Ministry of Health & Family Welfare
Government of India

World Health Organization
India

Training Module On

Extrapulmonary Tuberculosis 2023

डॉ. मनसुख मांडविया
DR. MANSUKH MANDAVIYA

सत्यमेव जयते
आज़ादी का अमृत महोत्सव

मंत्री
स्वास्थ्य एवं परिवार कल्याण
व रसायन एवं उर्वरक
भारत सरकार
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Health & Family Welfare
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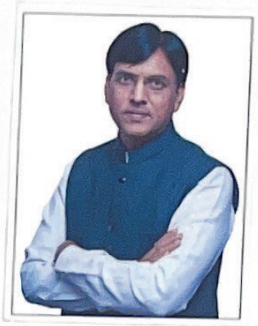
Government of India



FOREWORD

United Nations Sustainable Development Goals (SDGs) envisioned the ambitious goal of 'End TB by 2030' by suggesting an integrated patient-centered care and prevention strategy. Tuberculosis continues to present a critical challenge to society, considering its high incidence and mortality. The disease severely impacts the lives of those affected and the people surrounding them, like family, friends, and community. The considerable physical and mental health implications of tuberculosis also lead to a heavy economic burden on the individual and the nation. With the common global goal for TB elimination, India is committed to achieving the targets by streamlining the efforts towards the 2025 deadline of Pradhan Mantri TB Mukt Bharat Abhiyaan, flagged off by the Honourable President of India, Smt. Draupadi Murmu ji.

The multi-stakeholder collaboration between the Government, Private sector, Public Health workers, Caregivers, and Frontline Healthcare workers, among many others, makes it possible for services to reach the last mile. The National Tuberculosis Elimination Program (NTEP), with its continuous efforts, has been able to introduce and develop newer diagnostic tools, provide access to nutrition, decentralize access to care through Health and Wellness Centers (HWCs), look after the multitudes of population, including the most vulnerable and marginalized. Where data reporting and vigilance on the Ni-kshay portal have made the process of making concentrated plans more efficient, the Nikshay Poshan Yojana has achieved success in protecting the nutritional requirements of the patients by direct benefit transfers. Efforts like Ni-kshay Mitra have not only augmented the capacities of care by expanding the horizons of sponsorship, to include individuals and corporates alike but also have implicitly aimed at reducing the stigma attached to the illness.

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कार्यालय: 348, ए-स्कंध, निर्माण भवन, नई दिल्ली - 110011 • **Office:** 348, A-Wing, Nirman Bhawan, New Delhi - 110011
Tele.: (O): +91-11-23061661, 23063513 • **Telefax** : 23062358 • E-mail : india-hfm@gov.in

Working towards tuberculosis has also presented numerous challenges, like addressing multi-drug resistance, and latent and Extrapulmonary Tuberculosis (EPTB), which are difficult to diagnose and treat but require adequate and equal attention. India has prioritized the fight against TB as a Jan Andolan to ensure that a "whole of Government" approach is incorporated. The Ministry's flagship "Inter-Ministerial Task Force" program aims at better outreach, TB-free workplaces, and also addressing the socio-economic determinants of TB. The program has also prioritized innovation and diagnostics in the space of treatment and care, with the building of AI tools, vaccination trials, and newer diagnostic methods.

I believe that the launch of this strategy at this critical juncture, will allow the inclusion of those left behind and push the country forward to achieve the goals set forth by Honourable Prime Minister, Shri Narendra Modi ji. As a pillar of the national strategy of NTEP, "early diagnosis" paves the way for India's active response against EPTB as a covert barrier to TB elimination. Since this is one of the way for mitigating the excess burden and preventing the aggravation of TB cases, expanding access--and ensuring that no one is left behind--becomes the overarching strategy of battling with EPTB. The training manual on EPTB offer a standardized solution for capacity building and proper management of EPTB.

TB Harega, Desh Jeetega!

(Dr. Mansukh Mandaviya)

राजेश भूषण, आईएएस
सचिव
RAJESH BHUSHAN, IAS
SECRETARY

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण विभाग
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
Government of India
Department of Health and Family Welfare
Ministry of Health and Family Welfare

FOREWORD

The 'Mycobacterium Tuberculosis' bacteria affects millions of individuals yearly, and is considered one of the oldest diseases in the world. The burden of this disease is disproportionately high in low-and-middle-income Countries, and in India. To address this problem, India's Hon'ble Prime Minister gave a clarion call for a 'TB-Mukt Bharat' by 2025, five years ahead of the Sustainable Development Goals. There have been intensive efforts from the ministries, technical experts, multiple civil society and other organizations to realize this vision, and these have started showing results despite the difficulties and challenges posed by the COVID-19 pandemic.

To address the burden of tuberculosis, challenges at the diagnosis and treatment level must be addressed. Extra-Pulmonary TB (EPTB) accounts for around 40-50 percent burden in HIV-positive cases and affects immunocompromised individuals and also has a 15-20 percent burden among HIV-negative cases and is difficult to diagnose.

The non-clinical manifestation and lacunae in research lead to limited options for non-invasive testing in cases of EPTB. The delay in diagnosis often leads to intensification of the health issue, and inefficiency in the delivery of treatment services.

As we move towards a community-based approach, it is also essential to uphold a people-centered approach focused on early diagnosis and treatment to address the issue of EPTB. The detection for EPTB should improve across all health systems, especially in rural areas. There should also be focus on building awareness using evidence-based information to promote prompt diagnosis at all levels of healthcare systems to ensure that proper treatment is provided.

India is uniquely placed to address this challenge at a war footing. With the cadres of health workers and the public coming together in a Jan Andolan, we will work to achieve the goal set by our Hon'ble Prime Minister Shri Narendra Modi, to ensure equal attention to addressing the challenge of EPTB and make India TB free.

TB Harega Desh Jeetega!

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Date : 14-03-2023

(Rajesh Bhushan)

Room No. 156, A-Wing, Nirman Bhawan, New Delhi-110 011
Tele : (O) 011-23061863, 23063221, Fax : 011-23061252, E-mail : secyhfw@nic.in

भारत सरकार
स्वास्थ्य एवं परिवार कल्याण मंत्रालय
निर्माण भवन, नई दिल्ली - 110011
Government of India
Ministry of Health & Family Welfare
Nirman Bhavan, New Delhi - 110011

रोली सिंह, भा.प्र.से.
Roli Singh, I.A.S.
अपर सचिव एवं मिशन निदेशक (रा.स्वा.मि.)
Additional Secretary & Mission Director (NHM)

FOREWORD

United Nations (UN) has established the Sustainable Development Goals - with a renewed focus on ending poverty, ensuring prosperity for all, by 2030. Sustainable Development Goal 3 seeks to ensure good health and well-being for all with one of the primary targets being the eradication of TB by 2030. In pursuance of call for TB eliminationby Honourable Prime Minister Shri Narendra Modi, Ministry of Health and Family Welfare has left no stone unturned to achieve elimination by 2025- five years ahead of the global targets.

The disease of TB, in spite of its continued presence over thousands of years, presents challenges that require focused research and innovation. In its attempt to address high burden of TB, India has achieved breakthroughs with the introduction of newer diagnostic methods, shorter treatment regimens, and an extensive continuum of care.

Health is essential for welfare and achieving equity. We should continue to evolve the health care system to ensure services are available for all- door to door. The health infrastructure growing rapidly, and effectively using the public private model approach- is also an approach used extremely effectively to address the challenge of TB in India.

It is critical to understand how the social consequences of the disease severely differ and are determined based on an individual's socioeconomic situation. Keeping this in mind, the detection of TB often focuses on at-risk populations like people with HIV, people with diabetes, injection drug users, among others. The usual diagnostic methods allow testing a wide-ranging population. However, certain forms, like extra-pulmonary tuberculosis (EPTB), which involves organs other than the lungs, might evade clinical testing methods.

As we prepare to eliminate TB from India- an acute focus needs to be placed on addressing the challenge of EPTB- using a multi-sectoral approach to ensure timely diagnosis and treatment to all patients tested with EPTB; and also protect everyone with equipping them with knowledge and awareness. I strongly believe we can address these challenges- just the way we have responded to other health crisis in our times. I wish the program and all partners the very best as we implement strategies for this shift.

TB Harega Desh Jeetega

Roli Singh

(Roli Singh)

Tele : 011-2306 3693, Telefax : 011-2306 3687, E-mail : asmd-mohfw@nic.in

Department of Medicine
All India Institute of Medical Sciences
New Delhi - 110029
naveetwig@gmail.com
Office. No.011-2659-3303

Dr. Naveet Wig
Professor & Head

Tuberculosis (TB) has been a worldwide health problem since time immemorial and continues to be among the top ten causes of mortality, particularly in India which houses the world's highest TB burden. Efforts to curb the scourge of TB have been colossal under the strong leadership of our honorable Prime Minister who recently raised a clarion call to eliminate TB by 2025, five years ahead of the corresponding sustainable development goal. The National TB Elimination Programme (earlier known as the Revised National TB Control Programme) has been strengthened, The National Strategic Plan for Tuberculosis Elimination 2017-2025 is in effect and additional support is being provided to patients under the Pradhan Mantri TB Mukt Bharat Abhiyaan.

As opposed to pulmonary TB where effective strategies for diagnosis and treatment are readily available because of the ease of obtaining samples for diagnosis, extrapulmonary TB (EPTB), which accounts for 15-25% of all cases, remains a diagnostic and therapeutic challenge. Heterogeneous clinical presentations, difficulty in getting samples for establishing diagnosis, reduced drug efficacy because of poor penetration into certain tissues, difficulty in treatment response monitoring, and unclear duration of treatment are some of the factors which make EPTB management challenging. Each case of EPTB needs to be assessed holistically and a multidisciplinary, evidence-based, personalized approach is required to improve patient outcomes. Being a great masquerader that can involve almost any organ in the human body, EPTB can present first to any specialty. It is thus imperative for clinicians at all levels, irrespective of their specialty or level of training, to be trained in EPTB so that these cases can be picked up early and treated optimally. This EPTB training module represents a crucial step forward in this direction.

The Department of Medicine at AIIMS (New Delhi), which is a WHO collaborating centre and National Centre for Excellence in Extrapulmonary TB, has always been at the forefront in the country's battle against TB with publication of the first guidelines for EPTB in 2016 (the INDEX TB guidelines) which were instrumental in improving practices and standardizing care for EPTB patients in India and South East Asia. This EPTB training module, spearheaded by the Department of Medicine, AIIMS (New Delhi), represents the collective intelligence, shared vision and teamwork of experts across all specialties including medicine, infectious diseases, gastroenterology, pulmonology, cardiology, neurology, gynecology, surgery, orthopedics, neurosurgery, urology, ophthalmology, otorhinolaryngology, dermatology, radiology, microbiology, pathology and experts from central TB division and WHO country office. It is a culmination of tremendous effort that has been made over the last three years to review existing literature and synthesize it into a lucid document that can be readily used by clinicians to make informed management decisions regarding EPTB and facilitate uniformity in their practice. This module will also address important questions for primary care physicians including when to suspect EPTB, what basic investigations to order at the grassroots level and when to refer these patients to a higher centre.

We understand that the science of diagnosing and treating EPTB is constantly evolving. We thus plan to update our practice points in future editions of the module, as more robust evidence accrues and our understanding of this complex disease improves.

Finally, we hope this module will provide a much-needed push in the nation's renewed endeavor to end TB by 2025.

Dr. Naveet Wig

Dr. Rajendra P. Joshi
Deputy Director General
Central TB Division

भारत सरकार
GOVERNMENT OF INDIA
स्वास्थ्य और परिवार कल्याण मंत्रालय
MINISTRY OF HEALTH & FAMILY WELFARE
ROOM NO. G2 (GROUND FLOOR),
JEEVAN VIHAR BUILDING, 3, SANSAD MARG,
CONNAUGHT PLACE
NEW DELHI - 110011
ddgtb@rntcp.org
ddgtb-mohfw@gov.in
011-21400941

Owing to TB elimination being declared a national priority, the Revised National TB Control Program (RNTCP) has devised a National Strategic Plan (NSP) for the period 2017-2025. Under this, “Detection”, “Treatment”, “Prevention”, and “Building” have become the four pillars of the program for managing TB in India. With special emphasis on providing care to high-risk populations -- like HIV-positive populations or prisoners -- and also drug-resistant cases, the current NSP has been scoped out to be a promising endeavour. A strong system for notification, with checks at multiple levels, expands the reach of the program, with patients’ families and communities also being included in the ambit. The Ni-kshay portal has acted as a pioneer in tracking, and the free provision of diagnostic tests and drugs has shown an uptick in demand for accessing TB facilities.

Extrapulmonary TB (EPTB), which composes more than 20% of the TB burden in India, has continued to affect communities across India. Since it affects areas other than the lungs, contactless and/or convenient methods like sputum microscopy and chest x-rays fail to diagnose it, and as a result, it requires a more complex, invasive set of processes to confirm the infection. This significantly pronounces the index of suspicion. While the EPTB due to Mycobacterium Tuberculosis (MTB) is treatable by the general anti-TB drugs, the drug-resistant variant requires very specific profiling of the treatment course for each patient. The innate delays caused during the diagnosis aggravate the problem.

The National Tuberculosis Elimination Program (NTEP) is committed to invest in the awareness and delivery of services related to EPTB and ensuring that quality healthcare access is governed centrally. To enable this, the present document compiles evidence-based information related to EPTB and the standardized procedures followed from screening to the last leg of treatment for healthcare providers and medical staff across all verticals. Together, we aim to realize the vision of a TB-free India, by expanding the scope of the program beyond pulmonary TB by releasing these guidelines and efficiently utilizing the current state of infrastructure for EPTB.

TB Harega, Desh Jeetega.

(Dr. Rajendra P. Joshi)

Dr. Sanjay Kumar
MD (Public Health): DTCD
Adl Deputy Director General (ADDG)
NTEP, Central TB Division

भारत सरकार
Government of India
स्वास्थ्य और परिवार कल्याण मंत्रालय
Ministry of Health & Family Welfare
स्वास्थ्य सेवा महानिदेशालय
Dte. General of Health Services
निर्माण भवन, नई दिल्ली - 110011
Nirman Bhawan, New Delhi - 110011

Foreward

Tuberculosis has been a major obstacle to India's human and economic development over the past few decades. Though TB continues to be a leading cause of death with associated challenges of poor social economic growth and marginalization, amongst other- it is the multisectoral approach strategy implemented by the National Tuberculosis Elimination Program – that has resulted is India addressing this issue at a war footing. Taking everyone along.

Intersectoral engagement is a priority of the Government- as the program acutely understand that we need a multisectoral approach to eliminate TB by 2025. Some great and impactful achievements have been undertaken- with the Jan Andolan approach being implemented nationwide, social protection policies being introduced and delivered and innovative schemes like Direct benefit Transfer (DBT) reaching millions- under the leadership of Ministry of Health and Family Welfare and NTEP. The Nikshay Information System has allowed us to increase notification, monitor treatment adherence and ensure smooth transfer of cases between providers.

However, with successes we continue to work to address challenges. One such challenge is Extra Pulmonary TB (EPTB)- and we as a program are working to ensure we find solutions for this. It is absolutely critical that our strategies assist us in identifying, diagnosing, notifying and treating patients with extrapulmonary TB on an urgent basis- to ensure no hindrance in reaching the TB elimination by 2025.

Extra pulmonary TB is even more challenging for individuals with high morbidity and often occurs in both immunocompetent and immunocompromised patients. It is crucial that we reach the ones most at risk and this is why the NTEP looks at an equal investment of time for ensuring timely diagnosis and treatment for pulmonary and extra pulmonary TB.

There is new evidence and we have joined forces to address EPTB to ensure we not only meet targets but also save lives. Community and provider engagement both are critical pillars. Through our campaigns like TB Harega Desh Jeetega and Polio Eradication- India has proven its ability to address challenges of great magnitude. As we proceed further for a TB free India, the concerns of doctors and communities towards awareness generation and EPTB redressal are being addressed.

The Training module on Extra Pulmonary TB will support capacity building & boost the strategy to resolve the challenges in managing EPTB. I wish this strategy the very best and under the leadership of NTEP, team we will address this urgent challenge of EPTB.

Tel : 011-21401716, E-mail : mattoos@rntcp.org, sanjayk.mattoo@gov.in, sanjaykmattoo@gmail.com

Acknowledgements

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Several meetings were organized physically and virtually over the latter part of 2019 till 2022 by the Central TB Division (CTD), Ministry of Health and Family Welfare (MoHFW), GoI, with technical and organizational support from AIIMS Delhi, ICMR and WHO. The meetings involved discussions with several stakeholders. An extensive review of literature was undertaken, aligning with current and emerging evidence to address the prevailing epidemiology of extrapulmonary TB and the clinical updates, diagnostic tools, programmatic management, and care for children with TB, Index TB guideline, standard treatment workflow for management of EPTB, WHO Global TB report and their operational handbooks; and the National Strategic Plan for ending TB in India (2017–25) which in turn is aligned with the WHO End TB Strategy.

The Concept for the EPTB Module was initiated by Dr. Naveet Wig (Professor and Head, Department of Medicine AIIMS, New Delhi) and was supported by Ex DDG-TB Dr K.S. Sachdeva and ADG-TB, Dr Raghuram Rao along with members of Central TB Division, Ministry of Health and Family Welfare, Government of India. The EPTB Module Development Group (MDG) gratefully acknowledges the Subject Experts of different organ system groups (mentioned in list of contributors), under whose leadership this historical document could be prepared.
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List Of Contributors

Writing Team

Dr Naveet Wig	Professor & Head, Department of Medicine, AIIMS, New Delhi
Dr Ankesh Gupta	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Anivita Agrawal	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Ankit Mittal	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Manish Soneja	Additional Professor, Department of Medicine, AIIMS, New Delhi
Dr Neeraj Nischal	Additional Professor, Department of Medicine, AIIMS, New Delhi
Dr Pankaj Jorwal	Additional Professor, Department of Medicine, AIIMS, New Delhi
Dr Parul Kodan Ex	Assistant Professor, Department of Medicine, AIIMS, New Delhi
Dr Swati Gupta	Associate Professor, Department of Radiodiagnosis, MAMC New Delhi

Lymph Node TB Group

Dr Naveet Wig	Professor & Head, Department of Medicine, AIIMS, New Delhi
Dr Manish Soneja	Professor, Department of Medicine, AIIMS, New Delhi
Dr Anivita Aggrawal	Ex Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Ankesh Gupta	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Ayush Agrawal	Junior Resident, Department of Medicine, AIIMS, New Delhi
Dr Deepali Jain	Additional Professor, Department of Pathology, AIIMS, New Delhi
Dr Komal Singh	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Neeraj Nischal	Additional Professor, Department of Medicine, AIIMS, New Delhi
Dr Pankaj Jorwal	Additional Professor, Department of Medicine, AIIMS, New Delhi
Dr Pawan Goel	Ex Junior Resident, Department of Medicine, AIIMS, New Delhi
Dr S Anuradha	Professor, Department of Medicine, Maulana Azad Medical College, New Delhi

Pleural TB

Dr Anchal Kakkar	Associate Professor, Department of Pathology, AIIMS, New Delhi
Dr Animesh Ray	Associate Professor, Department of Medicine, AIIMS, New Delhi
Dr Ankesh Gupta	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Anuj Bhatnagar	Department of Pulmonology, RBTB, New Delhi
Dr Bharathi Arunan	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Gaurav Gupta	Assistant Professor, Department of Medicine, AIIMS, New Delhi
Dr Karan Madan	Additional Professor, Department of Pulmonary Medicine and Sleep disorder, AIIMS, New Delhi
Dr Nitesh Gupta	Assistant Professor, Pulmonary Medicine, VMMC Safdarjung
Dr Pranav Is	Assistant Professor, Pulmonary Medicine, VMMC Safdarjung
Dr Prerna Garg	Senior Resident, Department of Cardiology, AIIMS, New Delhi
Dr Rupak Singla	Head, Department of Pulmonology, NITRD, New Delhi
Dr Sanchit Kumar	Ex Senior Resident, Department of Medicine, AIIMS, New Delhi

Dr Sanjeev Sinha	Professor, Department of Medicine, AIIMS, New Delhi
Dr Shubham Sahni	Junior Resident, Department of Medicine, AIIMS, New Delhi
Dr Ved Prakash Meena	Assistant Professor, Department of Medicine, AIIMS, New Delhi
Dr Visakh C Keri	Ex Senior Resident, Department of Medicine, AIIMS, New Delhi

Pericardial TB

Dr Amandeep Singh	Assistant Professor, Department of Medicine, AIIMS, New Delhi
Dr Anunay Gupta	Associate Professor, Department of Cardiology, VMMC Safdarjung
Dr Binay Kumar	Consultant Cardiology, QRG Hospital, New Delhi
Dr Deepti Siddharthan	Assistant Professor, Department of Cardiology, AIIMS, New Delhi
Dr G Karthikeyan	Professor, Cardiology, AIIMS, New Delhi
Dr Kirtana Jonnalagadda	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Naval K Vikram	Professor, Department of Medicine, AIIMS, New Delhi
Dr Radhika Sarda	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Rohit Goel	Consultant, Fortis Hospital, Gurugram, Haryana
Dr Sandeep Seth	Professor, Cardiology, AIIMS, New Delhi
Dr Vivek Chaturvedi	Senior Consultant, Narayana Hrudayalaya Gurugram, Haryana

Central Nervous System TB Group

Dr Manish Soneja	Professor, Department of Medicine, AIIMS, New Delhi
Dr Ajay Garg	Professor, Department of Neuroradiology, AIIMS, New Delhi
Dr Aranya Kumar Das	Junior Resident, Department of Medicine, AIIMS, New Delhi
Dr Bhavesh Mohan Lal	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Debashish Chowdhury	Professor, Department of Neurology, MAMC, New Delhi
Dr Deepti Vibha	Associate Professor, Department of Neurology, AIIMS, New Delhi
Dr Himanshu Narang	Senior Resident, Department of Gastroenterology and Human Nutrition, AIIMS, New Delhi
Dr Karthik Kumar	Junior Resident, Department of Medicine, AIIMS, New Delhi
Dr M V Padma	Professor, Department of Neurology, AIIMS, New Delhi
Dr Manjari Tripathi	Professor, Department of Neurology, AIIMS, New Delhi
Dr Manoj Phalak	Associate Professor, Department of Neurosurgery, AIIMS, New Delhi
Dr Neera Chaudhary	Professor, Department of Neurology, VMMC Safdarjung
Dr Radhika Sarda	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Rohit Bhatia	Professor, Department of Neurology, AIIMS, New Delhi
Dr Rohit Garg	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Vinay Goyal	Ex Professor, Department of Neurology, AIIMS, New Delhi
Dr Vinod Puri	Senior consultant, MAX Hospital Saket, New Delhi

Gastrointestinal TB Group

Dr Aishwarya Ramprasad	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Govind K Makharia*	Professor, Department of Gastroenterology and Human Nutrition, AIIMS
Dr Mohit Chowdhury	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Parth Durgia	Junior Resident, Department of Medicine, AIIMS, New Delhi
Dr Piyush Ranjan	Additional Professor, Department of Medicine, AIIMS, New Delhi
Dr Praveen Trilangi	Senior Resident, Department of Medicine, AIIMS, New Delhi

Dr Prayas Sethi*	Assistant Professor, Department of Medicine, AIIMS, New Delhi
Dr Saurabh Kedia	Associate Professor, Department of Gastroenterology and Human Nutrition, AIIMS, New Delhi
Dr Souradeep Chowdhury	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Shubham Aggarwal	Senior Resident, Department of Pulmonary Medicine and Sleep disorder, AIIMS, New Delhi
Dr Vineet Ahuja*	Professor, Department of Gastroenterology and Human Nutrition, AIIMS, New Delhi
Dr Vishal Sharma	Associate Professor, Department of Gastroenterology, PGI Chandigarh

Bone and Joint TB Group

Dr Alok Thakkar	Professor & Head, Department of Otorhinolaryngology and Head and Neck Surgery, AIIMS, New Delhi
Dr Arvind Kairo	Associate Professor, Department of Otorhinolaryngology and Head and Neck Surgery, AIIMS, New Delhi
Dr Akansha Didwania	Junior Resident, Department of Medicine, AIIMS, New Delhi
Dr Anil Jain	Director Professor and Head, Orthopaedics, University College of Medical Sciences, New Delhi
Dr Ashutosh Biswas	Executive Director, AIIMS, Bhubaneshwar
Dr Bhawuk Garg	Additional Professor, Orthopaedics, AIIMS, New Delhi
Dr Harshith B Kudnur	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Kunal Sharma	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Neeren Ravela	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Praful Pandey	Senior Resident, Department of Medicle Oncology, AIIMS, New Delhi
Dr Rajesh Malhotra	Professor, Department of Orthopaedics, AIIMS, New Delhi
Dr S S Kale	Professor & Head, Department of Neurosurgery, AIIMS, New Delhi
Dr Soumendra Nath Haldar	Ex Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Sumit Sural	Professor, Department of Orthopaedics, Maulana Azad Medical College, New Delhi
Dr Tariq Maula	Junior Resident, Department of Medicine, AIIMS, New Delhi
Dr Umang Arora	Senior Resident, Department of Gastroentrology, AIIMS, New Delhi

Skin TB Group

Dr Kartik Vedula	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr M Ramam	Professor, Dermatology & Venerology, AIIMS, New Delhi
Dr Neetu Bhari	Associate Professor, Dermatology and Venerology, AIIMS, New Delhi
Dr Radhika Sarda	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Saurav Shekar Paul	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Shivdas Naik	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Upender Baitha*	Associate Professor, Department of Medicine, AIIMS, New Delhi
Dr V Ramesh	Ex- Professor, Department of Dermatology and STD, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi

ENT TB Group

Dr Alok Thakkar	Professor, Department of Otorhinolaryngology and Head and Neck Surgery, AIIMS, New Delhi
Dr Arvind Kairo	Associate Professor, Department of Otorhinolaryngology and Head and Neck

	Surgery, AIIMS, New Delhi
Dr Devashish Desai	Ex Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Kapil Sikka	Additional Professor, Department of Otorhinolaryngology and Head and Neck Surgery, AIIMS, New Delhi
Dr Megha Priyadarshi	Junior Resident, Department of Medicine, AIIMS, New Delhi
Dr Ranveer Singh Jadon	Associate Professor, Department of Medicine, AIIMS, New Delhi

Ocular TB Group

Dr Adarsh Aayilliath K	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Amit Khosla	Consultant Ophthalmology, Sir Gangaram Hospital, New Delhi
Dr Muhammad Tabish	Senior Resident, Department of Gastroenterology and Human Nutrition, AIIMS, New Delhi
Dr Pradeep Venkatesh	Professor, RP Centre for Ophthalmic Sciences, AIIMS, New Delhi
Dr Rohan Chawla	Additional Professor, RP Centre for Ophthalmic Sciences, AIIMS, New Delhi
Dr Sameer Abdul Samad	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Saurav Das	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Swasthi S Kumar	Ex Junior Resident, Department of Medicine, AIIMS, New Delhi
Dr Vinod Agarwal	Additional Professor, RP Centre for Ophthalmic Sciences, AIIMS, New Delhi

Urogenital TB Group

Dr Ankit Mittal	Ex Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Arvind Kumar	Additional Professor, Department of Medicine, AIIMS, New Delhi
Dr Ashwin Varadarajan	Junior Resident, Department of Medicine, AIIMS, New Delhi
Dr Chandan Das	Additional Professor, Department of Radiodiagnosis, AIIMS, New Delhi
Dr J B Sharma	Professor, Obstetrics & Gynaecology, AIIMS, New Delhi
Dr Neha Chopra	Senior Resident, Department of Cardiology, AIIMS, New Delhi
Dr Nikhil Vasudeva	Junior Resident, Department of Medicine, AIIMS, New Delhi
Dr Niranjan Mahishi	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Prabhjot Singh	Additional Professor, Urology, AIIMS, New Delhi
Dr Rishi Nayyar	Associate Professor, Urology, AIIMS, New Delhi
Dr Swati Gupta	Associate Professor, Department of Radiodiagnosis, MAMC, New Delhi
Dr Vidushi Kulshrestha	Associate Professor, Obstetrics & Gynaecology, AIIMS, New Delhi

Surgery TB Group

Dr Anita Dhar*	Professor, Surgery, AIIMS, New Delhi
Dr Mohit Joshi	Additional Professor, Surgery, AIIMS, New Delhi
Dr Sandeep Mathur	Professor, Department of Pathology, AIIMS, New Delhi

Microbiology Support Group/Diagnostic TB group

Dr Akashneel	Ex Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Amit Sehgal	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Ankesh Gupta	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Binit Kumar Singh	Consultant Microbiologist IRL (DSHM), Department of Medicine, AIIMS, New Delhi
Dr Ritu Singhal	Consultant Microbiology, NITRD, New Delhi

Dr Rohini Sharma	Consultant Microbiologist, The Union South-East Asia, New Delhi
Dr Charu Rajoria	Junior Resident, Department of Medicine, AIIMS, New Delhi

Radiodiagnosis and Nuclear Medicine Support Group

Dr Ankur Goyal	Associate Professor, Department of Radiodiagnosis, AIIMS, New Delhi
Dr Atin Kumar	Professor, Department of Radiodiagnosis, AIIMS, New Delhi
Dr Devasenatripathy K	Additional Professor, Department of Radiodiagnosis, AIIMS, New Delhi
Dr Madhvi Tripathi	Professor, Department of Nuclear Medicine, AIIMS, New Delhi
Dr Raju Sharma	Professor, Department of Radiodiagnosis, AIIMS, New Delhi
Dr Rakesh Kumar	Professor, Department of Nuclear Medicine, AIIMS, New Delhi
Dr Shivanand Gamanagati	Professor, Department of Radiodiagnosis, AIIMS, New Delhi
Dr Surabhi Vyas	Additional Professor, Department of Radiodiagnosis, AIIMS, New Delhi
Dr Swati Gupta	Associate Professor, Department of Radiodiagnosis, MAMC, New Delhi
Dr Smita Manchanda	Associate Professor, Department of Radiodiagnosis, AIIMS, New Delhi

Treatment and Follow-up TB group

Dr Animesh Ray	Associate Professor, Department of Medicine, AIIMS, New Delhi
Dr Baidnath Kumar Gupta	Junior Resident, Department of Medicine, AIIMS, New Delhi
Dr Bindu Prakash	Assistant Professor, Department of Medicine, AIIMS, New Delhi
Dr Imtiyaz Shareef	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Neeraj Nischal	Additional Professor, Department of Medicine, AIIMS, New Delhi
Dr Satish Swain	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Ankesh Gupta	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Anivita Agrawal	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Ankit Mittal	Senior Resident, Department of Medicine, AIIMS, New Delhi
Dr Manish Soneja	Additional Professor, Department of Medicine, AIIMS, New Delhi
Dr Naveet Wig	Professor, Department of Medicine, AIIMS, New Delhi
Dr Neeraj Nischal	Additional Professor, Department of Medicine, AIIMS, New Delhi
Dr Pankaj Jorwal	Additional Professor, Department of Medicine, AIIMS, New Delhi
Dr Parul Kodan	Ex Assistant Professor, Department of Medicine, AIIMS, New Delhi
Dr Swati Gupta	Associate Professor, Department of Radiodiagnosis, MAMC, New Delhi

Experts from Central TB Division (CTD)

Dr Rajendra P. Joshi	DDG (TB), CTD, The Ministry of Health and Family Welfare
Dr Sanjay Kumar Mattoo	ADDG (TB) CTD, The Ministry of Health and Family Welfare
Dr Alok Kumar Mathur	ADDG (TB) CTD, The Ministry of Health and Family Welfare
Dr Raghuram Rao	Asst.DG(TB), CTD, The Ministry of Health and Family Welfare
Dr Nishant Kumar	JD(TB), CTD, The Ministry of Health and Family Welfare
Dr Ravinder Kumar	Specialist (TB), CTD, The Ministry of Health and Family Welfare
Dr Pinky Singh	Technical Officer-TB & Comorbidity, CTD, The Ministry of Health and Family Welfare
Dr Pooja Tripathi	National Consultant,Pediatric TB and Gender, The Union
Dr Aman Gupta	National Consultant, TB comorbidities and AI, World Health Organization
Dr Dheeraj Tumu	National Consultant, Research, World Health Organization
Dr Vaibhav Shah	National Consultant, Nikshay & Digital Surveillance, World Health Organization
Dr Lalit Mehandru	National Consultant, TB & HIV Comorbidities, World Health Organization

Dr Lakshmi R	National Consultant TB Laboratories World Health Organization
Dr Sivavallinathan Arunachalam	National Consultant, Nikshay & Digital Surveillance, World Health Organization
Dr Sandeep Chauhan	National Consultant DR - TB, World Health Organization
Dr Hardik Solanki	National Consultant, TB Prevention, World Health Organization

Experts from World Health Organization - Country Office for India

Dr. Ranjani Ramachandran	National Professional Officer - TB & Labs, WHO Country Office for India
Dr. Malik Parmar	National Professional Officer – Drug Resistant and Latent TB, WHO Country Office for India
Dr. Kiran Rade	National Professional Officer (TB Epidemiology), WHO Country Office for India
Dr. Shibu Balakrishnan	National Professional Officer, PPM, WHO Country Office for India

Expert from National Technical working Group

Dr. Rohit Sarin	Member of National Technical working Group
Dr. Digamber Behera	Member of National Technical working Group
Dr Ira Shah	Member of National Technical working Group
Dr.Vikas Oswal	Member of National Technical working Group

Standard Treatment Workflow National Task Force

Paediatric Expert Group for STW

Prof. Sushil Kumar Kabra	Professor, Paediatrics, All India Institute of Medical Sciences, New Delhi
Dr Varinder Singh	Director Professor, Paediatrics, Lady Hardinge Medical College, New Delhi
Dr Amber Kumar	Assistant Professor, Paediatrics, All India Institute of Medical Sciences, Bhopal
Dr Jagdish Prasad Goyal	Professor, Paediatrics, All India Institute of Medical Sciences, Jodhpur
Dr Joseph L Mathew	Professor, Paediatrics Pulmonology, Postgraduate Institute of Medical Education and Research, Chandigarh
Dr Kana Ram Jat	Additional Professor, Paediatrics, AIIMS, New Delhi
Dr Krishna Mohan Gulla	Associate Professor, Paediatrics, All India Institute of Medical Sciences, Bhubaneswar
Dr Manjula Datta	Chief Scientist, ASPIRE Chennai
Dr Samriti Gupta	Assistant Professor, Paediatrics, All India Institute of Medical Sciences, Bilaspur
Dr Sangeeta Sharma	Professor, Paediatrics, National Institute of Tuberculosis and Respiratory Diseases, New Delhi
Dr Sarika Gupta	Professor (J.Gr.), Department of Paediatrics, King George's Medical University, Lucknow
Dr Tanu Singhal	Consultant, Paediatrics Infectious Disease, Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai

Extrapulmonary TB Expert Group

Dr Dhruva Chaudhry	Sr Professor & Head, Pulmonary & Critical Care Medicine, Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak
Dr Ashutosh N Aggarwal	Professor & Head, Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh
Dr Anil Kumar Jain	Professor, Orthopedics, University College of Medical Sciences, New Delhi
Dr Ashwani Khanna	Former State TB Officer and Consultant, National Tuberculosis Elimination Program, Govt of India, New Delhi
Dr Camilla Rodrigues	Consultant Microbiologist, Parmanand Deepchand Hinduja and Medical Research Centre, Mumbai
Dr Jai Bhagwan Sharma	Professor, Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi
Dr Jyotirmay Biswas	Director, Uveitis & Ocular Pathology Department, Sankara Nethralaya, Chennai
Dr Kusum Sharma	Associate Professor, Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh
Dr Mandira Varma-Basil	Professor, Microbiology, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi
Dr Manish Modi	Professor, Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh
Dr Manjula Datta	Chief Scientist, ASPIRE Chennai
Dr Narayan Jana	Professor & Head, Obstetrics and Gynaecology, Chittaranjan Seva Sadan College of Obstetrics, Gynaecology and Child Health, Kolkata
Dr Nitish Naik	Professor, Cardiology, All India Institute of Medical Sciences, New Delhi
Dr Priscilla Rupali	Professor, Infectious Diseases, Christian Medical College, Vellore
Dr Rajesh Malhotra	Professor, Orthopedics, All India Institute of Medical Sciences, New Delhi
Dr Ramprasad Dey	Professor, Obstetrics and Gynaecology, Chittaranjan Seva Sadan College of Obstetrics, Gynaecology and Child Health, Kolkata
Dr Ritesh Aggarwal	Professor, Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh
Dr Rohit Bhatia	Professor, Neurology, All India Institute of Medical Sciences, New Delhi
Dr Roy Thankachen	Professor, Cardio-thoracic and Vascular Surgery, Christian Medical College, Vellore
Dr Sambit N Bhattacharya	Director Principal, Dr Baba Saheb Ambedkar Medical College & Hospital, New Delhi
Dr Thangakunam Balamugesh	Professor, Pulmonary Medicine, Christian Medical College, Vellore
Dr Uday Pratap Singh	Associate Professor, Urology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India
Dr V Ramesh	Professor, Employees' State Insurance Corporation Medical College and Hospital, Faridabad
Dr Vineet Ahuja	Professor, Gastroenterology, All India Institute of Medical Sciences, New Delhi
Dr Vishal Sharma	Associate Professor, Gastroenterology, Postgraduate Institute of Medical Education and Research, Chandigarh
Dr Vishali Gupta	Professor, Advanced Eye Centre, Postgraduate Institute of Medical Education and Research, Chandigarh

