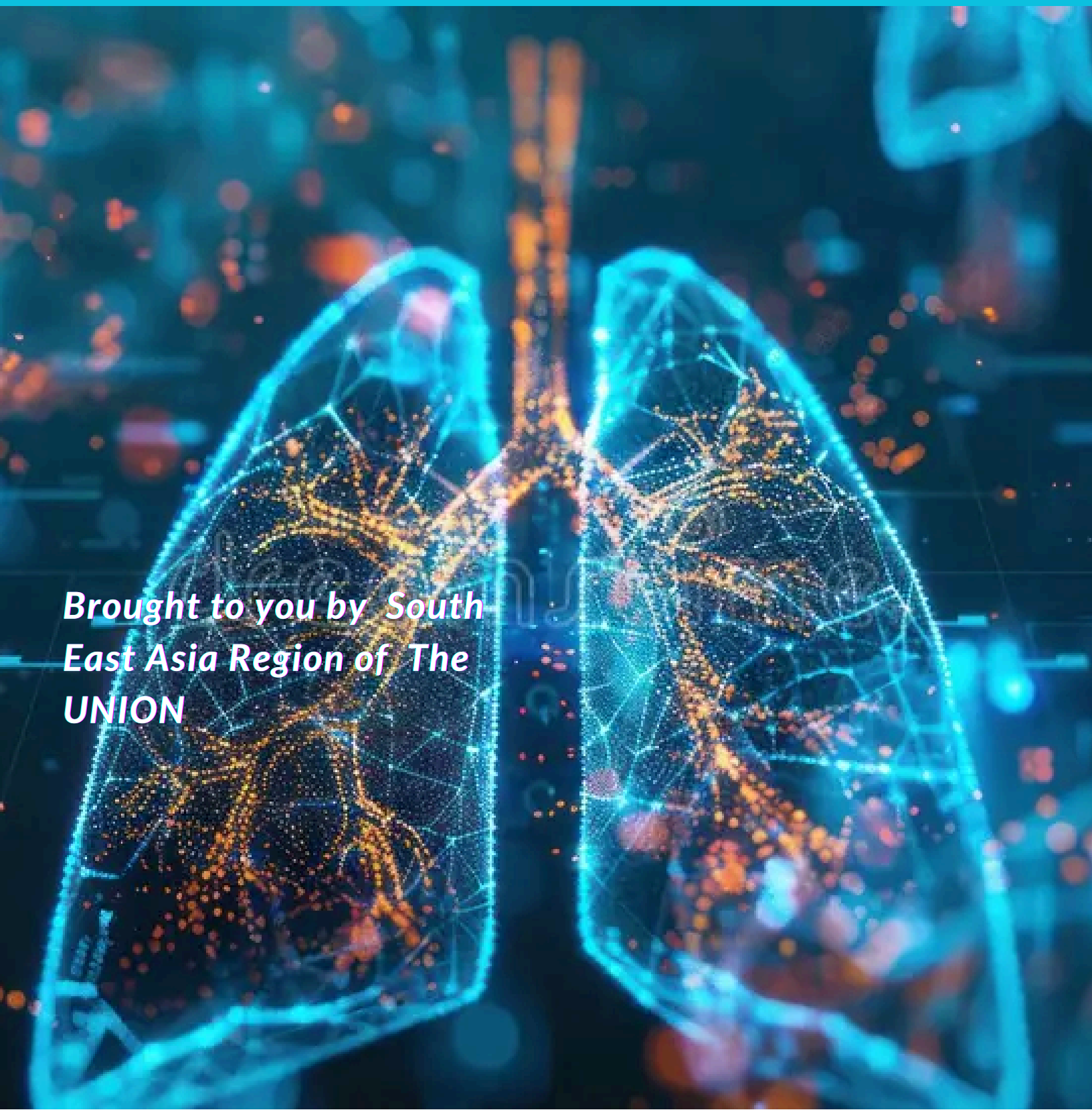
From Progressive Evolution to Revolutionary Shift



