0.5-3mm, closely, grouped lichenoid papules, usually skin coloured, but may be yellowish or reddish –brown, often perifollicular, and appears in groups or in an annular arrangement, the papules may have an adherent crust or small pustule, mainly found on the abdomen, chest and back and proximal limbs.
Diagnosis - D.D. all asymptomatic follicular lesions, with tendency to group to gather, which include; lichen nitidus, keratosis spinulosa, keratosis pilaris, popular or lichenoid sarcoidosis, 2ry syphilis, drug eruptions and follicular psoriasis. The tuberculin test is normally positive, but was negative in immunocompromised patients.

Treatment – with specific anti-TB. therapy the lesions usually clear with in 4-8 weeks without scarring.

4.b. Papulonecrotic tuberculide:
Definition - an eruption of necrotizing papules, mainly affecting the extensor aspect of the extremities, and occurring in symmetrical crops, individual lesions heal with varioliform scar.

Pathogenesis – an associated focus of TB. can be demonstrated in 38-75% of patients, the rapid response to anti-TB therapy usually leaves no doubt of the aetiology, when a TB. focus can not be found, mycobacteria are rarely demonstrated in skin lesions, M. TB. DNA has been demonstrated in skin lesions using PCR, TUBERCULIN TEST is normally positive, even with a severe, and even necrotic reaction appearing within 8-12 hours.

Pathology - in fully developed lesions, a large central zone of coagulation necrosis is surrounded by inflammation extending from superficial to deep dermis and sometimes into the subcutaneous tissues, with histiocytic palisade, similar to that of granuloma annular, is seen around larger lesions, the involvement of adjacent small vessels is striking, ranging from a mild lymphocytic vasculitis to fibrinoid necrosis and thrombotic occlusion.
**Clinical features** - the eruption consists of recurring crops of symmetrical, hard, dusky – red papules, which crust or ulcerate, leaving pigmented, sometimes atrophic, varioliform scars, over the course of a few weeks, lesions are usually asymptomatic, new crops may continue over months or years. **Young adults** are predominantly affected, but also seen in infants and young children, **conjunctivitis** may be present, the legs, knees, elbows, hands and face are the sites of predilection, but the ears, face, buttocks and penis – sometimes alone may be involved, and may be associated with other forms of TB. (LV).

**Diagnosis** - D.D. includes pityriasis lichenoides (palms and soles are involved), leukocytoclastic vasculitis and prurigo. Positive tuberculin test, biopsy, and therapeutic trial of specific anti-TB. therapy are usually decisive in doubtful cases.

**Treatment** – full specific anti-TB. therapy should be given.
4.c. Nodular tuberculides: which includes:

*erythema induratum: (Bazin): this was first described by Bazin in 1861, as a condition occurring on the legs of female with scrofulosorum, as recurrent nodular and ulcerative lesions, and occur secondary to TB. Elsewhere in the body, it is 4 times more common in women than men.

Pathogenesis: past or active foci of TB. are usually present, tuberculin test is positive 70% of skin biopsy specimens.

Histopathology: the features are those of either focal or diffuse, lobular or septolobular, granulomatous panniculitis in association with neutrophilic vasculitis or either large or small blood vessels.

Clinical features: an indolent eruption of ill defined nodules, usually affecting the backs of the lower legs of young or middle-aged women, however lesions may affect other body areas, such as the upper limbs, thighs, buttocks and trunk, follicular perniosis may be present, lesions may ulcerate, and this may be precipitated by cold weather, the ulcers are ragged irregular and shallow, with a bluish edge. Resolution may be slow, even with adequate therapy, if there are associated erythrocytotic features.

Treatment: full specific anti-TB therapy should be given.

*Nodular tuberculide: commonly seen in female patients with active pulmonary TB, as dull red or bluish–red non-tender, non-ulcerating, nodules of 1 cm or slightly larger in size, located on the lower legs. Pathological changes of granulomatous vasculitis were situated at the junction of the deep dermis and adjacent subcutaneous fat, with strongly positive Mantoux test, all lesions cleared promptly with anti-TB therapy.
Erythema nodosum: seen more frequently in countries where the TB. is still common specially in children, with non-respiratory TB.