Advisor from ICMR Headquarters

Prof. Dr Balram Bhargava	Secretary, DHR & Director General, ICMR
Dr Samiran Panda	Additional Director General, ICMR

ICMR Coordinating Unit, Headquarters

Dr R S Dhaliwal	Scientist G & Head(NCD), ICMR, New Delhi
Dr A M Khan	Scientist G, ICMR, New Delhi
Dr Manjula Singh	Scientist F, ICMR, New Delhi
Dr Ashoo Grover	Scientist F, ICMR, New Delhi
Dr Lokesh Kumar Sharma	Scientist E, ICMR, New Delhi
Dr Sudipto Pallab Roy	Scientist E, ICMR, New Delhi
Dr Jerin Jose Cherian	Scientist D, ICMR, New Delhi
Dr Saumya Srivastava Aggarwal	Scientist C, ICMR, New Delhi
Ms Saumya Deol	Scientist B, ICMR, New Delhi
Mr Neeraj Parmar	Technical Officer A, ICMR, New Delhi
Mr Dhiraj Kumar	Graphics Designer, ICMR, New Delhi
Mr Mahesh Chand	Sr Administrative Officer, ICMR, New Delhi
Mrs Harjeet Bajaj	Administrative Officer, ICMR, New Delhi
Mr Anil Lakhera	Section Officer, ICMR, New Delhi
Ms Ankita Bhakuni	Project Officer, ICMR, New Delhi
Mr Neeraj Kumar	Data Entry Operator, ICMR, New Delhi

Abbreviations

ADA	Adenosine deaminase or adenosine aminohydrolase
ALT	Alanine transaminase
AST	Aspartate transaminase
Am	Amikacin
AFB	Acid-fast bacilli
AF	Ascitic fluid
AIIMS	All India Institute of Medical Sciences
ART	Antiretroviral therapy
ATT	Anti-tuberculosis therapy
B/L	Bilateral
BMI	Body mass index
Bdq	Bedaquiline
BSC	Biosafety containers
CBC	Complete blood count
CP	Continuation phase
CBD	Common bile duct
CHC	Community health centre
Cfz	Clofazimine
Cm	Capreomycin
CLD	Chronic liver disease
CNS	Central nervous system
CRP	C Reactive Protein
CSF	Cerebrospinal fluid
CT	Computed tomography
Cy-Tb	Cy-Tb Skin Test (Serum Institute of India, India)
CXR	Chest X-ray
DGHS	Directorate General of Health Services
Dlm	Delamanid
DJS	Double J Stent
DST	Drug sensitivity test
E	Ethambutol
ECG	Electrocardiogram
ENT	Ear, nose and throat
EPTB	Extra-pulmonary tuberculosis
ESR	Erythrocyte sedimentation rate
FDC	Fixed Dose Combination tablets
FL-LPA	First line-Line probe assay
FFA	Fundus Fluorescein Angiography
FGTB	Female genital TB
FNAC	Fine-needle aspiration cytology

Abbreviations

FUO	Fever of unknown origin
GHA	Global health advocates
GI	Gastrointestinal
HIV	Human immunodeficiency virus
HAV	Hepatitis A virus
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
H	Isoniazid
HDN	Hydronephrosis
HDUN	Hydroureteronephrosis
HPE	Histopathological examination
HSG	Hysterosalpingography
ICP	Intracranial pressure
ICSOL	Intra-cranial space occupying lesion
IP	Intensive phase
INR	International normalized ratio
IGRA	Interferon-gamma release assay
IRIS	Immune reconstitution inflammatory syndrome
IS	Induced sputum
IVP	Intravenous pyelogram
JVP	Jugular venous pressure
KFT	Kidney function tests
Km	Kanamycin
Lfx	Levofloxacin
LDH	Lactate dehydrogenase
LFT	Liver function tests
LJ	Lowenstein-Jensen
LNTB	Lymph node tuberculosis
LOD	Limit of detection
LTBI	Latent TB infection
LUTS	Lower Urinary Tract symptoms
Mfx	Moxifloxacin
MGIT	Mycobacterium growth indicator tube
MRI	Magnetic resonance imaging
MRCP	Magnetic resonance cholangiopancreatography
Mtb	Mycobacterium tuberculosis
NAAT	Nucleic acid amplification test
NTEP	National TB elimination programme
OCT	Optical Coherence Tomography
PCR	Polymerase chain reaction

Abbreviations

PR	Paradoxical reaction
PT	Prothrombin time
PET-CT	Positron emission tomography–computed tomography
PHC	Primary health centre
PLHIV	People living with HIV/AIDS
R	Rifampicin
RAPD	Relative afferent pupillary defect
Rt.	Right
S	Streptomycin
SAAG	Serum ascites albumin gradient
SAD	Sagittal abdominal diameter
SAM	Severe acute malnutrition
SIADH	Syndrome of inappropriate antidiuretic hormone
SL-LPA	Second line-Line probe assay
SLID	Second-line injectable drugs (SLID)
SOL	Space occupying lesion
STW	Standard treatment workflow
TB	Tuberculosis
TBM	Tuberculous meningitis
TLC	Total leukocyte count
TPT	Tuberculosis prevention treatment
TST	Tuberculin skin testing (also referred to as Mantoux test)
TNF-alpha	Tumor necrosis factor-alpha
ULN	Upper limit of normal
USG	Ultra sonography
VCT	Voluntary counselling and testing
WHO	World Health Organization
WHO-CC	World Health Organization Collaborating Centre
XDR	Extensively Drug Resistant
Z	Pyrazinamide

Operational Definitions

A second-line TB drug: It is an agent reserved for the treatment of drug-resistant TB. First-line TB drugs used to treat drug-susceptible TB – ethambutol, isoniazid and pyrazinamide – may also be used in MDR-TB regimens (streptomycin is now considered a second-line TB drug and used only as a substitute for Amikacin when Amikacin is not available or there is confirmed resistance to it).

At-risk group is any group of people in whom the prevalence or incidence of TB is significantly higher than in the general population.

Bacteriologically confirmed TB is diagnosed in a biological specimen by smear microscopy, culture or a WHO-endorsed rapid molecular test and adopted by NTEP such as Xpert MTB/RIF®/Truenat®.

Contact investigation is a systematic process for identifying previously undiagnosed people with TB disease and TB infection among the contacts of an index TB patient and/or other comparable settings where transmission occurs. [Contact investigation consists of identification, clinical evaluation and/or testing and provision of appropriate anti-TB treatment (for people with confirmed TB) or TB preventive treatment (for those without TB disease)].

Close contact is a person who is not in the household but shares an enclosed space, such as at a social gathering, workplace or facility, for extended periods during the day with the index TB patient during the three months before commencement of the current TB treatment episode. This group will be included for all interventions as applicable for household contacts in these guidelines.

Cured: A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriological response and no evidence of treatment failed.

Drug susceptibility testing (DST) refers to in-vitro testing using either of the phenotypic methods to determine susceptibility.

Drug resistance testing (DRT) refers to in-vitro testing using genotypic methods (molecular techniques) to determine resistance.

Extensively drug resistant TB (XDR-TB): TB caused by Mycobacterium tuberculosis strains that fulfill the definition of MDR/RR-TB and are also resistant to any fluoroquinolone (levofloxacin or moxifloxacin) and at least one additional Group A drug (presently to either Bedaquiline or linezolid [or both]).

Extent or severity of disease: In patients older than 18 years, this is usually defined by the presence of cavities or bilateral disease on chest radiography or smear positivity. In children under 18 years, severe disease is usually defined by the presence of cavities or bilateral disease on chest radiography or extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression). In children, the occurrence of advanced malnutrition (defined

by syndrome or by metrics) or advanced immunosuppression or positive tuberculosis (TB) bacteriology (smear, NAAT, culture) may also be considered when determining disease severity.

Household contact (HHC): Is a person who shared the same enclosed living space as the index TB patient for one or more nights or for frequent or extended daytime periods during the three months before the start of current TB treatment. [For simplicity, close contacts may be considered inclusive in this term throughout the guidelines].

Index patient of TB: This is the initially identified person of any age with new or recurrent TB in a specific household or other comparable setting in which others may have been exposed. [An index TB patient is the person on whom a contact investigation is centered but is not necessarily the source.]

Isoniazid-resistant TB (Hr-TB): A TB patient, whose biological specimen is resistant to isoniazid and susceptibility to rifampicin has been confirmed.

Lost to follow up: A patient who did not start treatment or whose treatment was interrupted for one consecutive month or more.

Mono-resistant TB (MR TB): A TB patient, whose biological specimen is resistant to one first- line anti-TB drug only.

Multidrug-resistant TB (MDR-TB): A TB patient, whose biological specimen is resistant to both H and R with or without resistance to other first-line anti-TB drugs. MDR-TB patients may have additional resistance to any/all FQ or any other anti-TB drug

Not evaluated: A patient for whom no treatment outcome was assigned.

Presumptive TB: This refers to a person with any of the symptoms or signs suggestive of TB. [Diagnosis of TB is difficult in certain key groups of the presumptive TB patients like extra- pulmonary, PLHIV, children, smear -ve/NA with x-ray suggestive of TB, other vulnerable groups as defined in TOG-2016 and DR-TB contacts, hence, NAAT is offered upfront for diagnosis of TB among these presumptive TB patients.]

Presumptive DR-TB: This refers to the patient who is eligible for rifampicin resistant screening at the time of diagnosis OR/and during the course of treatment for DS-TB or H mono/poly DR-TB. [This includes all notified TB patients (Public and private), follow-up positive on microscopy including treatment failures on standard first-line treatment and H mono/poly DR-TB regimen and any clinical non-responder including paediatric.

Pre-extensively drug resistant TB (Pre-XDR-TB): TB caused by Mycobacterium tuberculosis strains that fulfill the definition of MDR/RR-TB and are also resistant to any fluoroquinolone.

Poly-drug resistant TB (PDR-TB): A TB patient, whose biological specimen is resistant to more than one first-line anti-TB drug, other than both H and R.

Rifampicin resistant TB (RR-TB): A TB patient, whose biological specimen is resistant to R, detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to R, in the form of mono-resistance, poly-resistance, MDR or XDR.

Treatment failed: A patient whose treatment regimen needed to be terminated or permanently changed to a new regimen option or treatment strategy.

Treatment completed: A patient who completed treatment as recommended by the national policy whose outcome does not meet the definition for cure or treatment failed.

Section 1

1. Extrapulmonary TB Overview

Tuberculosis (TB), an airborne communicable disease, before the COVID-19 pandemic, was the world's leading cause of death from a single infectious agent. As per The Global TB report 2022(1), 10.6 million people fell ill with TB worldwide in 2021, whereas there were 1.4 million TB deaths among HIV-negative people and an additional 1,87,000 among HIV-positive people. Out of the total notified cases globally, 87% belong to 30 high-burden countries. India contributed to 28% of TB cases globally. Although the lungs are the most typically affected site in TB (pulmonary TB), organ systems other than the lungs can also be affected. According to The Global TB Report 2020(2), Extrapulmonary tuberculosis (EPTB) constituted 16% of the 7.5 million reported TB cases globally and 19% in South-East Asia. However, these estimates may be the tip of the iceberg, as a considerable proportion remains undiagnosed or not notified.

While significant advances have been made in diagnosing pulmonary tuberculosis, EPTB diagnosis and management remain a considerable challenge. EPTB, which can involve almost any system of the body, along with the ambiguity regarding clinical management, has made it a formidable enemy in the war against TB. Clinical manifestations of EPTB range from nonspecific to mimicking any other disease. Moreover, due to the paucibacillary nature of Extrapulmonary specimens and sample collection often requiring invasive procedures, diagnosis of EPTB is often delayed. Varying responses to treatment and its duration further compound the management of EPTB. Therefore, the diagnosis and management of EPTB remains a challenge and a significant bottleneck in achieving TB elimination.

The inception of Index TB guidelines was the first step in tackling EPTB in an evidence-based manner. Further, in 2021, a Standard treatment workflow (STW) for the management of Extrapulmonary Tuberculosis was prepared. It was the culmination of a herculean effort taken by several leading experts, with an evidence-based approach to battle this deadly disease, address these issues and raise unanswered dilemmas. The next major step was preparing a comprehensive document for EPTB and disseminating the available knowledge far and wide. The diagnosis and management of EPTB have been primarily confined to tertiary care centres and medical colleges. The need of the hour is to sensitize and educate healthcare professionals across all levels of healthcare. The joint effort by everyone can be a big step forward in our battle against the Mycobacterium tuberculosis.

This Training Module is an effort to amalgamate the latest evidence and practices into a simple and understandable format and translate this guidance through capacity building of various health care professionals and staff towards efficient functioning of the diagnostics and treatment of the patients. One of the main objectives of the document is to strengthen the systematic management of EPTB for the healthcare providers at the secondary and tertiary care levels, both in the public and private sectors and TB Programme implementers in India.

This module's layout provides an overview and updated information on all essential aspects of EPTB. It is divided into four sections. Intending to provide the latest guidance and uniform, evidence-based practices for diagnosing and managing various types of EPTB at all levels of health care delivery, the Section 1 outlines the programmatic services offered by the National TB Elimination Programme (NTEP). While, Section 2 is dedicated to EPTB in organ systems, Section 3 illustrates Standard Treatment Work Flow and section 4 for annexures. The training module will also contribute to practices for providing the best possible patient care and includes guidance on screening, notification, diagnosis, initiation of treatment, adherence and completion whilst minimizing drug toxicity and overtreatment.

References:

1. Global Tuberculosis report 2022. Geneva: World Health Organization; 2022.

2. Global Tuberculosis report 2020. Geneva: World Health Organization; 2020

2. National TB Elimination Programme

The National TB Elimination Programme (NTEP) is one of the national flagship components of the National Health Mission (NHM), Ministry of Health & Family Welfare (MOHFW). The Central TB Division (CTD) under The MOHFW is the nodal agency for implementing the NTEP for coordinating the response to eliminating tuberculosis in India. The programme is being implemented in close coordination and support of the National Health Mission. The NTEP has a vision of achieving a "TB-free India" and aims to provide universal access to TB control services.

The programme provides various free-of-cost, quality TB diagnosis and treatment services across the country through the government health system. The underlying focus of the programme is on early diagnosis of all TB patients, prompt treatment with the right drugs and regimens, and suitable patient support systems, including financial and nutritional support. To achieve this goal, the NTEP is implementing the National Strategic Plan (NSP) for Tuberculosis Elimination (2017-2025), which consists of four pillars: Prevent — Detect — Treat — Build.

Pillar	Strategies
Prevent	
Prevent the emergence of TB in susceptible populations.	• TB Preventive Treatment Expansion to household contact of pulmonary TB • Intensively engaging with researchers, manufacturers for newer vaccines • Trial on newer skin test for diagnosis of TB infection is underway in India • Scale up air-borne infection control measures at health care facilities
Detect	

Find all DS-TB and DR-TB cases with an emphasis on reaching TB patients seeking care from private providers and undiagnosed TB in high-risk populations.	• Scale-up free, high sensitivity diagnostic tests and algorithms:
	  • Expansion of NAAT to shift to diagnosis of TB by molecular test
	• Universal testing for drug-resistant TB:
	  • Introduction of decentralized Drug Susceptibility Testing (DST) using newly available tools
	• Systematic screening of high risk populations
	• Facilitation of development of AI enabled tools for X-Ray, Line Probe Assay (LPA), cough sound-based results

Treat	
Initiate and sustain all patients on appropriate anti-TB treatment wherever they seek care, with patient-friendly systems and social support.	• Differentiated care & post treatment follow up of TB patients • Expand nutrition initiatives with assessment and improvement • Free TB drugs for all TB cases • Shorter oral BDQ containing MDR/RR-TB regimen • Patient-friendly adherence monitoring and social support to sustain TB treatment • Elimination of catastrophic costs by linkages of eligible TB patients with social welfare schemes including nutritional support
Build	
Build and strengthen enabling policies, empowered institutions and human resources with enhanced capacities.	• Community engagement • Inter-ministerial and corporate sector engagement • Integrated health system approach • Jan Andolan (People's movement) • Private sector engagement

Table 1: The Prevent — Detect — Treat — Build Approach of NSP 2017 -2025 and Key Initiatives for Achieving TB Elimination

2.1. Detect

All detected TB patients, whether from public or private sector need to be notified to the NTEP recording and reporting system. The process of the TB notification is described in details towards the end of this chapter.

Clinical Presentation:
TB could be suspected clinically based on any of the following symptoms:

- Fever for more than two weeks
- Cough for more than two weeks
- Significant weight loss (>5% weight loss over last three months or unintentional perceptible weight loss)
- Haemoptysis
- Night sweats

However, Extrapulmonary TB has a wide range of presentations, from non-specific signs and symptoms (for example, Ascites, Pleural effusion, and Gibbus deformity) to organ and system-specific symptoms based on the site involved.

Diagnosis of EPTB:
As per the NTEP NSP 2017-2025, timely detection of TB is one of the critical pillars to achieving TB elimination. Diagnostic services are provided free of cost.

All efforts should be made for bacteriological confirmation of TB, including for Extrapulmonary TB. However, in case of high clinical suspicion and the presence of supportive laboratory tests, the expertise of clinicians can be used to diagnose EPTB.

Tools for Microbiological Confirmation of EPTB:

1. Molecular (Genotypic) Testing: Nucleic acid amplification tests (NAATs) assays rely on the amplification of a targeted genetic region of the Mycobacterium tuberculosis (M. tb) complex, typically by Polymerase Chain Reaction (PCR). Molecular tests can detect TB and resistance to key anti-TB drugs, such as rifampicin (R) and isoniazid (H), fluoroquinolones (FQ) and second-line injectable drugs (SLID) more quickly than Culture and Drug Susceptibility Tests (C&DST).

Upfront NAAT are offered to all presumptive EPTB patients as per the NTEP programmatic guidelines. The following are the NTEP-approved NAAT tests:

a) GeneXpert MTB/RIF is a cartridge-based Nucleic Acid Amplification Test (CBNAAT) for the simultaneous detection of TB and Rifampicin Resistance (RRTB). It detects DNA sequences specific for the M. tb complex and mutations in the RNA polymerase related to drug resistant TB. Results are obtained from unprocessed sputum samples in 90 minutes, with minimal biohazard and minimal technical training required to operate.

b) TrueNat (Chip-based). TrueNat MTB and TrueNat MTB-Rif Dx are chip-based, micro real-time Polymerase Chain Reaction-based (PCR) NAAT for TB and rifampicin resistance detection, respectively. Resistance to rifampicin is detected by doing a second Reverse transcription polymerase chain reaction (RTPCR). For further detail, click on this link https://tbcindia.gov.in.

c) Line Probe Assay (LPA) uses PCR and reverse hybridisation methods to detect gene mutations associated with drug resistance. This is currently the only WHO and NTEP recommended rapid test to detect additional drug resistance in MDR-EPTB and XDR-EPTB patients. The First Line-LPA (FLLPA) detects M.tb and the presence of resistance to R and H. A second Line-LPA is available for testing for resistance to Levofloxacin (Lfx), Moxifloxacin (Mfx), Amikacin (Am), Capreomycin (Cm), and Kanamycin (Km).

2. Direct Microscopy:

- Ziehl-Neelsen (ZN) staining
- Fluorescent staining

Microscopy using ZN staining is a simple, cheap and quick valuable method for detecting acid-fast bacilli in smears prepared from various clinical samples. ZN staining is of limited diagnostic value. It requires more than 10^5 to 10^6 bacteria/ml samples to detect acid-fast bacilli (AFB). Most of the EPTB samples are usually paucibacillary. Furthermore, ZN staining usually cannot differentiate non-tuberculous mycobacteria from Mycobacterium tuberculosis.

3. Culture: The culture of *M. tuberculosis* on the Lowenstein Jensen (LJ) medium has been replaced by automated liquid culture systems as the turnaround time is shorter and has a better yield than the LJ medium. The most preferred liquid culture system is MGIT (Mycobacteria Growth Indicator Tube) 960, which is an automated liquid culture system. MGIT 960 system provides higher sensitivity in terms of the growth of mycobacteria along with a shorter turnaround time. MGIT liquid culture system contains an oxygen quencher for detecting fluorescence inside the culture tubes. Whenever there is a growth inside the tube, microorganisms utilise the oxygen in the quencher, leading to fluorescence. MGIT liquid culture system can be used for culture and drug susceptibility testing for all extrapulmonary and pulmonary specimens. There is a considerable contamination rate in the MGIT tube cultures; thus, an LJ culture is always performed in parallel as a backup.

4. As EPTB can be present in any part of the human body, other test modalities are also needed for diagnosis, apart from the test mentioned above. Other test modalities to detect EPTB which is used by

clinicians are:

1. Histopathology examination (Tissue biopsy)
2. Biochemical examination of body fluids (for Adenosine Deaminase (ADA), glucose, protein etc.)
3. Radiological examinations like CXR, CT scan, USG, MRI and PET Scan

Drug Susceptibility Test:

1. Phenotypic Drug susceptibility test (DST): DST on BACTEC MGIT 960 – an Automated Liquid Culture System. It can be used to test both the pulmonary & EP specimens for sensitivity to:
   - First-line drugs: Isoniazid (H); Rifampicin (R) and Pyrazinamide (z).
   - Second-line drugs: Levofloxacin (Lfx), Moxifloxacin (Mfx), Amikacin (Am), Capreomycin (Cm), Streptomycin (S), Kanamycin (Km), P-Aminosalicylic Acid (PAS) and Linezolid (Lzd).

2. Molecular (Genotypic) DST: Along with the diagnosis of TB/EPTB, both CBNAAT (one step, simultaneously) and TrueNat (second RTPCR) also detect rifampicin resistance.

All presumptive EPTB cases need to be diagnosed and appropriate sample should be taken from exact site. If sufficient samples are available, they can be sent for NAAT, Culture and LPA simultaneously, but in case NAAT is not available, they send directly for Culture and LPA. If liquid culture report is negative and clinical suspicion high, then other diagnostic test modalities need to be done to rule out clinically diagnosed cases and for all other alternate diagnosis.

2.2. Treatment of EPTB

In order to contribute to Universal healthcare, reduce out-of-pocket expenditure (OOP), and ensure zero catastrophic cost to patients, the NTEP provides free diagnostic and treatment services. The programme has been agile in adopting and adapting newer drugs and treatment modalities. In recent years, the country has made considerable progress in the management of TB. EPTB treatment regimen and duration are contingent upon the affected site and drug-susceptibility pattern: Drug-susceptible EPTB (DS-EPTB) or Drug-resistant EPTB (DR-EPTB).

For DS-EPTB the standard injection-free combination of four oral drugs treatment regimen is implemented across the country for the duration of 6 months. However, the regimen and duration of treatment could vary according to the affected site and at clinicians discretion.

Drug-resistant EPTB is managed by All Oral H Mono/Poly DR-TB Regimen shorter oral Bedaquiline (Bdq) containing MDR/RR-TB regimen and longer oral MDR/RR-TB regimen as per DST results.

As patient follow-up is an essential component, a coordinated effort by all State/District PPM coordinators, senior DR-TB TB-HIV supervisors, STS, and staff from PPSA (if present) is critical to ensure proper implementation of care cascade as per the NTEP guideline For further detail, refer to: Guidelines for Programmatic Management of Drug Resistant Tuberculosis in India-2021 :: Ministry of Health and Family Welfare (tbcindia.gov.in)

2.3. Prevention

Prevention is one of the critical pillars of NSP (2017-25) for ending TB by 2025, which aim to prevent TB's emergence in India's vulnerable population. NTEP took a significant step in 2021 by expanding the policy to offer TB Preventive Therapy (TPT) to accelerate prevention and decline in TB incidence in the next few years. TPT will be provided to all household contacts (HHC) of index pulmonary TB patients and other risk groups beyond the existing policy for People Living with HIV (PLHIV) and HHC children aged less than 5 years.

The current eligible population for TPT after ruling out active TB and positive for TB infection (TBI) is outlined in the table below.

Target population	Strategy
• People living with HIV • Adults and children >12 months • Infants <12 months with HIV in contact with active TB • HHC below 5 years of pulmonary* TB patients	TPT after ruling out active TB disease
• HHC 5 years and above of pulmonary* TB patients#	TPT among TBI positive# after ruling out TB disease

Table 2: Eligible population for TPT

*bacteriologically confirmed pulmonary TB patients
Chest X Ray (CXR) and TBI testing would be offered wherever available, but TPT must not be deferred in their absence

B. Other risk groups

Target population	Strategy
Individuals who are: • on immunosuppressive therapy • having silicosis • on anti-TNF treatment • on dialysis • preparing for organ or hematologic transplantation	TPT among TBI positive after ruling out TB disease

Table 3: Expanded population for TPT

Household contacts of EPTB patients are not one of the eligible populations for TPT currently, as per the programmatic guidelines. Eligibility for TPT relies on ruling out active TB and risk versus benefit assessment. Contact tracing of the HHC targeted population and other vulnerable populations is one of the main strategies for increasing the coverage of TPT in India.

Under the NTEP, the tests used for TBI are Tuberculin Skin Test (TST), Interferon-Gamma Release Assays (IGRA), or Cy-Tb. However, in places where testing services are yet to be made available, TPT may be considered after ruling out active TB based on symptom screening, CXR and NAAT results. For further details regarding eligibility criteria and the TPT regimen, refer to https://tbcindia.gov.in/showfile.php?lid=3625.

2.4. Public Health Actions

The NTEP staff coordinate and facilitate various concurrent public health actions to bolster TB elimination, such as, contact tracing and TPT provision, increasing support for patients seeking care in the private sector, enhance surveillance, treatment adherence, TB comorbidity management, routine follow up and patient support incentives.

2.4.1. Patient Support Systems:

Under the National TB Elimination Programme following schemes are currently ongoing:

1. Ni-Kshay Poshan Yojana (NPY)
2. Transport support for TB patients in notified tribal areas
3. Honorarium for Treatment Supporters
4. Notification & Treatment Outcome Incentive for Private Sector Providers
5. Pradhan Mantri TB Mukt Bharat Abhiyaan –Ni-Kshay Mitra

2.4.1.a. Nutritional Support: To provide nutritional support, the Government of India launched the Ni-Kshay Poshan Yojna (NPY) scheme in April 2018, giving financial incentives via DBT to all TB patients to support their nutritional requirements for the duration of their treatment. Direct Benefit Transfer (DBT) to beneficiaries is one of the critical initiatives taken by the Government of India, enabling targeted delivery of benefits to citizens directly to the bank account(s), thus enhancing efficiency, effectiveness, transparency, and accountability for each transaction.

2.4.1.b. Other Support Schemes: Tribal Support Scheme, a one-time financial incentive of Rs 750, is provided to the notified TB patients residing in tribal areas. In addition, Treatment Supporters are provided with an honorarium for supporting notified TB patients completing their treatment. Similarly, private providers are also provided financial incentives for notifying a TB patient and reporting their treatment outcome. The following are some details about these schemes mentioned below.

Schemes	Beneficiary	Benefit Amount
Ni-Kshay Poshan Yojana (NPY)	Confirmed TB Patients • DSTB & DRTB • Public Sector Patients • Private Sector Patients	• Rs 500 per month
Tribal Support Scheme	Confirmed TB Patients residing in Tribal TU	• Rs 750 (one time)
Treatment Supporter Honorarium	Treatment Supporter	• Rs 1,000 for DS TB patients • Rs 5,000 for DR TB patients
Incentive for Notification and Outcomes	• Private Health Facilities: • Practitioner /Clinic etc. (Single) • Hospital/Clinic/Nursing Home etc. (Multi) • Laboratories/Chemists	• Rs 500 as Informant or Notification Incentive • Rs 500 for Outcome declaration

Table 4: NTEP Support Schemes

2.4.1.c. Ni-kshay Mitra: For effective community engagement for ending TB in India, MoHFW is implementing Community Support to TB patients - Pradhan Mantri TB Mukt Bharat Abhiyaan. Ni-Kshay Mitra (Donor) for this programme includes co-operative societies, corporates, elected representatives, individuals, institutions, non-governmental organizations, political parties and partners who can support by adopting health facilities (for the individual donor), blocks/urban wards/ districts/states for accelerating response against TB to complement government efforts, as per the district-specific requirements in coordination with the district administration. The support provided to the patient under this initiative will improve the involvement of society, increase awareness, and community support for the treatment cascade, help in the reduction of stigma, reduction of out of pocket expenditure for family and overall will improve nutrition for TB patients resulting in better treatment outcomes. For further information, refer to "Pradhan Mantri TB Mukt Bharat Abhiyaan - Central TB Division".

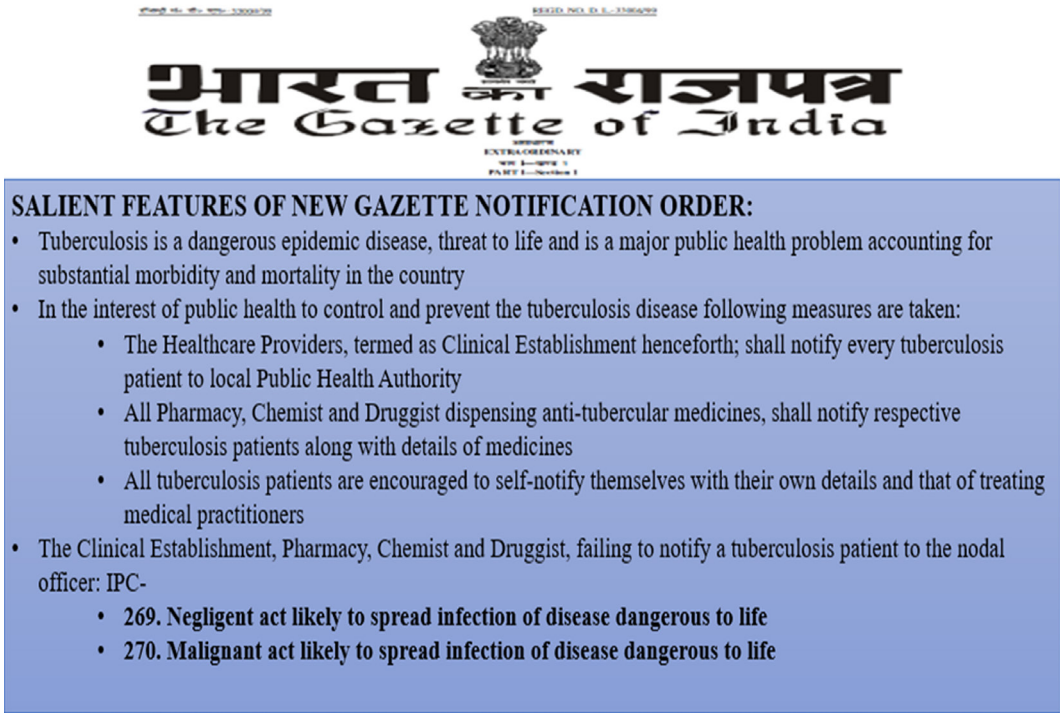
2.4.1.d. Psychosocial Support: People with TB may experience discrimination and stigma common with the diagnosis of TB. The stigma associated with TB could lead to isolation and weakening the social support system. Moreover, studies have shown high prevalence rates of psychiatric comorbidity in TB patients, ranging from anxiety, denial, hopelessness, tension, neglect by family and society and even depression. In addition, loss of employment and out-of-pocket expenditure on diagnostic and treatment services may cause financial constraints, further exacerbating the stress.
In order to provide rights-based, people-centred care, addressing the psychosocial needs of the people affected by tuberculosis is vital. Psychosocial support measures encompass the psychological, social and economic factors determining access to diagnosis, treatment adherence, and treatment outcome. The NTEP provides counselling support to all notified TB patients through a network of healthcare workers and Senior Treatment Supervisors.

Psychosocial support is an essential component of the management of adverse effects. Patient education, motivation by treatment supporters, and engagement with patient support groups are some of the core strategies for providing psychosocial support and empowering people affected by tuberculosis.

2.5. TB Notification

In the interest of public health, the Government of India, on 16th March 2018, through the TB Gazette Notification, made TB a notifiable disease, making notification of each TB case mandatory.

- The healthcare providers, termed as clinical establishment, shall notify every TB patient to the local public health authority, namely, District Health Officers or CMO of a District and Municipal Health Officers of urban local bodies in whatever way they are known or their designated DTO.
- All Pharmacy, Chemist and Druggist dispensing antitubercular medicines shall notify respective TB patients along with details of drugs. Considering the importance of patient support needed for complete and appropriate treatment, all TB patients are encouraged to self–notify themselves with their details and that of treating practitioners.
- If not notified and appropriate public health action is not taken, it is a punishable act under the provision of sections IPC 269 and IPC 270.


भारत का राजपत्र
The Gazette of India

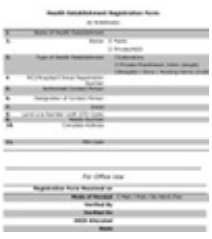
SALIENT FEATURES OF NEW GAZETTE NOTIFICATION ORDER:

- Tuberculosis is a dangerous epidemic disease, threat to life and is a major public health problem accounting for substantial morbidity and mortality in the country
- In the interest of public health to control and prevent the tuberculosis disease following measures are taken:
  - The Healthcare Providers, termed as Clinical Establishment henceforth; shall notify every tuberculosis patient to local Public Health Authority
  - All Pharmacy, Chemist and Druggist dispensing anti-tubercular medicines, shall notify respective tuberculosis patients along with details of medicines
  - All tuberculosis patients are encouraged to self-notify themselves with their own details and that of treating medical practitioners
- The Clinical Establishment, Pharmacy, Chemist and Druggist, failing to notify a tuberculosis patient to the nodal officer: IPC-
  - **269. Negligent act likely to spread infection of disease dangerous to life**
  - **270. Malignant act likely to spread infection of disease dangerous to life**

Figure 3. TB Gazette Notification

2.5.1 Methods of TB Notification:

TB notification can be done through any of the following ways:

Ni-kshay Portal	Call Centre	Physical Performa	District Nodal Officers
https://www.nikshay.in/	Nikshay sampark - 1800116666		http://tbcindia.gov.in/.

1. **TB Notification through Ni-kshay:** Any health facility/private practitioner/laboratory can notify TB cases by registering themselves on the Ni-Kshay portal, followed by notification of the diagnosed TB patients.

a. Registration of Health Facility:

Registration of a new health facility can be done through the Ni-Kshay portal via the following steps:

- For the public health facilities, the NTEP Program Manager of the district/state shall be approached for the generation of login ID and password.
- For the private sector, the login ID may be generated self or with assistance from the NTEP staff.