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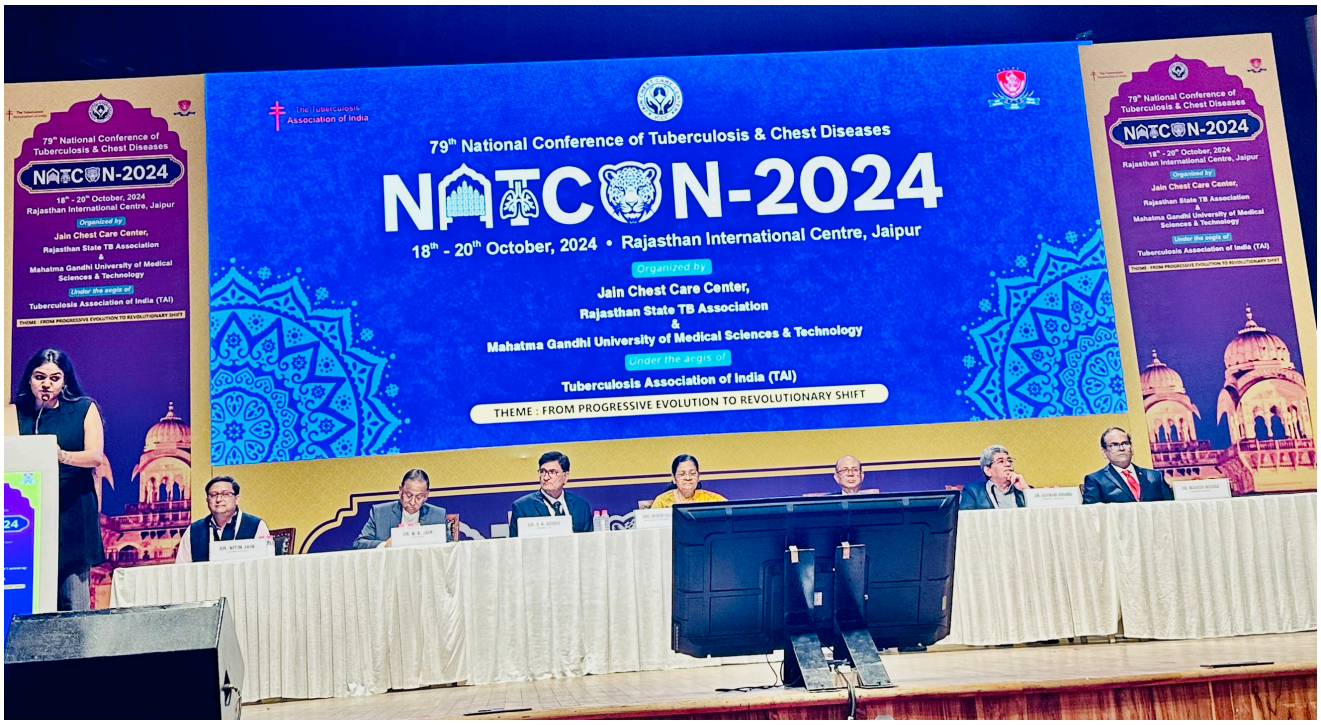
NATCON-2024