*Nodular vasculitis – most frequently seen in women, and the lesions are usually dusky, tender and persistent.

Prognosis of TB:
By modern therapy, the prognosis depends largely on early and accurate diagnosis. When TB. became generalized or affected the meninges, the prognosis must be doubtful. The mortality in patients with dual TB/HIV infection is higher than in HIV-negative patients, in infants and young children, TB. is always a serious disease. TB. confined to the skin usually responds well to multiple therapy, although the acute disseminated and orificial forms may respond less readily.

Diagnosis:
The only absolute criteria for diagnosis of Cutaneous TB. are: 
*positive culture of M. TB. from the lesions, 
*successful guinea-pig inoculation, 
*mycobacterial DNA identification by PCR. 
Other indications to ward the diagnosis which are by themselves unreliable, include the followings:
1-The presence of active proven TB. elsewhere in the body.
2-The presence of acid-fast bacilli in the lesion itself, which also seen in other mycobacterial infections.
3-The histopathology.
A positive tuberculin test.
4-The clinical and physical signs.
5-The effect of specific therapy.

TB. of the skin should be differentiated from: leprosy, leishmaniasis, deep mycosis, non-TB mycobacterial infections, syphilis and sarcoidosis.
Treatment:

1-General measures- search for an underlying focus of TB and coexistent infections like HIV.

2-Drugs therapy:

Patients non-compliance is currently the most important factor limiting successful treatment. Directly observed therapy (DOT), where the ingestion of every drug dose is witnessed, has shown improved cure rates in a number of countries, and is recommended for patients who are unlikely to comply, which include: * patients who are; * homeless, * alcoholics, * drug abusers, * drifters, * seriously mentally ill, * patients with multiple drug resistance, * patients with previous history of non-compliance with anti-TB therapy. DOT can be daily given, but an intermittent regimen is often more convenient.

Standard drug regimens are:

A-Six months regimens: including four drugs in the initial 2 months phase (rifampicin, isoniazid, pyrazinamide, plus streptomycin or Ethambutol), followed by continuation 4 months phase (rifampicin and isoniazid), are highly effective in patients with fully sensitive organisms. Combination tablets should be used whenever possible to aid compliance and to prevent monotherapy.

B-One year regimens: which include initial 2 months phase of 4 drugs and continuation 10 months phase of 2 drugs.
Drugs in present use: a standard 6-months regimen for adults is now recommended, it includes four drugs:

A- Isoniazid (300mg daily), for the full six months.
B- Rifampicin (450mg for those weighting <50kg and 600mg daily for those above this weight) for the full six months.
C- Pyrazinamide for the first 2 months (1.5g daily for those weighting <50kg and 2g for those weighting >50kg).
D- Ethambutol, for 2 months (15mg/kg body weight daily).

All drugs are taken on an empty stomach once daily.

Isoniazid (INH) remains the standard drug, given in all regimens, because of its efficacy, cheapness and low toxicity, the common side effects are peripheral neuropathy (commonly in elderly), controlled by pyridoxine (10mg/day), as prophylactic therapy from the start of treatment, and hepatitis in adults over 35 years of age.

Refampicin cause elevation of serum transaminases, orange colour of the skin, sweat and tears, reduce effectiveness of oral contraceptives.

Pyrazinamide cause hepatitis in 1%, arthritis and precipitate gout, Cutaneous hypersensitivity in 35%.

Ethambutol induce visual disturbance and rarely a retrobulbar neuritis, which is reversible.

Streptomycin may cause vertigo and tinnitus.

In HIV disease the same 6-months regimen is used, but with higher drug reaction rates, and higher reinfection rates.
Non-tuberculous (atypical) mycobacterial infections: These mycobacteria occurs much more frequently in immunocompromised hosts (AIDS), as pulmonary infections. Cutaneous infections can occur in immunocompetent patients and usually related to trauma and tend to be localized. *M. marinum* (swimming pool granuloma, Fish-Tank granuloma): *M. marinum* is natural habitant of water (swimming pool), and pathogenic on abraded skin. Old lesions shows well formed TB granuloma.

