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CURRENT STRATEGIES FOR TARGETING TUBERCULOSIS

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ABSTRACT

Due to the shortcomings of present TB therapy regimens, tuberculosis (TB) continues to be a common infectious illness worldwide despite substantial attempts to enhance treatment. Directly addressing host characteristics may be advantageous for the treatment of tuberculosis, according to recent research on innovative therapeutic approaches. These tactics, referred to as host-directed therapies (HDTs), centre on interactions between hosts and pathogens. HDTs may be more effective than the TB medications that are already on the market, which are constrained by the lengthy treatment times required and the rise of drug-resistant strains. Host factors like cytokines, immunological checkpoints, immune cell functions, and crucial enzyme activity are among the targets of HDTs.

KEYWORD: TB-Tuberculosis, RRTB- resistance to rifampicin, Tuberculosis, DALY disability-adjusted life year.

INTRODUCTION

Tuberculosis the leading cause of death worldwide from an infectious disease among adults has been considered a global public health emergency for the past 25 years.[1] Although public health approaches to tuberculosis have saved tens of millions of lives, modest progress has been made to control (let alone to end) tuberculosis. Drug resistant forms of tuberculosis are currently on course to be the world's deadliest pathogens, responsible for a quarter of deaths due to antimicrobial resistance.[2] Great ambition and radical action are needed to tackle this completely curable pathogen, which remains one of the greatest health problems in the world. The global tuberculosis situation is dire, but now is also a time of great promise and discovery for the disease. Numerous advances have been made in our understanding of the epidemiology, risk factors, and pathophysiology of tuberculosis, and new diagnostics and treatment for all forms of tuberculosis infection and disease are appearing on the horizon. Access to these innovations remains a substantial challenge for the majority of people living with the disease, but if the political will that seems to be building in the tuberculosis community and beyond[3] is put into action, with a focus on the rights of people affected by the disease, the next decade might finally see the devastation caused by this age-old disease start to abate. "A terrifying disease when the conflict between spirit and body is so gradual, silent, and solemn, and where the outcome is so certain, the mortal portion wastes and withers away day by day and grain by grain," A disease … which sometimes moves in giant strides and sometimes at a tardy sluggish pace, but, slow or quick, is ever sure and certain" Charles Dickens: Nicholas Nickleby. Till date the words of Charles Dickens are true. Tuberculosis; A scourge of the mankind from time immemorial, the dread disease was called consumption in Dickens time had a profound social and economic effect on human existence Globally, TB remains the ninth leading cause of global deaths, and the leading cause from a single infectious agent. In addition, in 2016, there were an additional 374,000 deaths among HIVpositive people. An estimated 10.4 million people fell ill with TB in 2016, and 56% of the total were living in 5 countries: India, Indonesia, China, Philippines, and Pakistan. Associated TB with HIV, as well as TB drug resistance remains a continuing threat and challenge. There were 600,000 new cases with resistance to rifampicin (RRTB), the most effective first-line drug, of which 490,000 were multidrug-resistant TB (MDR-TB), and almost half of these cases were in India, China, and Russia.[4,5] Globally, the TB mortality rate is now falling at a 3% per year rate. TB incidence is also decreasing at a rate of 2% per year. Between 2005 and 2015 the total TB mortality rate decreased by 17.4%. The global goal by 2020 is to improve to 4% to 5% per year and 10%, respectively.[6,7] The disability-adjusted life year (DALY) is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability, or early death.[21] In the communicable disease group TB DALYs ranked 13th as the leading cause of DALYs in 1990, 15th in 2005, and 18th in 2015. TUBERCULOSIS PRIMER TB is an obligate aerobic infectious bacterial organism (Mycobacterium tuberculosis or MTB).[8] The tubercle bacillus is a resistant infectious organism, in that it has a thick waxed cell wall that gives protection against external and host forces. Roy and Milton[9] stress that TB may be the only communicable disease that is initiated only through aerosols deposited in the distal lung. Pulmonary tuberculosis is the major target organ

involved in 85% of the victims, as it is transmitted by inhaling the infected droplets that are airborne with sneezing, coughing, speaking, or spiting.

HISTORY

TB or illnesses resembling TB have been described from different civilization since ancient times. The earliest such description can be found in Vedas, where TB was referred to as Yakshma meaning wasting disease. Literature in Greek, Chinese, and Arabic also discusses diseases similar to TB.[10] Mycobacterium has been present on earth for 150 million years. Mummies from the pre-Columbian periods in Peru and Egypt both have typical tubercular spinal lesions. A bone lesion discovered in a Turkish skull that is 500 000 years old provides the first tenuous proof of tuberculosis in humans. The first reliable evidence is the use of PCR sequencing to identify human TB in a Neolithic newborn and women from a 9000 year old settlement in the Eastern Mediterranean. Galen (131–201) was the first to hypothesise that TB might be contagious. Girolamo Fracastorius (1483–1553) demonstrated that some diseases could be spread by 'particles' through direct or indirect contact between humans after many centuries. Thomas Willis (1621-1675) first described miliary TB. Calmette extracted a protein (tuberculin) from large cultures of the bacillus and first used for therapy known as 'tuberculinisation', which failed as treatment for TB. The Tuberculin was also used for intradermal skin test which was described by Charles Mantoux & used in the diagnosis of TB. Later this intradermal skin test was named after Charles Mantoux and is known as Mantoux test. In his notion of "contagious living fluid," Benjamin Marten (1690-1752) proposed that TB is brought on by "wonderfully minute living beings." The transmission of TB from humans to animals and from animals to humans was effectively demonstrated by Jean Antoine Villemin (1827–1892), a French army physician. The term "tuberculosis," which is derived from the Latin word "tubercula," which means "a tiny lump," was proposed by Johann Lukas Schonlein in 1834. On 24th March 1882, Robert Koch announced in the meeting of the Berlin Society of Physiology that he had discovered causative agent responsible for pulmonary TB and named it as 'tuberkel virus' in his paper published 2 weeks later. Robert Koch won the Nobel Prize in medicine in 1905 for his two creative decisions: dyeing tuberculosis bacilli and growing it on solidified cow or sheep serum. Leon Charles Albert Calmette (1863-1933) and Camille Guerin (1872-1961) developed vaccine against TB by sub-culturing Mycobacterium bovis for more than 200 times in the Guinea pig model between 1908-1921. Arvid Wallgren, a professor from Royal Caroline medical institute, Sweden described clinical manifestations of tuberculous infection in an article titled 'The timetable of Tuberculosis' which helped in better understanding course of TB illness. The effective treatment for TB became a reality after the discovery of antitubercular drugs like Streptomycin, Para-amino salicylic acid (PAS) and isoniazid by the mid-1940s. By late 1970 it was believed that TB may no longer be a public health problem in the developed world. But the emergence of Acquired Immune Deficiency Syndrome (AIDS) in the early 1980s has ended this optimism and led to the resurgence of TB worldwide.[11]

TAXANOMY AND DESCRIPTION OF GENUS

Mycobacterium tuberculosis belongs to
ORDER- Actinomycetales
CLASS- Actinomycetes
FAMILY- Mycobacteriaceae
GENUS- Mycobacterium
Genera closely related to Mycobacterium are Gordomia, Tsukamurella, Nocardia and Rhodococcus.[12]

Table 1: Salient features of Mycobacterium genus.