Steps for self-registration of Health Facility on Ni-kshay

Step 1. For online registration visit https://www.nikshay.in/and click on New Health Facility Registration

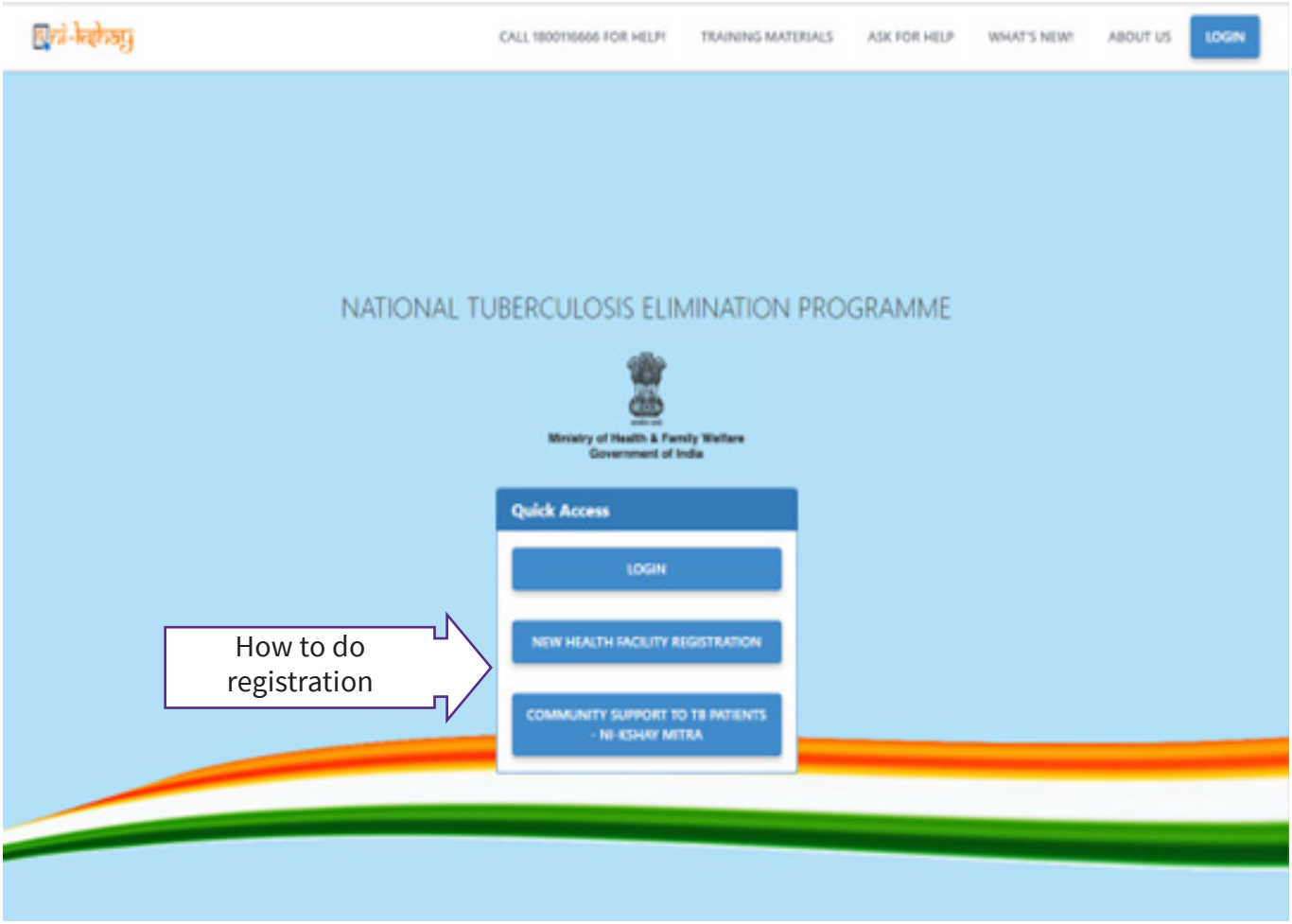


Figure 1. Dialogue box showing Informant or New Health Facility Registration

Step 2. Fill all details and correct mobile number to generate OTP (https://www.nikshay.in/Home/UserFacility)

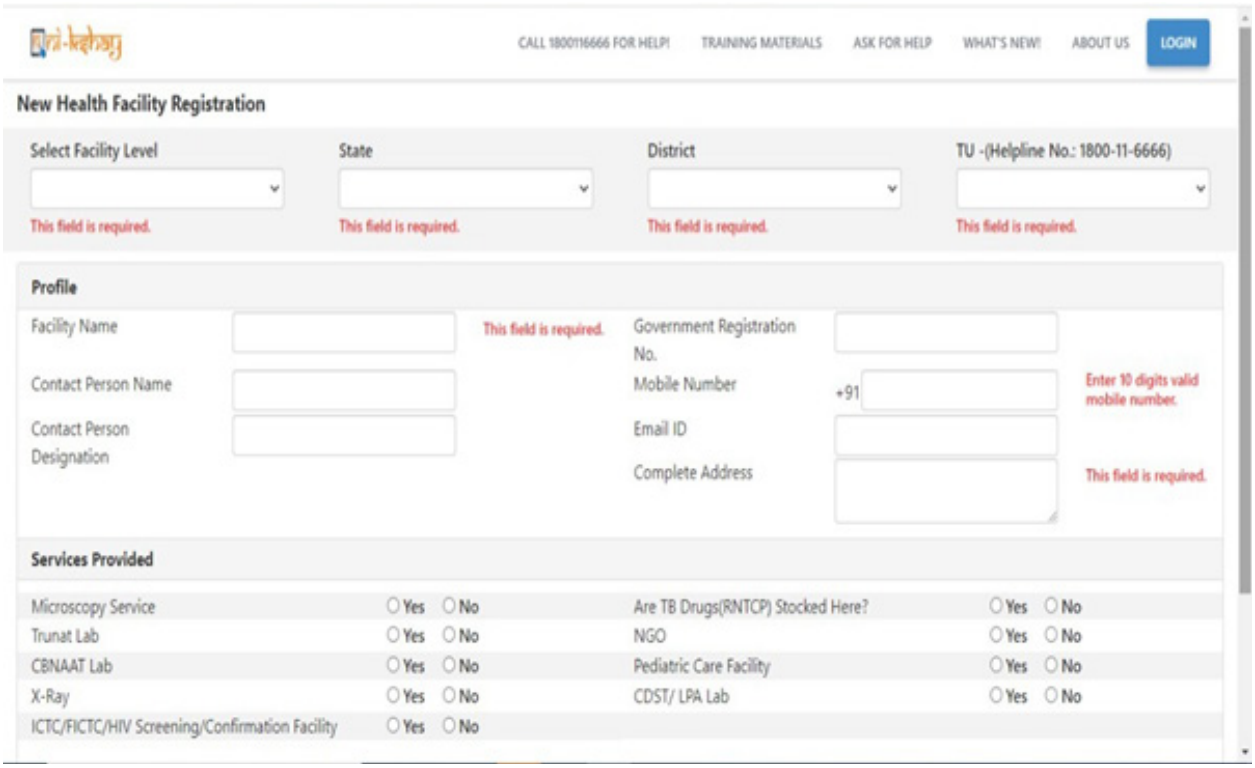


Figure 2. Dialogue box showing information for new health facility registration to get login details

Step 3. Enter OTP and then continue (https://www.nikshay.in/Home/UserFacility)

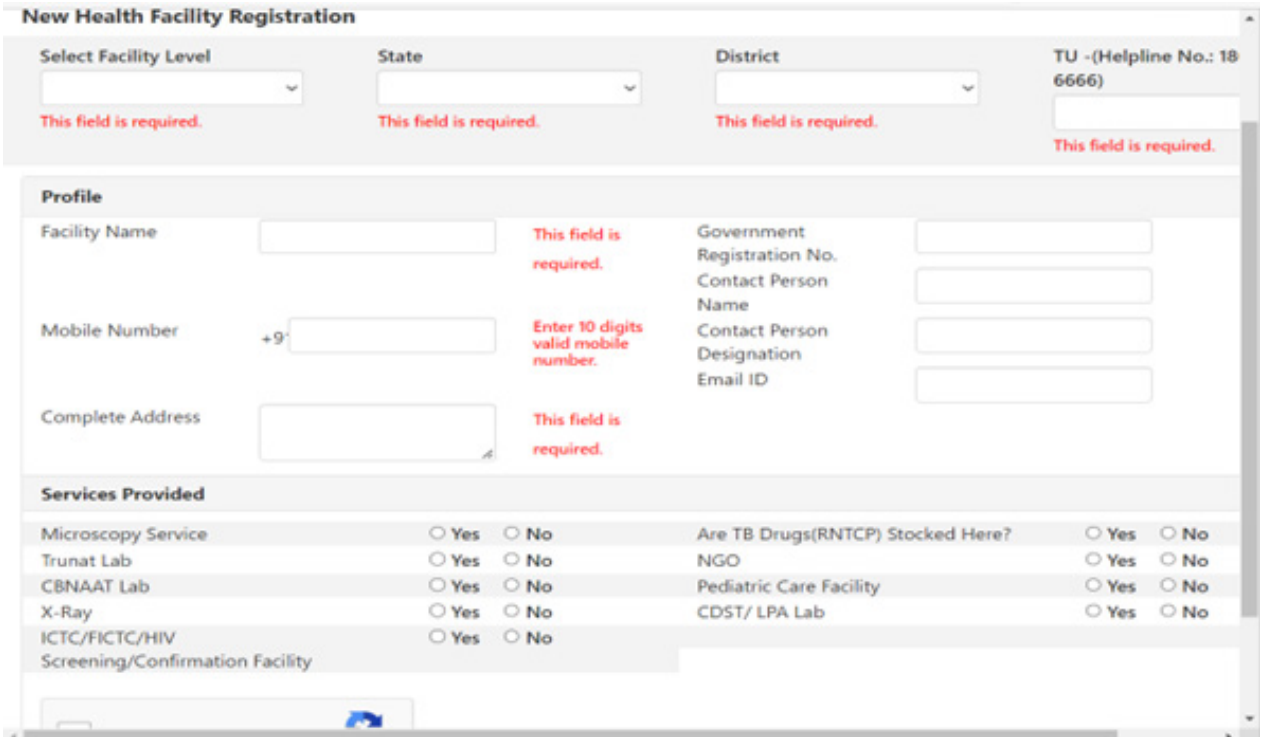


Figure 3. Dialogue box showing new health facility registration to get login detail for notifying presumptive TB cases

Step 4. Login ID and password will be generated on respective mobile no. and via email (https://www.nikshay.in/Home/UserFacility)

b. Notification of TB:

Step 1. Log In with respective Login ID and password through this link https://www.nikshay.in/

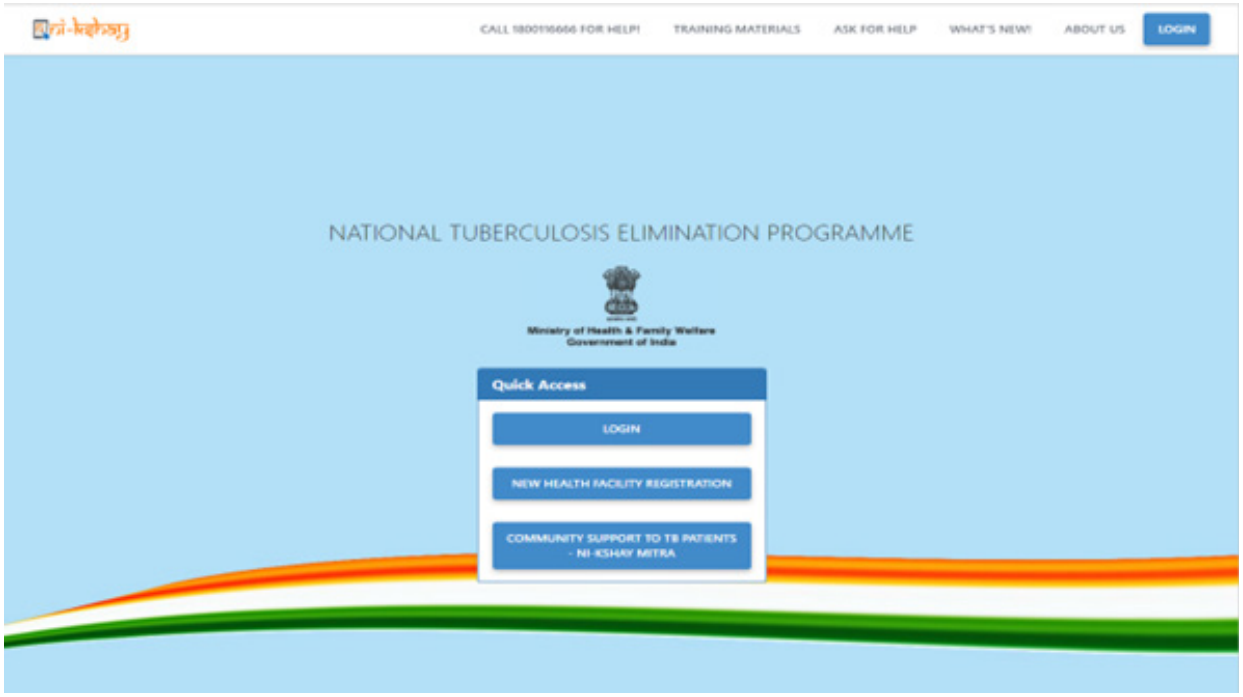


Figure 4. Dialogue box showing dashboard for login of health facility

Step 2. Click for new enrollment on the dashboard. (**Note:** This information can be filled by paramedical staff, not necessary to be filled by clinicians only)
https://nikshay.zendesk.com/hc/en-us/articles/360038200712-Enrollment-Notification-

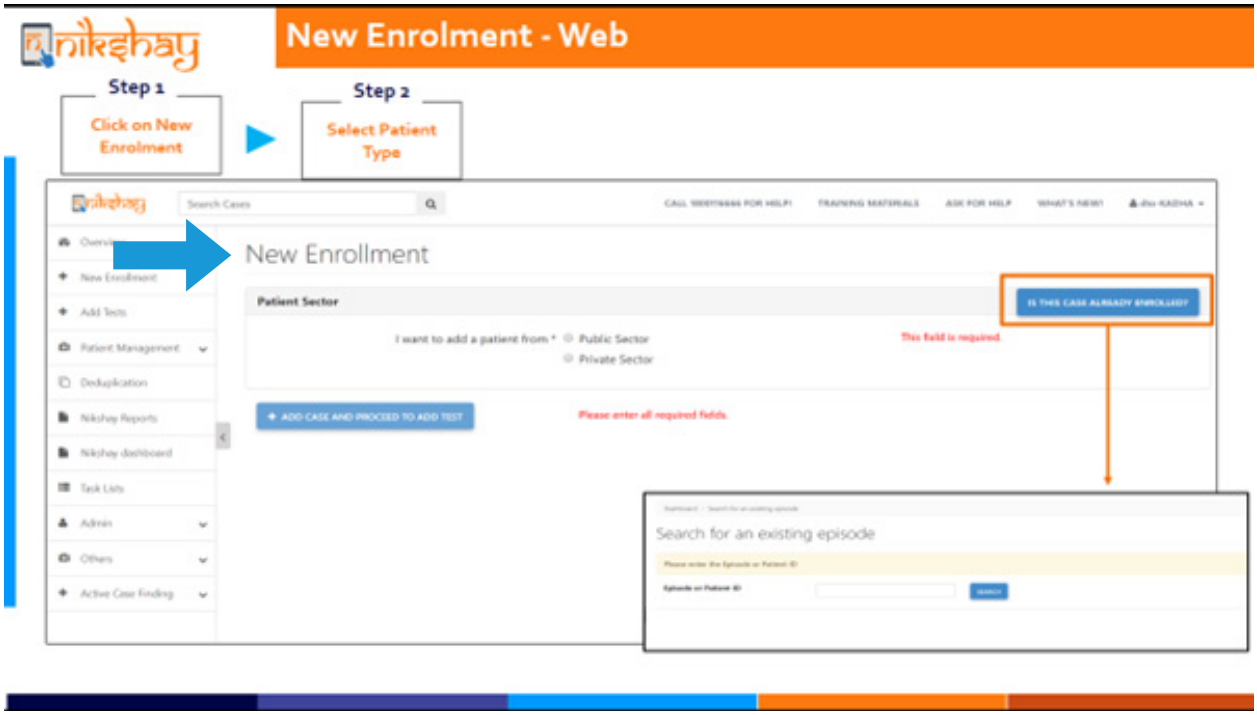


Figure 5. Dialogue box showing step for New Enrolment

Step3. Select the patient type from drop down menu (https://nikshay.zendesk.com/hc/en-us/articles/360038200712-Enrollment-Notification-)

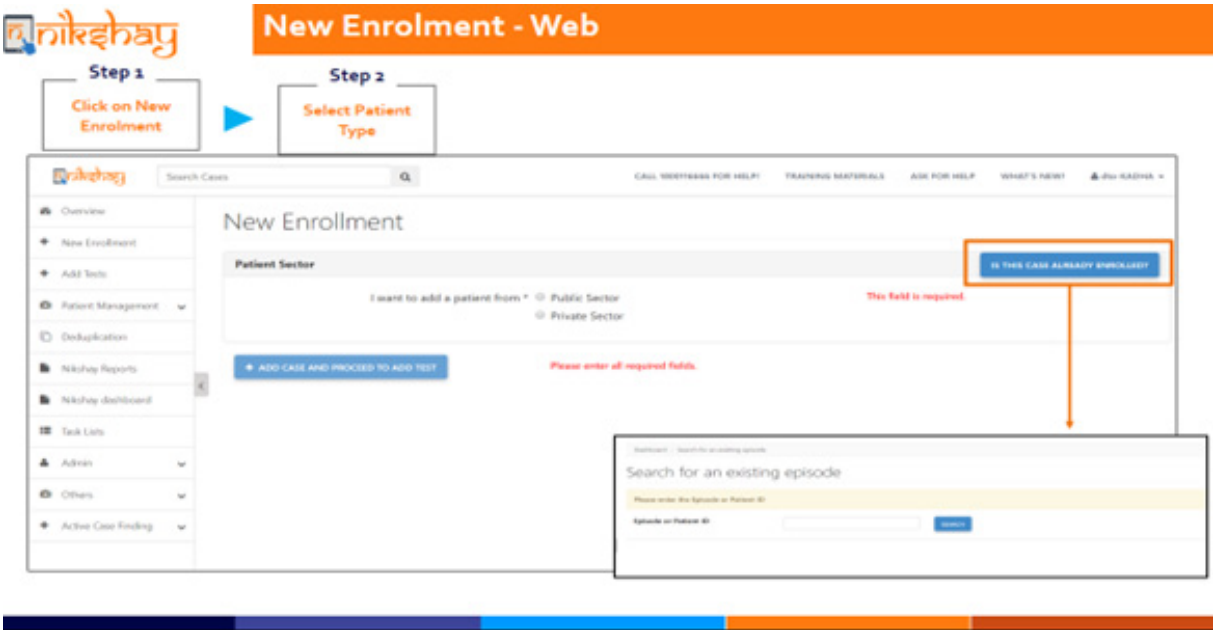


Figure 6. Dialogue Box showing to Select the patient type

Step 4. Add basic details of the patient (**Note:** This information can be filled by paramedical staff, not necessary to be filled by clinicians only)

Step 5. Deduplication the patient enrolled if intimated. (During enrolment, Nikshay shows duplicate records based on gender and mobile number. Users should review the possible duplicates carefully

before enrolling a new case) Enrollment Notification - Ni-kshay Knowledge Base

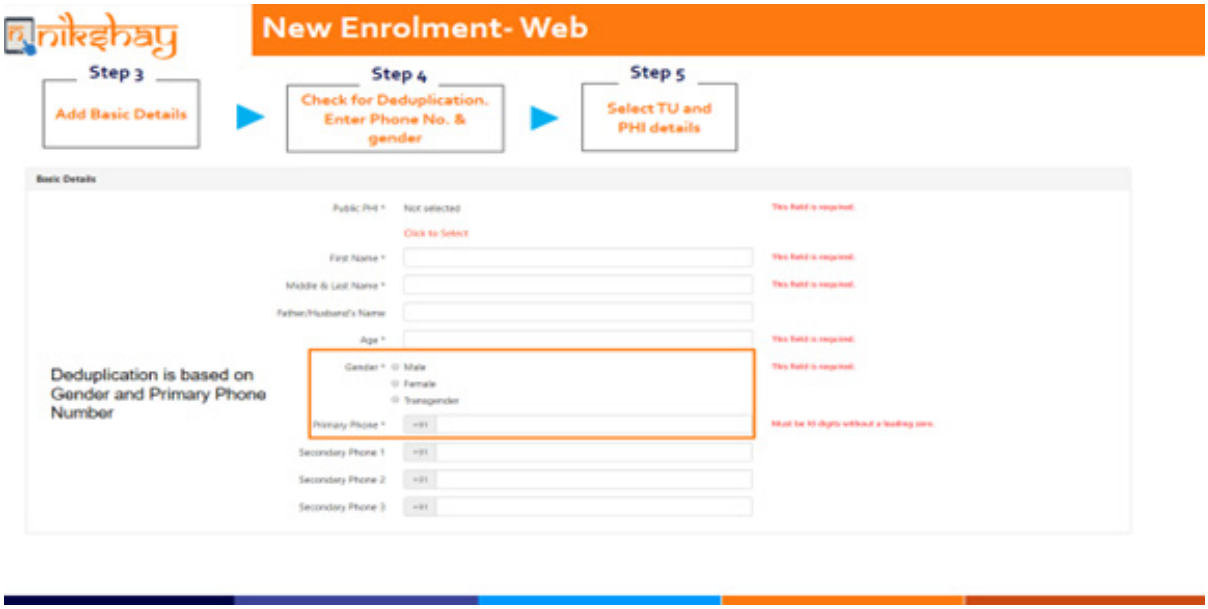


Figure 7. Dialogue Box showing to fill basic details of the patient and checking deduplication

Step 6. Add residence details (**Note:** This information can be filled by paramedical staff, not necessary to be filled by clinicians only)

Step 7. If no duplication, select Tuberculosis Unit (TU) and Peripheral Health Institute (PHI)

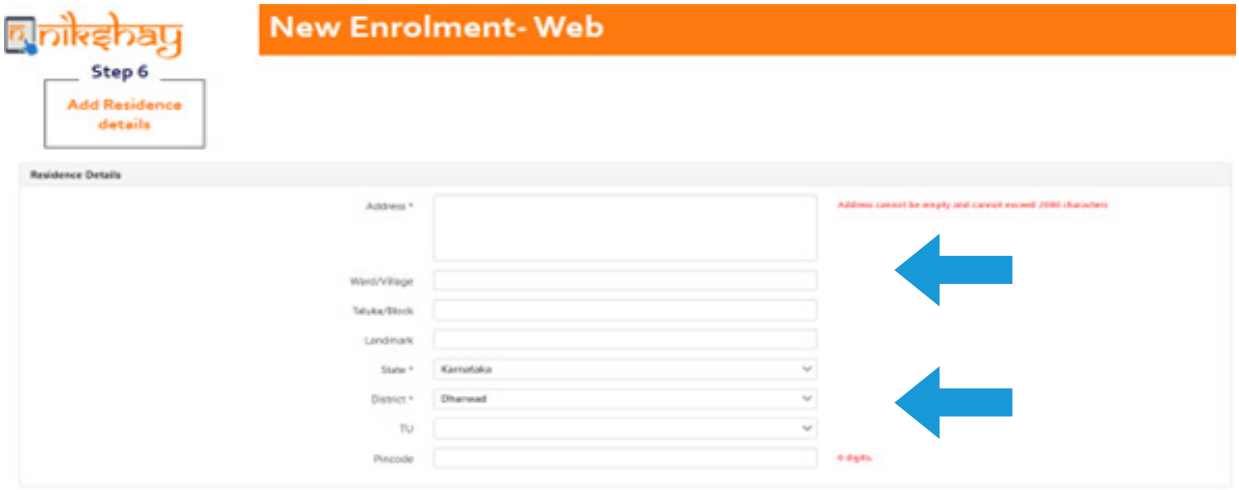


Figure 8. Dialogue Box showing to fill residence details and select Tuberculosis Unit

Step 8. Add demographic details (**Note:** This information can be filled by paramedical staff, not necessary to be filled by clinicians only)

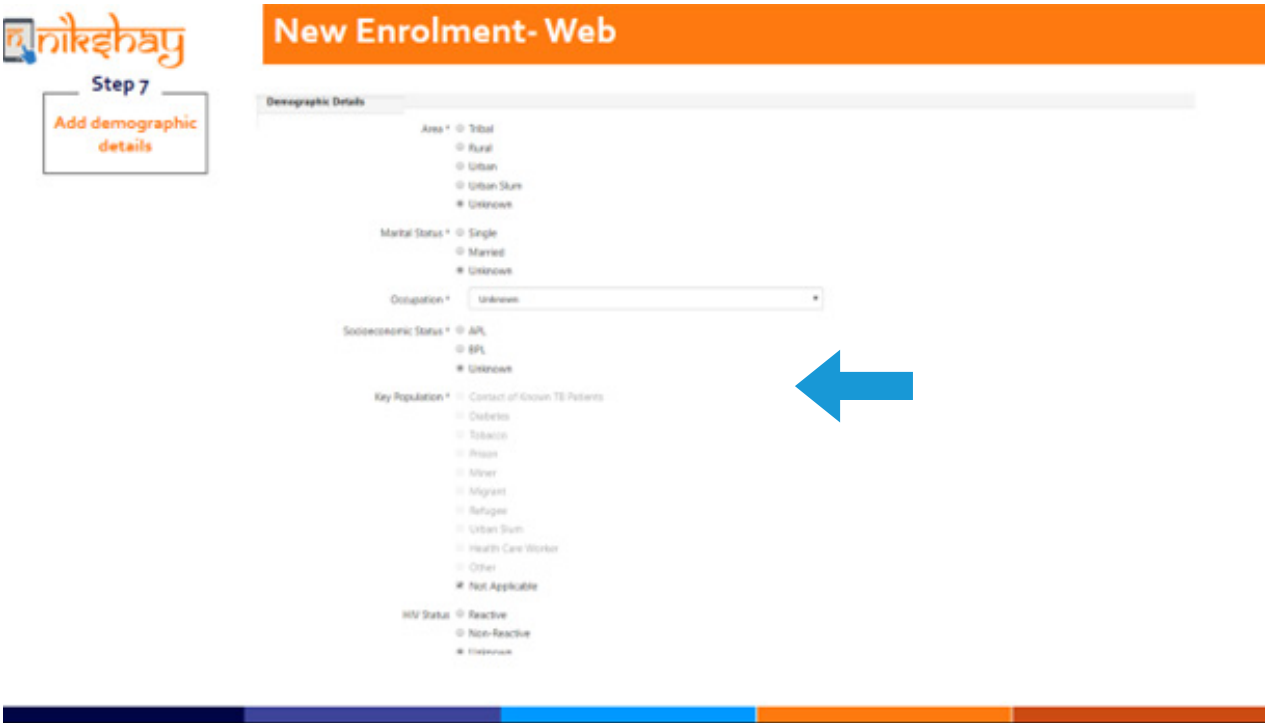


Figure 9. Dialogue Box showing to fill demographic details

Step 9. Add emergency contact details (**Note:** This information can be filled by paramedical staff, not necessary to be filled by clinicians only)

Step 10. Add case and notify the case

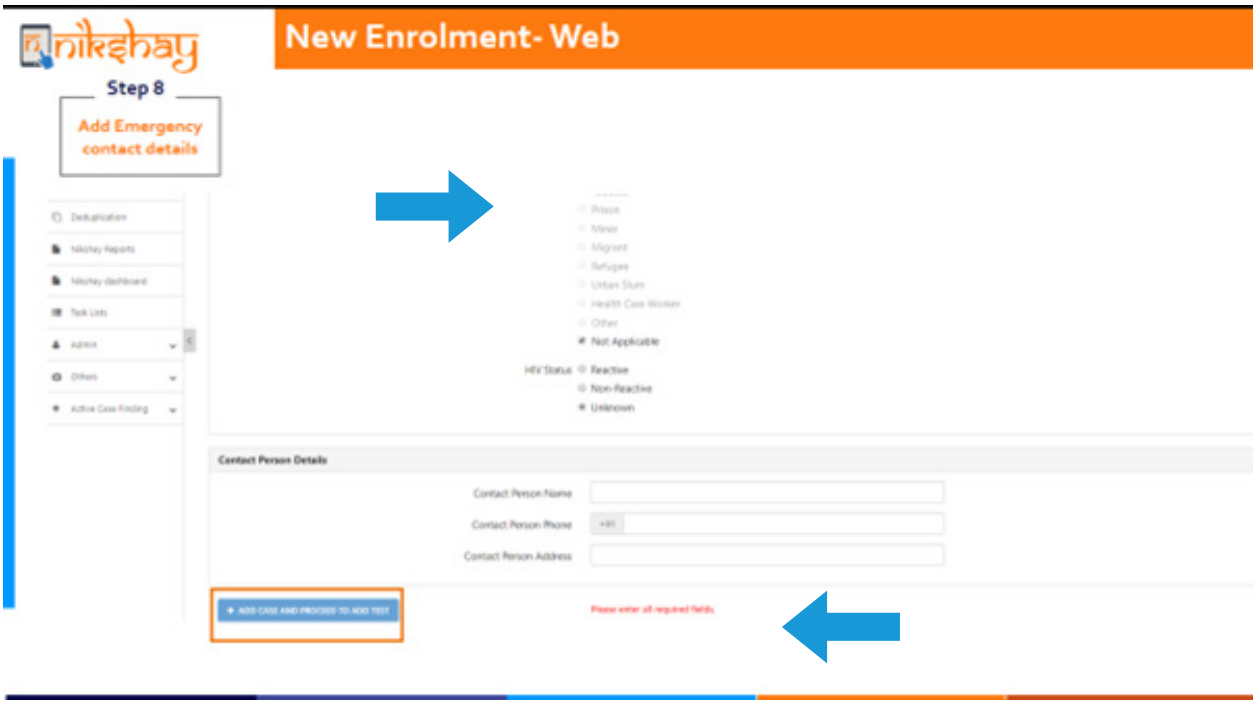


Figure 10. Dialogue Box showing to enter emergency contact details and Notify case

2. **Notification through Call Centre:** TB notification can be done through call centre on registered customer care number (1800116666). For further details click on this link http://tbcindia.gov.in

3. **Notification through physical Registration form:** For physical registration, registration form can be filled and submitted as a hard copy to the Nodal Officer for TB notification via (a) by post, (b) by courier and (c) by hand. Further details of nodal officer related to NTEP, can be obtained from directory of DTO/STO which can be accessed via click on this link http://tbcindia.gov.in

4. **Notification through District Nodal Officers:** Health establishments need to know the list of District TB officers in detail, which can be accessed by clicking (http://tbcindia.gov.in)on the directory of State TB Officer/District TB Officer. All relevant information is available in the directory of STO/DTO e.g., list of STO/DTO along with contact details.

References:

Central TB Division. National Tuberculosis Elimination Program: Central TB Division, Ministry of Health and Family Welfare, Government of India. https://tbcindia.gov.in/

Section 2

1. Tuberculous Lymphadenitis

KEY POINTS

- Tuberculous lymphadenitis is among the most frequent presentations of extrapulmonary tuberculosis.
- Clinical manifestations depend on the site of the lymphadenopathy and the immune status of the patient.
- In rural India, the prevalence of tuberculous lymphadenitis in children up to 14 years of age is approximately 4.4 cases per 1000.
- The most common presentation is isolated chronic non-tender lymphadenopathy in a young adult without systemic symptoms other than fever, most commonly in the cervical region.
- The yield of DNA appears to be highest in the setting of HIV infection and in regions where the prevalence of TB is high.
- Paradoxical reactions, such as Immune reconstitution inflammatory syndrome (IRIS) may occur in as many as 20 percent of patients, are usually culture negative, and do not usually represent treatment failure.

1.1. Introduction

Lymph node tuberculosis (LNTB, also called TB lymphadenitis) refers to *M. tuberculosis* infection of the lymph nodes and may occur as the sole manifestation of TB, or alongside pulmonary or miliary TB.

LNTB is the most common form of EPTB in India, accounting for around 35% of EPTB cases. Lymph node tuberculosis represents the most frequent localization and in some areas exceeds 80% of cases (1). The absence of defined prognostic criteria accentuates the therapeutic difficulties observed despite good drug compliance. Care should be taken to identify patients who need to be investigated for LNTB, as there are multiple differential diagnosis for lymphadenopathy e.g., sarcoidosis, lymphoma etc.

Among all tuberculous lymphadenitis, cervical adenopathy is most common (45-75% cases), but inguinal, axillary, mesenteric and mediastinal involvement have also been described.

In addition to common constitutional symptoms, TB of the deep lymph nodes in the chest (mediastinal TB) may present with cough or shortness of breath. Abdominal LNTB patients may have abdominal pain or distension.

1.2. Epidemiology

The epidemiology of tuberculous lymphadenitis varies between developed and developing countries. Previously, tuberculous lymphadenitis was considered a disease of childhood; however, the peak age of onset in developed countries has shifted from childhood to ages 20 to 40 years.

In developing countries where TB is endemic, extrapulmonary TB occurs in up to 60 percent of HIV-infected patients with TB and is frequently accompanied by signs of pulmonary involvement. Extrapulmonary TB cases (including tuberculous lymphadenitis) usually occur among patients with HIV at CD4 counts <300 cells/microL (usually below 100 cells/microL).

In rural India, the prevalence of tuberculous lymphadenitis in children up to 14 years of age is approximately 4.4 cases per 1000. The total estimated incidence of LNTB was 30.8 per 100 000 population in India in 2013 (2).

1.3. Pathogenesis

Tuberculous lymphadenitis may represent a spread of infection from the tonsils, adenoids, Sino-nasal or osteomyelitis of the ethmoid bone. In untreated primary tuberculosis, enlargement of hilar and paratracheal lymph nodes (or both) become apparent on chest radiographs.

Various portals of entries of infection are described for acquiring mycobacterium tuberculous lymphadenitis:

- Via respiratory tract - haematogenous and lymphatic dissemination. Hilar and mediastinal lymph nodes are usually involved initially.

- Via tonsil - spreads via the lymphatics to the draining cervical lymph nodes. It has been postulated that cervical tuberculous lymphadenitis occurs as a result of TB infection involving the tonsils, adenoids, and Waldeyer's ring, leading to cervical lymphadenopathy.

- Abdominal tuberculous lymphadenopathy may occur via swallowing of sputum or milk infected with *M. tuberculosis/M. bovis*

In the initial stage of superficial lymph node involvement, progressive multiplication of *M. tuberculosis* occurs. The onset of delayed hypersensitivity is accompanied by marked hyperaemia, swelling, necrosis and caseation of the centre of the nodes. This can be followed by inflammation, progressive swelling and matting with other nodes within a group. Adhesion to the adjacent skin may result in induration and purplish discolouration. The centre of the enlarging gland becomes soft and caseous material may rupture into surrounding tissue or through the skin with sinus formation.

Tuberculous mediastinal lymphadenitis may enlarge and cause compression of major blood vessels, phrenic or recurrent laryngeal nerves or cause erosion of bronchus.

Jones and Campbell classified peripheral tuberculous lymph nodes into following five stages:

- Stage 1: Reactive lymphadenitis - enlarged, firm, mobile, discrete nodes showing non-specific reactive hyperplasia

- Stage 2: Peri adenitis -large rubbery nodes fixed to surrounding tissue
- Stage 3: Cold abscess -central softening due to abscess formation
- Stage 4: Collar-stud abscess formation
- Stage 5: Sinus tract formation

1.4. History Taking Points

- Duration of swelling is usually variable, can be acute (1-2 weeks) in some cases to chronic (months) in some cases.
- Associated symptoms such as fever, weight loss and loss of appetite.
- Contact/past history of tuberculosis must be sought for.
- History of tobacco/alcohol/drug abuse treatment history includes the history of previous ATT intake (including drug, dose, duration and compliance).

1.5. Examination

On local examination, various factors like location, size, consistency etc. can be assessed. Specific areas can be evaluated in a patient with lymphadenopathy with various causes such as:

- Intraoral examination - cause of the swelling, odontogenic involvement or chronic ulcer
- Location of lymph nodes:
    - Generalized (>3 groups) can be present in HIV/NHL/TB/Infectious Mononucleosis/SLE.
    - Localized disease can be due to local infection and malignancy due to reactive changes and metastasis respectively.

Size of lymph node: Significant if >2 cm diameter in the inguinal region and >1 cm in other regions.

Consistency of lymph node:

- Hard – Malignancy/metastasis/Chronic infection
- Firm /Rubbery – Lymphoma/Chronic Leukemia
- Soft–Acute Leukemia

- Fixation:
    - Fixed seen in malignancy/inflammation
    - Matted seen in tuberculosis
- Tenderness:
    - Acute viral/bacterial infection
    - Rapid tumor expansion/bleeding into nodes
- Organomegaly:
    - Liver/spleen

Note: In case of deep-seated lymphadenopathy surveillance of all peripheral lymph node is also recommended.

Matted lymph node: Matted lymph nodes are described as a group of nodes that are conglomerated. They can be either due to benign (mycobacterial infection and sarcoidosis) or malignant (lymphoma and metastatic carcinoma) disorders.