**Clinical features** - average incubation period 2-3 weeks, occasionally as long as 9 months, the initial lesion is either a solitary nodule or pustule, which may break down to form an ulcer or abscess or remain as verrucous plaque. Lesions are often multiple, and in the sporotrichoid form (20%), nodules may extend along the line of lymphatic vessels, with enlarged regional lymph nodes (never breakdown), elbows, knees, and feet of swimmer are the common sites of lesions, and fingers of fish fanciers.

**Diagnosis** - is by clinical criteria and confirmed by positive culture (70-80%).

**Treatment** - is self limiting, minocyclin, rifampicin, clarithromycine, doxycicline and trimethoprim.
**Leprosy (Hansen's disease)**

**Definition** - a chronic granulomatous disease caused by *Mycobacterium leprae*, principally affecting peripheral nerves and skin, it is an old disease, imported in Europe in the fourth century BC.

**Etiology** - it is caused by *M. leprae*, which is non-culturable in vitro, but limited growth has been achieved in the mouse footpad, and more widespread growth and disease in immunosuppressed, and nude mice. It is an acid fast bacilli grows at 30-33 degree centigrade, with a doubling time of 12 days, it is a remarkably hardy organism, remaining viable in the environment for up to 10 days, has only two genes (*TB. bacilli has 22 genes*).

The incidence of leprosy remains stable at around 800,000 new cases annually, with a high rate of childhood cases. 86% of leprosy patients reside in 6 countries (India, Brazil, Indonesia, Myanmar, Madagascar, and Nepal).

An average incubation period of 2-5 years has been calculated for tuberculoid cases and 8-12 years for Lepromatous cases. Age, sex, household contact, and Bacilli – Chalmette-Guerin (BCG) vaccination are important determinates of leprosy risk. Leprosy incidence reaches a peak at the ages of 10-14 years, with an excess of male cases. Subclinical infection with *M. leprae* is probably common, but the development of established disease is rare. There is no-reliable test for determining whether a person has encountered *M. leprae* and mounted a protective immune response. Nasal discharge from untreated Lepromatous leprosy patients, who are often undiagnosed for several years, are the main source of infection in the community. After inhalation of *M. leprae*, it multiplies on the inferior turbinate and has a brief bacteremic phase before binding to Schwann cells and macrophages. Bacilli are not excreted by the skin and are rarely found in the epidermis, but direct inoculation via the skin is possible.
Pathogenesis and thus the clinical features of leprosy.

1. The degree to which cell mediated immunity (CMI) is expressed -

   * Lepromatous leprosy represents a failure of CMI specifically to words M. leprae, which result in bacillary multiplication, spread and accumulation of antigen in infected tissue, which means that nerve damage is slow and gradual in onset.
   * In tuberculoid leprosy, CMI is strongly expressed so that the infection is restricted to one or a few skin sites and peripheral nerves.
   * Borderline leprosy lies between the above two polar forms.

2. The extent of bacillary spread and multiplication.

   * In Lepromatous leprosy, haematogenous spread of bacilli occurs, to cool, superficial sites, including eyes, upper respiratory mucosa, testes, small muscles and bones of hands, feet and face, as well as peripheral nerves and skin.
   * In tuberculoid leprosy, bacillary multiplication is restricted to a few sites and bacilli are not readily found.

3. The appearance of tissue-damaging immunological complications.

   Lepra reactions: borderline patients (borderline tuberculoid BT, borderline BB, borderline Lepromatous BL), are immunologically unstable, and at risk of developing immune-mediated reactions.

   * Type 1 (reversal) reactions, are delayed hypersensitivity reactions by increase recognition of M. leprae antigens in skin and nerve sites.
   * Type 2 reactions – erythema nodosum leprosum (ENL), are due in part to immune complex deposition, and occurring in BL and LL patients who produce antibodies and have a large antigen load.
4. The development of nerves damage and its complications. Nerves damage occurs in two settings, in skin lesions and in peripheral nerve trunks. In skin lesions, the small dermal sensory and autonomic nerve fibers supplying dermal and subcutaneous structures are damaged, causing local sensory loss, and loss of sweating within the area of the skin lesions. Peripheral nerve trunks are vulnerable at sites where they are superficial or in fibro-osseous tunnels. Nerve damage leads to anesthesia, muscular weakness, contracture, and autonomic dysfunction, this permit trauma, brusing, burns, cuts and specially tissue necrosis and ulceration, secondary cellulites, ostiomyelitis and loss of tissue, so that deformity is added to disability.