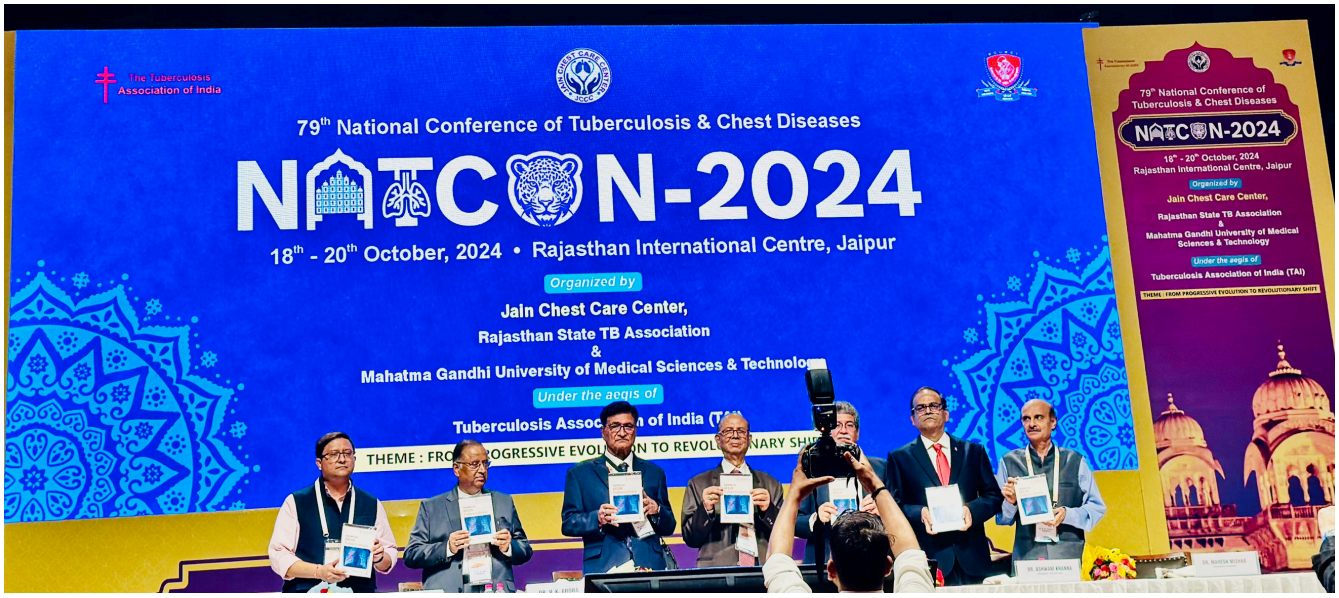
The Tuberculosis Association of India

Articles

The inauguration ceremony of the 2024 NATCON in Jaipur unfolded as a monumental event, marking the beginning of a pivotal conference dedicated to Tuberculosis and Lung Health. With the theme "From Progressive Evolution to Revolutionary Shift," the ceremony embraced a transformative vision for the future of respiratory health. Esteemed experts, policymakers, and healthcare professionals from across the globe gathered to exchange insights and forge collaborations aimed at combating these critical health challenges. The ceremony not only celebrated advancements made but also inspired innovative approaches to achieve groundbreaking solutions. Attendees enjoyed engaging keynote addresses, inspirational speeches, setting the tone for a conference poised to ignite revolutionary changes in lung health and tuberculosis care.



The Inauguration ceremony of the NATCON-2024



Release of Book on Update on MDR TB

Image Credit : Flickr creator Kent Clark

TB Vaccine Development landscape – An overview

Dr. V.V.Banu Rekha, Scientist F, ICMR-NIRT

Tuberculosis (TB) continues to be the major cause of mortality and morbidity from communicable disease worldwide. The end TB strategy envisages 95% reduction in TB mortality and 90% reduction in TB incidence rate in 2035 compared to 2015. To achieve these targets, it important to focus on strategies pertaining to TB diagnosis, treatment and prevention. Development of effective TB vaccine is essential to to achieve the goals of end TB strategy. Attributes of an ideal TB vaccine includes being efficacious and safe, protective against all forms of TB including drug resistant TB, logistically feasible to manufacture, store, transport and administer in field settings. Protection against TB in young children is offered by BCG vaccination but not so in adolescents and adults. Newer TB vaccines are essential to combat TB. The focus of new TB vaccines include prevent of infection (POI), prevention of disease (POD), prevention of recurrence (POR) or therapeutic vaccines. They can be priming vaccines to replace BCG or booster following BCG vaccination to address the inadequacy of BCG in offering long term protection. The TB vaccine development pipeline in the recent years is encouraging with more than a dozen vaccines in clinical trials in humans.

TB vaccines development platform has attenuated vaccine, inactivated vaccine, protein/adjuvant sub-unit vaccine, recombinant live vaccine, viral vector, mRNA vaccine etc. Intradermal, subcutaneous, intramuscular, intranasal routes of vaccine administration is being explored for safety, immunogenicity and efficacy. The vaccines in Phase III clinical trials include Immuvac (Mw), VPM1002, M72/AS01E, MTBVAC, GamTBvac and BCG revaccination. The following vaccines are in Phase II clinical trials: DAR-901, H56:IC3, ID93/GLA-SE, RUTI, AEC/BC02 and ChAdOx1 85A + MVA85A. Phase 1 clinical trials are ongoing for the following vaccines: AdHu5Ag85A (aerosol), BNT164, TB/FLU-05E (aerosol) and H107/CAF10b.