1.6. Differential Diagnosis of Lymphadenopathy

- Infectious
  - *Mycobacterium tuberculosis*
  - Bacterial: sinusitis, otitis externa, cellulitis, abscess, tonsillitis, pharyngitis
  - Viral: EBV, CMV, HIV
  - Others: fungal, parasitological

- Neoplasms
  - Primary hematologic malignancy: HL, NHL
  - Melanoma, SCC skin cancers
  - Solid-organ cancer metastatic
- Miscellaneous conditions
  - Sarcoidosis
  - SLE
  - Castleman disease
  - Histiocytic necrotizing lymphadenitis (Kikuchi-Fujimoto disease)
  - Drugs

1.7. Investigations

Key Points

- All patients should undergo a detailed clinical examination and routine evaluation (30% of cases will be missed if you don't examine them).
- In patients with deep lymphadenopathy, all peripheral lymph nodes must be assessed for the presence of lymphadenopathy and preferred for sampling.
- Chest radiograph to be performed in all patients to rule out pulmonary tuberculosis or any other primary pulmonary pathology.
- Chest radiograph may show findings in nearly 27.7% of LN TB patients (10).

1.7.1. Routine investigation:

- Routine (CBC, LFT/KFT, ESR)
- RBS
- Hemogram
- Liver and renal function tests
- HIV serology

1.7.2. Radiology:

- Chest X-ray
- Ultrasonography
- CT Scan
- MRI/PET- CT (subject to clinical indication and availability)

1.7.3. Sampling:

- FNA
- Biopsy
- EBUS-TBNA/cTBNA (subject to clinical indication and availability)

1.7.4. Microbiological and pathological:

- Microscopy (FNAC)
- Molecular (NAAT)
- Culture (solid/liquid)
- Cyto-histopathology

1.7.3. Sample Processing:

- If samples are insufficient, in case of high clinical suspicion, NAAT testing may be given priority.
- As per the clinician's suspicion, samples may also be sent for bacterial/fungal culture and microscopy.

Sampling from lymph node:

1.7.3.A Fine Needle Aspiration (FNA):

FNA is a simple and inexpensive procedure

Procedure:

  - FNA can be directly done from superficial nodes
  - Deep nodes: USG/CT/EBUS guided aspiration can be done
- Investigation to be sent from FNA
  - AFB
  - NAAT
  - MGIT/L-J media
  - Cyto-histopathology
- Limitations of FNA
  - Limited sample amount
  - Tissue morphology might be distorted in immunodeficiency i.e. HIV

1.7.3.B Biopsy:

Can be done where FNA is not diagnostic in the setting of strong clinical suspicion of TB or alternate diagnosis is suspected.

- Excisional biopsy is preferred over incisional biopsy as excisional biopsy has highest diagnostic yield and incisional biopsy later may be associated with sinus tract formation.
- Mycobacterium tuberculosis can be cultured in 70-90% cases in excisional biopsy (5).
- Mediastinal lymph node biopsy is done with help of Bronchoscopy/mediastinoscopy/EBUS.
- Merits:
  - Highest diagnostic yield
  - Adequate sample can be sent for AFB, microscopy, culture, molecular test and immunohistochemistry marker for lymphoma/carcinomas can also be done.
- Limitations:
  - Requires experience
  - Local complications like infection, sinus tract formation

Note: Finding of a caseating granuloma on histopathology with constitutional symptoms is highly suggestive of tuberculosis, ATT may be initiated in such cases even in absence of microbiological evidence.

Radiological Diagnosis:

Importance of radiological imaging

- Diagnosis in a relatively inaccessible site
- Assess the extent of disease
- Evaluate response to therapy
- Detect residual infection after completion of therapy
- Help in a guided procedure like FNA and biopsy

1.7.2.A. Chest X-ray:

Chest radiograph of the patient is done to rule out pulmonary tuberculosis or any other primary pulmonary pathology. It has been seen that chest X-ray may show findings in (5)-

- 0-10% of patients in a non-endemic area
- 20-40% of patients in an endemic area (pleural thickening, apical fibrosis)
- 90% of patients with retroviral disease

1.7.3.B. Ultrasonography:

- Can help differentiate reactive, malignant and tuberculous lymph nodes in appropriate clinical settings.
- Can aid in FNA from deeper nodes.
- Safe for pregnant women.
- Ultrasound is the first line investigation for cervical lymphadenopathy.
- Sonographic features that help to identify abnormal nodes include shape (round), absent hilum, intranodal necrosis, reticulation, calcification, matting, soft-tissue oedema, and peripheral vascularity.
- Tuberculous nodes tend to be hypoechoic, round, without echogenic hilus and tend to show intranodal cystic necrosis, nodal matting, and adjacent soft-tissue oedema.
- On colour doppler, power Doppler, and 3D sonography, the vascular distribution of tuberculous nodes is varied and simulates benign and malignant nodes.
- Displacement of hilar vascularity is common in tuberculous nodes and is due to the high incidence of intranodal cystic necrosis, which displaces the vessels, in tuberculous nodes.

1.7.3.C. Endobronchial Ultrasound (EBUS):

Endobronchial ultrasound (EBUS) transbronchial needle aspiration (TBNA) is a minimally invasive technique allowing sampling of mediastinal lymph nodes via fine needle aspiration under direct sonographic visualisation. It has a low rate of morbidity and has demonstrated utility in the diagnosis of mediastinal lymphadenopathy secondary to malignancy, lymphoma and sarcoidosis.

- EBUS-TBNA should be considered the procedure of choice for patients in whom mediastinal TB is suspected.
- EBUS- TBNA has been shown to have a sensitivity of 85% (9).
- Highly accurate (diagnostic yield, 92%) and safe procedure for diagnosing mediastinal lymphadenopathy (9).
- If culture and histological results are combined with high clinical suspicion, EBUS-TBNA demonstrates excellent diagnostic accuracy and NPV for the diagnosis of mediastinal TB lymphadenitis.

Patients were considered to have had a diagnosis of mediastinal tuberculous lymphadenitis if they met one or more of the following criteria:

- A positive culture result for Mycobacterium TB from EBUS-TBNA;
- A positive NAAT result with the high clinical index of suspicion;
- The diagnosis was achieved through culture or biopsy of sites other than mediastinal lymph nodes;
- Culture-negative, but the high clinical index of suspicion and demonstration of supportive histological changes (granulomatous inflammation)

1.7.3.D. Computed Tomography:

CT provides knowledge not only of the site and extent of tuberculous lymphadenitis but also the status of the affected lymph node. CT is more sensitive than plain radiography in detecting tuberculous lymphadenopathy. It reveals nodes often measuring more than 2 cm, with a very characteristic, but not pathognomonic, 'rim sign' that consists of a low-density centre, representing caseous necrosis, surrounded by a peripheral enhancing rim due to granulomatous inflammatory tissue.

CT in patients of lymph node tuberculosis:

- Lymph nodes showing peripheral enhancement with hypodense centres, secondary to caseous and/or liquefactive necrosis.
- Conglomerate lymph node masses with areas of necrosis secondary to perinodal inflammation.
- Increased number of normal-sized or mildly enlarged mesenteric nodes of homogeneous density.
- Calcified lymph nodes

Note: Calcified lymph nodes are also seen in metastases from teratomatous testicular tumours, non-Hodgkin's lymphoma and tuberculosis after treatment. However, nodal calcification in patients from endemic areas in the absence of known primary malignancy and presence of clinical suspicion suggests a tuberculous aetiology.

Table 1.1: Comparison between tuberculosis, sarcoidosis and lymphoma.

	Tuberculosis	Sarcoidosis	Lymphoma
Distribution	Rt. Hilar, Rt. paratracheal and subcarinal	Symmetrical B/L hilar most common	Perivascular, paratracheal most common; Hilar rare
Enhancement	Peripheral and heterogeneous enhancement	Homogenous	Homogenous
Size	<4cm	<4cm	>4cm
Conglomeration	Present	Discrete	Discrete
Calcification	Common	Egg-shell pattern	Not seen
Perinodal fat	Obscured	Clean	Clean
Lung involvement	Lung nodule, cavities	Peri lymphatic nodules	Uncommon

1.7.3.E. Magnetic Resonance Imaging (MRI):

- MRI is radiation-free and can be used in follow-up cases of mediastinal tuberculosis.
  - On MRI, tuberculous lymphadenopathy is mostly hyperintense on T2-weighted images. Central hyperintensity on T2-weighted images corresponds to liquefaction necrosis.
- Obliteration of the perinodal fat has been suggested to reflect capsular disruption.
- Enhancement patterns include peripheral enhancement visible as a uniform, thin or thick, complete or incomplete rim; and a conglomerate group of nodes showing peripheral and central areas of enhancement.
- Heterogeneous enhancement and, less frequently, homogeneous enhancement or no enhancement may also be seen.
- Can be done in selective follow-up cases after expert advice.

1.7.3.F. Positron Emission Tomography (PET):

Positron emission tomography/computed tomography with the use of 18F-fluorodeoxyglucose (18F-FDG PET/CT) is a non-invasive imaging method that has been used widely for the differentiation of malignant from benign lesions. But 18F-FDG uptake is also observed in PTB, in tuberculoma, and in other TB-related lesions.

During anti-TB treatment, some bacillus-negative tuberculomas do not decrease in size and may even increase, making it difficult for the physician to decide whether to modify treatment.

- 18F-FDG PET/CT imaging may help, as the changes in glycolytic activity within the inflammatory lesion, measured by 18F-FDG uptake, correlate well with the clinical markers of response.
- The value of 18F-FDG PET/CT is established in the follow-up and evaluation of the treatment response, especially in patients with extrapulmonary involvement and when drug resistance is prevalent.
- Can be done in selective cases only.

1.8. Treatment

1.8.1. Diagnostic definitions

1.8.1.a. Bacteriologically Confirmed LNTB case: Symptoms and signs of LNTB plus at least one of following

1. Positive validated NAAT (e.g. NAAT MTB/Rif)
2. Positive culture for *M. tuberculosis*
3. Positive microscopy for AFB

1.8.1.b. Clinically Diagnosed lymph node tuberculosis: Symptoms and signs of lymph-node tuberculosis plus

1. Negative microscopy, negative culture and NAAT based test
2. No other diagnosis explains signs and symptoms
3. Radiological evidence suggestive of LNTB
4. Histological findings and clinical features suggestive of tuberculosis

LNTB primarily requires medical management, adjunct surgical excision is generally associated with worse outcomes. LNTB patients can be managed at the primary care level. Referral to secondary care for specialist diagnostic sampling may be required.

Six months ATT standard first-line regimen is recommended for peripheral lymph node TB and can be

provided.

Initial 2 months as intensive phase- 4 drug regimen which includes isoniazid, rifampicin, pyrazinamide and ethambutol.

Continuation phase from 3rd month onward, for 4 months (total 6 months of therapy, after which continuation phase may be extended by 3 months) which includes 3 drug regimens (isoniazid, rifampicin and ethambutol).

Assess Response To Treatment At 4 Months

Treatment failure or alternative diagnosis should be considered in patients who have worsened or deteriorated after initial improvement. The most common cause of failure is compliance issues followed by poor absorption and drug resistance. After ruling out treatment failure or alternative diagnosis, the possibility of a paradoxical reaction should be considered. Some patients with LNTB have residual lymphadenopathy at the end of treatment. This does not indicate ongoing active TB infection if the largest node is less than 1 cm in size. Some patients have residual nodes more than 1 cm in size, and these patients are classified as partial responders. There is uncertainty about whether continuing ATT in these patients is beneficial. While some evidence suggests that these patients may not require further ATT, the data is insufficient at this stage.

The expert group suggested these patients should receive an additional 3 months of HRE, followed by a biopsy sent for histology and TB culture.

For mediastinal LNTB, improvement on ATT can be monitored with a chest X-ray, but a CT scan may be indicated if lymph nodes do not reduce in size after 4 months. In patients who fail to improve on ATT, the alternative diagnoses of lung cancer, lymphoma, sarcoidosis and fungal infection should be considered.

Current expert opinion on when to stop ATT in patients with persistently enlarged mediastinal lymph nodes is to stop when there is absence of interval change in CT/MRI of mediastinal lymph nodes for more than 4 months, with a resolution of all other clinical signs and symptoms.

Difficulties in managing lymph node tuberculosis also due to problems in obtaining the tissue for making definitive diagnosis of lymph node tuberculosis as mentioned earlier. Certain other problems that may be encountered include:

- The appearance of new lymphadenopathy
- Enlargement of the existing nodes
- Development of fluctuation
- Sinus tracts formation
- Residual lymphadenopathy after completion of treatment
- Relapse

Possible explanations for this suboptimal response of therapy in lymph node tuberculosis include:

- Poor patient compliance to treatment
- Unidentified drug resistance
- Poor drug penetration into the lymph node/absorption
- Unfavourable local milieu
- Nontuberculous mycobacterial infection

- Enhanced delayed hypersensitivity reaction in response to mycobacterial antigens released during medical treatment of the disease
- Superadded infection
- Drug resistance (INH mono-resistance/MDR TB)
- Alternative diagnosis e.g., malignancy, Kikuchi-Fujimoto, Kimura lymphadenitis

Table 1.2: Features of Peripheral Lymphadenitis Due to *M. tuberculosis* vs. Nontuberculous Mycobacteria.

	Tuberculosis	**Nontuberculous Mycobacteria**
Age range (years)	20–40	1–6
Sex distribution	F>M	F≥M
Birth country	TB-endemic	Non–TB-endemic
HIV infection	Common in HIV-endemic countries Uncommon in developed countries	Rare
Clinical features	Indolent painless swelling Systemic symptoms: uncommon in HIV-negative, common in HIV-positive	Indolent painless swelling Systemic symptoms: uncommon
Location	Cervical	Cervicofacial
Pulmonary disease	Common	Absent
Tuberculin skin test	Positive	Occasionally positive
Histology	caseating granuloma	More microabscess, ill defined granulomas(no classical caseating granuloma), less number of giant cells
Treatment	Antibiotics +/− excision	Excision +/− antibiotics
Paradoxical reactions	Common	Absent

1.9. Monitoring And Follow-Up LNTB Patients

- Baseline general examination to document all the possible sites of lymph-node involvement including nature and size of the involved lymph nodes.
- Appearance of fluctuation in one or more lymph nodes calls for aspiration under all aseptic precautions.
- Any secondary bacterial infection should be dealt with appropriately, that may include incision and drainage.
- Worsening after 8 weeks of therapy may call for en bloc resection of the involved lymph node chain to avoid the appearance of ugly sinus tracts. Non-healing sinus tracts may need resective surgery.
- Residual lymph nodes after completion of treatment should be observed closely. Any increase in size or appearance of symptoms calls for excisional biopsy for histopathology and culture. Most of these patients will respond to retreatment with the same regimen.

- All efforts should be made to isolate the causative agent and to obtain prompt sensitivity testing particularly in relapsed cases/non-responders and chemotherapy modified accordingly.
- Some patients with LNTB have residual lymphadenopathy at the end of treatment, >1 cm in size, such patients maybe:
    1) Partial responders: here additional 3 months of RHE, followed by a biopsy is to be sent for histology and TB culture.
    2) Residual fibrotic LN: ATT need not be extended.

1.10. Paradoxical Reaction

Paradoxical reaction (PR) in tuberculosis is defined by a clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions, in patients receiving anti-tubercular medication who initially improved on treatment. It is a diagnosis of exclusion as mentioned earlier.

This syndrome is often self-limiting yet its potential to cause serious morbidity and, on rare occasions, death is increasingly being recognised. Although the exact mechanisms are not understood it is most likely that PR is due to an abnormal immune response or reconstitution of the immune system. For this reason, PR is more commonly seen in HIV co-infected individuals.

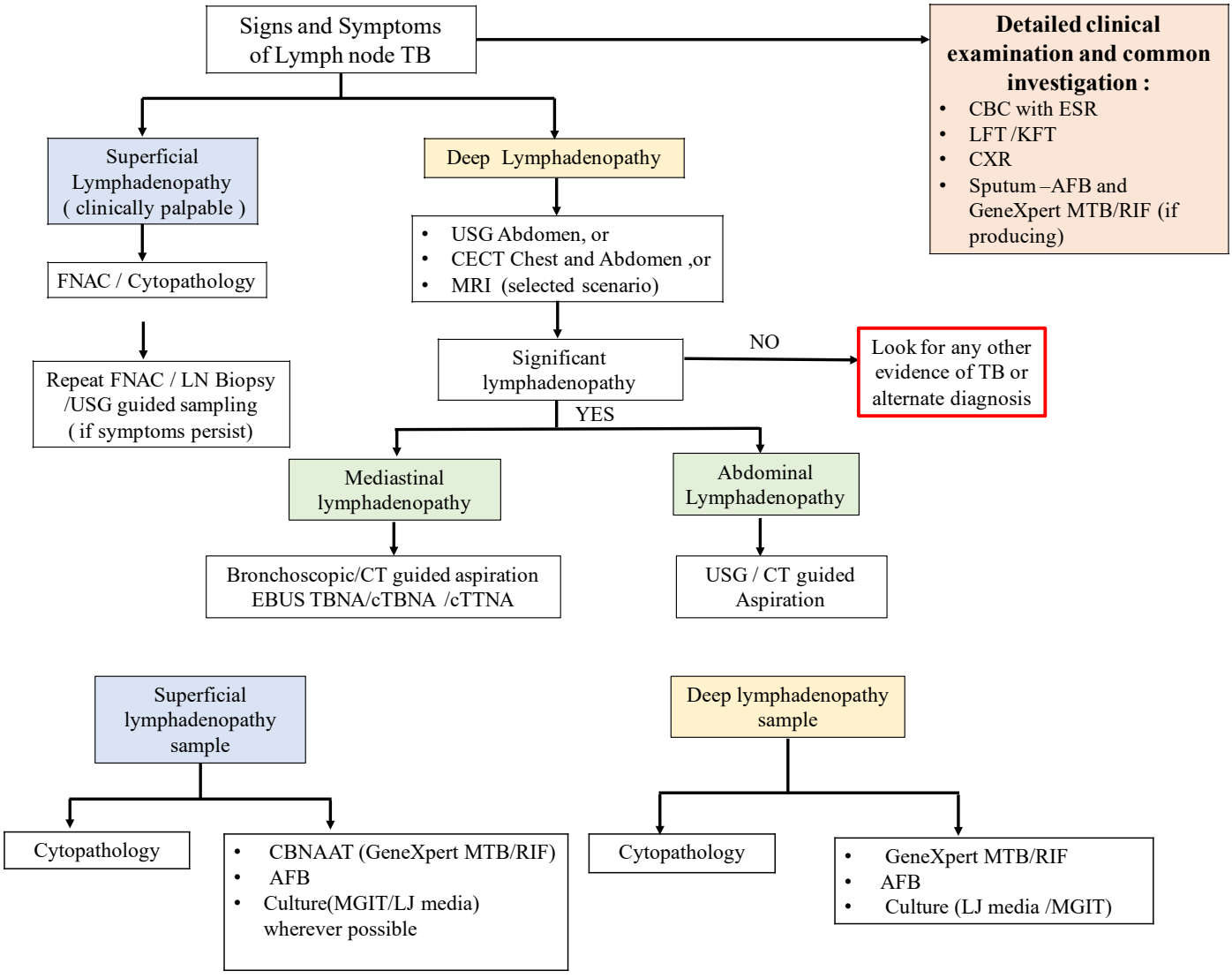
A rise in lymphocyte count, a tuberculin conversion during treatment and disseminated disease may all be associated with the development of PR. It is also recognised that cases of overwhelming or miliary TB can have poor skin reactivity to tuberculin skin tests in approximately half of such cases.

Key points:
- Deterioration in the first 3 weeks to 4 months may be due to paradoxical reaction
- Exclusion of alternative explanation for clinical deterioration
- More common in HIV infected (Within 2 months of combination antiretroviral therapy start)
- Management:
    - Continuation of ATT
    - Symptomatic treatment
    - NSAIDS for pain
    - USG guided aspiration in fluctuance

1.11. Follow Up

- Follow up of clinical response should be done at 1, 2, 4 and 6 months.
- Consider the possibility of treatment failure in patients who have worsened or deteriorated after initial improvement.
- Imaging to be repeated if clinically indicated.
- Development of fluctuation – should undergo aspiration.
- Sinus tracts- Any worsening after 8 weeks of therapy – en-bloc resection of the involved lymph node chain to avoid sinus tract formation.
- Some patients with LNTB have residual lymphadenopathy at the end of treatment, >1 cm in size:
    - Partial responders (clinical features have persisted or reappeared): additional 3 months of HRE, followed by a biopsy sent for histology and TB culture.
    - Residual fibrotic LN(clinical features have resolved): ATT need not be extended.

Flow chart 1.1: Diagnostic algorithm for Tuberculous Lymphadenitis



Bacteriologically Confirmed LNTB case	Clinically Diagnosed LNTB case
Symptoms and signs of LNTB and has at <u>least one</u> of the following: • Positive microscopy for AFB • Positive culture of M tb • Positive validated PCR-based test (such as Xpert MTB/RIF)	A LNTB patient who <u>has all of</u>: • Negative microscopy, negative culture and PCR- based tests • Strongly suggestive radiological findings, histopathological findings, clinical course • No other diagnosis made to explain signs and symptoms

Treat with drug sensitive ATT

References:

1. Sharma SK, Mohan A. Extrapulmonary tuberculosis. Indian J Med Res. 2004 Oct;120(4):316–53.

2. TB India 2014 Revised National TB Control Programme Annual Status Report. Ministry of Health and Family Welfare, Central TB Division, Directorate General of Health Services. New Delhi: Central TB Division.

3. Golden MP, Vikram HR. Extrapulmonary tuberculosis: an overview. Am Fam Physician. 2005 Nov 1;72(9):1761–8.

4. Clinical and cytological features in diagnosis of peripheral tubercular lymphadenitis - A hospital-based study from central India. - PubMed - NCBI [Internet]. [cited 2019 Oct 14]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28941854
5. Fontanilla J-M, Barnes A, von Reyn CF. Current Diagnosis and Management of Peripheral Tuberculous Lymphadenitis. Clin Infect Dis. 2011 Sep 15;53(6):555–62.

6. Chihota VN, Grant AD, Fielding K, Ndibongo B, van Zyl A, Muirhead D, et al. Liquid vs. solid culture for tuberculosis: performance and cost in a resource-constrained setting. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 2010 Aug;14(8):1024–31.

7. Gupta KB, Kumar A, Sen R, Sen J, Vermas M. Role of ultrasonography and computed tomography in complicated cases of tuberculous cervical lymphadenitis. Indian J Tuberc. 2007 Apr;54(2):71–8.

8. Ahuja AT, Ying M. Sonographic Evaluation of Cervical Lymph Nodes. Am J Roentgenol. 2005 May 1;184(5):1691–9.

9. Geake J, Hammerschlag G, Nguyen P, Wallbridge P, Jenkin GA, Korman TM, et al. Utility of EBUS-TBNA for diagnosis of mediastinal tuberculous lymphadenitis: a multicentre Australian experience. J Thorac Dis. 2015 Mar;7(3):439–48.

10. Skoura E, Zumla A, Bomanji J. Imaging in tuberculosis. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2015 Mar;32:87–93.

11. Joshi AR, Basantani AS, Patel TC. Role of CT and MRI in Abdominal Tuberculosis. Curr Radiol Rep. 2014 Sep 10;2(10):66.

12. Sharma SK, Ryan H, Khaparde S, Sachdeva KS, Singh AD, Mohan A, et al. Index-TB Guidelines: Guidelines on extrapulmonary tuberculosis for India. Indian J Med Res. 2017 Apr;145(4):448–63.
13. Campbell IA, Dyson AJ. Lymph node tuberculosis: a comparison of various methods of treatment. Tubercle. 1977 Dec;58(4):171–9.

14. Gupta PR. Difficulties in managing lymph node tuberculosis. Lung India. 2004 Oct 1;21(4):50.
15. Breen R a. M, Smith CJ, Bettinson H, Dart S, Bannister B, Johnson MA, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. Thorax. 2004 Aug;59(8):704–7.

2. Pleural Tuberculosis

KEY POINTS

- Pleural TB is a leading cause of exudative pleural effusion in our country
- The typical presentation is with cough, chest pain, fever and shortness of breath
- USG guided pleurocentesis and pleural fluid analysis play a key role in the diagnosis
- Pleural effusions causing respiratory embarrassment may require needle or intercostal tube drainage
- Pleural fluid ADA levels > 40 U/L raise suspicion for pleural TB
- Pleural fluid NAAT has low sensitivity for the diagnosis of pleural TB
- Management involves the introduction of ATT, pleural fluid drainage (if required) and pain management
- Corticosteroids have no role in the routine management of pleural TB

2.1. Introduction

While lymph nodes are the most common extrapulmonary site (33%) (1) involved, pleural involvement is the second most common.

2.2. Epidemiology

Pleural TB is one of the leading causes of exudative effusion in TB endemic areas and in the HIV – positive population. As opposed to pulmonary TB, pleural TB affects younger age groups (20-40 years) more commonly. A higher incidence is also found in the diabetic population.

2.3. Pathophysiology

The pathogenesis can be explained by:

- Immunological factors: Delayed hypersensitivity type phenomenon
- This occurs due to the rupture of subpleural foci with the entry of mycobacterial antigen into the pleural space.
- Contiguous spread from lung
- Haematogenous and lymphatic spread

2.4. Clinical Features

The most common clinical symptom is cough (94% of patients) followed by chest pain (78% of patients) (5). Fever for a duration of less than one month occurs in 66% of patients, a more acute onset fever occurring for less than one week is seen in 33% (6). Shortness of breath and constitutional symptoms such as night sweats are seen in 50% of individuals (7). The other constitutional symptoms like weight loss have a varying frequency ranging from 25-85% (7). On examination, around 90% of tuberculous effusions are unilateral (7) involving less than 2/3 of the hemithorax. Less than half (20-50%) (9) of the patients have associated pulmonary lesions.

2.5 Differentials

(i) Malignant pleural effusion
(ii) Empyema
(iii) Fungal related effusion
(iv) Chylothorax
(v) Hemothorax
(vi) Liver abscess
(vii) Sarcoidosis
(viii) SLE/Rheumatoid pleurisy
(ix) Viral pneumonia (influenza, COVID-19 etc.)

2.6. Diagnosis

- Blood investigations do not help much in making the diagnosis as they are normal in 94% of the patients (8).
- Pleural TB is considered as a differential in the setting of an acute to subacute disease process with symptoms presenting for less than a month in most patients. It may also present with a low-grade fever with constitutive symptoms such as weight loss and loss of appetite suggesting a chronic, inflammatory process that may be infectious, autoimmune or neoplastic in origin. Investigations include raised ESR, mild leucocytosis, mild anaemia, raised globulin/reduced albumin: globulin ratio may further point to an inflammatory process.
- A tuberculin skin test currently does not play a role in the diagnosis of pleural tuberculosis, as a negative test does not rule out its presence. The positive response rate shown in various studies ranged between 40.9% - 66.5% (5,8,12).
- A person with a positive skin test and tuberculous pleural effusion will still have a positive skin test at the end of 2 months of therapy. Immunocompromised and immunosuppressed patients may not show a response.
- Imaging can be useful in diagnosing an effusion and quantifying it and may also help in differentiating the cause. In the case of a tuberculous pleural effusion, 90-95% (4) of the time, only one hemithorax is involved and is usually one-half of the hemithorax volume.
- A chest radiograph should be done in all patients with suspected pleural effusion. PA view of chest x-ray requires at least 200ml of fluid for the effusion to be detectable. Stigmata of other tuberculous involvement such as pulmonary consolidation can give a clue to the diagnosis. Radiographs are also helpful in monitoring the treatment response and are advised 8 weeks (2 months) after commencement of therapy and at 6 months of therapy.
- Ultrasonographic examination is useful as a bedside tool for the diagnosis of pleural effusion. As little as 50ml of pleural fluid can be detected on ultrasound. It also has an advantage in diagnosis of septations and pleural thickening. Pleural fluid quantification and simultaneous pleurocentesis can also be done.

FINDINGS	USE	ADVANTAGE	DISADVANTAGE	SENSITIVITY (14)	SPECIFICITY (14)
Chest Radiograph Costo-phrenic angle blunting, with homogenous opacity in lung field	ALL patients	Detected when there is >200ml fluid on PA film. Pulmonary involvement can be seen and progress can be monitored.	Small amount of fluid may be missed Radiation exposure	SUPINE AP	
				33-92%	70-89%
				LATERAL DECUBITUS	
				94%	100%
				UPRIGHT PA	
				82%	81%
				UPRIGHT LATERAL	
				86%	88%
Ultrasound Anechoic region (black) below pleural line (white)	SELECTED patients*	Bedside investigation. Detects as little as 50ml pleural fluid. Septations visualised. No radiation.	Lung involvement cannot be ruled out in all cases	92-94%	93-100%

Table 2.1. Imaging for Pleural TB

2.6.1 Pleurocentesis

Surgical puncture of the chest wall to aspirate fluid or air from the pleural cavity.

2.6.1 A. Precautions:

1. Platelet count > 50,000/cumm
2. Check for clotting abnormalities, PT/INR
3. Severe cough or uncontrolled hiccoughs

2.6.1 B. Procedure:

Prior to starting, take informed consent from the patient and explain the procedure. The patient is then positioned in an upright sitting position, with arms resting on an elevated table in front at upper chest level. This ensures that intercostal spaces are widened.

Mark the site of insertion, either by counting the highest rib level on the x-ray or by percussing out the fluid level. Ideally ultrasound guided fluid visualization and marking of site is recommended.

The site should be located in the mid-scapular or mid-axillary line.

Using sterile precautions and after local anaesthesia (2% lignocaine), insert the needle along the superior margin of the lower rib, into the pleural space. Aspirate back on the needle till you see pleural fluid. Making sure that the needle is stabilised with one hand, using a 3-way connector, draw as much fluid as required. At least 20-40ml of fluid is required for all the recommended tests to diagnose a tuberculous pleural effusion. After aspiration, draw the needle out slowly with pressure over the site.

Ultrasound-guided pleurocentesis is advised in the following conditions:

- Minimal pleural effusion
- Atypical presentation
- Suspected loculation/adhesion

A post-procedure chest X-ray is warranted to look for any complications such as pneumothorax or hydro-pneumothorax.

2.6.1 C. Sample Collection And Transport:

The pleural fluid sample aspirated from pleurocentesis should be transferred to a sterile container and transported to the respective laboratories as soon as possible.

The maximum accepted time delay for the pleural fluid sample is 2 hours, but it can be stored for up to 48 hours at 4 degrees Celsius for most tests except for microbiological culture.

The recommendations for different tests are as follows:

- For cell counts about 3-4ml pleural fluid should be collected in an anti-coagulant coated tube. (EDTA/heparin)
- For biochemical analysis, 5ml of pleural fluid in any sterile container without any additive is required.
- For microbiological analysis, 2-5ml fluid has to be sent in a sterile container for gram stain and other standard processing (NAAT). The same amount of fluid can directly be inoculated into aerobic and anaerobic culture media as well. 5ml should also be inoculated into liquid culture media for *M. tuberculosis*.

For long term storage, the sample should be centrifuged and stored at -80 degrees Celsius. Samples can be viable for protein, LDH and ADA for at least for a few years and for cytokines up to 45 days.

2.6.1 D. Pleural Fluid Analysis:

The first line investigations to be sent are:

1. Cell count – total count/differential count
2. Protein
3. Glucose
4. ADA

Table 2.2: Pleural fluid examination for the diagnosis of pleural tuberculosis

Pleural Fluid	Frequency
Exudate with protein >3g/dL	Almost all (7)
Pleural fluid glucose >60mg/dL	80-85% (8)
>50% lymphocytes	93.3% (8)
Pleural fluid ADA >40 IU/L	81-100% (22)

Light's criteria are used to establish the nature of the pleural fluid with further workup based on the fluid being a transudate versus an exudate.

Pleural fluid in TB shows a high glucose value and an elevated LDH. Cytology of pleural fluid shows a lymphocytic predominance.

Culture: Pleural fluid-solid culture is positive in only 12- 30% (4) of cases whereas liquid cultures using MGIT display better sensitivity. MGIT cultures are also available within 2 weeks, unlike solid cultures which take at least a month.

Nucleic Acid Amplification tests (NAAT): NAAT for MTB/RIF has a sensitivity of 49.5% and specificity of 98.9% (23), when compared to culture. Using culture as a reference standard in a paucibacillary disease raises some concern. NAAT for MTB/RIF provides a higher sensitivity than conventional methods (culture and AFB staining).

Adenosine deaminase (ADA): ADA levels in pleural fluid is a semi-specific biochemical marker for diagnosis with a cut off level of 40 IU/l. It has a sensitivity of 92% and a specificity of 90% (25).

Level	Interpretation
> 70 IU/L	Highly likely to be pleural TB
40-70 IU/L	Indeterminate level, other risk factors to be considered
<40 U/L	Low likelihood of TB, investigate for other causes
Pleural fluid ADA >40 IU/L	81-100% (22)

Table 2.3. Pleural fluid ADA levels in diagnosis of TB

In cases with diagnostic uncertainty or nonresponse to treatment, other etiologies need to be ruled out using investigations which may include:

- Pleural fluid for bacterial/fungal culture, malignant cytology
- CT scan - CT scan is particularly helpful in patients with an uncertain diagnosis, suspected malignancy and in HIV positive individuals.
- Pleural biopsy

Table 2.4: CT-Scan in the diagnosis of pleural tuberculosis

FINDINGS	USE	ADVANTAGE	DISADVANTAGE
Hypodense effusion with pleural enhancement with/ without pleural thickening	Selected patients – When diagnosis not clear, suspected malignancy, HIV positive patients	Reference standard in most studies Sensitive than X-ray to check for primary lung involvement.	Difficult to distinguish small effusion and pleural thickening Low sensitivity for septations. High radiation exposure High cost.

2.6.2. Pleural Biopsy: Even with all the above-mentioned available tests, results may not always point to the right diagnosis. In such cases, the diagnostic test of choice is thoracoscopy with pleural biopsy.

2.6.2. A. Types Of Pleural Biopsy:

a. **Percutaneous pleural biopsy:** Includes closed pleural biopsy and CT guided cutting needle biopsy. The closed pleural biopsy may further be done blind or as an ultrasound-guided procedure.
b. **Thoracoscopic pleural biopsy:** Useful in cases with a negative percutaneous biopsy, suspicion for patchy disease or for a more detailed workup for malignancy. Rigid as well as semi-rigid thoracoscope may be used for thoracoscopy where the yield of the former has been reported to be higher.
c. **Open biopsy via thoracotomy:** Surgical procedure that has largely been supplanted by the above-mentioned methods.

2.6.2. B. Number: More than 6 biopsy specimens should be taken in suspected tuberculous pleural effusion to maximize yield.

2.6.2. C. Histopathology And Culture: Histopathology with evaluation for the presence of granulomas has a sensitivity of 72-80% in diagnosing tuberculosis while the use of culture in these specimens has a sensitivity of 60-67% (29). These modalities are used in conjunction and in such a scenario, there is an improved rate of detection of *M. tuberculosis* with a sensitivity of around 87% (30).

2.6.2. D. Use Of NAAT: Using NAAT on pleural biopsy specimens has been shown to greatly increase the yield and sensitivities- 45-85.5% with specificity 97.2% have been reported (31,32).
Proposed use: Patients with exudative pleural effusion with inconclusive initial workup have the option of undergoing thoracoscopy or a percutaneous pleural biopsy. While the yield of thoracoscopy has been found to be higher in such scenarios(93.2% vs 84.5% for percutaneous pleural biopsy), the cost and availability remain major issues (33). Therefore, in such scenarios, a percutaneous pleural biopsy may be used. A combination of ADA, lymphocytic predominance (>= 0.75) with closed needle biopsy has shown to have a sensitivity of nearly 93% and around 100% specificity (34).