**Histopathology:** according to CMI, leprosy is classified into five groups on the immunological spectrum, which are designated (TT, BT, BB, BL, LL). In this classification, epitheloid cells and lymphocytes at the tuberculoid end of spectrum, give place to macrophages, which appear increasingly foamy as the Lepromatous pole is reached.
1- **Tuberculoid leprosy (TT)**: tuberculoid granuloma collect in foci surrounding neurovascular elements and invades the papillary zone, and may even erode the epidermis, but acid fast bacilli (AFB) are not seen. Cutaneous nerves are not completely destroyed, but upper greatly swollen by epitheloid granuloma.

2- **Lepromatous leprosy (LL)**: skin lesions shows thinning of the epidermis and flattening of the rete ridges, the papillary dermis appears as clear band (granz-zone), whilst deeper in the dermis lies the typical diffuse libroma consisting of foamy macrophages, few lymphocytes and plasma cells, with enormous numbers of AFB singly or in clumps (globi), also there is bacillation of Schwann cells, leading to foamy degeneration of these cells, and nerve damage by fibrosis and hyalinization.

3- **borderline leprosy (BB)**: in borderline tuberculoid (BT) the epitheloid cell granuloma is more diffuse than in TT, with a free, but narrow papillary zone, AFB are usually absent or scanty. In mid-borderline (BB), there is diffuse epitheloid cell granuloma with very scanty lymphocyte and no giant cells, the papillary zone is clear, nerves are slightly swollen by cellular infiltrate, and AFB are present in moderate number. In **borderline Lepromatous (BL)** leprosy, macrophage may show slight foamy changes, with dense clumps of lymphocytes, and few epitheloid cells may be seen occasionally, AFB are numerous involving Schwann cells. The nerve damage in borderline leprosy results from combination of Lepromatous bacilliation and tuberculoid tissue damage.

4- **Indeterminate leprosy**: this early and transient stage occurs in those whose immunological state has not yet been determined, and histologically, there is a scattered non-specific histiocytic and lymphocytic infiltration, with some concentration around skin appendages. This type may last for months or years before resolving or giving way to one of the determinate types of leprosy described above.
Immunology: the immune response to M. leprae determines not only whether disease will develop, but also which type of leprosy. Both T-cells and macrophages play important roles in the processing, recognition and response to M. Leprae antigens. In TT leprosy, there is good evidence of a strong CMI response, in LL leprosy patients are unable to mount a CMI response to M. leprae, with a failure of T-cell response, and negative lepromin skin test, this is due to dysfunction of both T-cell and macrophage. 

Clinical features:
<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Tuberculoid leprosy</th>
<th>Lepromatous leprosy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of lesions</td>
<td>1-10</td>
<td>Hundreds, confluent</td>
</tr>
<tr>
<td>Distribution</td>
<td>Asymmetrical, anywhere</td>
<td>Symmetrical, avoiding, spared areas.</td>
</tr>
<tr>
<td>Definition &amp; clarity</td>
<td>Defined, edge, marked hypopigmentation</td>
<td>Vague edge, slight hypopigmentation.</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>Early, marked, defined, localized to skin lesions or major peripheral nerve</td>
<td>Late, initially slight, ill-defined, but extensive, over coal areas of body.</td>
</tr>
<tr>
<td>Autonomic less</td>
<td>Early in skin and nerve lesions.</td>
<td>Late, extensive as for anesthesia.</td>
</tr>
<tr>
<td>Nerve damage</td>
<td>Marked in a few nerves.</td>
<td>Slight but wide spread</td>
</tr>
<tr>
<td>Mucosal &amp; systemic</td>
<td>Absent</td>
<td>Common, severe during type 2 reaction.</td>
</tr>
<tr>
<td>Number of M. leprae</td>
<td>Not detectable</td>
<td>Numerous in all affected tissues.</td>
</tr>
</tbody>
</table>
1-Early lesions (indeterminate leprosy) – the early lesion is an area of numbness on the skin, or a visible skin lesion, which consists of one or more slightly hypopigmented or erythematous macules, a few CMs in diameter, with poorly defined margins, most commonly found on the face, extensor surface of the limbs, buttocks, trunk, scalp, axillae, groins, and lumber skin tend to be spared. Hair growth and nerve damage are unimpaired. A biopsy may show the perineurovascular infiltrate and reveal scanty acid-fast bacilli.