Developing new vaccines TB is a difficult task. This is largely due to a lack of understanding regarding the immune responses to TB, which results in failure to identify specific protective antigens. As a result, choosing the right antigens, as well as determining how many are needed for optimal vaccine effectiveness, is challenging. There is currently no suitable biomarker that effectively correlates with protection against TB for use in the early stages of vaccine development. Additionally, the absence of appropriate animal models for vaccine evaluation hampers predictive accuracy during pre-clinical testing. Conducting clinical trials to assess vaccine efficacy is time-consuming and requires significant funding. Countries with high rates of TB lack the necessary infrastructure and financial resources to support these clinical trials for vaccine development.

A strong political commitment and active involvement from various stakeholders—including industry, research institutions, academia, biotechnology companies, and manufacturers—would accelerate the TB vaccine development process. Securing funding from partners is essential to support different stages of vaccine development. Building capacity for clinical trials related to TB vaccines is also crucial. A favorable regulatory environment with expedited approval processes can help prevent delays in vaccine development. Additionally, community engagement and advocacy can promote, accelerate, and create demand for new TB vaccines.

Journey of Pediatric Tuberculosis in last 25 years

Dr. Sangeeta Sharma, Former Director of the National Institute of TB and Respiratory Diseases

Realisation that Pediatric TB is a nation wide problem started to emerge in the late nineties. This led to mere adoption of adult guidelines to manage children with TB disease. Diagnosis was sputum based, with little realisation from the programme managers that majority of children cannot produce sputum. Smear testing for diagnosis and treatment based on smear results was nothing but according mere executional priority to kids. But slowly and steadily, Global and National awareness to address the specific issues and gaps in knowledge lead to research for newer diagnostics, drugs and vaccines, including operational and implementational research on children of all ages. This targeted approach that "one size does not fit all" led to segregation of Pediatric guidelines as separate distinct from adults, a paradigm shift with policy changes towards better prevention and management strategies.

Diagnostic evaluation in a presumptive PTB case using chest X-ray (CXR) and microbiological assays can often be challenging in children presenting with vague symptomatology, pauci-bacillary disease and difficulties in specimen collection, though treatment initiation should not be delayed.Conventional tests, smear microscopy and solid culture have been replaced with highly sensitive, specific rapid WHO-approved newer diagnostics namely molecular genotypic nucleic acid amplification tests (NAAT eg. Xpert MTB/RIF, Truenat, Xpert ultra and XpertMTB/XDR), line probe assay (LPA eg. MTBDRplus, MTBDRsl) and liquid culture mycobacterial growth indicator tubes (MGIT) phenotypic DST. M. tuberculosis whole genome sequencing or targeted next generation sequencing allows rapid identification of mutations causing resistance. These tests pave way for faster microbiological confirmation and universal DST, having been validated on a wide range of pediatric samples, including nasopharyngeal aspirate and stool, making management at primary and secondary care settings easier in the future.

Recently updated WHO treatment recommendations, including shorter regimens for children and adolescents with non-severe drug sensitive disease, tubercular meningitis and injection free all oral regimens using newer reserve drugs, bedaquiline and delamanid, alongwith repurposed drugs linezolid, fluroquinolones, clofazimine for children of all ages with RR/MDRTB. WHO recommended 6BPaLM or 6BPaL regimens, are not yet available for children <15 y of age as pretomanid dosing and safety has not yet been established in children. Availability of child-friendly formulations of first line FDCs and most reserve drugs has improved compliance. But early inclusion of children in drug trials without compromising their safety is the need of the hour.