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Diagnosis

Table 2.5: Comparison of diagnostic modalities for pleural tuberculosis

TEST	PATIENTS	COMMENTS
X-ray chest	All	Look for blunting of costo-phrenic angle. Look for stigmata of pulmonary involvement – nodules/lymph nodes. Maybe used to monitor progress.
HIV testing	All	Due to association of EPTB with HIV, all suspected/diagnosed patients must undergo HIV testing as per the national program.
CT chest and abdomen	Selected	Useful in equivocal cases especially with suspected malignancy or HIV positive patients at higher risk of disseminated TB. More sensitive than CXR for detection of effusions/pulmonary/node involvement.
USG chest	Selected	Can detect smaller volumes of fluid. Loculation/adhesion/pleural thickening can be visualised. Fluid can be quantified and small volumes can be aspirated under guidance.
Pleurocentesis	All	Most do not require complete therapeutic drainage unless causing respiratory symptoms in which case specialist monitoring is required during and following a drain. All should have diagnostic samples taken for glucose, protein, ADA, LDH (with concurrent serum LDH), differential counts. Specific investigations include microscopy and culture for Mtb and cytology. Light's criteria is used to differentiate exudate from transudative effusion (table below) Yield from ADA levels depends on cutoff: > 70 U/L – highly likely to be pleural TB 40-70 U/L – Indeterminate level, other risk factors to be considered <40 U/L – Low likelihood of TB, investigate for other causes Due to a common differential of parapneumonic effusion in children, ADA may yield a higher proportion of false positives in this group and further investigation is required for defining the exact utility of the same in pleural TB in children.
Sputum samples	Selected	Send for NAAT, microscopy and culture as per pulmonary TB guidelines whenever concurrent pulmonary TB is suspected.
Pleural biopsy (closed or thoracoscopic)	Selected	Much higher yield than pleural fluid for microscopy and culture for Mtb, histopathology may also be performed. Thoracoscopically obtained specimens have a higher diagnostic yield than closed pleural biopsy. For patients where diagnosis is uncertain despite other tests or where pleural malignancy is a significant differential diagnosis.
NAAT	Can be considered if available	Sensitivity of NAAT is 46.1% whereas the specificity is 99.1%. In view of low sensitivity which can compromise treatment initiation, routine use is not recommended in pleural fluid.

2.7 Management

2.7.1 Anti Tubercular Therapy - 2HRZE + 4HRE (Total: 6 Months)

- Clinical improvement in most cases is seen in 2 weeks following the start of treatment with a significant reduction in pleural effusion in 6-8 weeks.
- Patients are monitored clinically and radiologically with defervescence, increase in appetite, weight gain, reduction in shortness of breath, decreasing pleural effusion and settling of inflammatory markers all pointing towards improvement.
- Follow-up CXR is recommended 8 weeks after starting treatment to assess progress. The increasing size of effusion or lack of response may be due to a paradoxical reaction or alternate diagnosis which requires further workup.
- Drug resistant TB – Drug Susceptibility testing is advised to guide treatment and patients must be referred to nodal/district TB centres for further workup and management.

2.7.2 Pleural Fluid Drainage:

- If the effusion is causing respiratory distress (shortness of breath, increase in respiratory rate) pleural fluid drainage can be done.
- Chest tube drainage/pigtail catheter drainage: Routine insertion is not required but special circumstances may necessitate insertion of chest tubes including the presence of an empyema, large/symptomatic pneumothorax, hemothorax or bronchopleural fistulas.

2.7.3 Role of Corticosteroids:

Recent meta-analysis that included 6 trials with 590 participants examining the role of corticosteroids in pleural tuberculosis found that while they might reduce the time to resolution of effusion and decrease the risk of chronic pleural changes (thickening/adhesions), there was no evidence to show difference in the relevant parameters such as long term respiratory function with the use of corticosteroids increases the risk of adverse events leading to discontinuation of therapy. In view of very low mortality in pleural tuberculosis and insufficient data to show major improvements in respiratory function or other clinically relevant outcomes, corticosteroids are not recommended for the treatment of pleural tuberculosis.

2.7.4 Nutritional Management:

Full description of management strategies as per existing guidelines is beyond the scope of this module and the reader is referred to the existing guidelines from WHO and their Indian adaptations. In general, a balanced diet rich in proteins and with adequate calories is needed for patients suffering from TB with emphasis on maintaining an adequate intake of pyridoxine to prevent isoniazid induced toxicity.

2.7.5 Testing for HIV:

All patients diagnosed with any form of TB must be tested for HIV according to national guidelines. Medications for drug-susceptible TB and ART are both available to the patients at the ART Centres to improve compliance.

2.8 Complications

2.8.1 Lack Of Response:

If the patient continues to have symptoms such as fever, loss of appetite and shortness of breath after 2 months of therapy they must be further investigated. After ensuring drug adherence and no interactions with other drugs being taken, the following possibilities must be considered:

a. Immune reconstitution inflammatory syndrome (IRIS):
   - Refers to paradoxical worsening of the clinical/radiological picture due to improved immune response as the disease mediated immune suppression reduces.
   - It usually starts after 2 weeks of therapy with a median of around 56 days.
   - Diagnosis revolves around repeat blood and radiological investigations and if necessary, a repeat thoracentesis with cultures to rule out a superadded infection.
   - Most cases can be managed conservatively while systemic corticosteroids are reserved for severe/life-threatening cases.

b. Drug Resistance:
   - Suspected based on lack of clinical improvement or history of contact with a resistant case
   - Microbiological evidence is needed for susceptibility guided treatment regimens.
   - Pleural fluid liquid culture can have a good yield for isolation of mycobacteria followed by drug susceptibility testing.
   - Lack of isolation may require more invasive procedures like pleural biopsy for microbiological diagnosis.
   - Treatment regimens for drug-resistant TB (DR-TB) to be provided as per national guidelines at District/Nodal DR-TB Centres.

c. Alternate diagnosis:
   - Fungal infections, malignancies, autoimmune disorders etc. can mimic tuberculous pleural effusions both clinically and on biochemical panels.
   - Repeat examination of the pleural fluid with specific testing for these etiologies may be required in case.

d. Superadded infection: Based on the clinical scenario, requires repeat cultures to establish etiologies and guide treatment.

2.8.2 Pleural Thickening: This is a common complication of pleural TB, which can occur in up to 50% of patients.This is mostly asymptomatic and causes no major limitation of lung function. However, severe cases may result in a marked restrictive lung pathology or development of fibrothorax which may need decortication.

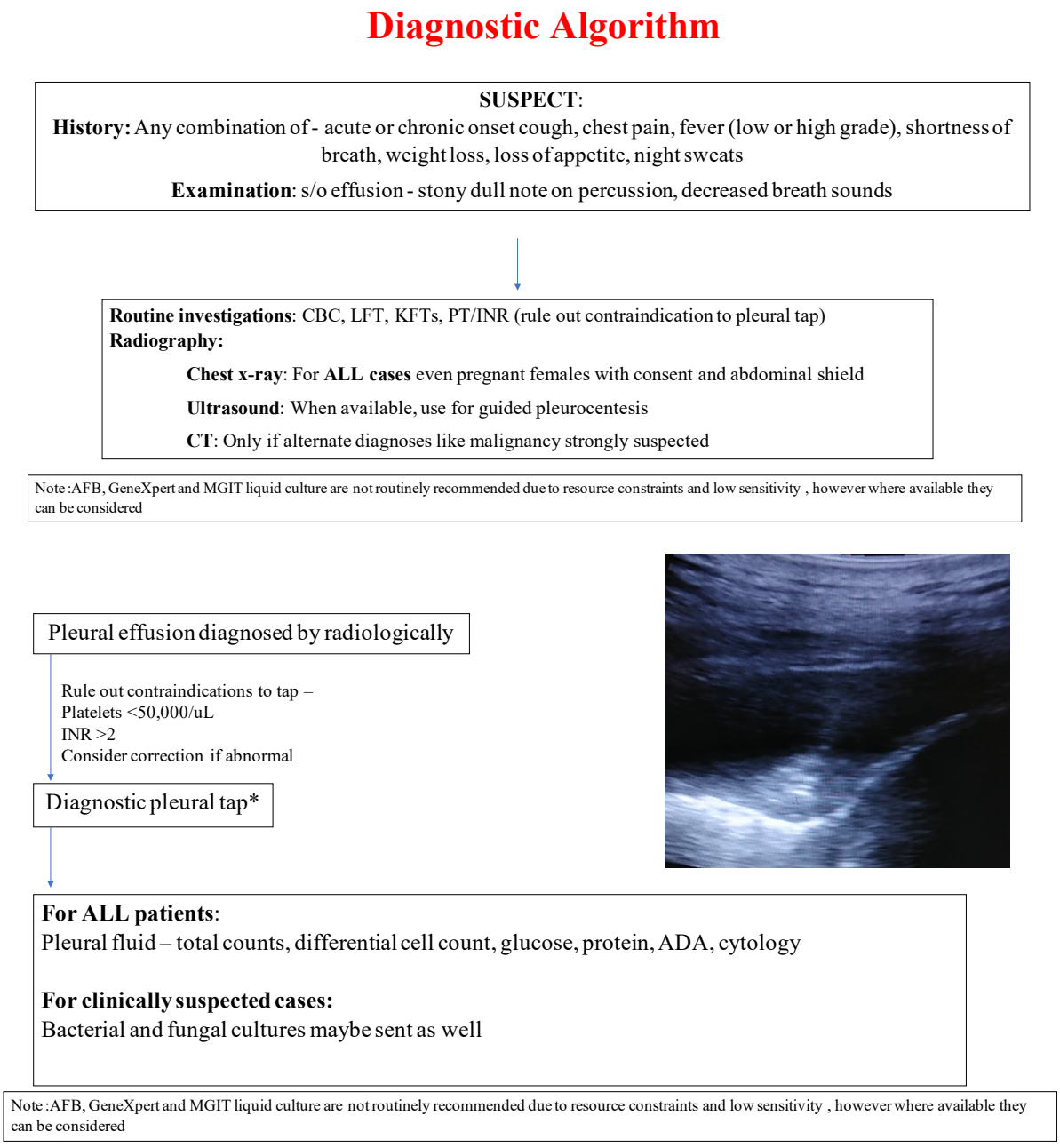
2.8.3 Empyema: Defined as the presence of frank pus in the pleural cavity as characterised by the presence of an exudate (Light's criteria) with polymorphonuclear cells on microscopy, low glucose, elevated lactate dehydrogenase >1000 and pH < 7.2. Such cases require management with tube thoracostomy along with anti-tubercular therapy and regular follow-up to assess the adequacy of drainage.

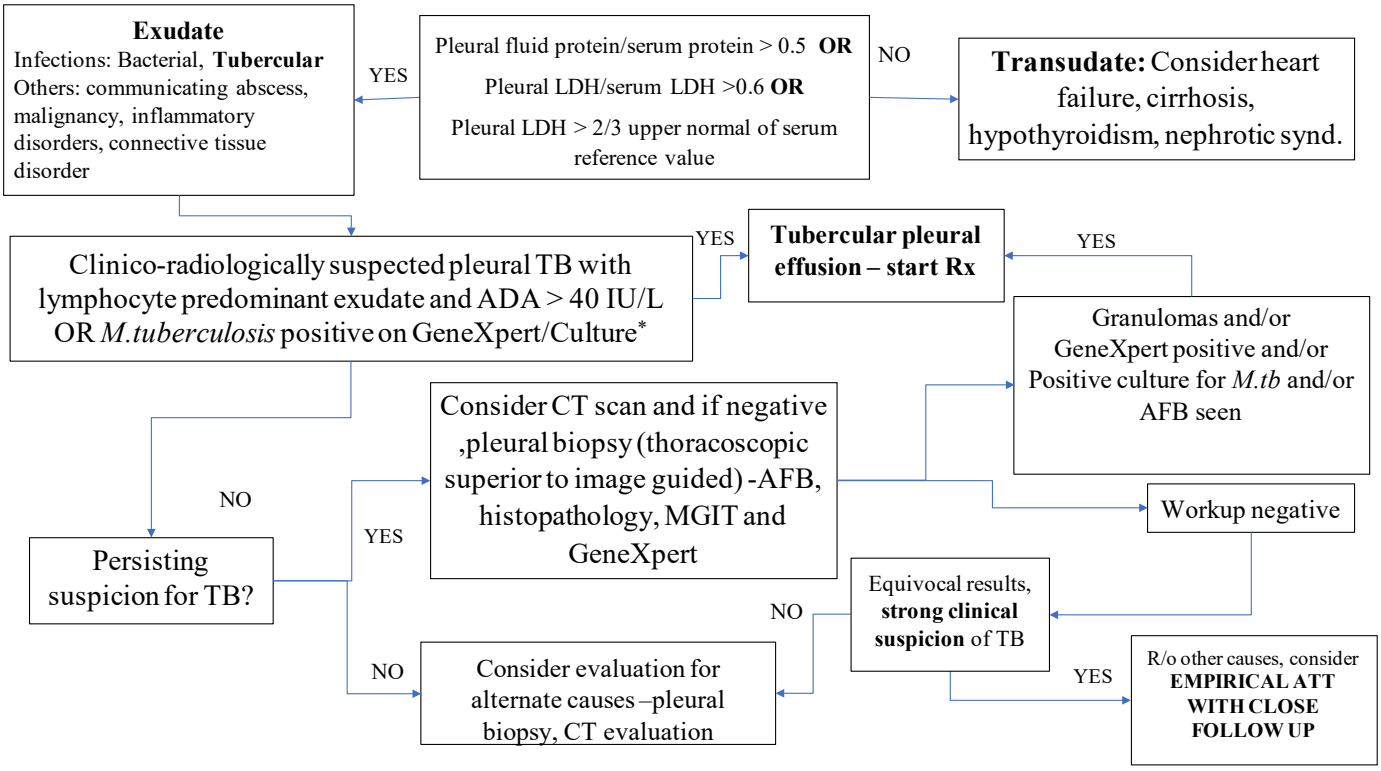
2.8.4 Hydro-Pneumothorax: It may result from rupture of a pulmonary cavity into the pleura. Patients present with breathlessness and cough which is managed with anti-tubercular therapy along with intercostal drainage.

2.9 Follow Up

- Monthly visits with monitoring for adverse drug events, documentation of vitals, fever, weight, examination findings.
- Chest radiographs should be done for monitoring at 2 months and 6 months. Improvement is suggested by significant/near-complete resolution of symptoms or calcification/pleural thickening. If there seems to be worsening of the disease alternative investigations like ultrasound to look for loculations or CT for complete assessment should be used.
- In spite of treatment for 2 months if the patient is having worsening of symptoms, lack of improvement or increasing effusion; clinical failure should be suspected. Such patients should be:
  - Evaluated for drug-resistant tuberculosis.
  - May require a pleural biopsy to rule out any other alternate diagnosis or to check for drug sensitivity.

Figure 1: Pleural TB Flowchart





*Note :AFB, GeneXpert and MGIT liquid culture are not routinely recommended due to resource constraints and low sensitivity , however where available they can be considered

Evaluation for alternate causes

Further workup depending on suspected etiology and CT/pleural biopsy findings. Differentials and evaluations may include-

Bacterial effusion: Bacterial culture and sensitivity, procalcitonin

Fungal effusion : Fungal culture and sensitivity, S. Galactomannan, Serum beta D glucan

Malignant effusion: Malignant cytology, PET

Sarcoidosis: Serum ACE levels, Urine Calcium, Biopsy

Rheumatoid arthritis: Rheumatoid factor, ESR/CRP, other stigmata

References:

1. India WHOCO for. Index-TB guidelines: guidelines on extra-pulmonary tuberculosis in India. 2016 [cited 2019 Aug 1]; Available from: https://apps.who.int/iris/handle/10665/278953.
2. Relkin F, Aranda CP, Garay SM, Smith R, Berkowitz KA, Rom WN. Pleural tuberculosis and HIV infection. Chest. 1994 May;105(5):1338–41.
3. Aljohaney A, Amjadi K, Alvarez GG. A Systematic Review of the Epidemiology, Immunopathogenesis, Diagnosis, and Treatment of Pleural TB in HIV- Infected Patients. Clin Dev Immunol. 2012;2012:1–9.
4. Vorster MJ, Allwood BW, Diacon AH, Koegelenberg CFN. Tuberculous pleural effusions: advances and controversies. J Thorac Dis. 2015;7(6):11.
5. Berger HW, Mejia E. Tuberculous Pleurisy. CHEST. 1973 Jan 1;63(1):88–92.
6. Levine H, Szanto PB, Cugell DW. Tuberculous pleurisy. An acute illness. Arch Intern Med. 1968 Oct;122(4):329–32.
7. Light RW, Lee YCG, editors. Effusions from infections: Tuberculosis. In: Textbook of Pleural Diseases. 3 edition. Boca Raton: CRC Press; 2016.
8. Valdés L, Alvarez D, San José E, Penela P, Valle JM, García-Pazos JM, et al. Tuberculous pleurisy: a study of 254 patients. Arch Intern Med. 1998 Oct 12;158(18):2017–21.
9. Gopi A, Madhavan SM, Sharma SK, Sahn SA. Diagnosis and treatment of tuberculous pleural effusion in 2006. Chest. 2007 Mar;131(3):880–9.
10. Cohen LA, Light RW. Tuberculous Pleural Effusion. Turk Thorac J. 2015 Jan;16(1):1–9.
11. Kobashi Y, Abe M, Mouri K, Obase Y, Miyashita N, Oka M. Usefulness of Tuberculin Skin Test and Three Interferon-Gamma Release Assays for the Differential Diagnosis of Pulmonary Tuberculosis. Intern Med. 2012;51(10):1199–205.
12. Chan CHS, Arnold M, Chan CY, Mak TWL, Hoheisel GB. Clinical and Pathological Features of Tuberculous Pleural Effusion and Its Long-Term Consequences. Respiration. 1991;58(3–4):171–5.
13. Ultrasound in the Diagnosis & Management of Pleural Effusions [Internet]. [cited 2019 Sep 9]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4715558/
14. Soni NJ, Franco R, Velez MI, Schnobrich D, Dancel R, Restrepo MI, et al. Ultrasound in the Diagnosis & Management of Pleural Effusions. J Hosp Med. 2015 Dec;10(12):811–6.
15. Tuberculous Pleural Effusion | IntechOpen [Internet]. [cited 2019 Aug 21]. Available from: https://www.intechopen.com/books/tuberculosis-current-issues-in-diagnosis-and-management/

tuberculous-pleural-effusion.
16. Pleural effusions. - PubMed - NCBI [Internet]. [cited 2019 Sep 19]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23374395.
17. Porcel JM. HANDLING PLEURAL FLUID SAMPLES FOR ROUTINE ANALYSES. Plevra Bul. 2013 Jul 10;7(2):19–22.
18. Menzies SM, Rahman NM, Wrightson JM, Davies HE, Shorten R, Gillespie SH, et al. Blood culture bottle culture of pleural fluid in pleural infection. Thorax. 2011 Aug;66(8):658–62.
19. von Groote-Bidlingmaier F, Koegelenberg CF, Bolliger CT, Chung PK, Rautenbach C, Wasserman E, et al. The yield of different pleural fluid volumes for Mycobacterium tuberculosis culture. Thorax. 2013 Mar;68(3):290–1.
20. Bielsa S, Esquerda A, Palma RM, Criado A, Porcel JM. Influence of storage time on pleural fluid adenosine deaminase activity. Clin Lab. 2014;60(3):501–4.
21. Bielsa S, Davies HE, Davies RJO, Taylor A, Lee YCG. Reproducibility and reliability of pleural fluid cytokine measurements. Eur Respir J. 2009 Oct;34(4):1001–3.
22. Macías A, Sánchez-Montalvá A, Salvador F, Villar A, Tórtola T, Saborit N, et al. Epidemiology and diagnosis of pleural tuberculosis in a low incidence country with high rate of immigrant population: A retrospective study. Int J Infect Dis. 2019 Jan;78:34–8.
23. Kohli M, Schiller I, Dendukuri N, Yao M, Dheda K, Denkinger CM et al. Xpert MTB/RIF Ultra and Xpert MTB/RIF assays for extrapulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2021 Jan 15;1(1):CD012768. doi: 10.1002/14651858.CD012768.pub3. PMID: 33448348; PMCID: PMC8078545.
24. Hillemann D, Richter E, Rüsch-Gerdes S. Use of the BACTEC Mycobacteria Growth Indicator Tube 960 Automated System for Recovery of Mycobacteria from 9,558 Extrapulmonary Specimens, Including Urine Samples. J Clin Microbiol. 2006 Nov;44(11):4014–7.
25. Aggarwal AN, Agarwal R, Sehgal IS, Dhooria S. Adenosine deaminase for diagnosis of tuberculous pleural effusion: A systematic review and meta-analysis. PLOS ONE. 2019 Mar 26;14(3):e0213728.
26. Mehta AA, Gupta AS, Ahmed S, Rajesh V. Diagnostic utility of adenosine deaminase in exudative pleural effusions. Lung India. 2014 Apr 1;31(2):142.
27. Sharma SK, Banga A. Diagnostic Utility of Pleural Fluid IFN-γ in Tuberculosis Pleural Effusion. J Interferon Cytokine Res. 2004 Apr;24(4):213–7.
28. Dhooria S, Singh N, Aggarwal AN, Gupta D, Agarwal R. A randomized trial comparing the diagnostic yield of rigid and semirigid thoracoscopy in undiagnosed pleural effusions. Respir Care. 2014 May;59(5):756–64.
29. Kirsch CM, Kroe DM, Azzi RL, Jensen WA, Kagawa FT, Wehner JH. The optimal number of pleural biopsy specimens for a diagnosis of tuberculous pleurisy. Chest. 1997 Sep;112(3):702–6.
30. Querol JM, Mínguez J, García-Sánchez E, Farga MA, Gimeno C, García-de-Lomas J. Rapid diagnosis of pleural tuberculosis by polymerase chain reaction. Am J Respir Crit Care Med. 1995 Dec;152(6 Pt 1):1977–81.
31. Christopher DJ, Dinakaran S, Gupta R, James P, Isaac B, Thangakunam B. Thoracoscopic pleural biopsy improves yield of Xpert MTB/RIF for diagnosis of pleural tuberculosis. Respirol Carlton Vic. 2018;23(7):714–7.
32. Du J, Huang Z, Luo Q, Xiong G, Xu X, Li W, et al. Rapid diagnosis of pleural tuberculosis by Xpert MTB/RIF assay using pleural biopsy and pleural fluid specimens. J Res Med Sci Off J Isfahan Univ Med Sci. 2015 Jan;20(1):26–31.
33. Maturu VN, Dhooria S, Bal A, Singh N, Aggarwal AN, Gupta D, et al. Role of medical thoracoscopy and closed-blind pleural biopsy in undiagnosed exudative pleural effusions: a single-center experience of 348 patients. J Bronchol Interv Pulmonol. 2015 Apr;22(2):121–9.
34. Diacon AH, Van de Wal BW, Wyser C, Smedema JP, Bezuidenhout J, Bolliger CT, et al. Diagnostic

tools in tuberculous pleurisy: a direct comparative study. Eur Respir J. 2003 Oct;22(4):589–91.
35. Sharma SK, Banga A. Pleural fluid interferon-gamma and adenosine deaminase levels in tuberculosis pleural effusion: a cost-effectiveness analysis. J Clin Lab Anal. 2005;19(2):40–6.
36. Novel tests for diagnosing tuberculous pleural effusion: what works and what does not? | European Respiratory Society [Internet]. [cited 2019 Sep 13]. Available from: https://erj.ersjournals.com/content/31/5/1098.
37. Moriwaki Y, Kohjiro N, Itoh M, Nakatsuji Y, Okada M, Ishihara H, et al. Discrimination of tuberculous from carcinomatous pleural effusion by biochemical markers: adenosine deaminase, lysozyme, fibronectin and carcinoembryonic antigen. Jpn J Med. 1989 Aug;28(4):478–84.
38. Jørstad MD, Dyrhol-Riise AM, Aßmus J, Marijani M, Sviland L, Mustafa T. Evaluation of treatment response in extrapulmonary tuberculosis in a low-resource setting. BMC Infect Dis. 2019 May 16;19(1):426.
39. Porcel JM. Chest Tube Drainage of the Pleural Space: A Concise Review for Pulmonologists. Tuberc Respir Dis. 2018 Apr;81(2):106–15.
40. Ryan H, Yoo J, Darsini P. Corticosteroids for tuberculous pleurisy. Cochrane Database Syst Rev [Internet]. 2017 [cited 2019 Sep 8];(3). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD001876.pub3/full
41. World Health Organization. Guideline. [Internet]. 2013 [cited 2019 Aug 2]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK189867/
42. Bhargava A, Bharti K, Kurpad A, Bhargava M, Rao R, Parmar M, et al. Guidance Document: Nutritional care and support for patients with Tuberculosis in India. 2017 Aug.
43. Cheng VCC, Yam WC, Woo PCY, Lau SKP, Hung IFN, Wong SPY, et al. Risk Factors for Development of Paradoxical Response During Antituberculosis Therapy in HIV-Negative Patients. Eur J Clin Microbiol Infect Dis. 2003 Oct 1;22(10):597–602.
44. Barbas CS, Cukier A, de Varvalho CR, Barbas Filho JV, Light RW. The relationship between pleural fluid findings and the development of pleural thickening in patients with pleural tuberculosis. Chest. 1991 Nov;100(5):1264–7.
45. Candela A, Andujar J, Hernández L, Martín C, Barroso E, Arriero JM, et al. Functional sequelae of tuberculous pleurisy in patients correctly treated. Chest. 2003 Jun;123(6):1996–2000.
46. Karkhanis VS, Joshi JM. Pleural effusion: diagnosis, treatment, and management. Open Access Emerg Med OAEM. 2012 Jun 22;4:31–52.
47. Shen KR, Bribriesco A, Crabtree T, Denlinger C, Eby J, Eiken P, et al. The American Association for Thoracic Surgery consensus guidelines for the management of empyema. J Thorac Cardiovasc Surg. 2017;153(6):e129–46.
48. Kasargod V, Awad NT. Clinical profile, etiology, and management of hydropneumothorax: An Indian experience. Lung India Off Organ Indian Chest Soc. 2016;33(3):278–80.
49. Chest tuberculosis: Radiological review and imaging recommendations Bhalla AS, Goyal A, Guleria R, Gupta AK - Indian J Radiol Imaging [Internet]. [cited 2019 Oct 22]. Available from: http://www.ijri.org/article.asp?issn=0971-3026;year=2015;volume=25;issue=3;spage=213;epage=225;aulast=Bhalla
50. Philip KEJ, Kon OM, Roddie M, Ross C. Pleural tuberculosis: a key differential diagnosis for pleural thickening, even without obvious risk factors for tuberculosis in a low incidence setting. Case Rep. 2018 Oct 26;2018:bcr-2018-224992.
51. World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care: 2017 update. 2017.
52. Marjani M, Yousefzadeh A, Baghaei P, Tabarsi P, Moniri A, Masjedi MR, et al. Impact of HIV infection on tuberculous pleural effusion. Int J STD AIDS. 2016 Apr;27(5):363–9.
53. Hussein MM, Mooij JM, Roujouleh H. Tuberculosis and Chronic Renal Disease. Semin Dial.

2003;16(1):38–44.
54. Ahluwalia G. Exudative pleural effusion in chronic kidney disease: An aetiological dilemma. Indian J Med Res. 2015 Mar;141(3):269–70.
55. Global Tuberculosis Programme. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. [Internet]. 2018 [cited 2019 Aug 4]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK531235/
56. Sugarman J, Colvin C, Moran AC, Oxlade O. Tuberculosis in pregnancy: an estimate of the global burden of disease. Lancet Glob Health. 2014 Dec 1;2(12):e710–6.
57. Loto OM, Awowole I. Tuberculosis in Pregnancy: A Review [Internet]. Journal of Pregnancy. 2012 [cited 2019 Aug 2]. Available from: https://www.hindawi.com/journals/jp/2012/379271

3. Pericardial Tuberculosis

KEY POINTS

- The most common presentation of pericardial tuberculosis is in the form of pericardial effusion.
- Tuberculous pericarditis should be considered in the evaluation of patients with pericarditis who do not have a self-limited course.
- Pericardiocentesis is warranted for routine evaluation of suspected tuberculous pericarditis; cardiac tamponade is an absolute indication for pericardiocentesis.

3.1 Introduction And Epidemiology

Tuberculous pericarditis accounts for 60–80% [1] of cases of acute pericarditis in high TB burden countries, and 75% [1] cases of constrictive pericarditis.

In the developed world, TB is a relatively rare cause of pericardial disease in HIV negative, immunocompetent persons and accounts for ≤4% percent cases of pericardial disease. [2]

3.2 Pathophysiology

Tubercle bacilli can enter the pericardium via one of the following routes:

1. Retrograde lymphatic spread from adjacent lymph nodes
2. Hematogenous spread
3. Adjacent spread from lung, spine or pleural involvement

In immunocompetent individuals, it is a paucibacillary disease, where tubercular bacilli incite a cell-mediated immune response via Th1 cells and cytokines, while in immunodeficient individuals, there can be high bacillary load and replication.

Spectrum:
Tuberculous pericarditis can present as a spectrum of diseases including pericardial effusion, constrictive pericarditis, myopericarditis and cardiac tamponade. The most common presentation is in the form of pericardial effusion which is of variable duration, followed by constrictive pericarditis, myopericarditis and rarely cardiac tamponade. Constrictive pericarditis may have a subacute or chronic presentation. Myopericarditis usually presents as pericarditis with concurrent abnormal cardiac ejection fraction and/or elevated serum levels of cardiac enzymes.

3.3 Clinical Features

The nature of symptoms depends upon the stage of infection, extent of tuberculous disease outside the pericardium, and the degree of pericardial involvement.

3.3.1 Clinical features attributable to pericardial disease:

- Chest discomfort, shortness of breath, orthopnoea
- Features of congestive heart failure, ascites out of proportion to minimal or absent pedal oedema
- Tamponade – hypotension, tachycardia, raised JVP

3.3.2. Clinical/radiological features pointing towards tuberculous aetiology:

- Constitutional symptoms: fever with night sweats, significant weight loss, loss of appetite
- Pericardial calcification, cardiomegaly

3.3.3 Clinical features indicating other system involvement:

- Chronic cough with expectoration, hemoptysis, swelling over the neck, abdominal distension/ discomfort

According to the duration of symptoms:

- Acute- New-onset
- Incessant- persistent for 4-6 weeks but <3 months without remission
- Chronic - >3 months
- Recurrent- Recurrence of pericarditis after a documented first episode of acute pericarditis and a symptom-free interval of 4-6 weeks or longer

3.4 Diagnosis

Tuberculous pericarditis should be considered in the evaluation of patients with pericarditis who do not have a self-limited course. Patients may have non-specific and varied symptoms as mentioned above. Clinically patients with tuberculous pericarditis may have fever, tachycardia, increased jugular venous pressure, hepatomegaly, ascites, and peripheral oedema.

Investigations

Table 3.1. The following investigations are recommended in a patient with suspicion of pericardial TB.

TEST
Complete blood counts, liver and renal function tests.
ECG: May reveal evidence of pericardial effusion (low voltage trace, T wave flattening or inversion). Patients are at risk of atrial arrhythmia.
Chest X ray: Features suggestive of pericardial disease include hilar widening, and a globular or “water bottle” heart shadow. In some cases the cardiac shadow may appear normal. Evidence of pulmonary TB or pleural effusions may be noted.
Echocardiogram: (TTE) Reveals or confirms pericardial effusion and/or constriction, and can detect signs of impending tamponade which requires urgent intervention.

CECT Chest: Useful for demonstrating pericardial thickening or calcification, or associated lung/mediastinal abnormalities. Not required routinely. **Features of mediastinal nodes in pericardial tuberculosis:** · Aortopulmonary, paratracheal, and carinal nodes are most often involved. · Typically coalesced (matted) with a hypodense centre. · Hilar involvement is rare hence nodes are not seen on routine chest radiographs. · Nodes seen only on chest computed tomography or MRI. · Nodes disappear or regress with specific treatment.
Cardiac MRI: Only required in patients where a diagnosis of restrictive cardiomyopathy is being considered as a significant differential diagnosis.

3.4.1 Pericardiocentesis:

- Rule out other causes of pericardial involvement before proceeding with a diagnostic pericardiocentesis in consultation with an expert (Cardiologist etc).
  Eg. ANA(Autoimmune), TSH(Hypothyroidism), Renal function tests (Uremic pericardial disease)

- Mantoux test: Does not have diagnostic utility but negative result in the absence of immunosuppression status may be used to rule out tuberculous aetiology.

Table 3.2. Pericardial Fluid Analysis:

	Investigation
1.	Cell counts and Differential counts: Predominantly lymphocytic
2.	Protein, LDH[with paired serum values]: Exudative [uncertainty in diagnostic utility with discriminative evidence]
3.	Malignant cytology: At least 3 samples
4.	Cultures: MGIT Culture positive in 2/3rd of cases
5.	GeneXpert: Discriminative evidence regarding utility

3.4.1 A. Characterization As Exudate Or Transudate By Light's Criteria (Refer to Pleural TB chapter):

Caution is needed when interpreting pericardial fluid LDH and total protein according to Light's criteria, because pericardial transudates may have levels of these parameters in the exudative range.
Characteristic findings in pericardial fluid:

- Straw coloured or serosanguinous; exudative
- High count of lymphocytes and monocytes
- Direct examination – AFB, rarely may be positive

Culture reveals *M. tuberculosis* in up to 2/3rd of cases, biopsy has a higher yield

3.4.1 B. Pericardial Fluid ADA utility:

According to a study done by Reuter et al [5], pericardial fluid ADA ≥40 U/l had 87% sensitivity and 89% specificity. A Meta-analysis by Tuon et al [6] in the same year showed a sensitivity of 88% and a specificity of 83%.

3.4.1 C. NAAT:

A study by Pandie et al [7], showed NAAT had a sensitivity and specificity of 63.8% and 100%, respectively. A similar study by Sharma et al [8] in 2014 on NAAT in different extrapulmonary tuberculosis samples showed a sensitivity of 25% and specificity of 94% for pericardial fluid.

3.4.2 Pericardial Biopsy:

Diagnostic biopsy: In areas where tuberculosis is endemic, a diagnostic biopsy is not required prior to commencing empiric antituberculosis treatment. In areas where tuberculosis is not endemic, a diagnostic biopsy is recommended in patients with >3 weeks of illness and without etiologic diagnosis having been reached by other tests.

Empirical treatment for Tuberculosis may be started in these patients in case of inconclusive investigations, after ruling out evidence of malignancy in pericardial fluid cytology.

3.5 Treatment

- 2HRZE + 4HRE (for a total duration of at least 6 months).
- Use of Corticosteroid: an initial adjuvant corticosteroid therapy may be used (Conditional recommendation, very low certainty in the evidence).
- HIV negative – **corticosteroids may reduce deaths from all causes and the need for repeat pericardiocentesis.**
- Prednisone in a dose of 1mg/kg for 4 weeks followed by 0.5mg/kg for 4 weeks and tapers gradually over next two to four weeks.

Surgical Intervention:

- Pericardiocentesis – indicated as an urgent intervention in cardiac tamponade
- Pericardiectomy – on treatment option in constrictive pericardial disease as a late complication

3.5.1 Predictors Of Improvement:

3.5.1 A. Clinical:

- Normal Jugular Venous Pressure
- Resolution of Pedal Edema
- Symptomatic Improvement

3.5.2 B. Radiology (USG/ECHO):

- IVC normal diameter and collapsibility
- Decrease in dimensions of effusion on Echo

3.5.2 Causes of Poor response to ATT:

1. Alternate diagnosis
2. Inappropriate dosing
3. Co-existing other infection
4. Non compliance

5. Poor drug absorption or penetration
6. Immunocompromised status
7. Paradoxical reaction
8. Drug interactions

In cases of poor or non-response to treatment, re-evaluate for alternate diagnosis and rule out drug-resistant TB.

3.6 Cardiac Tamponade

- Life-threatening, slow or rapid compression of the heart due to the pericardial accumulation of fluid, pus, blood, clots or gas as a result of inflammation, trauma, rupture of the heart or aortic dissection.