	Features
Mycobacteria	aerobic, non-spore forming, non-motile
Shape	slightly curved or straight rods
Shape	0.2-0.6 mm by 1-10 mm
Colony morphology	varies from species to species, ranging from rough to smooth and from non-pigmented to pigmented (carotenoid pigment)
Cell wall	N-acetyl muramic acid High content of Mycolic acid (70e90 carbon atoms)-renders acid fastness
DNA	High G+ C content (61-71 mol %)
Generation time	Slow- ranging from 20 hours to 36 hours for Mycobacterium Tuberculosis

EPIDEMEOLOGY

M. tuberculosis bacilli have infected nearly 1/3rd of the world's population with 10% lifetime risk of developing TB disease.19 Globally 10.4 million cases of TB reported in 2017, accounting to 133 cases/1,00,000 population, of which 90% of cases were adults (aged≥ 15 years), 64% were male, 9% were people living with HIV (72% of them in Africa). An estimated 558 000 new cases (range- 483 000e639 000) of Rifampicin resistant TB (RR-TB), of which almost half were in three countries: India (24%), China (13%) and the Russian Federation (10%).[13] Among 0.8 million new EPTB cases reported worldwide (2013), maximum cases were from India accounting for 0.35 million cases. In India, according to Revised National Tuberculosis Control Programme (RNTCP) data, the prevalence of EPTB is 50% in HIV infected patients and 15-20% in non-HIV patients. The distribution of EPTB was in lymph node 47%, pleural cavity 30%, abdomen 10%, bones and joints 8%, CNS 2% and others 3%. Between 2000 and

2017, TB mortality rate reduction is 42%. TB incidence has fallen by an average of 2% per year and case fatality rate of 16% in 2017, down from 23% in 2000.6 In 30 high burden countries, India has managed to reduce the prevalence rate by 50% as set by Stop TB Partnership Programme. Drug resistant TB has been reported from early days of introduction of ART, but multidrug-resistant tuberculosis (MDR-TB) and more recently extensively drug resistant tuberculosis (XDR-TB) posing a threat to TB control program globally.[14]

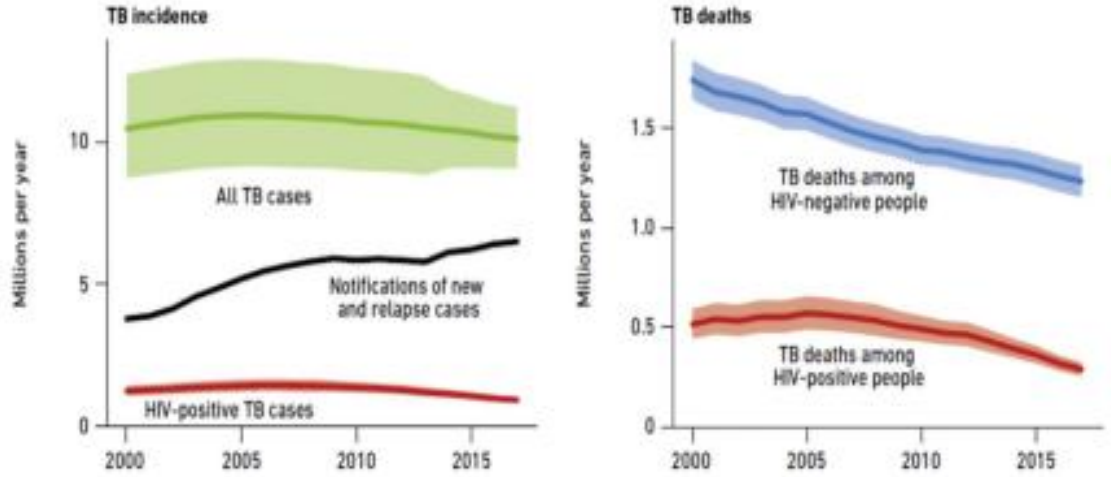

Fig. 1: Shows an estimated number of incident TB cases and TB deaths (in millions) from 2000 to 2017.

MECHANISM/PATHOPHYSIOLOGY

Ongoing transmission of M. tuberculosis infection30 and LTBI reactivation31 are globally responsible for TB disease. M. tuberculosis (sensustricto) or a closely related pathogen is thought to be responsible for the majority of TB cases. A small percentage of cases are caused by zoonotic strains of the Mycobacterium TB complex, like Mycobacterium bovis or Mycobacterium caprae. The sole known reservoir for M. tuberculosis is people; it has no recognised environmental reservoir. As a result, M. tuberculosis has ramifications for our comprehension of host-pathogen relationships since it functions as both a pathogen and a symbiont.[15]

HOST-PATHOGEN INTERACTION

Genomic studies have shown substantial genetic variability among isolates from around the world (several thousand single-nucleotide polymorphisms across a genome of 4.4 million base pairs), which reflects either accumulated genetic drift associated with patterns of human migration or variable pathogenicity of different lineage. It has been proposed that hypervirulent strains exist, based on epidemiological studies. If true, genomic study of such strains could uncover lineage-specific virulence factors that can ultimately be used to prioritize patient care and infection control decisions. Although specific strains have been linked to a number of characteristics of M. tuberculosis, including increased human transmissibility, drug resistance, and mortality in an experimental model[16], results varied between studies, making it difficult to immediately apply these findings to clinical care. In addition, complicated interactions exist between the host and M. tuberculosis. In order to avoid obscuring synergistic interactions, it is best to research M. tuberculosis virulence factors in the absence of host determinants of susceptibility. For instance, a specific host–pathogen interaction might explain why strains of the East-Asian lineage are highly infective and pathogenic in Asian populations[17] but have a normal clinical and epidemiological presentation when imported into Canada or Switzerland. On the other hand, given the right social and epidemiological circumstances, strains that are otherwise unremarkable according to genomic and laboratory characterisation can be linked to outbreaks.

PATHOGENESIS

Most MTB-containing droplet nuclei from infected individuals are retained in upper airways and ejected by ciliated mucosal cells: Almost none of it reaches the alveoli.The mycobacteria then bind to cell surface of alveolar macrophages through complement receptors, mannose receptor or type A scavenger receptor. Mycobacteria diminish the phagosome's acidity after phagocytosis, and a component of the cell wall called lipoarabinomannan interferes with the Ca+/calmodulin pathway, preventing the fusion of the phagosome and the lysosome. After phagosome maturation has been successfully stopped, bacilli start to multiply. Eventually, the macrophage bursts to release its bacilli, which are then ingested by other macrophages, continuing the infection cycle and widening the spread.[18] The major Ghon's complex is formed when MTB bacilli spread through hematogenous and lymphatic means, affecting the hilar and mediastinal lymph nodes. Bacilli eventually enter the bloodstream and travel to other organs. Extrapulmonary tuberculosis is caused by this lympho-hematogenous spread either during the initial infection or

later on in life when the illness reactivates.[19] EPTB can involve any site in the body & the most common site is lymph node. However pleural, neurological, synovial, pericardial, abdominal, genitourinary involvement has been described. a. Tubercular Lymphadeniti.

MECHANISM OF SPREAD

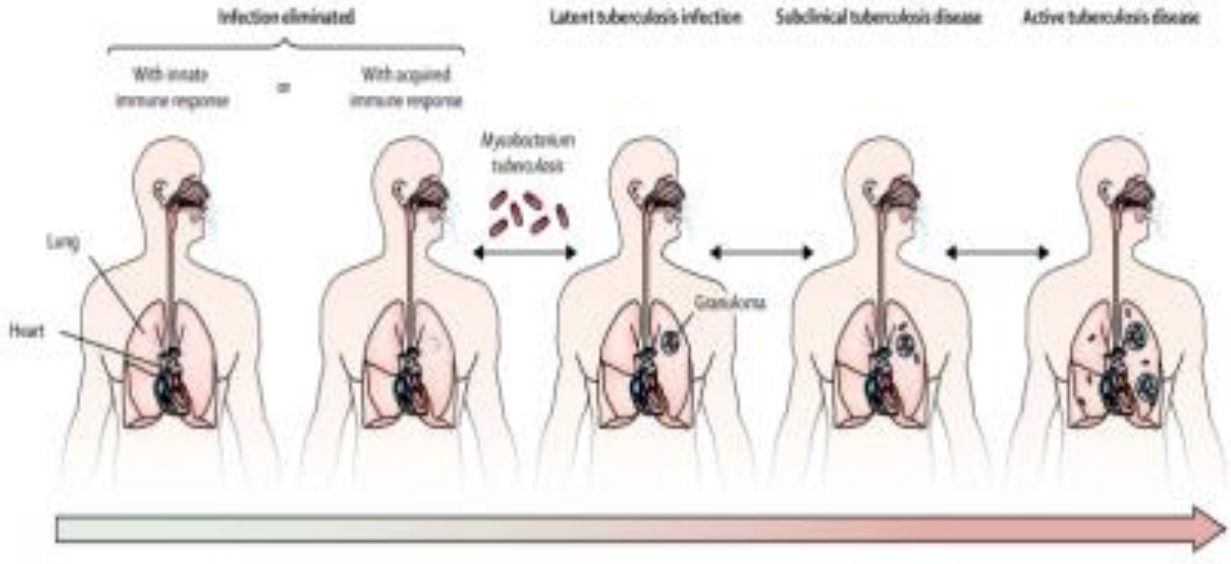

Fig 2: Spread of TB from person to person.