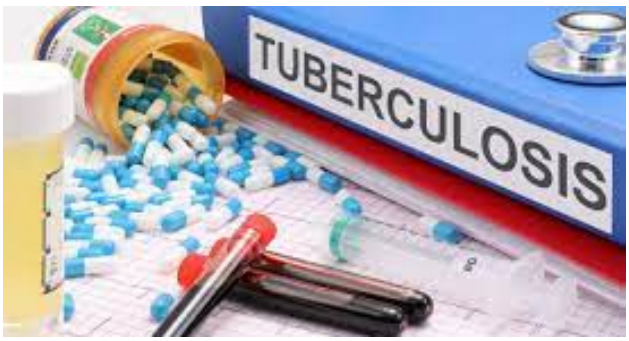


Image Credit : The Blue Diamond Gallery

Transition towards shorter rifamycin based TPT regimens (weekly 3HP, daily 1HP) with better safety profiles, higher completion rates as compared to 6H, the only available safe regimen till now. 6Levofloxacin is the only recommended RR/MDR TPT regimen. Nineteen newer TB vaccine candidates in different phases of development with four in Phase I, eight in Phase II, six in Phase III, and one in Phase IV clinical trial. rBCGs are emerging suitable safer immunogens while no vaccine exists against the DRTB strains till date.

Mismanagement of TB cases still continues to create a havoc on the most vulnerable with mounting global efforts towards TB elimination.

The National TB Elimination Programme (NTEP) of India, the goals of which are to eliminate TB as a public health problem by 2030, five years before the global target of 2035.

The Pulmonologist's Role in Diagnosis of Extra-Pulmonary Tuberculosis – Current Perspective

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Extra-Pulmonary Tuberculosis (EPTB) collectively refers to Mycobacterium tuberculosis infection and disease affecting organs or organ systems apart from the lungs. Risk factors include extremes of age, immunosuppression, diabetes, close contact with known cases of Tuberculosis and homelessness. Commonly affected sites in clinical practice include lymph nodes, pleura, bones and joints (osteo-articular TB), abdominal, genito-urinary tuberculosis and the central nervous system. From the historical perspective, EPTB was believed to contribute only 20% to the tuberculosisburden, with the remaining 80% being equally divided between smear-positive and smear-negative pulmonary cases. Recent evidences point to changing paradigms in the epidemiology of TB that challenge this conventional trend, and it is now established that EPTB may account for nearly half of the TB cases notified from peripheral health institutes (PHI), which are considered tertiary referral centres and contribute more than 25% of all diagnosed TB cases in India.

Several factors lead to delay in diagnosis of EPTB diagnosis, which include (but are not limited to) non-specific signs and symptoms, overlapping clinical presentations, and paucibacillary samples for smear, culture and molecular tests. While a definitive diagnosis for TB in terms of positive microbiologic and/or histopathologic findings should always be attempted, several factors that hinder tissue sampling (low sensitivity, difficulty in site accessibility, denial of consent, etc.) often come into play, which pose a dilemma for the treating physician, who; in the absence of definitive diagnosis, is compelled to rely on supportive pathological findings such as granulomatous inflammation, caseous necrosis, tuberculin skin testing and characteristic imaging features along with clinical correlation to establish a subjective or presumptive diagnosis of EPTB.

Quite often, the diagnosis of EPTB is made by the concerned specialist treating the affected organ or organ system (except for pleural disease) and a pulmonologist's (chest physician's) referral is thereafter sought mainly for anti-TB treatment, which may be either definitive or empiric, decided on a case-to-case basis. The author wishes to clearly emphasize the leading role of the pulmonologist in diagnosis and management of EPTB, rather than merely a contributory role, with a genuine conviction that the pulmonologist, being a trained expert specialist in TB with the capacity to provide a good and advanced standard of care, should occupy the centre-stage of EPTB diagnosis.

Such a strategy establishing the pulmonologist as the key specialist for diagnosis in addition to treatment would not only reduce the turn-about-time to TB diagnosis, but also pave the way for prompt initiation of anti-TB treatment, thereby reducing the morbidity and mortality due to TB, and help to achieve the public health objectives of TB Control programmes across the world, in particular, the National TB Elimination Programme (NTEP) of India, the goals of which are to eliminate TB as a public health problem by 2030, five years before the global target of 2035.

TUBERCULOSIS: THE PHOENIX OF THORACIC SURGERY

Dr. Nasser Yusuf, Cardiothoracic Surgeon,
Sunrise Hospital, Kochi

From the time of Hippocrates, Tuberculosis was known as phthisis, a term derived from the Greek language which means “decaying”. There is no more dangerous disease than pulmonary phthisis, and no other is so common, it destroys a very great part of the human race. Antoine Portal, Paris, 1832. The swollen glands of the neck were known as scrofula and the King's evil.