3.6.1 Aetiology:

3.6.1 A. Common Causes:

- Pericarditis
- **Tuberculosis**
- Iatrogenic(post cardiac surgery/invasive procedure)
- Trauma
- Neoplastic

3.6.1 B. Uncommon Causes:

- Connective tissue diseases
- Post MI
- Aortic dissection
- Radiation induced

3.6.2 Clinical Features:

- Chest pain/discomfort, dyspnea, orthopnea progressive in nature
- Becks Triad:
  - Elevated JVP
  - Hypotension
  - Muffled Heart Sounds
- Tachycardia
- Kussmaul's Sign: Paradoxical elevation of JVP on inspiration
- Pulsus Paradoxus: >10 mmHg drop in SBP during Inspiration

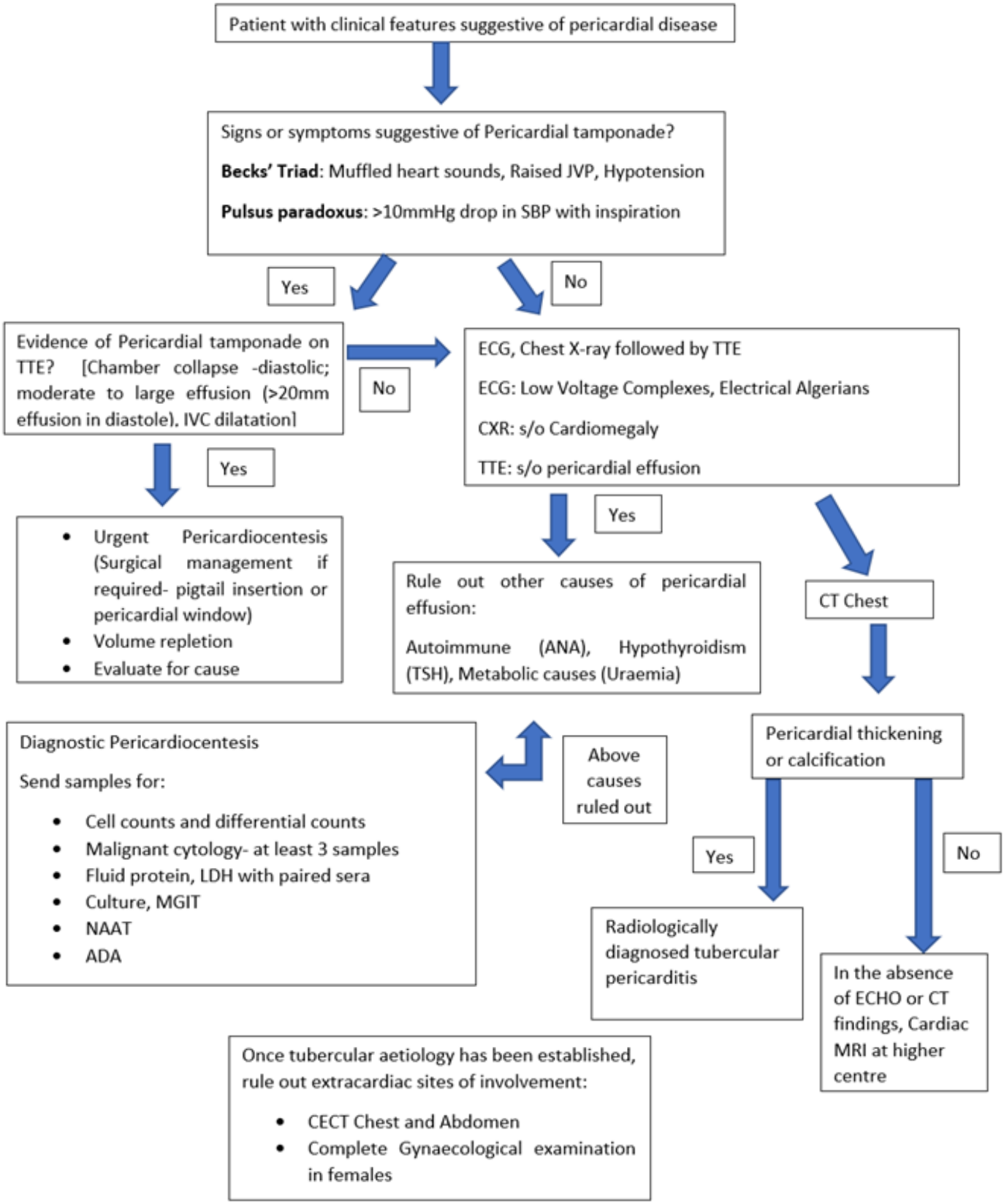
Two-dimensional echocardiogram shows illustrating cardiac tamponade with right atrium collapse or indentation

3.6.3 Treatment:

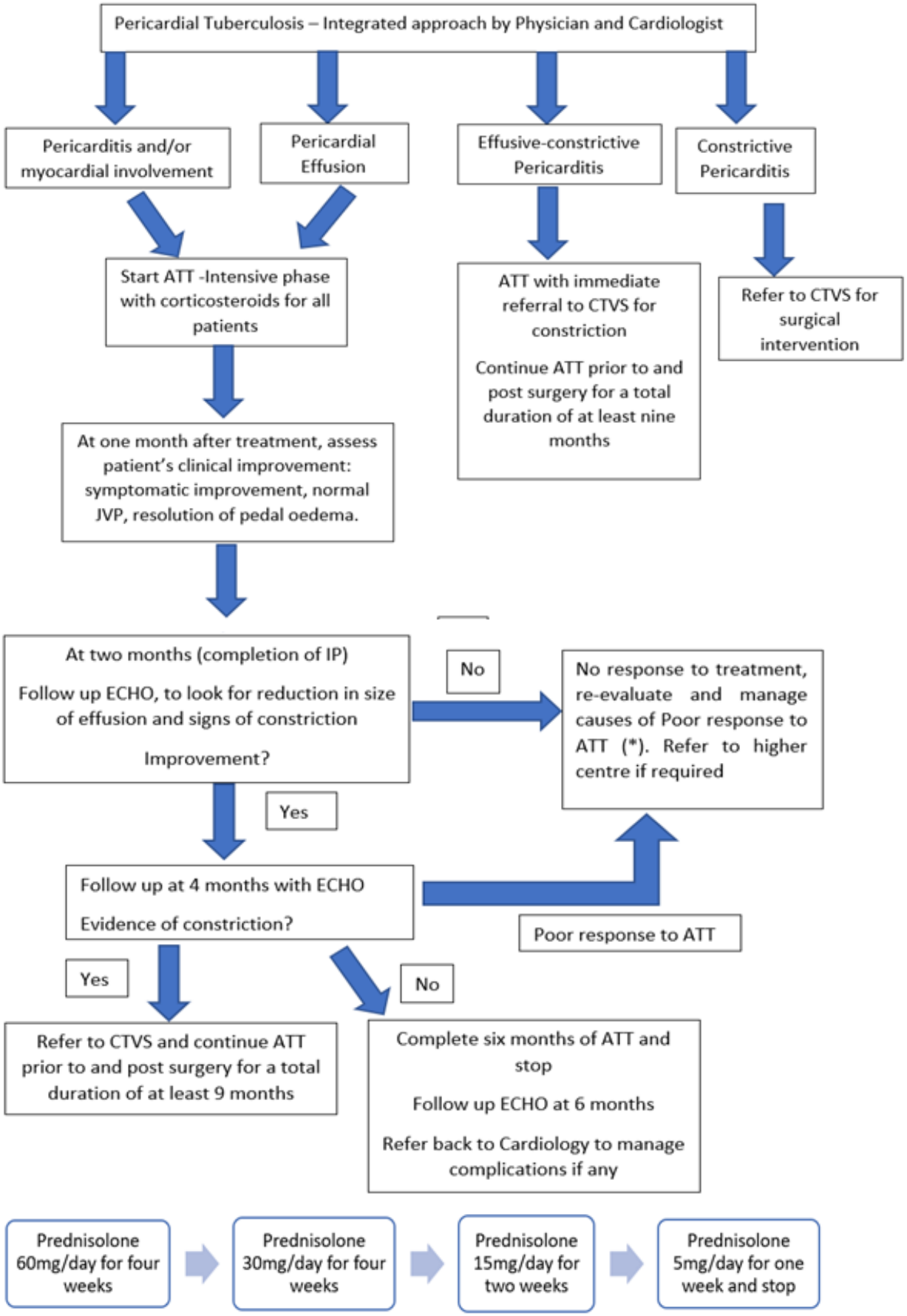
- Needle Pericardiocentesis – preferably under echocardiographic guidance
  - Contraindications:
    - Uncorrected Bleeding Diathesis
    - Severe Pulmonary Hypertension (PASP>70mmHg)
    - Specific Indication for surgery: Aortic dissection repair, trauma, purulent effusion
- Volume Repletion with fluids

- Inotropes – ineffective because endogenous adrenergic stimulation is already enhanced under tamponade conditions

3.7 INVESTIGATION ALGORITHM



3.8 MANAGEMENT ALGORITHM



References:

1. Sharma, Surendra K., H. Ryan, Sunil Khaparde, K. S. Sachdeva, Achintya D. Singh, Alladi Mohan, Rohit Sarin, et al. “Index-TB Guidelines: Guidelines on Extrapulmonary Tuberculosis for India.” The Indian Journal of Medical Research 145, no. 4 (April 2017): 448–63. doi: 10.4103/ijmr.IJMR_1950_16.

2. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. European Heart Journal. 2015 Nov 7 ;36(42):2921–64. doi:10.1093/eurheartj/ehv318.

3. Pannu AK, et al. Tuberculous Pericarditis: A Review. Cell Cellular Lif Sci J 2018, 3(2):000130. doi:10.23880/cclsj-16000130.

4. Milevoj Kopcinovic L, Culej J. Pleural, peritoneal and pericardial effusions – a biochemical approach. Biochem Med. 2014 ;123–37; doi:10.11613/BM.2014.014.

5. Reuter H, Burgess L, van Vuuren W, Doubell A. Diagnosing tuberculous pericarditis. QJM. 2006 Nov 3;99(12):827–39.doi:10.1093/qjmed/hcl123.

6. Tuon FF, Litvoc MN, Lopes MIBF. Adenosine deaminase and tuberculous pericarditis—A systematic review with meta-analysis. Acta Tropica. 2006 Aug;99(1):67–74; doi:10.1016/j.actatropica.2006.07.004.

7. Pandie S, Peter JG, Kerbelker ZS, Meldau R, Theron G, Govender U, et al. Diagnostic accuracy of quantitative PCR (Xpert mtb/rif) for tuberculous pericarditis compared to adenosine deaminase and unstimulated interferon-γ in a high burden setting: a prospective study. BMC Med. 2014 Dec;12(1):101; doi:10.1186/1741-7015-12-101.

8. Sharma SK, Kohli M, Chaubey J, Yadav RN, Sharma R, Singh BK, et al. Evaluation of Xpert MTB/RIF assay performance in diagnosing extrapulmonary tuberculosis among adults in a tertiary care centre in India. Eur Respir J. 2014 Oct; 44(4):1090–3; doi:10.1183/09031936.00059014.

9. Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumedze F, et al. Prednisolone and Mycobacterium indicus pranii in Tuberculous Pericarditis. N Engl J Med. 2014 Sep 18;371(12):1121–30.doi:10.1056/NEJMoa1407380.

10. Wiysonge CS, Ntsekhe M, Thabane L, Volmink J, Majombozi D, Gumedze F, et al. Interventions for treating tuberculous pericarditis. Cochrane Infectious Diseases Group, editor. Cochrane Database of Systematic Reviews. 2017 Sep 13;2017(9). doi:10.1002/14651858.CD000526.pub2.

11. Strang JIG, Nunn AJ, Johnson DA, Casbard A, Gibson DG, Girling DJ. Management of tuberculous constrictive pericarditis and tuberculous pericardial effusion in Transkei: results at 10 years follow-up. QJM. 2004 Aug 1;97(8):525–35. doi:10.1093/qjmed/hch086.

12. Strang JIG, Gibson DG, Mitchison DA, Girling DJ, Kakaza HHS, Allen BW, et al. Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous

pericardial effusion in transkei. The Lancet. 1988 Oct;332(8614):759–64.doi: 10.1016/s0140-6736(88)92415-4.

13. Strang JIG, Gibson DG, Nunn AJ, Kakaza HHS, Girling DJ, Fox W. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in transkei. The Lancet. 1987 Dec; 330(8573):1418–22 ; doi: 10.1016/s0140-6736(87)91127-5.

14. Singh S, Tiwari K. Use of corticosteroids in tuberculosis. J Assoc Chest Physicians . 2017;5(2):70. doi: 10.4103/jacp.jacp_40_16.

15. Bozbuga N, Erentug V, Eren E, Erdogan HB, Kirali K, Antal A, et al. Pericardiectomy for chronic constrictive tuberculous pericarditis. Tex Heart Inst J. 2003 ;30(3):180–5.

16. Chowdhury UK, Sankhyan LK. Pericardiectomy for Chronic Constrictive Pericarditis: Where are we after 100 Years? World J Surg Surgical Res. 2018; 1: 1027.

17. Jensen' 'Jesper K., Poulsen' 'Steen Hvitfeldt, Mølgaard' 'Henning. Cardiac tamponade: a clinical challenge. Available from: https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-15/Cardiac-tamponade-a-clinical-challenge.

18. Cherian G. Diagnosis of tuberculous aetiology in pericardial effusions. Postgraduate Medical Journal. 2004 May 1;80(943):262–6; doi:10.1136/pgmj.2003.013664.

19. Cale-Subia, Laarnie N. and Arlene M. De Luna. "Applicability of Light ' s Criteria in the Biochemical Analysis of Pericardial Fluid." (2012).

4. Central Nervous System Tuberculosis

KEY POINTS

- TB of Central Nervous System (CNS) is the most severe form of TB and is almost always fatal if left untreated.
- The exact mechanism of pathogenesis is not known, however, the proposed mechanism includes primary infection and seeding into CNS followed by a latent period and then rupturing of primary foci leading to re-activation and disease activity.
- The leptomeningeal form is the most common and most severe form of CNS TB.
- Tuberculomas and brain abscesses are less common than Tuberculous meningitis (TBM) and have lower mortality and morbidity.
- Diagnosis of CNS TB is based upon clinical assessment, CSF analysis which includes cytology, biochemistry, microbiology and ADA levels, imaging studies like CT and MRI and other investigations to exclude other diagnoses.
- British MRC grading for Severity assessment helps to stratify patients and is useful to predict prognosis.
- CSF findings in usual cases of TBM include raised protein with lymphocytic pleocytosis and decreased glucose.
- CSF ADA levels are not recommended as a rule in or rule out test for TB meningitis.
- Imaging modalities can be employed to aid the diagnosis of CNS TB as well as the presence of complications and to evaluate the dissemination of TB disease.
- The primary therapy for CNS TB includes medical therapy in the form of antitubercular drugs.
- The treatment course is divided into intensive phase (IP)- 4 drugs HRZE for 2 months and a continuation phase (CP) - 3 drugs HRE for at least 8-9 months. ATT should be continued for a minimum duration of 12 months, which may be further extended in case of partial or no response in confirmed cases.
- Steroids are indicated in TBM. Dexamethasone at a dose of 0.4mg/Kg per day in 3-4 divided doses, to be tapered over 6-8 weeks to reduce significant inflammation in TBM manifesting in the form of meningeal reaction, basal exudates, vasculitis of intracranial vessels.
- Hydrocephalus is one of the commonest complications of TBM due to the formation of basal exudates. Medical management includes osmotic agents however surgery (CSF diversion-VP shunt/EVD) is the main modality of management.
- In case of tuberculomas or abscesses, therapy for a duration of at least 12-18 months is recommended. Lesions may persist after therapy; therefore, extended therapy beyond 18 months may not be required in most cases.

4.1 Introduction

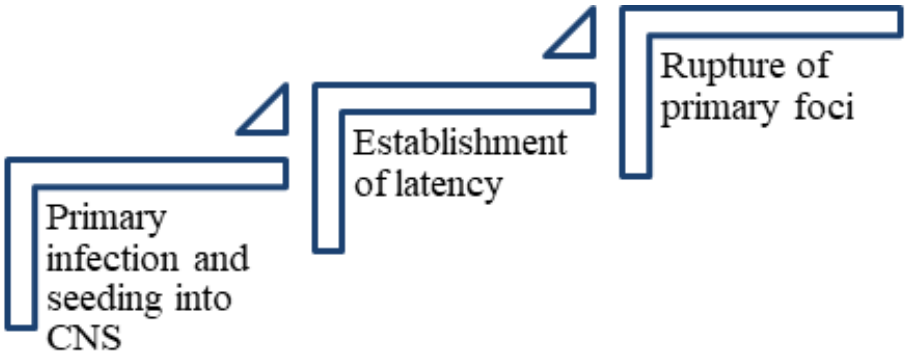
CNS TB is the most severe form of TB. It is almost always fatal if left untreated, and even with currently available ATT, mortality rates remain high. It results in high mortality or morbidity in the form of severe neurological sequelae in almost 50% of people, despite treatment.

It accounts for around 5%–10% of EPTB cases; and around 1% of all TB cases (1). The prognosis of the disease is further complicated by nonspecific clinical features, the number of complications, diagnostic challenges and delay in treatment. These factors, singly or in combination result in increased mortality and morbidity associated with the disease (2).

4.2 Pathogenesis

Most of the information regarding the pathogenesis of CNS TB is derived from in-vitro or in-vivo (animal models) studies. The exact mechanism as to how TB bacilli reach the CNS and establish disease is not known. However, the pathogenesis of CNS tuberculosis is described in a three-step process.

Figure 4.1: pathogenesis of CNS TB – 3 essential steps



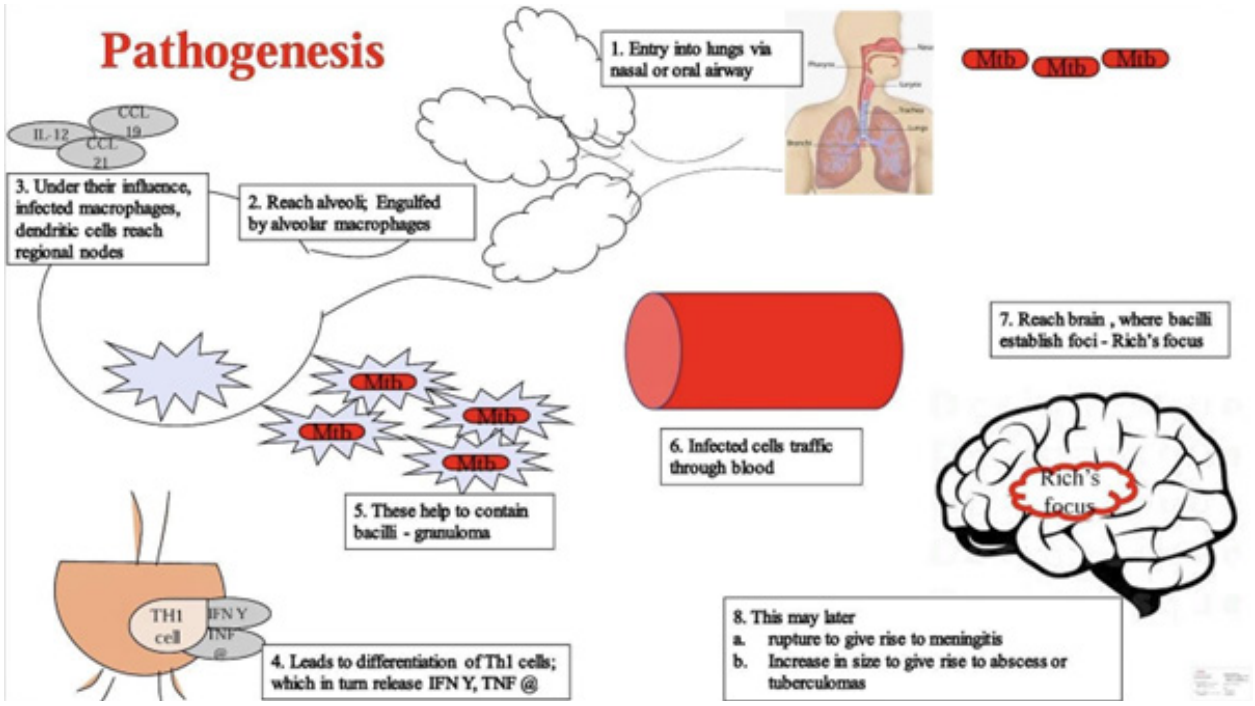
4.2.1 Primary Infection And Seeding Into CNS: After primary infection i.e. after the acquisition of bacilli through inhalation route, TB bacilli enter lungs, reaching alveoli where they are encountered by macrophages which try to contain the bacilli.

4.2.2 Establishing The Latency: Infected macrophages reach regional lymph nodes; from where they may get disseminated via the bloodstream to various organs including the CNS. In an immunocompetent host, macrophages are able to contain the bacilli in granuloma, establishing a focus of latency with dormant bacilli within.

4.2.3 Rupture Of Primary Foci: Due to certain unknown mechanisms, dormant bacilli gets reactivated leading to rupture of focus; manifesting in the form of TB meningitis. Alternatively, latent foci may enlarge at their original site, leading to the formation of tuberculoma. This mechanism has also been represented in the form of a diagram (Figure 2).

According to studies, various cytokines, chemokines, interleukins etc. play a key role in the pathogenesis of TBM. Also, there is the interplay of several host factors, metabolic factors, genetic factors, virulence factors, which may modulate the immune response, overall affecting the possibility of developing the disease or severe disease.

Figure 4.2: Pathogenesis of CNS TB



4.3. Spectrum Of CNS TB

CNS TB may involve any part of the nervous system.

4.3.1 Meningeal Involvement: Tt is the most common form of CNS TB. Meningeal involvement may be further divided into:-

4.3.1 A. Leptomeningeal involvement: It implies the involvement of pia-arachnoid layers and it is the **most severe form** of CNS TB. Complications may include:-

i. Hydrocephalus – due to the formation of basal exudates, there is impaired CSF absorption and this, in turn, leads to the development of hydrocephalus
ii. Severe inflammation may lead to vasculitis resulting in infarcts
iii. Multiple cranial neuropathies
iv. Arachnoiditis

4.3.2 B. Patchy-meningeal involvement: It implies the involvement of dura mater.

4.3.2 Parenchymal involvement – it includes

4.3.2 A. Cerebritis & TB abscess
4.3.2 B. Tuberculomas
4.3.2 C. Miliary TB
4.3.2 D. TB encephalopathy

4.3.3 Spinal TB

4.3.3 A. TB radiculomyelitis
4.3.3 B. Myelitic tuberculomas
4.3.3 C. Extrinsic (epidural abscess)

(Involvement of these sites may or may not be exclusive)

4.4. Clinical Features

4.4.1 TB Meningitis:

The leptomeningeal form is the most common and most severe form.
Symptoms depending on site of involvement and macroscopic complications (Table 1)

Table 4.1: Symptoms in Tuberculous meningitis and their relative frequency(2)

Symptoms	Frequency (%)
Vomiting	69.7
Altered sensorium	69.2
Anorexia	57.1
Seizures	34.4
Vision impairment	21.2
Meningeal signs	81.8
Papilledema	48.5
1 or more cranial nerve palsy	47
Optic atrophy	14.6

4.4.1 A. History and Clinical Features supporting the diagnosis of TBM:

- Weight loss (or poor weight gain in children), night sweats or persistent cough for more than 2 weeks.
- History of recent (within the past year) close contact with an individual with PTB or positive TST or IGRA (only in children <10 years of age).

4.4.1 B. Differential diagnosis:

- Partially treated bacterial meningitis
- Cryptococcal meningitis
- Viral meningoencephalitis
- Carcinomatous meningitis
- Neuro-sarcoidosis
- Neurosyphilis

4.4.2 Tuberculomas And Abscess:

- It is less common than TBM and has lower morbidity and mortality
- It can arise anywhere in the brain or spinal cord
- It may present as:
  - Mass lesion causing focal neurological deficits depending on anatomical location and/or seizure
  - It may be found in concurrence with TBM

4.5 Diagnosis

4.5.1 Clinical assessment: for evaluation of history and clinical features to suspect CNS TB, assess the severity and presence of complications.

4.5.2 CSF analysis: to confirm the presence of meningeal involvement and for etiological evaluation.

- Cytology; biochemical
- Adenosine deaminase (ADA)
- Microbiological
    i. AFB staining, CSF culture (LJ/MGIT)
    ii. Molecular – NAAT, Line probe assay (LPA)

4.5.3 Imaging:

4.5.3 A. CNS imaging: to look for findings suggestive of CNS infection, findings favouring TB meningitis as well as presence of complications.

i. NCCT/CECT head
ii. MRI Brain + spine

4.5.3 B. Imaging of other systems: to evaluate for dissemination of disease.

4.5.4 Other Investigations: to exclude other diagnoses.
CSF culture (bacterial/fungal),VDRL, CSF Cryptococcal Antigen, Malignant cytology.

4.5.5 TBM diagnostic criteria[3]:

A. Clinical

- Fever and headache lasting for more than 14 days (mandatory).
- Vomiting, alteration of sensorium or focal deficit (optional).

B. Cerebrospinal fluid

- Pleocytosis with more than 20 cells, predominantly (greater than 60%) lymphocytes, protein greater than 100mg%, sugars less than 60% of corresponding blood sugars.
- Negative India ink studies and cytology for malignant cells (in relevant situations).

C. Radiological

- CT head showing 2 or more:
    1. Exudates in basal cisterns or in Sylvian fissures
    2. Hydrocephalus
    3. Infarcts
    4. Gyral enhancement

D. Extra neural tuberculosis

- Active TB of lungs, G.I.T, G.U.T, lymph nodes, skeletal system or skin - by radiological or microbiological tests or by presence of caseation necrosis on histopathological examination.

Based on presence of these features in combination of one or more, TBM can be clinically categorised as:

1. Definite tuberculous meningitis
    (i) Clinical criteria (A)

(ii) Bacterial isolation from CSF or diagnosis at autopsy

2. Highly probable tuberculous meningitis
   (i) Clinical criteria (A)
   (ii) All 3 of (B), (C) and (D)
3. Probable tuberculous meningitis
   (i) Clinical criteria (A)
   (ii) Any 2 of (B), (C) and (D)
4. Possible tuberculous meningitis
   (i) Clinical criteria (A)
   (ii) Any one of (B), (C) and (D)

Accuracy and positive predictive value were 91.7% 66.7% and 38.5% in the highly probable, probable and possible TBM groups respectively(3).

British MRC Grading (Severity)

- Grade 1 TBM: MILD - Glasgow coma score (GCS) of 15 with no focal neurological deficit; those without altered consciousness or focal neurological signs
- Grade 2 TBM: MODERATE - GCS of 15 with a focal neurological deficit, or a GCS of 11–14; those with altered consciousness who are not comatose and those with moderate neurological signs, e.g. single cranial nerve palsies, paraparesis, and hemiparesis
- Grade 3 TBM: SEVERE - GCS of ≤10; for comatose patients and those with multiple cranial nerve palsies, hemiplegia or paraplegia, or both.

► Severity assessment helps to stratify patients and is useful to predict prognosis

4.5.2 CSF analysis[2]: at least 6ml of CSF should be collected for adults, 2–3ml for children, under aseptic precautions.
CSF sample should be examined:

- grossly for appearance, turbidity,
- microscopy, biochemical evaluation, cultures,
- special staining (as indicated),
- molecular tests, antigen-antibody detection based tests (as indicated).

Table 4.2 CSF Findings in TB Meningitis

Appearance	clear CSF/Cobweb may form due to high protein
Leucocyte count	usually 100 - 500 cells/µl, can exceed 1000 cells/µl ^
Protein	generally 100 - 500mg/dl #
Glucose	may be less than 40% of corresponding blood glucose level

^ In acute stage, a polymorphonuclear response may occur transiently and is replaced by lymphocytic reaction in the course of days to weeks

if allowed to stand, a pellicle or cobweb may form, indicating presence of fibrinogen -highly suggestive but not pathognomonic of TBM.

CSF AFB staining - to demonstrate AFB in CSF

The staining technique has a low rate of detection from 12.5 to 69 % due to the low limit of detection (LOD) i.e around 10000 bacilli. However, increasing CSF volume being tested increases Limit of detection (LOD) (i.e staining multiple CSF samples enhances the sensitivity to about 86%)(4).

Moreover, centrifuging CSF [around 5ml] for 30 minutes and thick smear examination from pellicle and repeat CSF examination enhances the detection rate

4.5.2 A. Culture - LJ/MGIT: Using solid media (LJ) or liquid media (MGIT). The positivity of CSF culture varies from 25 - 70 % (LJ or MGIT). However, the advantage of liquid culture is that it has a shorter time to positivity(4).

It has been seen that repeated cultures using different CSF samples is associated with increased sensitivity from 52 % for the first culture to up to 83 % after four cultures. A positive culture from CSF samples also helps in guiding antitubercular therapy based on sensitivity reports(4).

4.5.2 B. CSF NAAT[5]:

- **Exclusion of alternative diagnoses**
- CSF Bacterial culture
- CSF VDRL
- Toxoplasma PCR
- CSF Cryptococcal Ag (CrAg); fungal culture
- CSF wet mount examination
- Malignant cytology
- CSF – viral PCR (according to suspicion)

4.5.3 Imaging – Imaging is employed to aid the diagnosis of CNS TB by

- findings suggestive of TB meningitis as well as the presence of complications
- imaging of other systems – to evaluate for dissemination of TB disease

4.5.3 A. CT Head: A plain CT may aid the diagnosis of CNS TB. However contrast-enhanced CT may be used wherever available, and no contraindication to contrast agents exist. Following CT findings may suggest TBM -

- Presence of ventricular dilatation – due to communicating hydrocephalus
- Presence of basal meningeal enhancement
- Presence of hyper-density in basal cisterns on non-contrast scans
- Presence & location of infarctions
- Ring enhancing lesions

4.5.3 B. MRI - MRI findings suggestive of TBM are:

- Hydrocephalus
- Basal meningeal enhancement and exudates on T1 post contrast image
- Ischemic infarct
- Dural venous sinus thrombosis - with resultant hemorrhagic infarct
- Cranial nerve involvement - appear thickened, especially in proximal segments, high signal intensity on T2-weighted images and marked enhancement on postcontrast images.

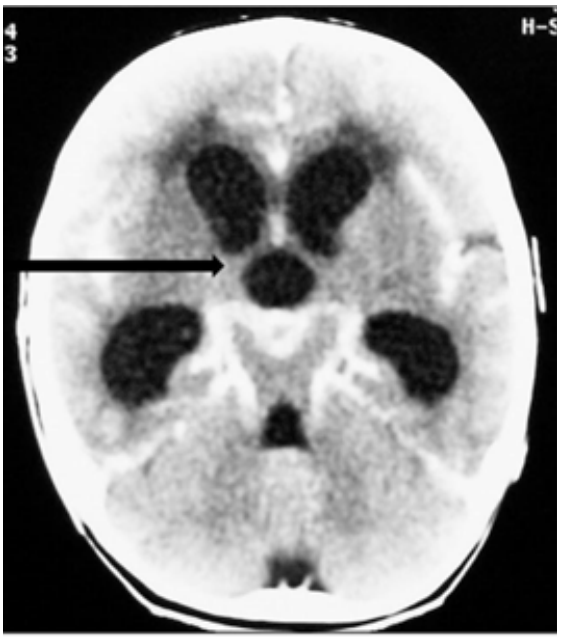


Figure 4.3: CT scan of the head showing the presence of hydrocephalus

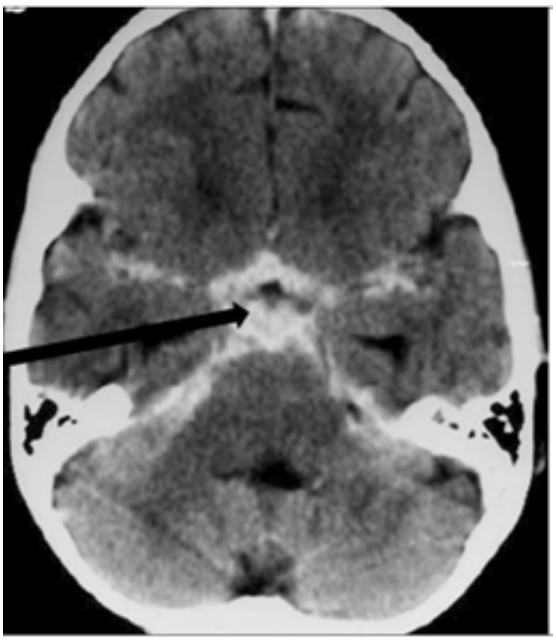


Figure 4.4: CT scan of the head showing basal meningeal enhancement

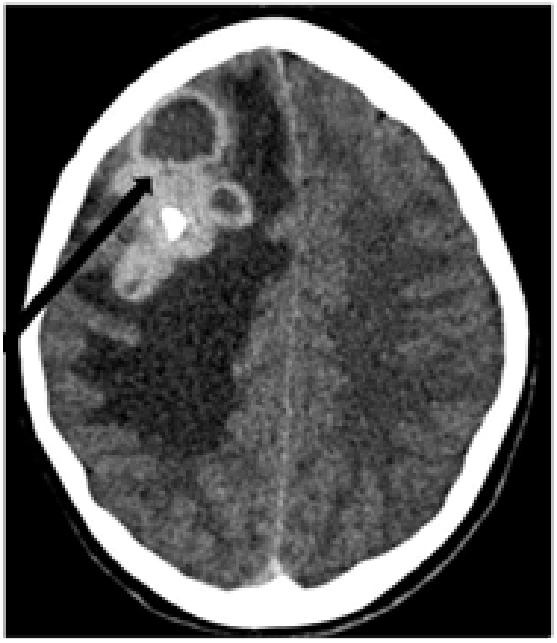


Figure 4.5: CT scan of the head showing the presence of a conglomerated tuberculous abscess

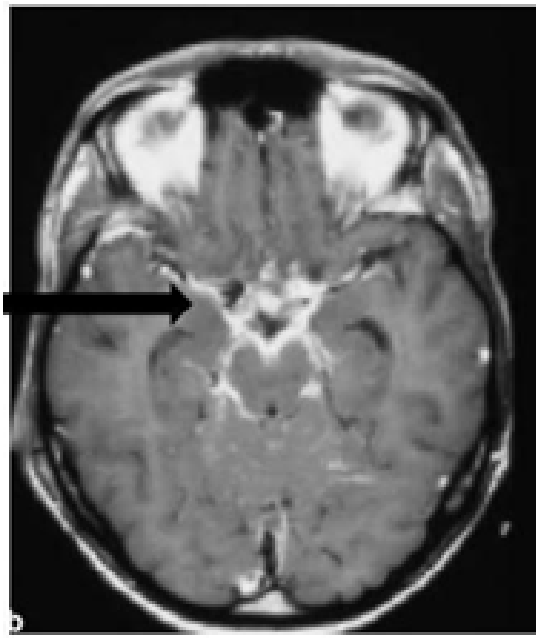


Figure 4.6: MRI brain showing basal meningeal enhancement on T1 post contrast image

4.5.3 C. Other findings in CNS TB

Focal tuberculous cerebritis - T1 hypo and T2 hyper signal intensities; small areas of patchy enhancement on postcontrast images.

Tuberculous abscess – the central area of liquefaction with pus. May be solitary or multiple and is frequently multiloculated. It appears hypodense with peripheral oedema and mass effect on CT.

- On T2-weighted images, the central necrotic area has increased signal intensity.
- Postcontrast - ring enhancement, usually thin and uniform, may be irregular and thick.

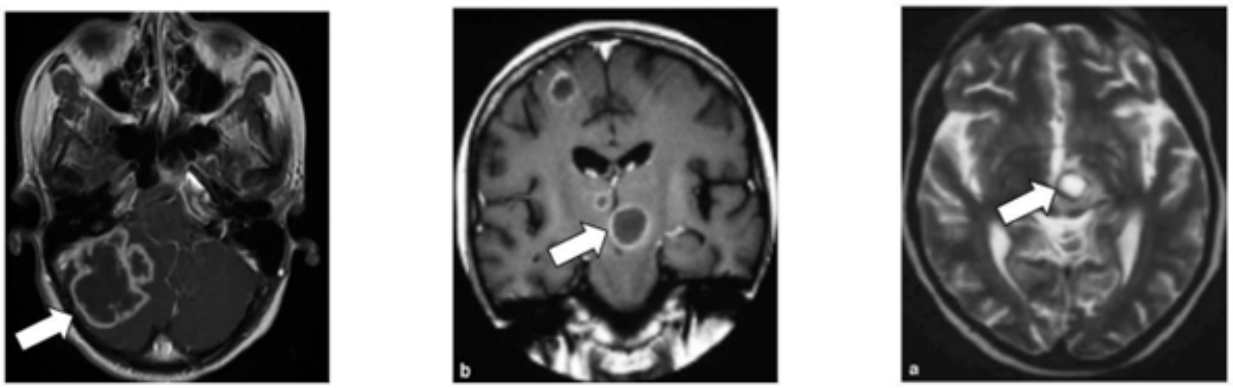


Figure 4.7: MRI brain showing tuberculous abscesses

4.6 Management

Management of suspected or confirmed cases of TBM includes the following considerations:

1. Primary therapy – Medical therapy in form of antitubercular drugs are the mainstay
2. Complications – physician need to assess and manage the metabolic or pathological complications such as
   a) Metabolic - electrolyte disturbances, Pituitary dysfunction
   b) Medical – vasculitis related stroke, drugs toxicity & interactions, seizures, co-infections
   c) Surgical – hydrocephalus, raised intracranial pressure.