When people with active pulmonary TB cough, sneeze, speak, sing, or spit, they expel infectious aerosol droplets 0.5 to 5.0 μm in diameter. A single sneeze can release up to 40,000 droplets. Each one of these droplets may transmit the disease, since the infectious dose of tuberculosis is very small (the inhalation of fewer than 10 bacteria may cause an infection).

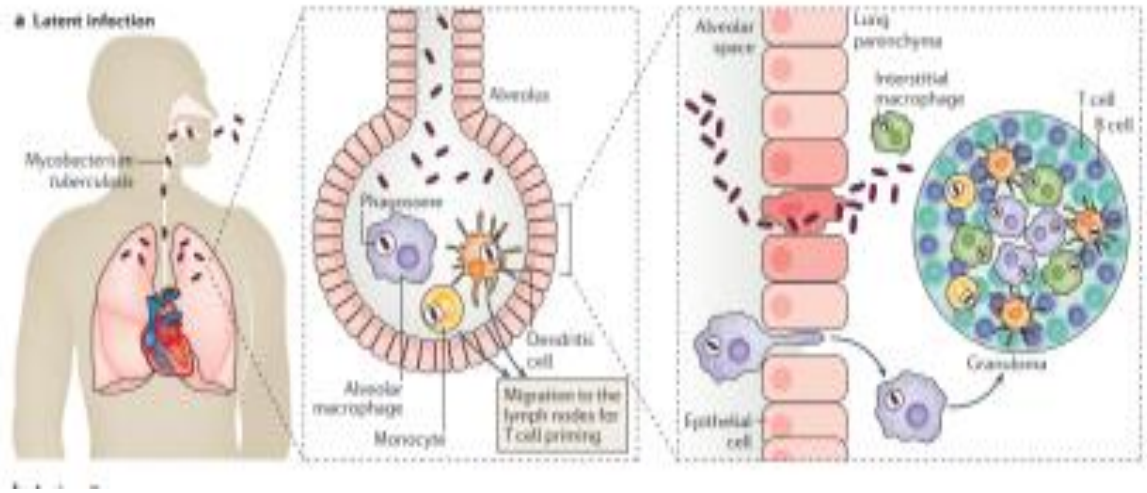

Fig. 3: Mycobacterium infection: how the infection begins.

MYCOBACTERIUM TUBERCULOSIS INFECTION

Infection begins when Mycobacterium tuberculosis enters the lungs via inhalation, reaches the alveolar space and encounters the resident alveolar macrophages. If this first line of defence fails to eliminate the bacteria, M. tuberculosis invades the lung interstitial tissue, either by the bacteria directly infecting the alveolar epithelium or the infected alveolar macrophages migrating to the lung parenchyma. Subsequently, either dendritic cells or inflammatory monocytes transport M. tuberculosis to pulmonary lymph nodes for T cell priming. This event leads to the recruitment of immune cells, including T cells and B cells, to the lung parenchyma to form a granuloma.

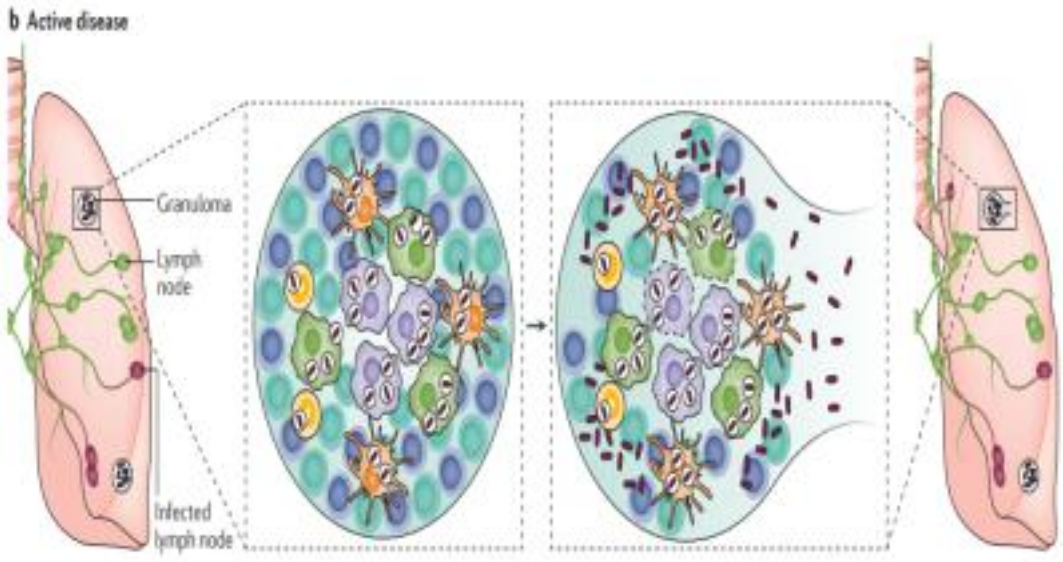

Fig 4: spread of infection in the lungs.

The bacteria replicate within the growing granuloma. If the bacterial load becomes too great, the granuloma will fail to contain the infection75 and bacteria will disseminate eventually to other organs, including the brain. At this phase, the bacteria can enter the bloodstream or re-enter the respiratory tract to be released — the infected host is now infectious, symptomatic and is said to have active TB disease.[20]

SIGNS AND SYMPTOMS

Pulmonary tuberculosis frequently develops slowly, without a definite date of onset. The disease has a wide spectrum of manifestations ranging from skin positivity with negative X rays to far advanced tuberculosis. Ordinarily, until the disease is moderately or far advanced, as shown by changes on the roentgenogram, symptoms are minimal and often attributable to other causes, such as excessive smoking, hard work, pregnancy, or other conditions. Symptoms may be divided into two categories, constitutional and pulmonary. The frequency of these symptoms differs according to whether the patient has primary tuberculosis or reactivation tuberculosis. Subjects with primary tuberculosis are much more likely to be asymptomatic or minimally symptomatic. For a list of the most common symptoms and their relative frequencies in representative case series of both primary and reactivation tuberculosis. The constitutional symptom most frequently seen are: fever, low grade at the onset but becoming quite marked as the disease progresses. Characteristically, the fever develops in the late afternoon and may not be accompanied by pronounced symptoms. With defervescence, usually during sleep, sweating occurs—the classic "night sweats." Other signs of toxemia, malaise, irritability, weakness, unusual fatigue, headache, weight loss may be present. With the development of caseation necrosis and concomitant liquefaction of the caseation, the patient will usually notice cough and sputum, often associated with mild hemoptysis.

- Chest pain may be localized and pleuritic. Shortness of breath usually indicates extensive disease with widespread involvement of the lung and parenchyma or some form of tracheobronchial obstruction and therefore usually occurs late in the course of the disease.
- Physical examination of the chest is ordinarily of minimal help early in the disease. At this stage, the principal finding over areas of infiltration is one of fine rales detected on deep inspiration followed by full expiration and a hard, terminal cough (posttussive rales). This sign is found particularly in the apexes of the lungs, where reactivation disease has its onset in a large majority of patients.

