Mycobacterial infections

Prof. Dr. Khudair Al-Kayalli

Introduction

The genus **mycobacterium** contains more than 80species , 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 mycibacteria 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 , there for treatment must continue for at least 6months , 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 sub clinical 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. burulin from **M. ulcerancs) .**

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 , 5or10 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 48-72hours , 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 =4-6papules , 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 out side 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 3-6weeks 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 , 3-6weeks 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 **lymphadenepathy** 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 in to 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 3ways :** *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 **symptom less , indurated , warty papule , with slight inflammatory areola , by gradual extension , a verrucuse plaque is formed .** Irregular extension at the edges leads to serpiginous out line 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. .
Differentia diagnosis – 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- with out 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. <u>Scrofuloderma:</u>
***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 of 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. <u>Orificial TB. :</u> (TB. cutis orificialis , acute tuberculous ulcer) .
Definition and pathogenesis- it is TB infection of the mucosa or the skin adjoining orifices in a patients 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 , genetalia , 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 2cm 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 in to 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 person 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 adult 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 cassation 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 to8% of patients .

Diagnosis- early stage lupus may easily be confused with lymphocytoma , Spitz naevus , DLE , 3ry syphilis , deep mycosis , lupoid leishmaniasis , on the face rocacea , 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 bacteriological 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 immunosupressed 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 done 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 4-8weeks with out 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 sever , and even necrotic reaction appearing within 8-12hours .

Pathology- in fully developed lesions , a large central zone of coagulation necrosis is surrounded by inflammation extending from superficial to deep dermis and some times in to 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 , some times atrophic , varioliform scars , over the of 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 – some times 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 .** **P**ositive 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 4times 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 erythrocynotic 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 1cm 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 . Diractly 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 2months phase*** (rifampicin , isoniazid , pyrazinamide , plus streptomycin or Ethambutol) , followed by ***continuation 4months 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 2months phase of 4drugs** and **continuation 10months phase of 2drugs .**

Drugs in present use: a standard 6months 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 2months (1.5g daily for those weighting <50kg and 2g for those weighting>50kg .

D-Ethambutol ,for 2months (15mg/kg body weight daily) .

All drugs are taken on an empty stomach once daily .

Isoniaizd **(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 35years of age .**

Refampicine **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 retro bulbar neuritis , which is reversible .**

Streptomycin **may cause vertigo and tinnitus .**

In HIV disease the same 6months 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 2-3weeks , occasionally as long as 9months , 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 swimmier 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 forth 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 immunosupressed , and nude mice . It is an acid fast bacilli grows at 30-33 degree cent grate , with a doubling time of 12days , it is a remarkably hardy organism , remaining viable in the environment for up to 10days , has only two genes (TB. bacilli has 22genes) .

The incidence of leprosy remains stable at around 800000 new cases annually , with a high rates of childhood cases . 86% of leprosy patients reside in 6 countries (India , Brazil , Indonesia , Myanmar , Madagascar and Nepal) .

An average incubation period of 2-5years has been calculated for tuberculoid cases and 8-12years 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 10-14years , with an excess of male cases . **Sub clinical** 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 bacteramic 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 with in the area of the skin lesions . Peripheral nerve trunk are vulnerable at site 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 in to 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 **CIM** response , in **LL leprosy**
patients are unable mount a CMI response to M. leprae , with a failure of T –cell response , and negative negative lepromin skin test , this is due to dysfunction of both T-cell and macrophage .

Clinical features:

Clinical features	Tuberculoid leprosy	Lepromatous leprosy
Number of lesions	1-10	Hundreds, confluent
Distribution	Asymmetrical, anywhere	Symmetrical, avoiding, spared areas .
Definition & clarity	Defined, edge , marked hypopigmentation	Vague edge, slight hypopigmentation .
Anesthesia	Early, marked, defined, localized to skin lesions or major peripheral nerve	Late , initially slight, ill-defined, but extensive , over coal areas of body .
Autonomic less	Early in skin and nerve lesions .	Late, extensive as for anesthesia
Nerve damage	Marked in a few nerves .	Slight but wide spread
Mucosal & systemic . Number of M. leprae	Absent Not detectable	Common, sever during type 2reaction . Numerous in all affected tissues .

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 shows 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 coloure , 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 , hair less 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 coloure , 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 incicisor 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 8years . **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 **dapson 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 104/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 6-10years** 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 time 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 than 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 **48hours (Fernandez reaction , which id delayed hypersensitivity)** or **3-4weeks (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 , there by 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 6weeks after starting therapy , as exfolative dermatitis , lymphadenepathy , 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 6-12months 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 22daily doses killing 99.99% of viable *M. leprae* in multibacillary cases . Daily minocyclin(100mg) , treatment of multibacillary patients for 3months , 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 (prednisolone40-60mg/day) is used for treatment of neuritis , reduced by 5mg every 2-4weeks for 2-4months in patients with BT leprosy and for 6months in BL leprosy reactions . ENL should be treated by high dose steroids (80mg/day prednisoline , tapered down rapidly) , o thalidomide (400mg/day) is superior to steroids in controlling ENL , and is the drug of choice for young men with sever 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 .*

Type of leprosy	Monthly supervised	Daily self administered	Duration of treatment	Duration of follow –up
Paucibacillary	Refampicin 600mg	Dapson 100mg	6 months	2 years
Multibacillary	Rifampicin 600mg. cloazimine300 mg	Clofazimine 50mg . dapson 100mg	24 months	5 years