Although Tuberculosis (TB) is essentially a medical disease, a sizeable proportion of patients fall in the realm of surgery, may it be due to the primary disease or its sequelae. TB was the leading cause of death in the 17th century. Patients were nursed in sanatoriums and treated with plenty of sunlight and good food. Surgery then became widely prevalent as a treatment modality. With the discovery of Streptomycin and Isoniazid in the mid 20th century, surgery faded away. However, concerted efforts have not yielded desired results in the control of TB, owing to the burgeoning Multi-Drug Resistant Tuberculosis (MDR-TB) and Extensively Drug Resistant Tuberculosis (XDR-TB). TB remains the foremost cause of death from an infectious agent. Current drug regimens achieve a cure rate >85%, with poorer outcomes in geographical areas where multi-drug resistant (MDR) strains are prevalent. In this critical global scenario, surgery could be crucial in the treatment of the sequelae of TB as well as for clinically and bacteriologically severe forms of pleuro-pulmonary MDR-TB.

The need for surgery is estimated to have increased from 5% to 15% over the last twenty years.

INDICATIONS FOR SURGERY

Referrals for surgery are often made when treatment has been failing for a long time, a large part of the lung parenchyma has already been destroyed and the patient is extremely symptomatic. In this sense, the physician's awareness should be increased to identify and call for early surgical evaluation before the disease is too far advanced denying the patient the benefits of resection – relief of symptoms and/or possible cure. Although specific practical guidelines concerning surgical indications and approaches are currently unavailable, a summary of the evidence is listed.

Emergency indications where without surgery, death is imminent and unavoidable, include:

profuse lung haemorrhage - massive hemoptysis

tension spontaneous pneumothorax

Elective indications are

A. Complications of Scarring

Massive hemoptysis

Cavernoma (cavity)

Lung cancer

Tracheoesophageal or bronchoesophageal fistula

Bronchiectasis

Extrinsic airway obstruction by tuberculous lymph nodes

Endobronchial tuberculosis and bronchostenosis

Middle lobe syndrome

Aspergilloma

B. Failure of Medical Therapy
Progressive disease, lung destruction and left bronchus syndrome
Drug resistance
C. Pleural Tuberculosis
Undiagnosed pleural effusion
Empyema
Bronchopleural fistula
D. Surgery for Diagnosis
Pulmonary lesions of unknown cause
Mediastinal adenopathy of unknown cause
E. Miscellaneous
Cold Abscess and Osteomyelitis of the Chest Wall
Consequences of insufficient surgery
Thoracoplasty
Delayed complications of plombage

Although Tuberculosis (TB) is essentially a medical disease, a sizeable proportion of patients fall in the realm of surgery, may it be due to the primary disease or its sequelae

A multi-disciplinary approach should be adopted when surgery is contemplated. The considered opinion of pulmonologists, radiologists, surgeons, anesthesiologists and other identified specialists is taken into account.
Surgery is always considered as an adjunct to proper medical therapy. A diagnostic surgical approach is recommended when pleural effusion occurs without any radiologic signs or established cause. VATS or mediastinoscopy with ex tempore histological examination may be helpful to distinguish between malignant and TB lesions. With proper indications for surgery, sputum conversion rates of more than 90% can be obtained. In established cases of TB, patients are operated on with proper antibiotic coverage of at least 3 months' duration, and surgeries are always followed by complete courses of therapy, the lengths of which are dictated by the resistance of the organisms and the susceptibilities of the hosts. One of the main indications for surgery is massive hemoptysis along with known destructive pulmonary sequelae such as destroyed lung. It may occur due to infection, cavity, aspergilloma or bronchiectasis. Surgery is also recommended for cases with major residual pleural thickenings. The role of surgery is to remove the burden of mycobacteria in actively infected patients or to treat debilitating consequences caused by the ongoing scarring process that characterizes the healing of TB. It is indeed very difficult to sterilize cavities or destroyed lungs, probably because the disease is too far advanced or medications are unable to penetrate the lesions. Surgery would also benefit patients who have extreme patterns of drug resistance who are left with residual cavities and destroyed lung despite maximum medical treatment. These lesions pose a risk of relapse which are difficult to manage. Excision of such localized pathology can significantly improve the chances of cure in this group.