2-Tuberculoid leprosy – only nerves and skin show clinical evidence, lesions are few, often solitary, may be purely neural with pain, swelling of the affected nerve followed by anesthesia and or muscular weakness and wasting, alternatively, a skin lesion appears with or without evidence of nerve involvement. The typical lesion is a plaque that is conspicuous, erythematous, copper or purple in colour, with raised and clear cut edges sloping to word a flattened and hypopigmented center. Dark skins may not show the erythema, the surface is dry, hairless, and insensitive, and in some times scaly. Just beyond the outer edge, a thickened sensory nerve may be palpated or a thickened nerve trunk may be felt in the vicinity, e.g. thickened ulner nerve, with lesion on the arm. Less commonly the lesion is a macule, erythematous in light skin and hypopigmented (never depigmented), in dark skin, such macules have a dry, hairless and insensitive.

3-Lepromatous leprosy – the first clinical manifestation are usually dermal (because early nerve involvement is usually a symptomatic) other early symptoms are nasal stuffiness, discharge and epistaxis, oedema of legs and uncles. Dermal signs comprise macules, diffuse papules, infiltration or nodules or all four. Macules are small, multiple, erythematous or faintly.
hypopigmented, with vague edges and shiny surface, **papules** and **nodules** usually have normal skin colour, but sometimes are erythematous, with bilateral symmetrical distribution on **face, arms, legs, and buttocks**, but may be anywhere apart from **hairy, scalp, axillae, groins and perineum** (regions of skin with the highest temperature). Hair growth and sensation are not initially impaired over the lesions. **The longest peripheral nerve fibers** are first affected, causing numbness and anesthesia on the dorsal surface of the hands and feet, latter on extensor surface of the arms and legs, and finally the trunk. **Infiltration of corneal nerves** causes anesthesia, which predisposes to injury, infection and blindness, if there is also **lagophthalmos** due to damage to the facial nerve. **Radiographs may show osteoporosis** in the phalanges, small osteolytic cysts and often hairline or compression fractures. **The hands and the feet** swell and become oedematous, **the fingers** become crooked or short, **nails** thin and brittle. **If the patient remained untreated**, the lines of forehead became deeper as the skin thickens (**leonine facies**), eye lashes and brows became thinned or lost (**madarosis**), ear lobes are thickened, the nose became **misshapen**, and may collapse due to septal perforation, and loss of anterior nasal spine, the voice becomes hoarse, and the **upper incisior teeth** loosen or fall out. **The skin of the legs** becomes ichthyotic and thickened, **ulcers** may form on the legs when nodules break down, and also fibrosis of the peripheral nerves results in nerve thickening, and **bilateral gloves and stocking anesthesia**, palms and soles sensation affected late in the disease. **Leprous deposits in the eyes causes keratitis, iridocyclitis and iris atrophy, testicular atrophy** causes sterility, impotence and gynaecomastia. **Histoid lesions** are distinctive round, regular, Cutaneous nodules that stand out on normal skin, they are characteristic of relapses after treatment.
4- Borderline leprosy – skin lesions are intermediate in number between those of the two polar types already described (TT, LL), depending on the position of the patient on the border line spectrum, and are distributed a symmetrically. They may take the form macules, plaques, annular lesions or bizarre –shaped bands, plaques with punched –out appearance are characteristic of the middle of the spectrum. Towards the tuberculoid end of the spectrum, lesions are fewer and drier, have more hair loss and anhidrosis are more insensitive, and have fewer bacilli in smears and biopsies, and vice versa towards the Lepromatous pole. One or more nerves are likely to be thickened and non-functioning, neural symptoms may precede the appearance of skin lesions by as much as 8 years. When borderline leprosy downgrades to Lepromatous, the resulting subpolar Lepromatous leprosy (LLS), can be differentiated from polar Lepromatous (LLP), because in addition to typical Lepromatous skin lesions, there are several a symmetrical thickened nerves and one or more typical borderline skin lesions. Damage to structures other than skin and nerves will not manifest clinically in borderline leprosy, but bacilli may be present in other tissue. Borderline leprosy is the commonest type of the disease encountered, with BT predominating in Africa and BL in Asia. Borderline leprosy is unstable and down-grades towards LL, especially if untreated or upgrades towards TT, the clinical changes lags behind the immunological and histological changes.
5-Pure neuritic leprosy – present with asymmetrical involvement of peripheral nerve trunks, and no visible skin lesions, on histology of Cutaneous nerve biopsy, all types of leprosy are seen, most frequently but not exclusively seen in India and Nepal.