As the disease progresses, more extensive findings are present, corresponding to the areas of involvement and type of pathology. Allergic manifestations may occur, usually developing at the time of onset of infection. These include erythema nodosum, phlyctenular conjunctivitis, Erythema induratum, involvement of the lower leg and foot with redness, swelling, and necrosis, probably represents a combination of local subcutaneous bacterial infection with an allergic response and should not be confused with erythema nodosum, the latter considered to be due to circulating immune complexes with resultant localized vascular damage. Initially, erythema nodosum occurs in the dependent portion of the body and, if the reaction is severe, may be followed by a more disseminated process.[21]

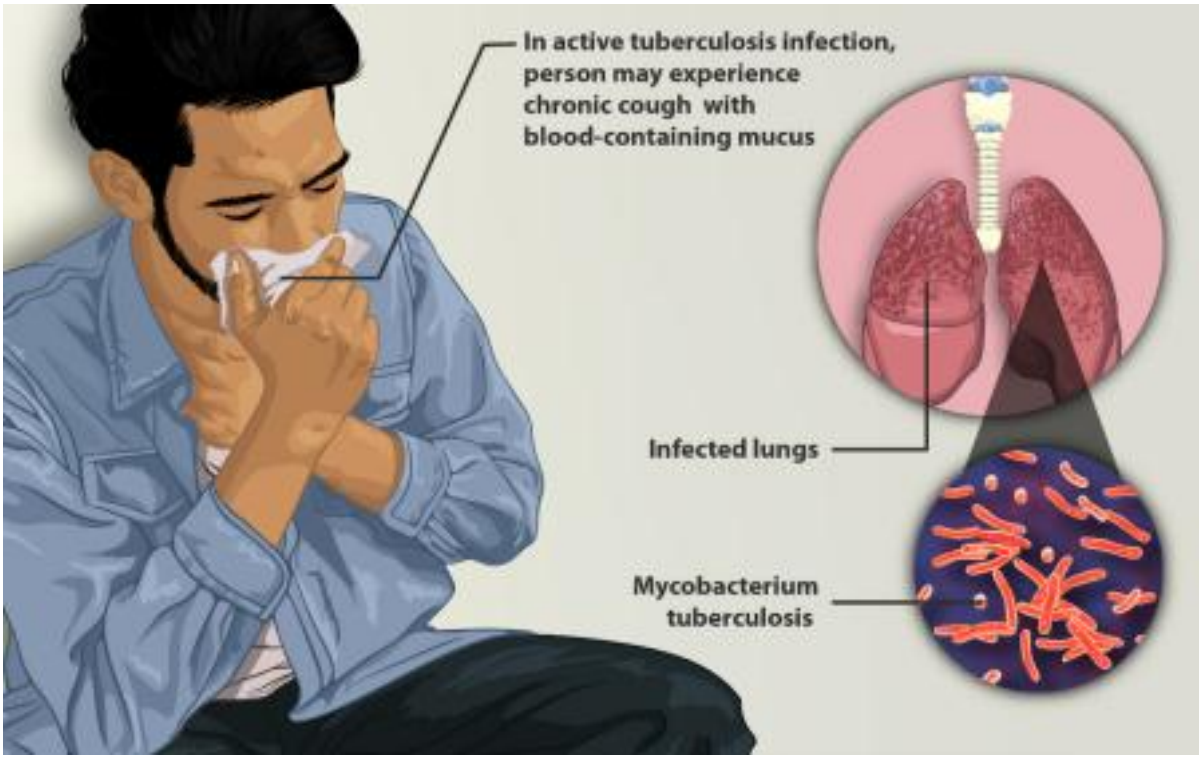

Fig 4: Infected individual.

RISK FACTORS

● Nonspecific decrease in resistance
1. Adolescence
2. Senescence
3. Malnutrition
4. Postgastrectomy state
5. Diabetes mellitus
6. Renal failure

● Decrease in resistance due to
1. hormonal effects
2. Pregnancy Therapy with adrenocortical steroids

● Decrease in local resistance
1. Silicosis
2. Decrease in specific immunity
3. Lymphomas Immunosuppressive therapy
4. Sarcoidosis
5. Live-virus vaccination
6. HIV infection Transplantation.[21]

TYPES OF TUBERCULOSIS

EPTB is less common when compared to PTB, thus less commonly encountered by clinicians and difficult to diagnose clinically.

1. Miliary TB

The clinical features are usually non-specific and may present with fever, weight loss, night sweats, anorexia and weakness. The physical findings in descending order are fever, wasting, hepatomegaly, pulmonary findings, lymphadenopathy and splenomegaly. A granuloma in retinal choroid is strong suggestive feature of disseminated TB.

2. TB Lymphadenitis

It presents as painless swelling in cervical region (supraclavicular fossa). Usually the process is bilateral and with progression of disease, the lymph node fuse and become matted. The overlying skin gets inflamed, ultimately enlarged lymph node rupture through inflamed skin forming sinus tract. Intra thoracic adenopathy may cause atelectasis by compressing bronchi or bronchiectasis (common in children).

3. Pleural TB

The presentation in tubercular pleurisy depends on number of bacteria infecting pleural space. If few MTB bacilli gain entry into pleural space, then it leads to hypersensitivity response causing pleural effusion. The process may resolve spontaneously or may lead to large effusion causing fever, pleuritic pain, dyspnea and weight loss. If large number of MTB bacilli gain entry from rupture of a cavity or the adjacent parenchymal fistula, then it leads to tubercular empyema. The presentation of pleural TB in HIV seropositive patients is chronic with additional symptoms like tachypnea, night sweats, fatigue, diarrhea and have more hepatomegaly, splenomegaly, lymphadenopathy as compared to seronegative patients.

4. Abdominal TB

The clinical presentation depends on site of involvement as TB can affect any location from mouth to anus. The most common site of involvement is terminal ileum or caecum and manifest as pain abdomen, a palpable mass sometimes with weight loss, fever and loss of appetite. Tubercular peritonitis presents with classic doughy abdomen, ascites, pain abdomen and fever. In esophageal

TB, additional symptoms seen are dysphagia, odynophagia and retrosternal pain/discomfort. Patient also suffers from life threatening complications like broncho-esophageal fistula/hematemesis. Gastric TB is rare because of acidic pH, few lymphoid tissues in mucosa and rapid gastric emptying. Duodenal TB presents with dyspepsia, duodenal obstruction and duodenal ulceration. Other reported complications are perforation, fistulae and obstruction jaundice. The common presenting feature in rectal TB is hematochezia followed by constitutional symptoms and complication. It may also present as anal fissure, fistulae or perirectal abscess.

5. CNS TB

The most common manifestation of CNS TB are meningitis (95%), tuberculomas (2%) and abscess (1%). Clinical features include those related cranial nerve involvement as well as headache, vomiting, decreased level of consciousness, neck stiffness and in the absence of medical care coma and death.

6. Skeletal TB

Pain is the most common presenting feature. The involved joints have limited motion of range with or without the presence of swelling. The patient may present with sinus tract. Involvement of spine leads to chronic backache, fever and more than 50% of patient suffer from neurological symptom due to compression of spinal cord. Delayed diagnosis may further complicate the situation due to spinal deformity and severe, irreversible neurological sequelae like paraplegia.

7. Genito-urinary TB

Patient usually presents with local symptoms like dysuria, hematuria, flank pain and increased frequency of micturition. In women, genital involvement presents with pelvic pain, menstrual irregularities and infertility whereas in men the most common presentation is scrotal swelling/mass with or without pain. Symptoms of prostatitis, orchitis or epididymitis may also occur depending on site of involveme.[23]