There is also a higher percentage of non-conversion with lobectomy and segmentectomy compared to pneumonectomy, suggesting that a more radical procedure may be more effective than a smaller resection.

However maximal parenchymal sparing should be exercised in cases of MDRTB due to the possibility of relapse. The mortality rate after lobectomy is about 2–3%, after pneumonectomy is 7-8% and surgery for empyema has complications of about 8–11%. The post-operative complications of surgeries is 9–26%, the commonest being persistent air leakage (40%).

THORACOTOMY, VATS AND RATS

Video-assisted thoracoscopic surgery (VATS) was first reported in 1992. Thoracoscopy has an amplifying action and a deep illumination effect. Further, in addition to the advantage of cosmetic appearance, pain is minimal as there is little injury to the ribs, muscles and sub-cutaneous tissues. VATS therapeutic resection could be safely performed in selected patients with medically failed pulmonary TB as an effective adjunct with satisfactory results. Similarly, Robotic Assisted Thoracoscopic Surgery (RATS) may be employed. However, there is no clear conclusion whether RATS can achieve an equal or even better surgical effect when compared with VATS. Further a recent paper stated that in the setting of a comprehensive enhanced recovery protocol, patients undergoing VATS versus open lobectomy exhibited similar short-term outcomes. Incompleteness of interlobar fissures and solid pleural symphysis and dense fibro-vascular adhesions, common in tuberculous destroyed lung, are among “technical contraindications” for thoracoscopy.

However there is no role for VATS or RATS in the emergency setting of massive hemoptysis; instead, a full posterolateral thoracotomy is to be performed. Most of the available literature is from North America and Europe where the incidence of TB is low in comparison to the developing countries. India has the dubious distinction of having the largest estimated number of MDR-TB cases in the world, responsible for around 20% of the global burden. In our series of over 1,000 patients during the past 25 years, the most common indications for Surgery in TB were the sequelae - Bronchiectasis, Aspergilloma, Empyema, Bronchopleural fistula and Destroyed lung. Emerging indications are resection of localized lesions in patients with persistent sputum AFB positive and MDRTB. A significant number of patients belonged to ASA Class IV. Outcomes were on par with existing literature.

Successful treatment of TB depends on prompt diagnosis and proper medical therapy. Sequelae of TB forms the major chunk of patients requiring surgery. The increase in the number of new TB cases and the number of patients with MDRTB are the present challenges for medical providers. When patients fail medical therapy or are at high risk to do so, surgery remains a very effective tool in the management of this difficult problem. Relevant indications, appropriate timing of referrals and proper selection of patients are crucial to the final outcome.

The role of surgery in the treatment of TB is unquestionable.

Artificial Intelligence in TB Control

Dr. V. K Arora, Dr. Sanjay Rajpal, Dr. Kamal Kishore Chopra and Dr. Ankita Anand

Traditional tuberculosis (TB) diagnostic methods face challenges due to time and resource constraints, especially in regions with prevalent TB and underdeveloped healthcare systems. Culture-based diagnosis, once the gold standard, is time-consuming. Rapid molecular tests like GeneXpert and Truenat, which detect Mycobacterium tuberculosis DNA and rifampicin resistance, are underutilized globally, with only 33% used for initial diagnostics in 2022. With advancing technology, there's increased interest in AI, particularly in image recognition, to complement current diagnostic methods. AI systems, capable of mimicking human intelligence, offer improved accessibility, cost-effectiveness, and sensitivity in diagnostics.

Efforts in TB treatment have surged, focusing on precision medicine, AI-supported early diagnosis, and patient care optimization. An estimated 23% of the global population has latent TB infection (LTBI), with higher numbers in India. Identifying who to test is tough due to absent symptoms, but AI can forecast LTBI progression to active TB, enhancing early intervention. AI can also accelerate TB diagnoses by quickly analyzing chest X-rays, as demonstrated by the qXR software, which identifies lung abnormalities swiftly. However, AI-assisted X-ray reading has limitations in differential diagnosis.

Medication adherence in TB treatment is vital, and AI can enhance electronic monitors and VDOT systems by recognizing patterns and gestures reliably, aiding remote treatment observation.