Reactions:

A-Type-1 reaction: occurs in borderline disease and are characterized by acute neuritis and/or acutely inflamed skin lesions, nerves often becomes tender with loss of sensory and motor functions, existing skin lesions becomes erythematous or oedematous and may desquamate or rarely ulcerate, new lesions may appear. Occasionally, oedema of face, hands or feet is the presenting symptom, but constitutional symptoms are unusual. Although type-1 reaction can occur spontaneously, the commonest time is after starting treatment and during the puerperium.

B-Type-2 reaction (ENL) – erythema nodosum leprosum, occurs in patients with multibacillary disease (LL, BL), they may occur spontaneously (roseolar leprosy) or whilst on treatment. During the dapsone monotherapy era, an estimated 50% of LL patients experienced ENL reactions. ENL manifests most commonly as painful red nodules on the face and extensor surfaces of limbs, the lesions may be superficial or deep, with suppuration, ulceration or brawny induration when chronic. ENL is a systemic disorder producing fever and malaise, adenitis, dactylitis, arthritis, neuritis, lymphadenitis, myositis and orchitis, cataract and glaucoma are the most serious complications.
**Prognosis**- antibacterial treatment for leprosy is highly effective, with low relapse rates, but needs to be taken over many months. **But without treatment**, borderline patients will downgrade towards the LL end of the spectrum with its complications (type-1,2 reaction, nerve damage and eye damage with blindness).

**Diagnosis** – is usually made clinically on the basis of two out of three characteristic findings, or by demonstration of AFB in slit–skin smears, or by histology typical of leprosy. The cardinal signs are:

1. **Anesthesia of skin lesion**, or in the distribution of a peripheral nerve, or over dorsal surfaces of hands and feet.
2. **Thickened nerves**, specially at the sites of predilection.
3. **Typical skin lesions**.

The AFB load of a patient is determined by modified Zichl-Neelson staining of slit-skin smears, suspect lesions and sites commonly affected in LL should be sampled. The number of AFB per field is scored according to a logarithmic scale, a mean score is the bacterial index (BI).

In untreated LL, the BI is 5+ or 6+, the BI falls to zero in TT.

Slit-skin smears only detect bacilli present at concentration greater than $10^4$/g of tissue, and so can not be used as a test of microbiological cure. With **treatment** bacilli disappear from BB lesions in **few months**, and from BL lesions in a **year or two**, it may take 6-10 years for the last bacillary remnants to disappear from the skin in LL.
The investigations include:

1- **Slit-skin smears** – an incision of 5mm long and 3mm depth, is made by a small-bladed scalpel (size 15), and scraping the wound by the blade several times in one direction, the incision is made by griping of the skin by fingers to make a fold, to render it blood free. The smear is then fixed over a flame and stained.

2- **Skin biopsy** – the incision should be made down to subcutaneous fat, so the whole depth of the dermis is included and fixed in 10ml of 40% formaldehyde.

3- **Nerve biopsy** – it is necessary in pure neural leprosy, to establish the diagnosis, e.g. radial nerve at the wrist, superficial peroneal in front of the ankle or sural nerve at the ankle.

4- **Lepromin test** – is a crude, semi-standardized preparation of heat killed bacilli, from a Lepromatous nodule or infected armadillo liver. The lepromin test is a **non-specific test** of occasional value in classifying a case of leprosy. It is strongly +ve in TT, weakly +ve in BT, -ve in BB, BL and LL, and unpredictable in indeterminate leprosy. Technique is lepromin 0.1ml injected intradermally, and the reaction is read at 48 hours (Fernandez reaction, which is delayed hypersensitivity) or 3-4 weeks (Mistuda reaction which is granulomatous response).
DD: macular lesion: from vitiligo, pityriasis alba, TV, T. corporis.