DIAGNOSIS

A firm diagnosis of tuberculosis requires bacteriological confirmation. It is important to remember that a positive acid-fast smear is not specific for Mycobacterium tuberculosis. Other mycobacteria, both saprophytes and potential pathogens, can be acid fast. Thus, culture of M. tuberculosis is the only absolute way of confirming the diagnosis. Freshly expectorated sputum is the best sample to stain and culture for M. tuberculosis. Sputum samples 24 h old are frequently overgrown with organisms of the mouth flora and are much less useful. If the patient is not spontaneously producing sputum, induced sputum is the next best specimen for study. It can be obtained by having the patient breathe an aerosol of isotonic or hypertonic saline for 5 to 15 min. If the patient cannot cooperate to give a spontaneous sputum sample, a gastric aspirate to obtain swallowed sputum may be useful. This sample must be obtained in the morning before the patient arises or eats. For the majority of patients, the above-mentioned procedures are successful in obtaining positive material for culture. Smears of gastric contents for acid-fast bacilli are of limited value because of the presence of nontuberculous ingested acid-fast bacilli. In a few cases, one may have to resort to bronchoscopy. For 41 patients proven to have tuberculosis, cultures of specimens, taken during fiber-optic bronchoscopy, were positive in 39 cases[24,25] Stainable mycobacteria were seen in 14 of the cases, and in 8 cases, granulomas were seen on biopsy. Similar results have been obtained in another study of 22 patients with proven mycobacterial disease and negative smears prior to bronchoscopy.[26] The local anesthetics used during fiber-optic bronchoscopy may be lethal to M. tuberculosis, so specimens for culture should be obtained using a minimal amount of anesthesia. However, irritation of the bronchial tree during the fiber-optic bronchoscopy procedure frequently leaves the patient with a productive cough. Thus, collection of the post bronchoscopy sputum can provide another valuable source of diagnostic material. In nine (13%) of the above-mentioned cases, the post bronchoscopy sputum was the only source of positive material. Nucleic acid amplification (NAA) testing can be used for rapid diagnosis of M. tuberculosis complex in respiratory specimens. Current CDC recommendations suggest that at least one respiratory sample be tested using NAA testing for smear-negative patients in whom active pulmonary tuberculosis is considered. In smear-positive samples, NAA testing can be used to differentiate M. tuberculosis from nontuberculous mycobacteria and has a positive predictive value of more than 95%[27] However, if the NAA test is positive but the smear is negative, clinical judgment must be used in interpreting the test. A recent review of Xpert MTB/RIF, loop mediated isothermal amplification, and simultaneous amplification testing methods found a sensitivity and specificity of 98% and 68% in the smear-positive subgroup but only a sensitivity and specificity of 72% and 93% in the smear-negative subgroup[28] Importantly, a negative NAA result is insufficient to exclude a diagnosis of pulmonary tuberculosis Both positive and negative NAA results should be evaluated within the individual clinical context and local laboratory capabilities. In 2014 in the United States, sputum culture confirmed the diagnosis in 77% of cases. In 16% of cases, the diagnosis was confirmed by a clinical response to therapy. Thus, in a significant number of cases, the diagnosis of tuberculosis is made in the absence of bacteriological confirmation.

DIFFICULTIES IN DIAGNOSIS

While diagnosis of tuberculosis certain errors and difficulties occurs which are enlisted below.

- Lack of organisms for culture.
- Slow growth of culture.
- Chest X-ray findings absent or misinterpreted.
- Biopsy material may not be specific.

- Decreased tuberculin sensitivity.
- Symptoms and signs of tuberculosis easily attributed to a pre-existing disease.[29]

DIFFERENTIAL DIAGNOSIS

Since tuberculosis today is a disease frequently present in older individuals, as well as immigrants, one major differential diagnosis is usually between tuberculosis and carcinoma of the lung. An important concept to remember is that carcinoma may cause a focus of tuberculosis to spread; thus, carcinoma of the lung and tuberculosis may be present simultaneously. In cases with the simultaneous presentation of carcinoma and tuberculosis, the diagnosis of tuberculosis frequently is made first, and the diagnosis of carcinoma is delayed for several months. Thus, if radiograph and clinical findings suggest carcinoma but the sputum has acid-fast bacilli, further procedures to diagnose carcinoma may still be indicated. Isolated involvement of the anterior segment of the upper lobe, isolated lower lobe involvement, or the presence of irregular cavities would suggest carcinoma, and further diagnostic workup may be indicated despite acid-fast bacilli in the sputum smear. Any type of infectious or granulomatous disease may be radiographically identical to tuberculosis. Three broad categories of infectious disease must be distinguished: those involving fungi (histoplasmosis, coccidioidomycosis, and blastomycosis), bacteria (Pseudomonas pseudomallei), and atypical mycobacteria (mainly Mycobacterium kansasii and Mycobacterium intracellulare). Culture of the organism from the patient's sputum is the best way to differentiate these diseases, although titers of serum antibody to fungi are also valuable. Common bacterial pneumonias are usually easily differentiated from tuberculosis. The localized alveolar infiltrate on the chest radiograph and the prompt response to antibiotic therapy usually differentiate bacterial pneumonia from tuberculosis. When in doubt, treatment for a bacterial pneumonia should be given first and tuberculosis therapy withheld until adequate sputum samples have been obtained and the response to antibiotics determined. Lung abscesses can usually be differentiated from tuberculous cavities by prominent air-fluid level, more common lower lobe distribution, and clinical findings (i.e., associated with seizures, alcoholism, dental caries, etc.). While sarcoidosis is a non-infectious granulomatous disease which can present with radiographic similarities to tuberculosis, it does not typically cause cavitary disease and is distinguished from tuberculosis on histopathology by the presence of noncaseating granulomas and the absence of acid-fast bacilli and negative culture results.[30]

TREATMENT

RNTCP (now known as National tuberculosis elimination programme) has introduced daily regimen for drug sensitive TB in PLHIV, Pediatric TB cases in the entire country and for all TB cases in 104 districts. In drug sensitive TB, for all new TB cases, 8 weeks of intensive phase (IP) with Isoniazid(H), Rifampicin(R), Pyrazinamide(Z), Ethambutol(E) in daily doses as per 4 weight band categories whereas except Pyrazinamide, other 3 drugs are continued in continuation phase (CP) for another 16 weeks as daily doses. For previously treated cases of TB, 12 weeks of IP with Isoniazid(H), Rifampicin(R), Pyrazinamide(Z), Ethambutol(E) and injection Streptomycin only for first 8 weeks of IP whereas 20 weeks of CP with Isoniazid, Rifampicin and Ethambutol MDR/RR-TB cases (with or without additional resistance): The duration of treatment consists of 6-9 months of IP with Kanamycin(Km), Levofloxacin(Lfx), Ethionamide(Eto), Cycloserine(Cs), Pyrazinamide(z), Ethambutol(E), Isoniazid(H) and 18 months of CP with Levofloxacin, Ethionamide, Cycloserine, Ethambutol, Isoniazid on daily bases under supervision**.**

NEW APPROACHES AND STRATERGIES FOR TARGETING TUBERCULOSIS BEDAQUILINE AND DELAMANID

The treatment landscape for tuberculosis has changed dramatically over the past 5 years, with the introduction of two new drugs, bedaquiline and delamanid, and multiple clinical trials whose results are being used to radically alter the care of people with all forms of tuberculosis. More tuberculosis treatment studies are happening than ever before in the history of the disease, and not only will these studies help improve the care of people living with tuberculosis[31], but they should also help show aspects of tuberculosis pathophysiology that can be used to develop better, targeted therapies for people with tuberculosis. To date, no major changes in treatment of drug-susceptible tuberculosis have been made. For pansusceptible tuberculosis, treatment still consists of four dr`ugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) given for a total of 2 months followed by two drugs (isoniazid and rifampicin) given for an additional 4 months. Data from a 2014 study show that a so-called hard-to-treat phenotype, defined by high smear grades and cavitation, can require durations of more than 6months to achieve cure.[32] Studies have shown that daily administration of therapy results in improved treatment outcomes compared with thrice-weekly treatment, and WHO recommends all people diagnosed with tuberculosis be offered daily treatment with fixed-dose combinations.[33] Of note, studies show that some combination tablets can result in subtherapeutic concentrations of certain key drugs (especially rifampicin)[34] but the clinical implications of this occurrence are not entirely clear. Therapeutic advances in the treatment of drug susceptible tuberculosis have focused on two areas: high-dose rifampicin and the addition or substitution of fluoroquinolones in the regimen. Although high-dose rifampicin shows early promise for treatment shortening, randomised controlled trials with the fluoroquinolones did not show a treatment-shortening benefit.[35-39] Multiple studies to assess shorter tuberculosis treatment regimens are ongoing, including regimens containing rifapentine, clofazimine, and the novel drugs bed