4.6.1 Anti-Tubercular Therapy (Details in therapeutics chapter):

ATT is the mainstay of medical therapy in any form of tuberculosis. The goal of therapy is CSF sterility with clinical and radiological improvement; however, the neurological deficit may persist.

Choice of drugs is governed by susceptibility results (if available) along with the bactericidal activity of individual drugs, associated toxicity profile (important in certain population such as pregnancy, chronic liver disease, chronic kidney disease); drug interactions (in cases co-infected with HIV or Hepatitis B/C or transplant patients). However, some aspects warrant special mention with respect to CNS TB; the most important is drug penetration across the blood-brain barrier.

Table 4.3: First line Antitubercular drugs with their preferred doses and route of administration

Isoniazid	5-10mg/kg/day	oral
Rifampicin	10-15g/kg/day	oral
Rifampicin	15mg/kg/day	oral
Pyrazinamide	20-25mg/kg/day	oral
Streptomycin	15-25mg/kg/day	Injectable (i.m)

Comparison of 1st line and 2nd line ATT drugs along with their bactericidal activity and CSF penetration is shown in Table 3 and Table 4.

Table 4.4: First line Antitubercular Drugs with their bactericidal activity and CSF penetration[6]:

1st line drugs	Activity	CSF Penetration
Pyrazinamide	Cidal	95-100%
Isoniazid	Cidal	90-95%
Ethambutol	Static	10-50%
Streptomycin	Cidal	10-20%
Rifampicin	Cidal	5-25%

Table 4.5: Second line Antitubercular Drugs with their bactericidal activity and CSF penetration[6]:

2nd line drugs	Activity	CSF Penetration
Linezolid	Cidal	80-100%
Ethionamide	Cidal	80-95%
Moxifloxacin	Cidal	70-80%
Levofloxacin	Cidal	60-80%
Cycloserine	Static	40-70%
Amikacin	Cidal	10-25%
Kanamycin	Cidal	0-43%

Drug regimen - Based on above considerations and available evidence, following treatment is recommended as per NTEP guidelines and INDEX TB guidelines):

Treatment course is divided into intensive phase (IP) and continuation phase (CP). In IP – a minimum of 4 drugs should be used, consisting of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol. Experts also recommend use of Streptomycin/amikacin in place of ethambutol as the 4th drug in critically ill patients. In the continuation phase, at least three drugs should be continued.

Intensive phase - 4 drugs HRZ + E/S x 2 months
Continuation phase - 3 drugs HRE x at least 8-10 months

4.6.1 A. Response To Therapy And Duration:

- With the effective ATT, therapeutic response is expected within 6-8 weeks.
- Clinical response precedes radiological response.
- ATT should be continued for a minimum duration of 12 months, which may be further extended in case of partial or no response in confirmed cases. In addition, such cases require additional investigations to exclude drug resistance or alternative diagnosis.

4.6.1 B. Follow Up:

- All suspected or confirmed cases of TBM should be followed clinically.
- On every visit, patients should be assessed for clinical status, treatment compliance, drug toxicities.

- During follow-up, repeat CSF examination or brain imaging is not desirable; these are only to be done when clinically indicated i.e worsening of symptoms, partial or no response or new neurological symptoms.

4.6.1 C. Drug Resistant - tuberculous Meningitis:

Drug-resistant TB is an emerging problem all over the globe with drug resistance rates reaching alarming proportions, particularly in developing countries with high TB endemicity. It complicates the management of CNS TB further due to the limited arsenal of drugs with high bactericidal activity and good penetration in CNS along with less toxic profiles. TB meningitis due to drug resistance TB is not common as is exemplified by the number of case reports, case series and cohorts with variable sample sizes; concrete data on individual drug resistance is lacking (7).

According to available data, resistance to one or more drugs may be present; with Isoniazid monoresistance as most common across various studies. Therefore, it is noteworthy that all CSF samples in suspected TBM cases should be subjected to appropriate investigations to detect drug resistance.

Treatment - therapy in drug-resistant cases is guided by drug susceptibility reports and basic principles as outlined above.

For details, refer to PMDT (Programmatic management of Drug Resistant Tuberculosis) guidelines for the management of drug-resistant TB.

4.6.2 Role Of Steroids [8]:

TBM is characterised by significant inflammation, manifesting in the form of meningeal reaction, basal exudates, vasculitis of intracranial vessels. According to a study by Prasad et al, the use of steroids was found to be associated with a reduced risk of death (32 v/s 41%) (8). However, such benefits were not statistically significant in HIV positive patients. Therefore, based on this limited data, the following recommendations have been made regarding the use of steroids in TBM -

- HIV negative patients – recommended for at least 4 weeks
- HIV positive patients – may be used after ruling out opportunistic infections e.g., cryptococcal meningitis and cerebral toxoplasmosis – as these are associated with increased mortality with the use of steroids.

Steroids are indicated in TBM at a dose of 0.4mg/Kg (dexamethasone), to be tapered over 6-8 weeks. Following is the most accepted regimen -

- IV dexamethasone – 0.4mg /Kg x 2 weeks followed by 0.3mg/kg x 1 week followed by 0.2mg/Kg x 1 week followed by 4mg/day x 1 week followed by 3mg/day x 1 week followed by 2mg/day x 1 week followed by 1mg/day x 1 week and stop.

4.7 Management Of Complications

4.7.1 Hydrocephalus: It is one of the commonest complications of TBM due to formation of basal exudates, which in turn impair CSF absorption. Therefore, it is more commonly a communicating type in TBM. Salient points in managing hydrocephalus includes -

- Medical - Anti-edema or osmotic agents. Following agents may be used - Mannitol, Acetazolamide, Frusemide, steroids.

- Surgical (CSF diversion) – main modality of management. Various approaches to manage TBM may be -
  - Ventriculoperitoneal shunt – best surgical approach
  - External ventricular drain – may be considered as an acute intervention; bridge procedure till VP shunt is done
  - Endoscopic 3rd ventriculostomy-avoided in acute TBM

4.7.2 Raised Intracranial Pressure (ICP):

- Intracranial pressure may increase secondary too
- Diffuse oedema consequent to encephalitic process
- Infarcts, micro and macro, secondary to vasculitis
- Hydrocephalus
- Space-occupying effect of associated tuberculomas

This leads to decreased cerebral blood flow causing cerebral ischemia which is majorly responsible for poor outcomes. Osmotic agents (mannitol and hypertonic saline) and steroids are the mainstays of treatment.

4.7.3 Others

4.7.3 A. Hyponatremia (Sodium <135 mmol/L): 40 to 50% patients of TBM may develop hyponatremia(9). This may be secondary to (i) SIADH or (ii) Cerebral salt wasting syndrome. Manage according to onset– acute or chronic hyponatremia (48 hours).

4.7.3 B. Seizures: 5% of adults with TBM may develop seizures (9). Benzodiazepines should be used as acute abortive treatment. Maintenance therapy with antiepileptic drugs may be required (levetiracetam is the most favourable drug).

4.7.3 C. Vasculitis/stroke [10]: (15-57%); Occurs due to arteritis, arterial spasm, intraluminal thrombus, external compression of proximal vessels by the exudates in the basal cisterns. 51 % of the infarcts involve the head of the caudate nucleus, anteromedial thalami & anterior limb & genu of the internal capsule ('tubercular zone').

Role of aspirin in TB vasculitis[10]: Due to anti-inflammatory, antioxidant, antiaggregatory properties aspirin may have a role in preventing strokes due to vasculitis in TBM. A Systematic review and meta-analysis by Rizvi et al (2019) concluded that aspirin reduced the risk of new infarction, however, no overall benefit on all-cause mortality (11). Currently there is no consensus on using aspirin as a preventive strategy for vasculitis in TB meningitis.

4.8 Tuberculomas & TB Abscess

Management of TB abscess or tuberculoma is challenging due to the following reasons –

I. Diagnostic dilemma - as presenting features are relatively non-specific. Diagnostic uncertainty always remains. Imaging may aid in the diagnosis, however, confirmation of the diagnosis is made on histopathological analysis. Therefore, therapy is empirical i.e. based on clinical and radiological features.
II. Majority of lesions require surgical intervention as part of a diagnostic strategy or for management of space-occupying lesions or complications.

III. Most of the lesions tend to persist on serial radiological images albeit they may become smaller with treatment. Therefore, the optimal duration of therapy is not known.
IV. Lack of evidence to show that surgical removal without ATT is beneficial over ATT with or without surgery.

Management of TB abscess or tuberculoma includes –

- Medical management - ATT with steroids is the mainstay(12)
- Surgery - indicated in special situations -
  - Presence of associated obstructive hydrocephalus
  - Features of raised ICP
  - Large space-occupying tuberculomas with raised ICT
  - In addition – if features of associated compartmental shifts

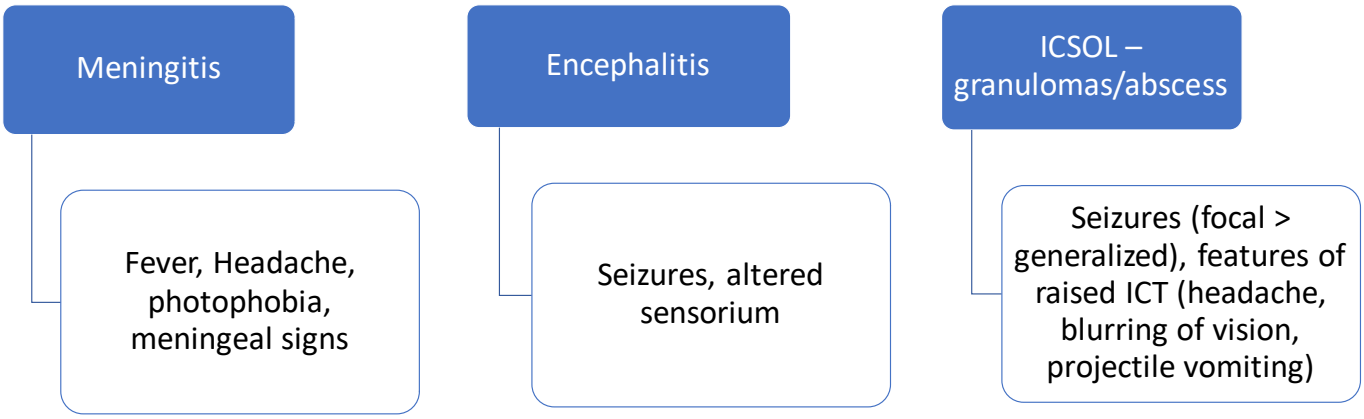
Experts recommend therapy for a duration of at least 12-18 months in case of tuberculomas or abscesses. Also, a noteworthy point here is that the lesions may persist after therapy; therefore, extended therapy beyond 18 months may not be required in most of the cases (13).

For further follow-up, repeat imaging may not be required unless clinically indicated (new-onset seizures, neurological signs or symptoms).

Assessment for response to therapy is based on clinical assessment. If clinically no response within 6 - 8 weeks of effective therapy, further evaluation should be done to rule out the following:

- Drug-resistant TB
- Other infectious causes
- Neurocysticercosis, toxoplasmosis
- Cryptococcomas
- Malignancy – primary or metastatic
- IRIS – usually within 3-6 months of therapy

Figure 4.8: Different types of CNS Tuberculosis



- Causative organisms – Bacterial, Viral, Fungal, Mycobacterial, Parasitic

Figure 4.9: Algorithm for Diagnosis of CNS TB

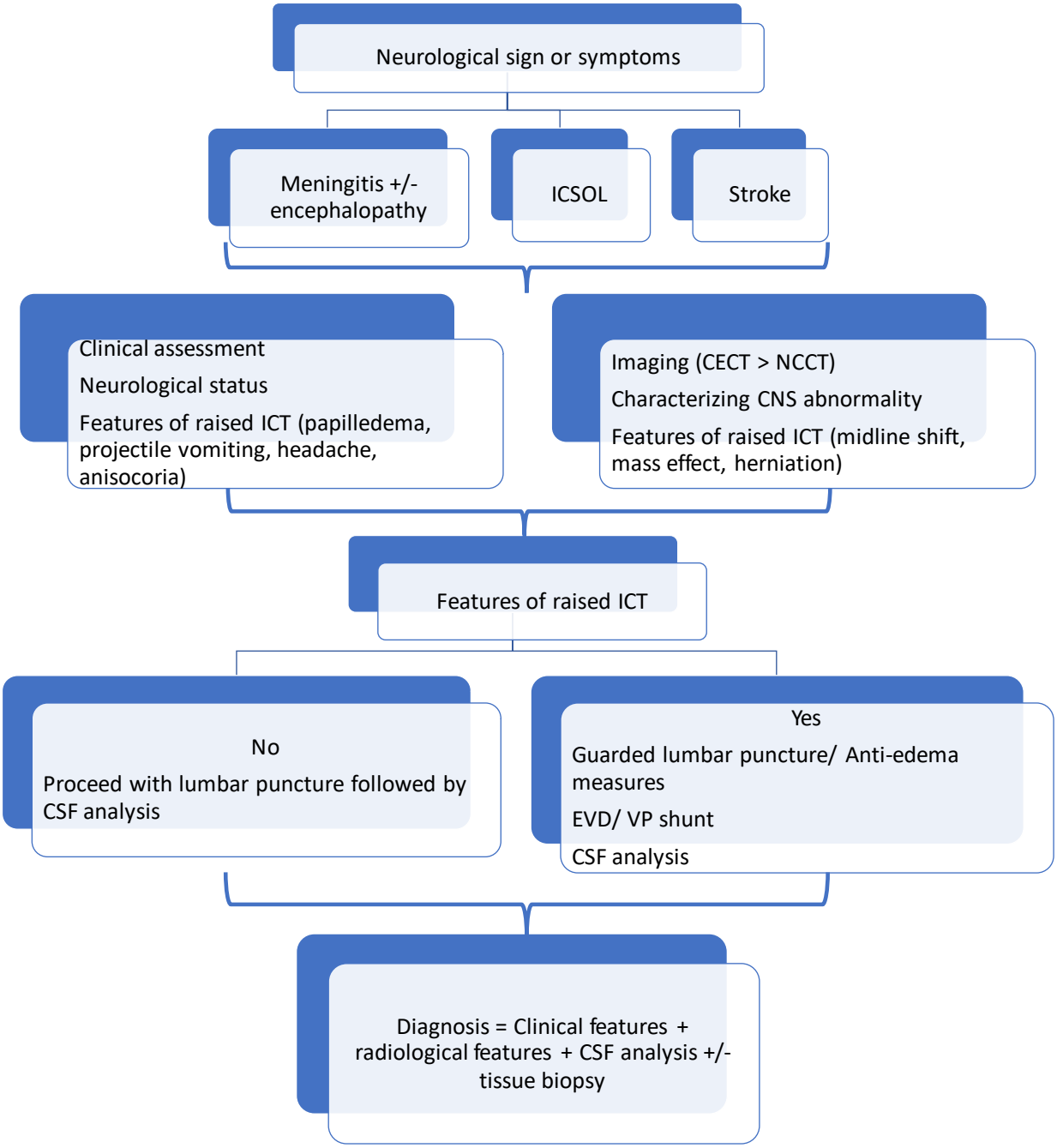
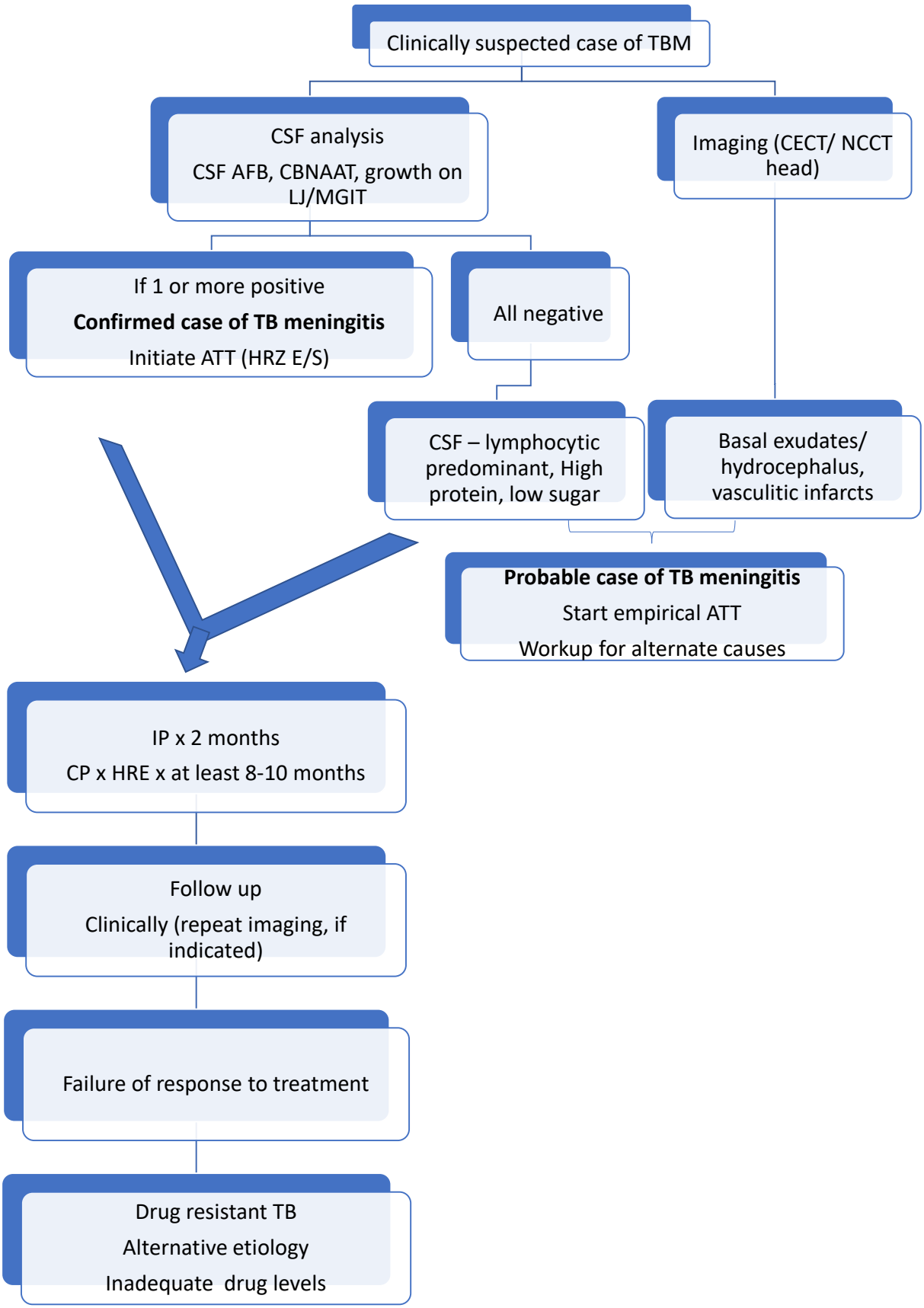


Figure 4.10: Approach to CNS TB



References:

1. Khadilkar SV, Kadam ND, Kulkarni RV, Meshram CM, Meshram AR, Patel BA, et al. Guidelines versus ground lines: Tuberculosis of the central nervous system. Neurology India. 2019 May 1;67(3):787.

2. Goyal V, Elavarasi A, Abhishek null, Shukla G, Behari M. Practice Trends in Treating Central Nervous System Tuberculosis and Outcomes at a Tertiary Care Hospital: A Cohort Study of 244 Cases. Ann Indian Acad Neurol. 2019 Mar;22(1):37–46.

3. Ahuja GK, Mohan KK, Prasad K, Behari M. Diagnostic criteria for tuberculous meningitis and their validation. Tuber Lung Dis. 1994 Apr;75(2):149–52.

4. Tuberculosis, by Surendra K Sharma, Second edition, Chapter 21, pg.309.

5. Sharma SK, Kohli M, Chaubey J, Yadav RN, Sharma R, Singh BK, et al. Evaluation of Xpert MTB/RIF assay performance in diagnosing extrapulmonary tuberculosis among adults in a tertiary care centre in India. European Respiratory Journal. 2014 Oct 1;44(4):1090–3.

6. Marx GE, Chan ED. Tuberculous Meningitis: Diagnosis and Treatment Overview. Tuberculosis Research and Treatment. 2011 Dec 21;2011:e798764.

7. Nagarathna S, Rafi W, Veenakumari HB, Mani R, Satishchandra P, Chandramuki A. Drug susceptibility profiling of tuberculous meningitis. Int J Tuberc Lung Dis. 2008 Jan;12(1):105–7.

8. Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2016 Apr 28;4:CD002244.

9. Goyal V, Elavarasi A, Abhishek null, Shukla G, Behari M. Practice Trends in Treating Central Nervous System Tuberculosis and Outcomes at a Tertiary Care Hospital: A Cohort Study of 244 Cases. Ann Indian Acad Neurol. 2019 Mar;22(1):37–46.

10. Misra UK, Kalita J, Nair PP. Role of aspirin in tuberculous meningitis: a randomized open label placebo controlled trial. J Neurol Sci. 2010 Jun 15;293(1–2):12–7.

11. Rizvi I, Garg RK, Malhotra HS, Kumar N, Uniyal R. Role of Aspirin in Tuberculous Meningitis: A Systematic Review and Meta-analysis. Neurol India 2019;67:993-1002.

12. Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TTO, Nguyen TCT, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med. 2004 Oct 21;351(17):1741–51.

13. Nair BR, Rajshekhar V. Factors Predicting the Need for Prolonged Antituberculous Treatment in Patients with Brain Tuberculomas. World neurosurg. 2019;125:e236-e247.

5. Abdominal Tuberculosis

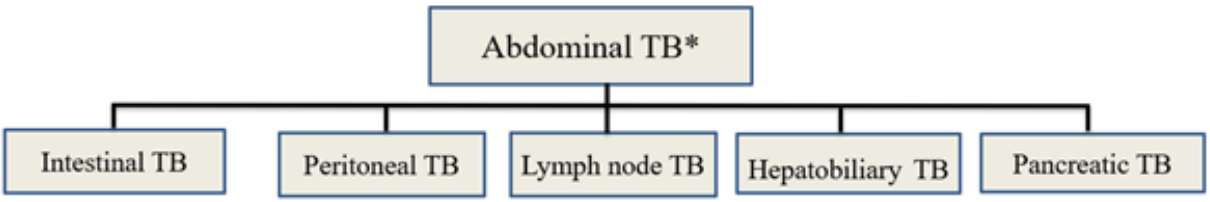
KEY POINTS

- Abdominal tuberculosis constitutes 11-13% of EPTB in India. It poses a diagnostic challenge because it presents with a myriad of manifestations.
- Intestinal TB is the most commonly encountered sub-type, followed by peritoneal and lymph node TB.
- Imaging is the primary modality of diagnosis as microbiological yields are classically low.
- Clinical expertise and diagnostic armamentarium are needed to differentiate it from its close mimics.

5.1 Introduction

Abdominal tuberculosis refers to Mycobacterial infection of any organ in the abdominal cavity, including the intestine & peritoneum. It is the sixth most common form of EPTB, constituting ~3% of all EPTB cases globally, and 11-13% of cases in India. Like PTB, it is common in the younger age group (25-44 years). It has varied presentations based on the site of involvement, stage of illness and complications, and poses a vast diagnostic challenge. (3)

5.2 Classification



*other uncommon types include esophageal, gastro-duodenal and peri-anal TB

5.3 Case Definitions Of Abdominal Tuberculosis

5.3.1 Presumptive Abdominal TB:

- A patient with abdominal pain, distension, fever, unexplained weight loss, chronic diarrhoea or an abdominal mass.

5.3.2 Bacteriologically Confirmed Case:

- A patient who has a microbiological diagnosis of abdominal TB, based on positive microscopy, culture or NAAT MTB/RIF.

5.3.3 Clinically Diagnosed Case:

- A patient with negative microbiological tests but with strong clinical suspicion and other evidence of abdominal TB, such as compatible imaging, histological findings, ancillary diagnostic tests or

response to anti-TB treatment.

5.4 Clinical Features

The following signs and symptoms may be present for **weeks to months**:
Symptoms such as abdominal distension (most common), abdominal pain with constitutional symptoms like fever, weight loss or loss of appetite.

Signs suggestive of tuberculosis such as conjunctival pallor, poor nutrition at times, icterus or peripheral lymphadenopathy (dissemination) are usually present. Signs suggestive of abdominal tuberculosis such as ascites (most common), tenderness at times, rarely hepato/splenomegaly or localised fullness/lumpiness (doughy abdomen) are observed. The ascites is out of proportion to pedal oedema, differentiating it from other causes like chronic liver disease or constrictive pericarditis.

5A Peritoneal Tuberculosis

5A.1 Classification:

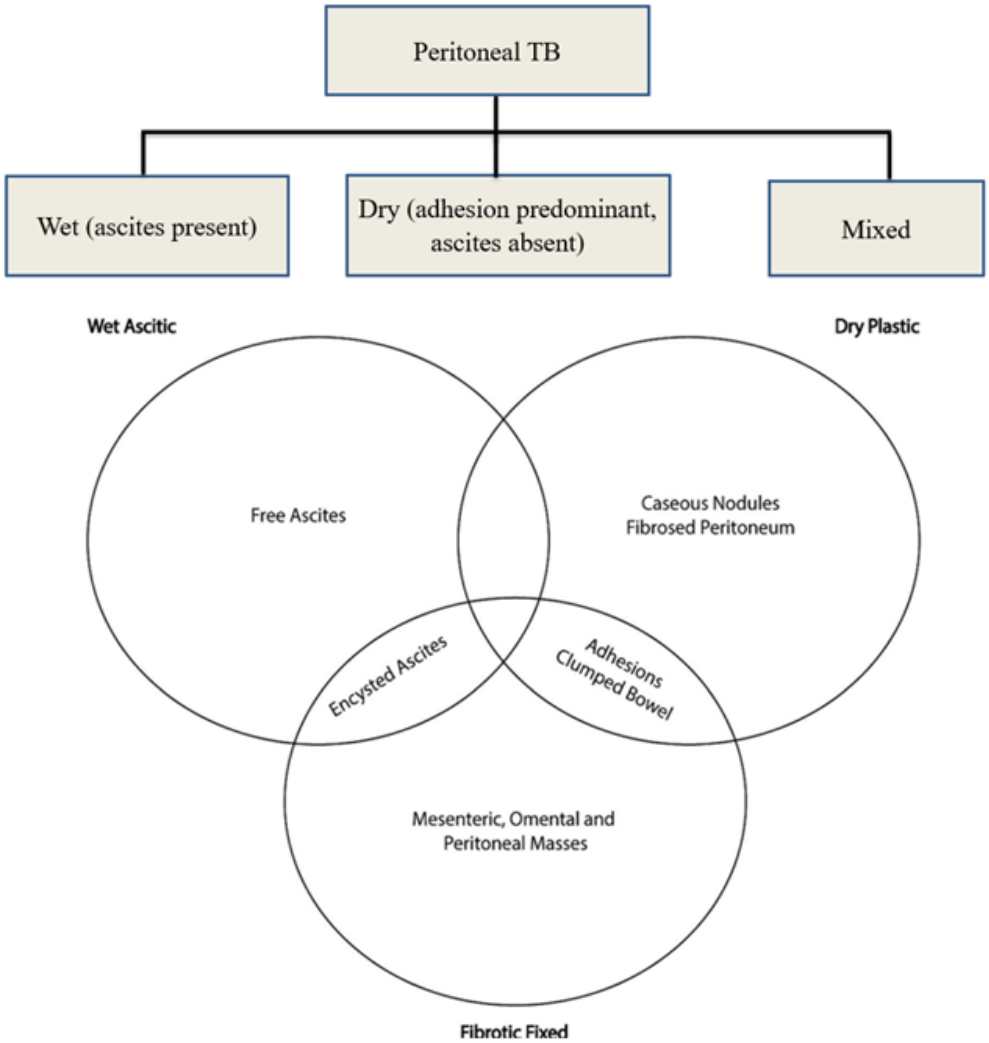


Figure 5A.1: Overlap between the various patterns of peritoneal TB. Adapted from: Ahamed Z R, Shah J, Agarwala R, Kumar-M P, Mandavdhare HS, Gupta P, et al. Controversies in classification of peritoneal tuberculosis and a proposal for clinico-radiological classification. Expert Review of Anti-infective Therapy. 2019 Aug 3;17(8):547–55.

5A.2 Pathogenesis Of Peritoneal Tuberculosis:

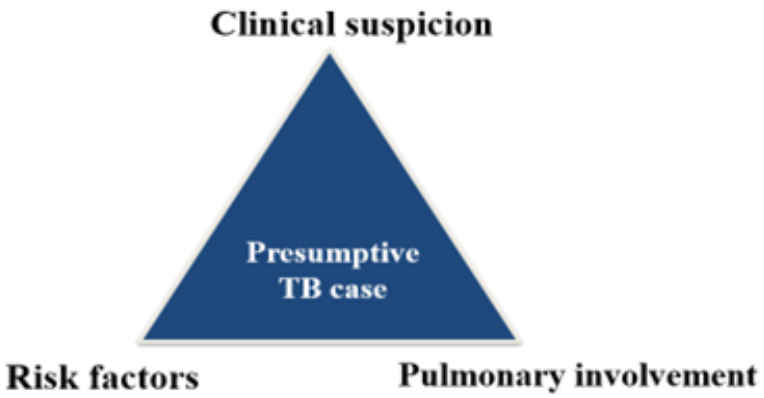
There are mainly 3 mechanisms of pathogenesis of peritoneal tuberculosis. The most common mechanism is that of hematogenous seeding from primary focus i.e. lungs, which leads to immune reaction and healing of the lesion with few *M. tuberculosis* bacilli remaining dormant. Reactivation of these dormant bacilli can occur during the event of impairment of cell-mediated immunity. The second mechanism is that of contiguous spread for adjacent sites i.e. fallopian tube or intestine. The third mechanism is that of direct seeding into the peritoneum in patients undergoing peritoneal dialysis.

5A.3 Risk Factors For Peritoneal Tuberculosis:

In addition to the common risk factors, the following are certain factors that specifically pertain to peritoneal tuberculosis:

- Alcohol use
- Cirrhosis (Chronic Liver Disease)
- HIV
- Patients on peritoneal dialysis

5A.4 Diagnostic Approach



5A.5 Investigations

All cases of presumptive peritoneal TB **must undergo:**

5A.5.1 Ancillary blood tests:

- CBC with peripheral smear: Normocytic normochromic anemia (of chronic disease), thrombocytosis, relative monocytosis
- ESR (raised)
- Baseline LFT, KFT

5A.5.2 Chest X Ray- to look for current or past evidence of Pulmonary TB

5A.5.3 HIV Testing- greater likelihood of dissemination, EPTB and MDR-TB

5A.5.4 USG Abdomen

5A.5.5 Ascitic Fluid Analysis

5A.5.4 Ultrasound Abdomen in Abdominal Tuberculosis

Ultrasound abdomen in typical cases can show:

- Free or loculated fluid in the abdomen, in which fine septations may be seen (MC differential-malignant ascites).
- Enlarged lymph nodes (mesenteric, retro-peritoneal) which, if hypoechoic, increase the likelihood of tuberculosis.
- Diffuse peritoneal and omental thickening.
- Interloop ascites (club sandwich sign).
- At times, a loculated mass may be seen, showing an encapsulated fluid collection with thick septa.
- Most common differential: tubo-ovarian mass.
- Bowel wall thickening (concomitant intestinal disease).
- Clumping of bowel loops to each other or onto the abdominal wall.

5A.5.5 Ascitic Fluid Analysis:

Ascitic Fluid Should Be Sent for:

- Cytology
- Biochemistry (protein, albumin, sugar)
- **ADA**
- Microscopy for AFB (sensitivity <2%) (6)
- Culture for TB (liquid/ solid); Sensitivity ~20% (6)
- PCR based methods like NAAT were not routinely recommended in the Index TB guidelines in view of poor sensitivity
    - A Cochrane meta-analysis (2018) showed a sensitivity of NAAT to be 59% in peritoneal fluid (8)
    - Ascitic fluid for NAAT MTB/Rif may be employed in research settings. With regard to clinical diagnosis, it is currently a conditional recommendation depending on feasibility.
- Gram stain and culture for bacterial/ fungal organism (case to case basis)
- Malignant cytology (case to case basis, at least 3 samples if high suspicion)

Complete panel comprising AFB, TB culture and NAAT MTB/Rif increases the overall diagnostic yield.

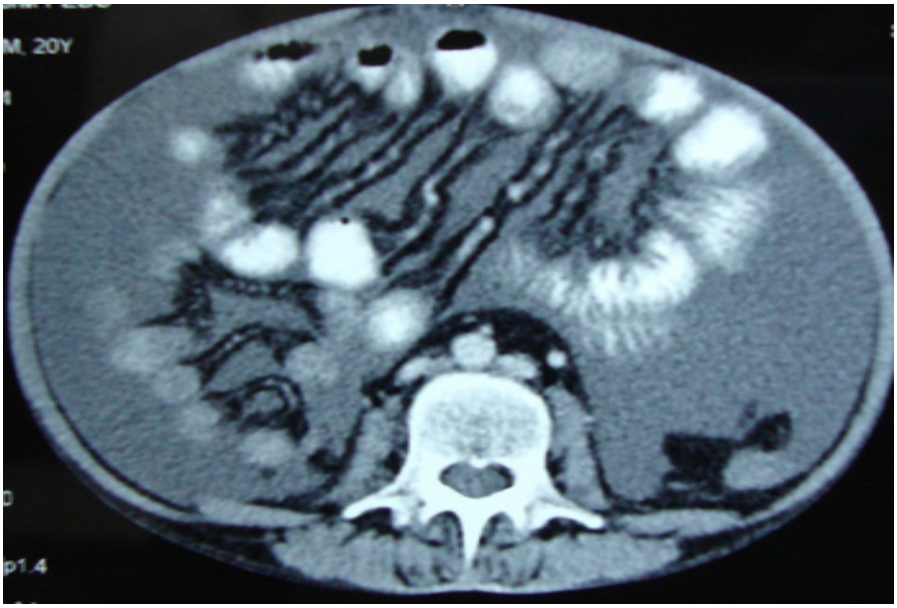
Ascitic fluid analysis can show:

- Straw coloured fluid
- Cytology showing raised TLC with lymphocytic predominance
- Low SAAG (<1.1)
- High protein (>=2.5 g/dL)
- ADA > 39 (sensitivity and specificity 93% and 94%) (2)
- In cirrhosis: sensitivity is poor and ADA can be low, as they mount a weak inflammatory response.

5A.5.6 CT Scan In Peritoneal Tuberculosis:

CECT abdomen is sufficient for evaluation of peritoneal TB, and in typical cases can show:

- Ascitic fluid with high attenuation value (more grey as compared to urine in bladder).
- **Smooth thickening and enhancement of peritoneum.** Nodular implants and irregular peritoneal thickening suggest carcinomatosis.
- Matting of loops, fibrous adhesions, omental caking/masses and abdominal cocoon formation (small bowel loops matted together, encased by an enhancing membrane). Thickened mesentery with mesenteric lymph nodes which usually have a hypodense center **(necrotic)**.



Gross ascites: Ascitic fluid separating the leaves of the mesentery

Figure 5A.2: CECT image of abdomen shows ascitic fluid seen here separating the leaves of the mesentery (thin arrow). These findings are suggestive of wet type of peritoneal tuberculosis. Image Courtesy: Professor Raju Sharma, Dept of Radiology AIIMS.