Plaque and annular lesions – from T. corporis, granuloma annular, sarcoidosis and TB.

Nodules – from diffuse leishmaniasis, post-kalaazar dermal leishmaniasis.

Nerves – from hereditary sensory neuropathy type -3, amyloidosis AIDS, DM, alcoholism heavy meta poisoning.

Eyes – from trachoma.

Treatment: There are five main principles of treatment:
1- Stop the infection with chemotherapy.
2- Treat reactions and reduce the risk of nerve damage.
3- Educate the patient to cope with existing nerve damage in particular anesthesia.
4- Treat complications of nerve damage.
5- Rehabilitate the patient socially and psychologically.

These objectives can only be achieved with the patients co-operation and confidence. In endemic countries this may be done through the leprosy outpatient clinic.

*Rifampicin: is a potent bactericidal for M. leprae, four days after a single 600mg dose, bacilli of M.laprae from a previously untreated multibacillary patient are no longer viable, it acts by inhibiting DNA dependent RNA polymerase, thereby interfering with bacterial RNA synthesis. It is hepatotoxic.
*Dapson (DDS, 4,4-diaminodiphenyl sulphone), act by blocking folic acid synthesis, it is weakly bactericidal, commonly caused mild haemolysis, rarely anemia or psychosis, G6PD deficiency is one of relative contraindication, other side effects are DDS syndrome (start 6 weeks after starting therapy, as exfoliative dermatitis, lymphadenopathy, hepatosplenomegaly, fever, hepatitis and may be fatal), agranulocytosis, hepatitis, and cholestatic jaundice occurs rarely.

*Clofazimine – is a brick-red fat-soluble crystalline dye, it is weakly bactericidal, of unknown mechanism of action. It has an anti-inflammatory effect, which is useful in the management of ENL. The most noticeable side effect is a red to purple–black skin discoloration (which persist up to 6-12 months after stopping therapy), also urine, sputum and sweet may become pink. Other side effects are ichthyosis on the shins and forearms, GIT side effects (mild cramps, diarrhea and weight loss).

Relapsed multibacillary patients – are also retreated with triple therapy regardless of any change in classification. Relapse rates have been reported from zero-2.04/100 person-years.
Several new drugs bactericidal for *M. leprae* have been identified: fluroquinolones, minocycline and clarithromycine. The fluroquinolones (pefloxacin, ofloxacin), have a remarkable degree of bactericidal activity with 22 daily doses killing 99.99% of viable *M. leprae* in multibacillary cases. Daily minocyclin (100mg), treatment of multibacillary patients for 3 months, killed all viable *M. leprae*.

*Clarithromycin 500mg/day give the same results. These drugs are established as second-line drugs, and may replace dapsone and Clofazimine.*

**Reactions and neuritis** treatment is amid to control acute inflammation, easing pain, reversing nerve and eye damage, and reassuring the patient.

Multidrug therapy should be continued, corticosteroids (prednisolone 40-60mg/day) is used for treatment of neuritis, reduced by 5mg every 2-4 weeks for 2-4 months in patients with BT leprosy and for 6 months in BL leprosy reactions. ENL should be treated by high dose steroids (80mg/day prednisolone, tapered down rapidly), oral thalidomide (400mg/day) is superior to steroids in controlling ENL, and is the drug of choice for young men with severe ENL, but in young women it need double contraception to avoid teratogenecity to the fetus if pregnancy occurs.

BCG vaccination give significant but variable protection (ranging from 20-80%) against *M. leprae*.
<table>
<thead>
<tr>
<th>Type of leprosy</th>
<th>Monthly supervised</th>
<th>Daily self administered</th>
<th>Duration of treatment</th>
<th>Duration of follow–up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paucibacillary</td>
<td>Refampicin 600mg</td>
<td>Dapson 100mg</td>
<td>6 months</td>
<td>2 years</td>
</tr>
<tr>
<td>Multibacillary</td>
<td>Rifampicin 600mg, cloazimine 300mg</td>
<td>Clofazimine 50mg + dapson 100mg</td>
<td>24 months</td>
<td>5 years</td>
</tr>
</tbody>
</table>