aquiline and PA-824, also known as pretomanid (an experimental nitroimidazole agent for drug-resistant tuberculosis).[40] Although there are no data-driven recommendations on whether to routinely test people for isoniazid-resistant tuberculosis, isoniazid-resistant forms of tuberculosis are the most prevalent drug-resistant tuberculosis in the world. Isoniazid-resistant tuberculosis is projected to be diagnosed more frequently in the upcoming years as a result of the introduction of molecular diagnostics. Despite the lack of formal trials to direct therapy, a 2017 meta-analysis indicated that fluoroquinolone-containing regimens led to better outcomes despite the high degree of variability in treatment practise (more than 55 regimens were utilised). WHO has recommended that fluoroquinolones be given to people with isoniazid-resistant tuberculosis, but also note the need for formal clinical studies to assess the optimal therapy for this form of tuberculosis. Rifampicin mono-resistant tuberculosis (with retained susceptibility to isoniazid) is increasingly documented, and this strain might constitute an important population of patients with mono-resistant tuberculosis in the future. The treatment of these two entities will be discussed jointly in this Seminar since the treatment guidelines are the same for patients with multidrug-resistant tuberculosis (although this scenario may change in the future). With the development of bed aquiline and delamanid, as well as the growing usage of repurposed medications like linezolid and clofazimine, the treatment of rifampicin-resistant tuberculosis has undergone significant shift. For the first time, WHO has recommended all-oral therapy for a majority of people with rifampicin-resistant tuberculosis, and regimens of 9–12 months' duration (compared with the standard 18–24 months of therapy) are also being rolled out for the treatment of rifampicin-resistant tuberculosis. These therapeutic advances have already been shown to greatly improve the treatment of rifampicin-resistant tuberculosis. Ongoing trials aim to assess new and repurposed drugs for the treatment of rifampicin-resistant tuberculosis.[41]

Table 2: Summary of new and repurposed drugs for treating rifampicin-resistant tuberculosis.

	Class and mechanism of action	Phase completed and regulatory approval	Summary of findings	Adverse events	Drug–drug interactions and overlapping toxicities	Access and pricing[a]	Ongoing trials[a]
Bedaquiline[7–9]	Diarylquinoline; inhibits mycobacterial ATP synthase	Phase 2b US FDA, EMA, SAHPRA, multiple other countries	Significantly faster time to culture conversion; significantly higher culture conversion; significantly improved treatment outcomes when compared with placebo	QTc prolongation (moderate), hepatitis	Cannot use with efavirenz; use with protease inhibitors results in increased bedaquiline concentration but clinical significance not clear; cannot use with rifampicin; caution when used with other QTc prolonging agents	Available to <20% of individuals that need it; US$400 for a 6-month course via GDF	endTB (NCT02754765), TB PRACTECAL (NCT02589782), NIX-TB (NCT02333799), STREAM 2 (NCT02409290), NeXT (NCT02454205), ZeNix (NCT03086486), Janssen C211 (NCT02354014), ACTG 5343 (NCT02583048), Janssen Japan Trial (NCT02366623), SimpliciTB (NCT03338621), P1101B (NCT02906007)
Delamanid[10–12]	Nitroimidazole; inhibits mycolic acid synthesis	Phase 3 EMA, Japanese Regulatory Authority	Faster time to culture conversion compared with placebo; no differences in final outcomes but study did not have statistical power for detection	QTc prolongation (mild), generally well tolerated	No clinically significant drug–drug interactions	Available to <5% of individuals that need it; $1700 for a 6-month course from GDF	endTB, MDR-END (NCT02639994), ACTG 5453, Otsuka 213 (NCT01424670), Otsuka 233 (NCT01859923), Otsuka 232 (NCT01856634), IMPAACT 2005 (NCT03141060)
Pretomanid[10–12]	Nitroimidazole; inhibits mycolic acid synthesis, generates mycobacterial nitrogen oxide	Phase 2b; currently undergoing regulatory review	Has only been tested in combination regimens and not as a single agent	Hepatitis, animal studies show ocular and reproductive toxic events	No clinically significant drug–drug interactions	Not available	SimpliciTB, NIX-TB, TB PRACTECAL, ZeNix

DENDRIMERS AS NANO CARRIERS

Nanotechnology represents a multidisciplinary field encompassing various domains such as chemistry, materials, biology, physics, diagnosis and engineering, including the synthesis of nanodevices. The pharmaceutical industry adopts nanotechnology throughout the R&D process. Thus, nano-formulations and nanocarriers have made a significant impact on the delivery of therapeutic agents and diagnostics through the development of several nanodevices such as liposomes, nanocrystals, nanoparticles and dendrimers. These nano-delivery platforms can improve the solubility and, consequently, the bioavailability and pharmacokinetic/pharmacodynamic (PK/PD) ratio, reduce the therapeutic dosage (by increasing the drug exposure level over a long period of time) and minimize off-target effects (adverse side effects) of carried drugs such as small molecules, macrocycles and peptides. Finally, the use of nanoparticles can simplify the treatment versus, for example, drug combinations. These therapeutic agents can be encapsulated within nanoparticles, conjugated to them or complexed on their surface. Genes and vaccines can also be carried. In addition, many efforts have been devoted to developing targeted nanoparticles to deliver therapeutic agents to the right tissues (e.g., brain, kidney, lung), cells (e.g., tumour cells) and inside cell compartments (e.g., nucleus, mitochondria, cytosol). A global view of the modulation of several physicochemical properties has been proposed by Choi, named 'Choi criteria']. Composition of the nanoparticles manage their biodegradation and toxicity effects, surface properties control their targeting and biodistribution properties, whereas size and shape govern their excretion and clearance profiles. Besides polymeric, metal-based nanoparticles, polymeric micelles and linear polymers, dendrimer and dendron nanostructures represent ideal delivery vehicles and offer high hopes for the future of nanomedicine. Dendrimers (from the Greek words "dendros" and "meros") are a family of nanosized macromolecules characterized by a highly homo-structural, branched three dimensional (3D) architecture and compact, spherical geometry in solution. Dendrimers represent globular macromolecules, with a highly branched 3D architecture, whose shape and size can be precisely controlled. They display an exponential number of dendritic branches (hydrophobic and hydrophilic moieties) radiating from a central core. The dendrimer diameter increases linearly, while the number of surface groups increases exponentially with each generation. Low-generation dendrimers are usually flexible, while higher generation compounds are denser and increasingly rigid. A schematic of a typical dendritic structure for biomedical applications is illustrated in Figure 3. The dendritic macromolecular structure can be divided into four main components: (a) a central core moiety; (b) interior layers (generations, Gn, where n is 0, 0.5, 1, 1.5, …) made of regularly repeating branching units attached to the core; (c) terminal functionalities distributed in a 3D space; (d) void spaces, which are rooms for molecular cargo, such as anti-cancer agents.[18]

The main dendrimer types used are PAMAM dendrimers (Starbust®), poly-etherhydroxyl-amine (PEHAM) dendrimers (Priostar®), PPI dendrimers (Astramol®) carbosilane dendrimers, and phosphorus-based dendrimers developed by J-P. Majoral and A-M. Caminade.[19] Figure 2. Delamanid, Pretonamid, Rifampicin (RIF), and Isoniazid (INH) chemical structures. A multidisciplinary field, nanotechnology includes the creation of nanodevices as well as chemistry, materials, biology, physics, diagnosis, and other fields. The pharmaceutical industry adopts nanotechnology throughout the R&D process. Thus, nano-formulations and nanocarriers have made a significant impact on the delivery of therapeutic agents and diagnostics through the development of several nanodevices such as liposomes, nanocrystals, nanoparticles and dendrimers. These nano-delivery platforms can improve the solubility and, consequently, the bioavailability and pharmacokinetic/ pharmacodynamic (PK/PD) ratio, reduce the therapeutic dosage (by increasing the drug exposure level over a long period of time) and minimize off-target effects (adverse side effects) of carried drugs such as small molecules, macrocycles and peptides. Finally, the use of nanoparticles can simplify the treatment versus, for example, drug combinations. These therapeutic agents can be encapsulated within nanoparticles, conjugated to them or complexed on their surface. Genes and vaccines can also be carried. In addition, many efforts have been devoted to developing targeted nanoparticles to deliver therapeutic agents to the right tissues (e.g., brain, kidney, lung), cells (e.g., tumor cells) and inside cell compartments (e.g., nucleus, mitochondria, cytosol). Choi's "Choi criterion" is a broad perspective on how many physicochemical parameters are modulated. Nanoparticle composition controls biodegradation and toxicity, surface characteristics influence targeting and biodistribution, and size and shape control excretion and clearance profiles. Along with polymeric micelles, linear polymers, and polymeric, metal-based nanoparticles, dendrimer and dendron nanostructures serve as perfect delivery systems and hold great promise for the future of nanomedicine. A family of nanosized macromolecules known as dendrimers—from the Greek words "dendros" and "meros"—are distinguished by their compact, spherical geometry in solution and highly homogeneous, branching three-dimensional (3D) architecture. Dendrimers are globular macromolecules that have a highly branching 3D architecture and can have exquisite control over their size and structure. They exhibit a central core that is surrounded by an exponential number of dendritic branches with hydrophobic and hydrophilic moieties. With each generation, the number of surface groups grows exponentially while the dendrimer diameter increases linearly. The majority of low-generation dendrimers are elastic., while higher generation compounds are denser and increasingly rigid. A schematic of a typical dendritic structure for biomedical applications. The dendritic macromolecular structure can be divided into four main components: (a) a