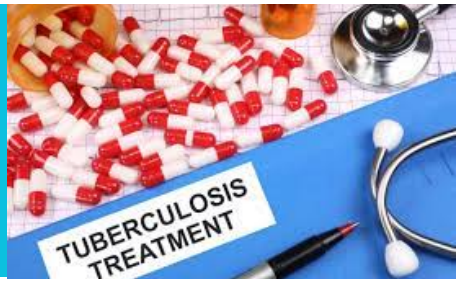

Image Credit: Pix4free

AI ventures further with hypotheses like distinct TB cough sounds, leading to innovations like "Swaasa," a mobile platform recording cough sounds for rapid TB detection. Yet, large cohort studies are needed before universal application. AI-enabled diagnostics, like reading Line Probe Assay strips for drug-resistant TB, show promise but require widespread test availability.

Medication adherence in TB treatment is vital, and AI can enhance electronic monitors and VDOT systems by recognizing patterns and gestures reliably, aiding remote treatment observation. Drones, integrated with AI, improve healthcare access by transporting samples and information efficiently, particularly in rural areas. Studies show significant time savings in urban and rural models using drones, as evidenced in Ghana, where AI-enhanced drones supported healthcare supply chains.

AI's future in healthcare, notably with Generative-AI, promises real-time clinical decision support and personalized patient interaction. It holds great potential in enhancing TB prevention, diagnosis, treatment, and eradication, by improving the accuracy of diagnostic tests, assisting in drug discovery, optimizing treatment, and enhancing public awareness.

However, integrating AI into healthcare requires careful consideration of data privacy, equity, and implementation barriers. An ethical and regulatory framework is necessary to ensure AI benefits all TB-affected communities. Collaboration among stakeholders is crucial to overcome these challenges, leveraging AI's potential for early diagnosis, effective treatment, and ultimately, TB eradication.

MDR TB: New Drugs, Research and Policy

Dr. V.K. Arora et al.

Managing multidrug-resistant tuberculosis (MDR TB) is increasingly challenging, despite rapid advancements in diagnostic tools and treatment options. As of 2021, there were approximately 410,000 MDR/RR-TB cases globally, with India accounting for a significant 26% of these cases in 2022. While the global treatment success rate for drug-resistant TB has improved to 63%, several barriers persist.

Timely and accurate diagnosis is crucial, yet the private healthcare sector often lacks awareness and access to the latest rapid molecular tests. A stronger focus on preventing drug resistance is needed, including policies emphasizing drug adherence and newer regimens for drug-sensitive cases to curb resistance emergence. The traditional treatment for MDR/RR-TB involves a lengthy 20–24 months duration, burdened by toxicity and cost concerns. However, the introduction of bedaquiline and delamanid has led the WHO to endorse an oral regimen of 9–10 months, giving hope for improved treatment outcomes.

India's guidelines, updated in 2021, align with WHO's recommendations, offering two regimens: a shorter bedaquiline-based regimen (9 months) and a longer 18-month regimen for those ineligible for the shorter course. Although these have shown up to 80% success in trials, real-world outcomes are around 60-65%, highlighting issues like treatment adherence and resource availability. Rising fluoroquinolone resistance, observed in regions like Delhi, further complicates eligibility for these regimens.

Recent clinical trials, such as TB-PRACTECAL, ZeNix, and NeXT, are exploring shorter and more effective regimens, including the promising BPaLM (bedaquiline, pretomanid, linezolid, and moxifloxacin) regimen. The WHO recommended this 6-month regimen in 2022, showing an 89% success rate. However, its adoption has been slow in India and other countries due to logistical and regulatory challenges.

Rapid adoption of these new treatments is crucial, requiring streamlined regulatory processes and evidence generation by healthcare bodies. With potential new drugs in development, focus should also shift to trying preventive treatments for drug-resistant TB contacts, leveraging novel drug combinations due to existing fluoroquinolone resistance. Additionally, accelerating the development of a TB vaccine remains a vital strategy.

To effectively manage MDR TB, accessible drug sensitivity testing, proper referral to specialized centers, updated national guidelines based on evidence, and availability of new treatments are essential steps. Addressing these factors can significantly enhance MDR TB management.

Tuberculosis workshop done in79th NATCON under Aegis of TAI 18th October 2024 Jaipur