centrawith the aim of improving the bioavailability of anti-TB drugs in general and RIF in particular, several studies have been developed using drug delivery system approaches (nano-formulations) such as.
(1) Nano-dispersions including nanosuspensions, nano-emulsions, solid dispersions and niosomes.
(2) polymeric and non-polymeric nanoparticles.
(3) polymeric micelles and analogues and.
(4) liposomes and dendrimers (vide infra)

The main anti-TB drugs carried by liposomes are streptomycin, gentamycin, sparfloxacin, amikacin, clofazimine, INH, RIF, PZA, rifabutin (RFB) and capreomycin; by niosomes, RIF and by nanoparticles and microparticles, INH, RIF, PYZ, ETB, streptomycin, moxifloxacin, PZA, ETB and econazole.

Encapsulation of Anti-TB Drugs within Dendrimers
Early studies were performed by Palanirajan Vijayaraj Kumar and co-workers on the development of mannosylated dendritic architectures (G5 EDA-PPI dendrimers) for the selective delivery of RIF to alveolar macrophages. The mannosylated G5 EDA-PPI dendrimer is a fifth-generation poly(propyleneimine) (PPI, 64 amino groups on the surface) dendrimer with an ethylene diamine (EDA) core and grafted on the surface with ~30 D-mannose groups RIF is an essential component of the cocktail of anti-TB combination drugs, The component of the cocktail of anti-TB combination drugs, as shown in Figure 1. The mechanism of action of RIF is related to the inhibition of the subunit of the bacterial RNA polymerase, which inhibits gene transcription. It is emphasized that several side effects of RIF are related to its poor pharmacokinetic profile, mainly due to its low solubility in water. In addition, under gastric conditions (pH 4–5), RIF is hydrolysed into the less soluble compound 3-formyl-rifampicin Mannose was chosen because it is recognised by lectin receptors on the surface of phagocytic cells, which enhances immune system cells' ability to absorb nanocarriers with mannose on their surfaces and medicines in their empty spaces. Pharmaceutics 2018, 10, x FOR PEER REVIEW 5 of 10 poor pharmacokinetic profile, mainly due to its low solubility in water. In addition, under gastric conditions (pH 4–5), RIF is hydrolysed into the less soluble compound 3-formyl-rifampicin. Mannose was selected because this sugar molecule is recognizable by lectin receptors on the surface of phagocytic cells and consequently improves the uptake of nanocarriers bearing mannose on their surface and drugs in theirvoid spaces by the cells of the immune system. Using the very well-known dissolution technique, about 37 RIF have been incorporated into PPI dendrimers. SEM studies showed an irregular shape and agglomerated mannosylated dendrimers with a median diameter less than 5 μm. Differential scanning calorimetry studies suggested that loaded mannosylated PPI dendrimers did not form a physical mixture. A drop in solubility was seen when RIF was enclosed in a mannosylated dendrimer (5 mg/mL), although this solubility level is still double that of the aqueous solubility of RIF alone. The nanodevice created by including RIF within the PPI dendrimer had a solubility of around 50 mg/mL. RIF and the mannosylated dendrimer were seen to interact non-covalently. Both hydrogen bonding and hydrophobic interactions (~37%) with the core were observed. Haemolytic toxicity of the G5 EDA-PPI mannosylated dendrimer was evaluated against red blood cells emphasizing the significant decrease in toxicity of mannosylated versus non-mannosylated dendrimers (2.8% versus 15.6%) due to inhibition of the interaction of the charged quaternary ammonium ion with cells. The high haemolytic toxicity of unmodified PPI dendrimers, with all the surface bearing amino groups, precludes their clinical applications. Similarly, PAMAM dendrimers must be modified on their surface by the introduction of groups that decrease the cationic surface aspect and, consequently, toxicity. Mannosylated dendrimers displayed negligible cytotoxicity against Vero cells at a concentration of 100 μg/mL, as did the RIF-loaded mannosylated dendrimer (~85% viability). In the same assay, the group of RIF alone showed a viability of ~50% at the sameconcentration.[42]

AUTOPHAGY
The autophagy process plays a fundamentally important basal housekeeping function in diverse physiological conditions. Autophagy activation is required for the maintenance of cellular homeostasis and survival by providing energy building blocks during a variety of stresses via the cell autonomous digestion of intracytoplasmic cargo (i.e., large macromolecular aggregates and damaged organelles). Innate immunity, inflammation, and the antibacterial defences of macrophages are just a few of the immunological responses that autophagy is essential for controlling. A global threat, human tuberculosis (TB) is an infectious illness with a high fatality rate. The standard treatment for TB is a regimen of frontline combination chemotherapy with multiple antibiotics for at least 6 months. Current anti-TB therapy has many limitations such as prolonged treatment duration, drug toxicity, and potential risk for the development of drug-resistant strains if patients are noncompliant. Therefore, there is an urgent need to develop new therapeutic drugs to control infection more effectively.[3] TB treatment effectiveness may be increased by using host-directed therapy (HDT) to combat bacterial infections. Additionally, by therapeutically targeting a variety of clinically significant biological processes in hosts, HDT-TB may be useful in the treatment of multidrug (MDR)- or extensively drug-resistant (XDR) TB. Numerous immune system elements and immune system pathways are key players that support therapeutic targets for HDT against TB based on the control of pathogenic or protective responses in hosts. Modulators of pathological inflammation, antimicrobial effectors, and medications/reagents for the preservation of homeostasis are examples of potential targets. Because autophagy is critical for maintaining intracellular homeostasis and acts

as a crucial immune arm, autophagy modulators/molecules could represent promising candidates in the context of HDT against TB with or without adjunctive agents for standard therapeutics. In this review, we focus on current advances in the identification of autophagy-activating agents exhibiting antibacterial activity as potential therapeutics to eradicate Mtb infection. More attention should be paid to the identification of key players and mechanisms by which autophagy-activating agents target Accepted to enhance antimicrobial responses. Finally, we discuss the challenges and perspectives of autophagy-adjunctive therapeutics for their clinical use.

Selective autophagy (xenophagy) targeting mycobacteria

During mycobacterial infection, xenophagy against Mtb infection is triggered by the cytoplasmic release of bacteria through its ESX-1 system. The xenophagic eradication of Mtb is significantly aided by the STING-dependent cytosolic pathway and the autophagic receptors p62 and NDP52. The subsequent ubiquitination and host defence against Mtb are dependent on the ubiquitin ligase Parkin. The ubiquitin ligase Smurf1, which functions primarily in K48-linked ubiquitination, was recently found to play an essential role in the activation of selective autophagy, host defence against Mtb, and lung inflammation. Additionally, TRIM16 participates in autophagic defence against Mtb infection and is necessary for ubiquitination and autophagy in response to lysosomal damage along with Galectin-3 and Atg16L1. Previous research has shown the significance of murine immunity-related p47 guanosine triphosphatase family M protein 1 (IRGM1) (also known as LRG47) in IFN-γ-dependent host defence against several intracellular infections, including mycobacterial infection. IRGM1 and human IRGM (the human equivalent of mice Irgm/Lrg47) both play a part in the autophagic removal of mycobacteria and are genetically linked to TB and Crohn's disease. Recent research has uncovered the molecular pathways by which IRGM controls autophagy and encourages the antimicrobial effects. IRGM works by stabilizing AMP-activated protein kinase (AMPK) and maintaining and associating with autophagy factors ULK1, ATG14, and ATG16L1. However, further information is needed to determine the precise role of IRGM in the control of selective autophagy during mycobacterial infection. In terms of infection and inflammation, the IRGM/murine ortholog IRGM1 may also have additional regulatory roles in addition to autophagy. Furthermore, a recent study by Kimmey et al. demonstrated that a number of genes related to autophagy did not contribute to host resistance to Mtb infection in mice models in vivo. It's significant that the authors could not rule out the possibility that autophagy limits mycobacterial development. Future research is necessary to determine the routes and components that are crucial for the antimicrobial responses induced by autophagy activation in mouse and human cells.[43]

α-GLUCAN BIOSYNTHESIS

In the search for a new Achilles heel of M. tuberculosis, we discovered a previously unknown metabolic pathway that converts the disaccharide trehalose (an abundant and essential metabolite in M. tuberculosis) to α-glucans (α-1,4-linked glucose polymers exhibiting α-1,6-linked branches) (3). Trehalose is interconverted to maltose in this four-step process by the enzyme trehalose synthase (TreS), as shown in Figure 1.

Step 1. which is then phosphorylated in a subsequent ATP-dependent process by the maltokinase Pep2.

Step 2: producing maltose 1-phosphate, a phosphosugar. The main enzyme in this route is maltosyltransferaseGlgE, which releases the phosphate moiety while polymerizing maltose 1-phosphate to linear 1,4-glucans by adding the maltosyl unit to the nonreducing end 4′-hydroxyl group of an acceptor substrate.

Step 3. Finally, the branching enzyme GlgB introduces α-1,6- linked branches into the linear polymer chain

Step 4. forming it into a structure like glycogen. This -glucan pathway, also known as the GlgE pathway, is not necessary in and of itself for M. tuberculosis viability. TreS and Pep2 are the first two stages in the process, and their inactivation has no effect on either in vitro growth or in vivo pathogenicity**.**

Thus, at first sight, this pathway appears to be an unlikely candidate to provide viable targets for chemotherapeutic intervention. However, the last two steps in this pathway, catalysed by GlgE and GlgB, are, surprisingly, essential in M. tuberculosis. The accumulation of the hazardous intermediate maltose 1-phosphate serves as the basis for essentiality. Normally, this phosphosugar is immediately converted by the metabolising enzyme GlgE and never reaches large intracellular quantities. However, when GlgE activity is compromised, hazardous quantities of maltose 1-phosphate quickly accumulate, which causes pleiotropic stressors in the cells. Upregulation of a route that releases trehalose from -glucans and uses the enzymes TreX, TreY, and TreZ is one of the stress reactions brought on by the buildup of maltose 1-phosphate (3, 4).This reaction likely represents a stress protection mechanism, since trehalose serves as a stress-protectant in many pro- and eukaryotic organisms. Ironically, when GlgE function is blocked, however, the increased trehalose level further promotes the conversion of trehalose into maltose 1-phosphate, thus accelerating the accumulation of this toxic phosphosugar and increasing, instead of mitigating, the stress on the cells. This "derailed" protective reaction is therefore likely to lock the cells in a catastrophic self-amplifying spiral of self-poisoning that ultimately results in cell death. The accumulation of linear, unbranched oligoglucans, which are themselves not poisonous to the bacteria, is the initial result of the inactivation of GlgB, the second crucial enzyme in this pathway. These unbranched oligoglucans, however, are no longer available as acceptor substrates for GlgE because they quickly become insoluble. Thus,

the absence of branching enzyme activity indirectly slackens the function of GlgE by acceptor substrate limitation, thereby curbing its conversion of maltose 1-phosphate, causing accumulation of this toxic phosphosugar and leading to cell death. Therefore, GlgB is also a potential therapeutic target, but it is less desirable due to the existence of a human branching enzyme orthologue. The maltosyltransferaseGlgE, on the other hand, satisfies several of the criteria for a promising novel anti-TB target. First, we have demonstrated that GlgE inactivation is a bactericidal event, which results in the death of the cells, rather than merely inhibiting the development of M. tuberculosis cells. Second, we have demonstrated that this killing effect is seen not only with cells grown in vitro, but also when cells are grown in lungs and spleens of infected mice in vivo. These findings suggest that the target GlgE would be exposed and susceptible in vivo, and that the -glucan route serves a vital, albeit unidentified, role for M. tuberculosis during infection. Third, except for Mycobacterium leprae, the cause of leprosy, where it is present as a pseudogene that probably does not code for an active enzyme, GlgE is found in practically all mycobacterial species whose genome sequences are publically available. GlgE, on the other hand, is not present in humans or in the usual gut flora bacteria. These findings imply that medications created particularly to inhibit GlgE may also exhibit efficacy against a variety of pathogenic mycobacteria without having adverse effects on the individuals receiving the medication. Fourth, chemotherapeutics have never specifically targeted -glucan production in the management of TB. Additionally, it is likely that GlgE inhibitors would have resistance-breaking properties and thus be effective against MDR- and XDR-TB strains since suicidal self-poisoning by the accumulation of a toxic phosphosugar that causes multiple stresses in the cells is a novel mode of action fundamentally different from those of all anti-TB antibiotics currently in clinical use. In addition, GlgE combines several other beneficial properties, which will be discussed below.[44]

CONCLUSION

Robert Koch once said that "amidst the persistently great variety in the ways and means of combating tuberculosis, it is yet necessary to ask what measures do indeed best satisfy the scientific requirements," and those words still ring true more than a century after the discovery of tubercle bacilli. Medical professionals, pathologists, and microbiologists are still faced with a variety of problems related to early detection and treatment of tuberculosis in all of its forms. WHO END TB strategy wishes to achieve 95% reduction in absolute number of tuberculosis deaths by 2035 which needs thorough understanding of tuberculosis and systemic filling of gaps in TB detection and treatment. The war is set on a platform of real knowledge; mankind equipped with experience of past and armed with present medicine to win against this ancient foe in its all forms. This review articles are a sincere effort towards increasing awareness about TB. I conclude by repeating the words of Sigmund Freu. The future is bright for TB treatment. Never before has there been such a global effort to develop new technologies and treatment for TB patients. Combining these advancements, it is possible that we will base each patient's treatment on their own protein biosignatures in conjunction with the genomic expression of mutations in the Mtb strain they have been affected with. If we are to achieve our goal of global eradication of TB, it is essential that we continue to collaborate and share our expertise on an international GlgE combines a number of favourable properties that qualify it as a highly attractive novel drug target candidate for the treatment of TB, based on its unique essential function within a synthetic lethal pathway. Drugs targeting GlgE could have bactericidal activity against replicating—and possibly also against nonreplicating and persistent—TB bacilli. They could induce death of M. tuberculosis by causing a suicidal self-poisoning cycle that provokes pleiotropic stresses and eventually leads to DNA damage. This novel mode of action, which is completely different from those of currently used anti-TB drugs, is expected to provide a novel chemotherapeutic regimen for the treatment of MDR-TB and XDR-TB strains. During an infection, the target, GlgE, is expressed, active, and susceptible. Additionally, GlgE inhibitors may have broad effectiveness against other mycobacterial infections in addition to their effect against M. TB while having very minor adverse effects on people and commensal flora. Most noticeably, discovery of a synthetic lethal interaction with an alternative α-glucan pathway enables the rational design of a novel combination therapy that would not only boost the killing properties of GlgE inhibitors but also eliminate a potential resistance mechanism Dendrimers have a polymeric architecture with tuneable defined structures and represent versatile drug delivery systems. Thus, in the dendrimer domain, few articles have highlighted the encapsulation of anti-TB drugs such as RIF (vide supra). No conjugation of anti-TB drugs was described to date. Extensive application of dendrimers as nano carriers has been described essentially in the oncology domain.

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