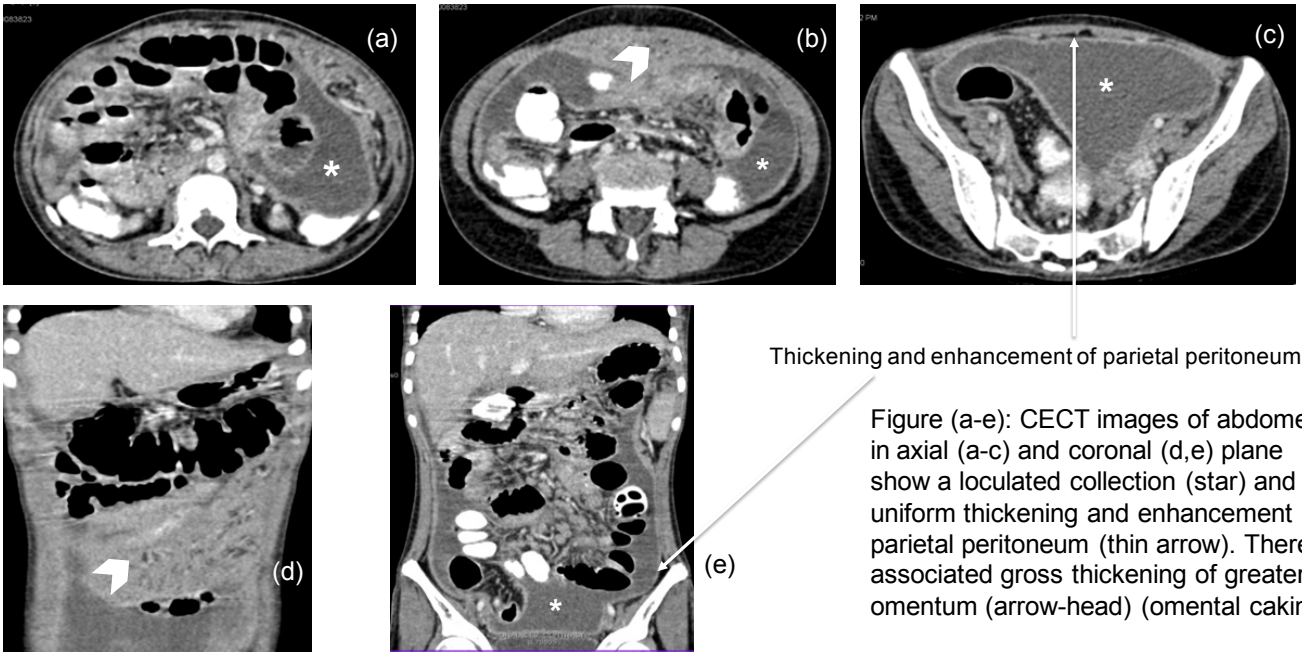


Figure (a-e): CECT images of abdomen in axial (a-c) and coronal (d,e) plane show a loculated collection (star) and uniform thickening and enhancement of parietal peritoneum (thin arrow). There is associated gross thickening of greater omentum (arrow-head) (omental caking)

Figure 5A.3 (a-e): CECT images of abdomen in axial (a-c) and coronal (d,e) in coronal plane show loculated ascites (star) and uniform thickening and enhancement of parietal peritoneum (thin arrow). There is associated gross thickening of greater omentum (outlined arrow) (omental caking). The ascitic fluid analysis suggested tuberculosis and the patient responded to ATT. Peritoneal carcinomatosis can also present with omental caking and peritoneal thickening which is a close differential diagnosis. Image Courtesy: Professor Raju Sharma, Dept of Radiology AIIMS.

5A.5.7 USG Guided FNAC/Biopsy:

- Indications
  - Few selected cases which remain a diagnostic dilemma may require an additional FNAC/ core biopsy from peritoneal or omental thickening or from the intra-abdominal lymph nodes. Such features may include:
    - Atypical radiological findings
    - No ascites
    - Ascitic fluid analysis not suggestive of TB
    - No response to trial of ATT till 4-8 weeks
- Specimens should be sent for histopathology (formalin), microscopy for AFB, culture for M. tb and GeneXpert (all 3 in **sterile saline**).

5A.5.8 Diagnostic Laparoscopy:

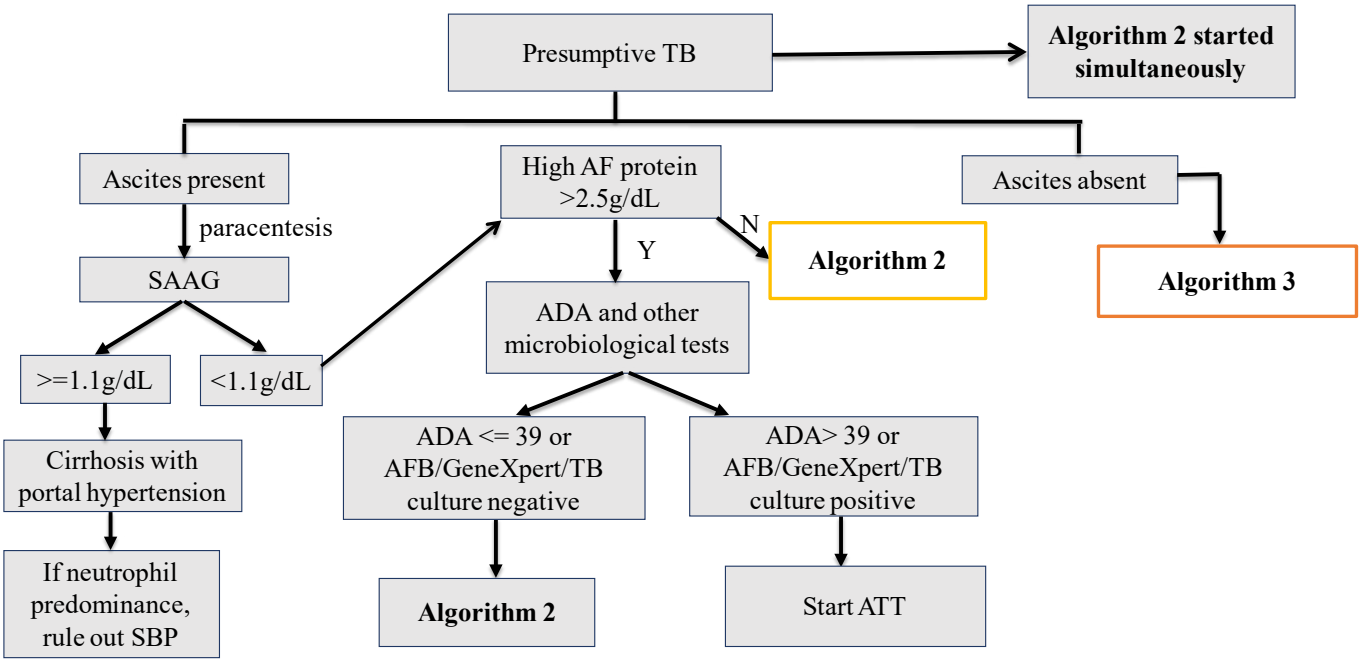
If the diagnosis is still doubtful after a battery of investigations, visual appearance on laparoscopy can be resorted to. Laparoscopic appearance can be highly suggestive of peritoneal Tuberculosis.

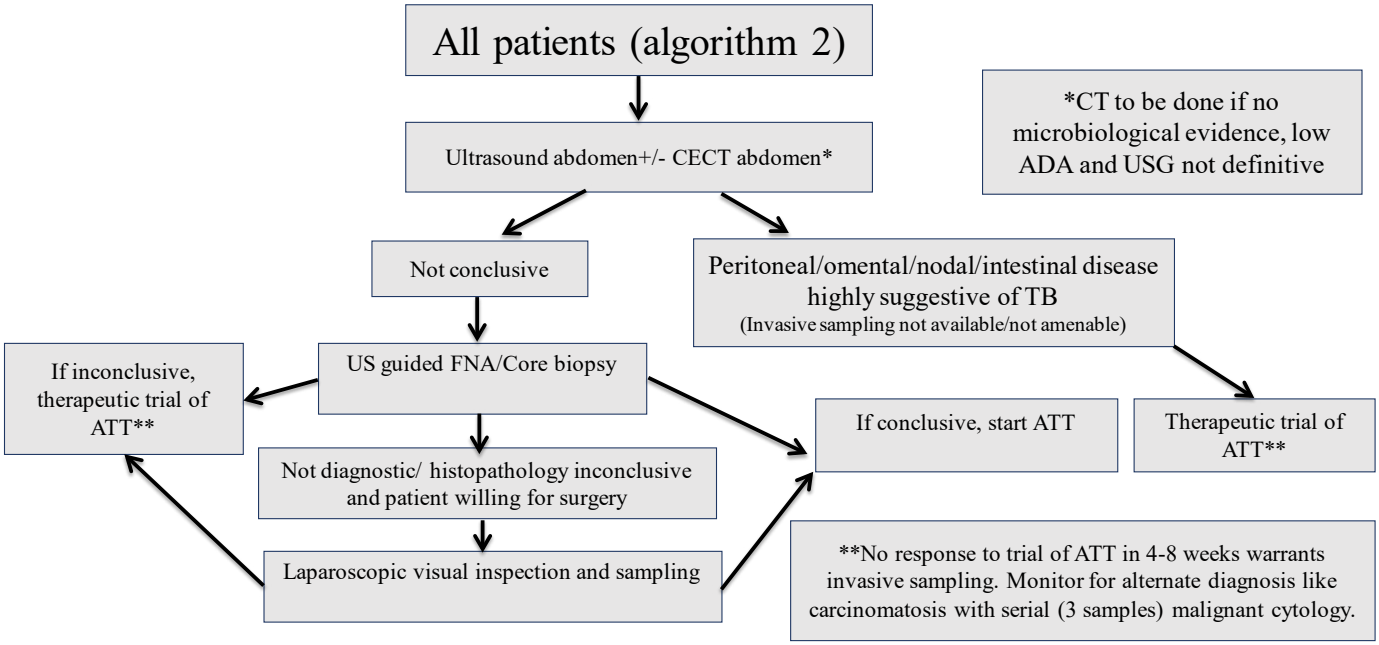
Typical laparoscopic findings include:

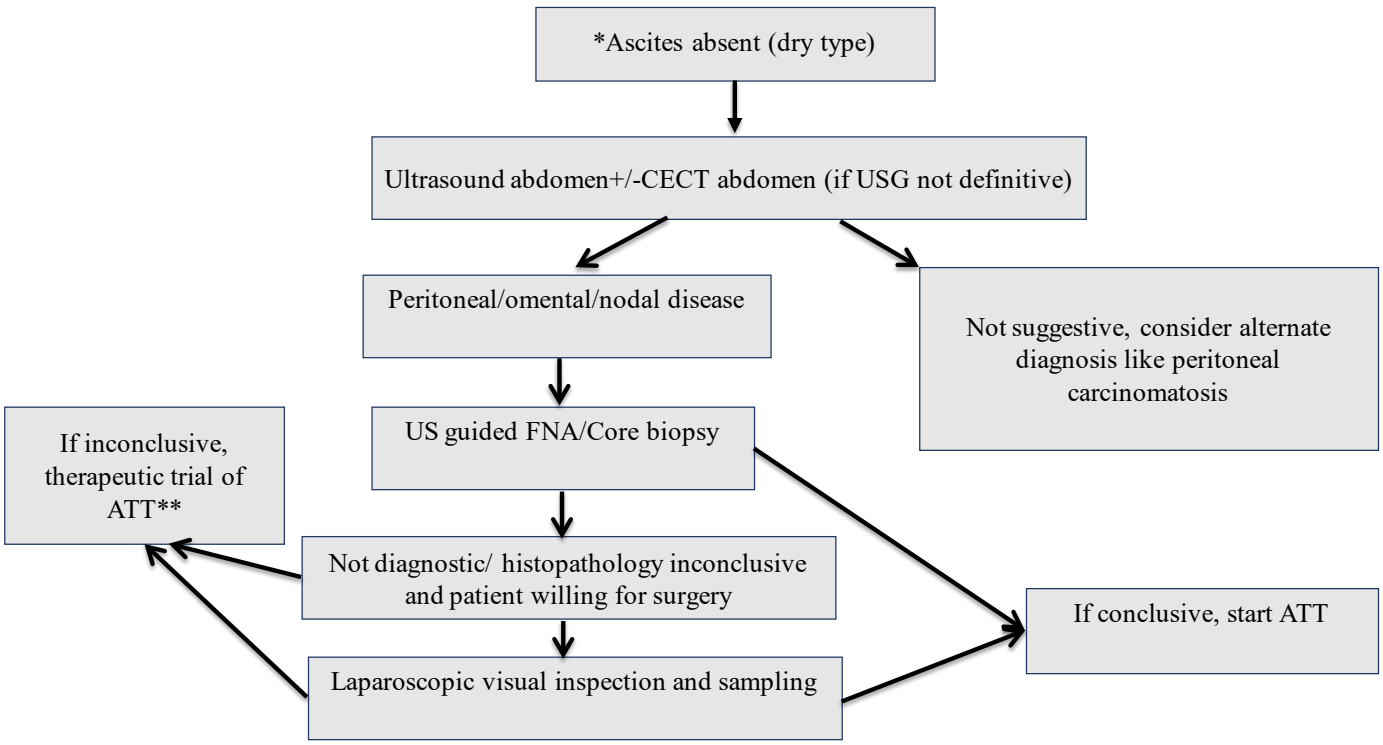
- Thickened peritoneum with or without tubercles:
  - Multiple, yellowish-white, uniform-sized (~ 4-5mm) tubercles diffusely distributed on the parietal peritoneum
- The peritoneum is hyperaemic and lacks its usual shiny lustre.
- The omentum, liver and spleen can also be studded with tubercles.
- Fibro-adhesive peritonitis with markedly thickened peritoneum and multiple thick adhesions fixing the viscera.
- Tissue must be sent for microscopy and culture for M. tb, NAAT (in sterile saline) and histopathology (in formalin).

Laparoscopy is **not** routinely recommended due to the high cost and invasive nature of the procedure.

5A.6 Diagnostic Algorithm:




All patients (algorithm 2)
Ultrasound abdomen+/- CECT abdomen*
*CT to be done if no microbiological evidence, low ADA and USG not definitive
Not conclusive
Peritoneal/omental/nodal/intestinal disease highly suggestive of TB
(Invasive sampling not available/not amenable)
If inconclusive, therapeutic trial of ATT**
US guided FNA/Core biopsy
If conclusive, start ATT
Therapeutic trial of ATT**
Not diagnostic/ histopathology inconclusive and patient willing for surgery
Laparoscopic visual inspection and sampling
**No response to trial of ATT in 4-8 weeks warrants invasive sampling. Monitor for alternate diagnosis like carcinomatosis with serial (3 samples) malignant cytology.


*Ascites absent (dry type)
Ultrasound abdomen+/-CECT abdomen (if USG not definitive)
Peritoneal/omental/nodal disease
Not suggestive, consider alternate diagnosis like peritoneal carcinomatosis
If inconclusive, therapeutic trial of ATT**
US guided FNA/Core biopsy
Not diagnostic/ histopathology inconclusive and patient willing for surgery
If conclusive, start ATT
Laparoscopic visual inspection and sampling

5A.7 Management Of Abdominal Tuberculosis

Medical management (the cornerstone of treatment):

- **Intestinal and peritoneal: 6 months** of first-line ATT (2 HRZE+ 4 HRE), with the decision to extend treatment made on a case to case basis.
- **Pancreatic and hepato-biliary TB:**
  - 6 months with the decision to extend treatment made on a case to case basis.
- **Referral:** Presumptive intestinal and presumptive peritoneal TB where the diagnosis is uncertain require referral to a gastroenterologist or radiologist for further evaluation and tissue sampling for testing.
- **Follow-up:** Patients are assessed at 2 months (end of IP) and at 6 months after starting treatment.

References:

1. Sanai FM, Bzeizi KI. Systematic review: tuberculous peritonitis--presenting features, diagnostic strategies and treatment. Aliment Pharmacol Ther. 2005 Oct 15;22(8):685–700.

2. Makharia GK, Srivastava S, Das P, Goswami P, Singh U, Tripathi M, et al. Clinical, endoscopic, and histological differentiations between Crohn's disease and intestinal tuberculosis. Am J Gastroenterol. 2010 Mar;105(3):642–51.

3. Sharma SK, Mohan A. Tuberculosis. 2nd ed. Jaypee Brothers; 2009. 1078 p.

4. Sharma MP, Bhatia V. Abdominal tuberculosis. Indian J Med Res. 2004 Oct;120 (4):305–15.

5. Riquelme A, Calvo M, Salech F, Valderrama S, Pattillo A, Arellano M, et al. Value of adenosine deaminase (ADA) in ascitic fluid for the diagnosis of tuberculous peritonitis: a meta-analysis. J Clin Gastroenterol. 2006 Sep;40(8):705–10.

6. Debi U, Ravisankar V, Prasad KK, Sinha SK, Sharma AK. Abdominal tuberculosis of the gastrointestinal tract: Revisited. World J Gastroenterol. 2014 Oct 28;20(40):14831–40.

7. Kohli M, Schiller I, Dendukuri N, Dheda K, Denkinger CM, Schumacher SG, et al. Xpert® MTB/RIF assay for extrapulmonary tuberculosis and rifampicin resistance. Cochrane Database Syst Rev. 2018 Aug 27;8(8):CD012768.

8. Chou CH, Ho MW, Ho CM, Lin PC, Weng CY, Chen TC, et al. Abdominal tuberculosis in adult: 10-year experience in a teaching hospital in central Taiwan. J Microbiol Immunol Infect. 2010 Oct;43(5):395–400.

5B Intestinal Tuberculosis

5B.1 Introduction:

Intestinal tuberculosis is a form of extrapulmonary TB. This increasingly common disease poses significant diagnostic challenges as the features are often non-specific and diagnostic modalities are not sensitive enough. India has one of the highest burdens of TB and is home to a large number of patients with abdominal TB.

5B.2 Epidemiology:

Abdomen is involved in 11% of patients with extra-pulmonary tuberculosis. The most common site of involvement is the ileocaecal region.

Risk factors for development of abdominal TB: Intestinal TB can affect apparently normal people. However, the following sub group of patients are at increased risk.

- Persons living with HIV
- Cirrhosis
- Type II DM
- Alcoholism
- People with prior pulmonary TB
- Chronic kidney disease, renal transplant
- Use of steroids or biologicals
- Poor socioeconomic status, malnutrition
- Underlying malignancy
- Treatment with antitumor necrosis factor (Anti TNF-a) agents
- Corticosteroids
- Use of continuous ambulatory peritoneal dialysis (CAPD)

5B.3 Case Definitions:

1. **Presumptive Case:**
   Any patient with recurrent intestinal colic, partial or complete bowel obstruction, chronic diarrhea, unexplained weight loss, palpable lump per abdomen, lower GI bleed.
2. **Confirmed Case:**
   Clinical, endoscopic and radiological findings consistent with abdominal tuberculosis with one of the following
   - Typical histology (Caseation with granulomas)
   - Confirmed microbiological findings from tissue obtained by biopsy, fine needle aspiration, fluid aspirate or surgery/laparoscopy with demonstration of AFB by stain or culture or positivity by NAAT*.
3. **Probable Case**
   Clinical, endoscopic and radiological findings consistent with abdominal tuberculosis with the following
   - Consistent findings on histology or cytology (granulomas without caseation, chronic

inflammation) or fluid analysis.
- Exclusion of other differential diagnosis including (but not limited to) inflammatory bowel disease (Crohn's disease), malignancy, etc.

5B.4 Pathophysiology

5B.4.1 Mode Of Acquisition:

1. Majority of cases are from reactivation of primary infection caused by *Mycobacterium tuberculosis.*
2. TB bacteria reach the gastrointestinal tract via
    - Haematogenous spread (from a pulmonary focus acquired during primary infection in childhood).
    - Ingestion of infected sputum.
    - Direct spread from infected contiguous lymph nodes and fallopian tubes.

5B.4.2 Common Sites Affected:

- Intestinal TB can involve any part of the alimentary tract (from oesophagus to the anus).
- Gastro-duodenal TB is uncommon (1%) due to
    - Bactericidal properties of gastric acid
    - Scarcity of lymphoid tissue in the mucosa
    - Rapid emptying of gastric contents
- The ileocaecal region is the most common site of involvement (75%) (2) because of
    - Increased physiological stasis
    - Fluid and electrolyte absorption
    - Minimal digestive activity
    - The abundance of lymphoid tissue (Peyer's patches)
- Other locations of involvement, in order of descending frequency, are the ascending colon, jejunum, appendix, duodenum, stomach, oesophagus, sigmoid colon, and rectum.

Table 5B.1.Spectrum/Classification: Depending on gross morphology, the predominant types are

Ulcerative form	Ulcero-hypertrophic form	Hypertrophic form
• Single or Multiple transverse mucosal ulcers • Long axis of the ulcers is perpendicular to the long axis of the bowel.	• Combination of ulceration and hypertrophy	• Thickening of the bowel wall with scarring fibrosis and a rigid, mass like appearance • May mimic carcinoma on colonoscopy

5B.5 Clinical Presentation

Common symptoms include recurrent and chronic abdominal pain, fever, weight loss, diarrhea or constipation. ITB can also present with symptoms of obstruction (Constipation, obstipation, severe abdominal pain).

Table 5B.2.Symptoms depend upon the site(s) of involvement and the type of lesions

Site	Type	Symptoms
Small intestine	Ulcerative	Diarrhoea, malabsorption
	Stricturous	Obstruction
Large intestine	Ulcerative	Bleeding Per rectum
	Hypertrophic	Lump, obstruction

5B.6 Diagnosis:

The disease is insidious and has nonspecific and protean manifestations, thus a high degree of clinical suspicion is necessary.

- Routine evaluations may reveal anemia, raised ESR and CRP and hypoalbuminemia. But these tests are of little diagnostic help.
- Chest X-ray is mandatory for all patients of ITB.
- HIV testing should be offered to all patients of ITB.
- All patients with suspected intestinal TB should be offered endoscopic evaluation, unless contraindicated.
- All attempts should be made to get a histological or microbiological diagnosis by means of radiologically guided biopsy.

5B.6.1 Radiological Findings

USG

Nonspecific and operator dependent and is often not useful in diagnosis. However, it is usually the first investigation and might help in excluding other etiologies.

Following features when present are supportive of a diagnosis of ITB.

- Abdominal Lymphadenopathy
- Ascites
- Bowel thickening: best appreciated in the ileocaecal region
- **"Club sandwich" or "sliced bread" sign:** seen due to localized fluid between radially oriented bowel loops
- **Pseudo-kidney sign:** Pseudo kidney sign is a nonspecific sign seen in bowel obstruction. There is bowel wall thickening which opposes mucosal surfaces, giving an echogenic stripe.

CT Enterography

- It is the investigation of choice when intestinal TB is suspected.
- It enables us to identify intraluminal and extramural abnormalities.
- Typical findings of ITB on CT Enterography are
  - Involvement of ileocaecal region
  - Short segment involvement
  - Symmetric bowel wall thickening and enhancement
  - Presence of large lymph nodes (> 1cm, often necrotic)
  - Pulled up contracted caecum with wall thickening
- Findings supportive of a diagnosis include
  - Presence of ascites
  - Peritoneal thickening and enhancement
  - Omental nodularity or thickening

CT Enterography Protocol

- The technique of CT enterography combines small bowel distension with a oral contrast mixture and abdomino-pelvic CT examination during the enteric phase following administration of intravenous contrast.
- Neutral oral contrast agents such as water, polyethylene glycol solution, mannitol or Volumen (low density barium in sorbitol) are used.
- 20% Mannitol prepared by diluting 300ml of mannitol in 1200ml of water is preferred.
- The solution intake protocol is 450ml at 60 min and 40 min prior to scanning and 225ml at 20 and

10 min prior to scanning. The remaining is ingested on the table, just prior to scanning.

- Intravenous iodinated contrast agent should be given at a rate of 4ml/s.
- Scanning is done in single phase (venous, at 70s) and shows mural features, wall thickening, and extraluminal abnormalities.

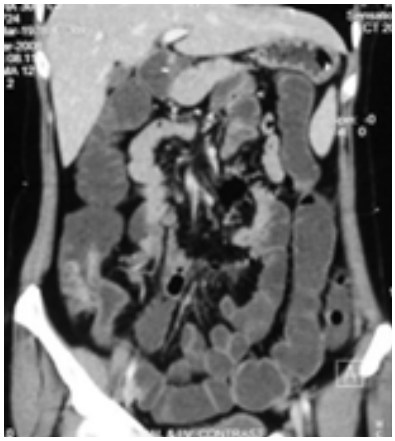


Figure 5B.1. shows the CT scan of a patient with Intestinal TB: note the characteristic ileocecal involvement. Image Courtesy: Professor Raju Sharma, Dept of Radiology AIIMS

Barium meal follow through may be performed when facilities for performing a CT Enterography are unavailable.

Typical features of active ITB on barium meal follow through

- Irregular and nodular narrowing of ileocecal junction with the involvement of adjacent terminal ileum and cecum. Often, deep ulcers are seen.
- The extent of involvement of cecum is often more than that of ileum.
- The cecum is contracted and pulled-up due to associated fibrosis.
- Dilatation of the proximal bowel segment.

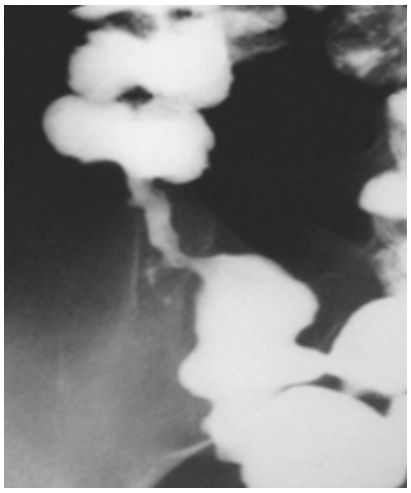


Figure 5B.2. Barium meal follows through showing severe narrowing of ileocecal junction, contracted cecum, and adjacent ascending colon. Image Courtesy: Professor Raju Sharma, Dept. of Radiology AIIMS.

MR enterography has also been shown to perform well in comparison to CT. However, it is not routinely done

5B.6.2 Colonoscopy

- It is the most important tool for evaluation of ITB as it helps in the characterisation of lesions, as well as in obtaining samples for microbiological and histological analysis
- **Typical Endoscopic Findings:** transverse ulcers, patulous ileocecal valve, short. segment

involvement.

- **Other Features:** pseudopolyps, strictures, and nodularity may be seen but these are not pathognomonic of TB and may be found in CD.
- **Features Against ITB:** Recto-sigmoid involvement, longitudinal ulcers, aphthous ulcers, cobblestone appearance, mucosal bridges and skip lesions (favor CD).

5B.6.3 Microbiological Diagnosis

- ITB is a paucibacillary disease and thus the sensitivity of microbiological diagnostics is poor. This is one of the biggest challenges of ITB diagnosis.
- Pooled Indian data indicate that the sensitivity of ZN staining is only 2.7-37.5%. (9).
- Use of NAAT MTB/Rif
  - NAAT MTB/Rif is of limited benefit in the diagnosis of ITB.
  - A recent systematic review and meta-analysis determining the diagnostic accuracy of Xpert MTB/Rif for the diagnosis of intestinal TB reported the sensitivity to be only 23%. (1).
  - In a report on ITB, only 3 out of 37 patients had a positive Xpert MTB/Rif test, suggesting that the sensitivity of the test for ATB would be low.

5B.7 Histopathology

- In patients with clinically confirmed ITB, only 50-80% have demonstrable granuloma on intestinal mucosal biopsies. (2), (6)
- **Characteristic features:** large confluent granuloma, often more than 5-10/hpf with caseous necrosis.
- **Typical but not characteristic:** Submucosal granulomas, ulcers lined by a band of epithelioid histiocytes and disproportionate submucosal inflammation.

5B.8 Common differential diagnosis

1. ITB vs Crohn's Disease (CD)

- Both these chronic granulomatous disorders have similar clinical, endoscopic, radiologic, and histologic pictures.
- However, the natural history of both these disorders is strikingly different with serious implications regarding management.
- Misdiagnosis of one disease as another may be associated with multiple problems, including unnecessary immune suppression, drug toxicity, and delay in appropriate treatment.

Radiological (Table 5B.3) and histopathological (Table 5B.4) features that help in differentiating ITB vs CD

Table 5B.3 - Radiological features characteristic of intestinal tuberculosis and Crohn's disease

Parameter	ITB	CD
Site of involvement	Cecum more than ileum	Ileum more than caecum
Length	Short segment	Long segment
Multiple site	Uncommon (<4)	Common
Skip lesions	Uncommon	Common
Enhancement	Homogeneous	Stratified
Fistulae	Rare	Common

Mesenteric abscess	Very rare	May be seen
Strictures	Concentric	Eccentric and sacculations
Fibrofatty proliferation	Rare	Common
Mesenteric nodes	Larger, necrotic	Small, homogeneous
Omental involvement	Common	Rare

Table 5B.4: Histopathological features characteristic of intestinal tuberculosis and crohn's disease

Tuberculosis granuloma	**Granuloma in crohn's disease**
Caseating	Non-caseating
Organisms seen on AFB staining (5 to 15 % cases)	Not seen
5 or more granulomas in biopsies from one Segment	infrequent (< 5) Granulomas in biopsies from one segment
Granulomas larger than 400 µm in diameter	Granulomas usually less than 200 µm in diameter
Granulomas located in the submucosa or in granulation tissue, often as palisaded epithelioid histiocytes, and disproportionate sub mucosal inflammation	Granulomas located in the mucosa. Poorly organized and discrete or isolated. Micro granulomas, or aggregates of histiocytes and crypt centred inflammation such as pericryptal granulomas and focally enhanced colitis is a feature.
Confluent granulomas	No confluent Granulomas
lymphoid cuff around granulomas	Not present

5B.9 Concomitant Pulmonary TB:

In a prospective study from AIIMS, among treatment naïve patients with suspected ITB (unpublished data) in whom a differentiation between CD and ITB couldn't be made, 24% of patients had evidence of active TB on CT chest.

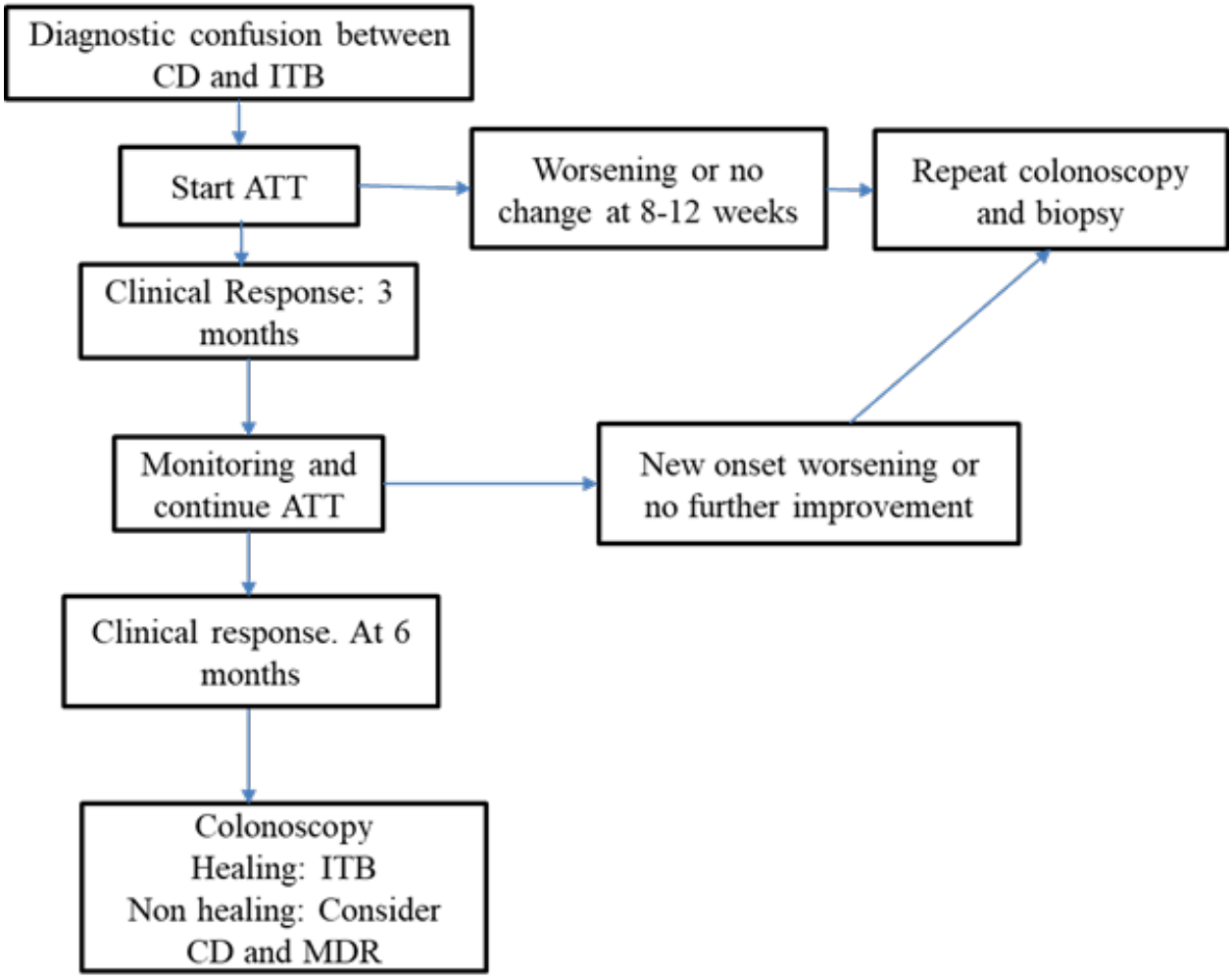
Thus, a CT chest may help in making a diagnosis of ITB when a differential between CD and ITB cannot be made based on other features.

ATT as a therapeutic option for differentiating ITB and CD:

- A definite differentiation of ITB and CD may not always be possible
- In a recent study that evaluated empirical ATT for differentiation of ITB from CD revealed the following findings: (9)
  - In patients with ITB, clinical response was seen in 94% at 3 months and in 99% at the end of 6 months.
  - All ITB patients had mucosal healing at the end of ATT, while only 5% of CD patients showed mucosal healing.
  - Interestingly in patients with CD, symptom response was seen in 38% and 37% in patients at 3 and 6 months, respectively. This may be due to the waning and waxing nature of CD
- Therefore, ATT may be used as a therapeutic option for differentiating ITB and CD.
- After a course of 8-12 weeks at ATT, a clinician may decide after evaluation to continue to treat the patient as ITB or otherwise as CD.

- Persistent symptoms after 3 months of ATT may indicate a diagnosis of CD
- However, the presence of a clinical response to ATT does not exclude the possibility of CD and mucosal healing should be sought.

Figure 5B.3 shows an algorithm for differentiating between intestinal tuberculosis and Crohn's disease in patients with diagnostic confusion between the two diseases. Adapted from Pratap Mouli V, Munot K, Ananthakrishnan A, et al. Endoscopic and clinical responses to anti-tubercular therapy can differentiate intestinal tuberculosis from Crohn's disease. *Aliment Pharmacol Ther.* 2017.



5B.10 Treatment of intestinal TB

- Recommended standard treatment for adult and children with ITB: **2RHZE/4RHE.**
- **Duration:** Standard 6 months treatment is recommended.
- This is based on the meta-analysis of 3 RCTs (Cochrane systematic review) (9) which concluded that
  - Rate of clinical cure was the same between those treated for 6 months and 9 months.
  - Relapse was uncommon in both groups, but couldn't be assessed due to small sample size.
  - Patients with HIV and those with prior ATT exposure were excluded from the study, no recommendation couldn't be made for these patient groups.
- Duration of the treatment may be extended depending on the clinical response as per clinician discretion.

5B.11 Monitoring Response

- Routinely, patients should be monitored for drug induced liver injury(DILI) at 2, 3 and 6 months.
- There are no standard guidelines regarding the frequency and modality of assessing response and is left to the discretion of the treating physician.
- In a confirmed case response should be monitored clinically at 3 and 6 months, if required imaging may be done in selected patients. Worsening or no clinical response after initial treatment may indicate treatment failure.
- However, in the first 3 months deterioration may be due to paradoxical reaction.

5B.12 People living with HIV

- Higher incidence of EPTB and abdominal tuberculosis, and may have atypical presentation.
- Less common but an important differential in this subpopulation is disseminated MAC infection.
- Duration of therapy: There is a lack of data and these patients may need to be treated for longer duration based on clinical response.

5B.13 Management of complications

Strictures can be managed with endoscopic dilatation, but some cases require resection of the stricture or hemicolectomy.

Oesophageal and gastroduodenal TB patients rarely require surgery; ATT alone is usually adequate. Duodenal strictures may be treated with balloon dilatation. Bypass surgery may be required if this is not successful.

It is also important to understand that successful treatment of ITB need not necessarily result in resolution of strictures.

- Endoscopic evaluation when feasible may show mucosal healing which can be taken as an end point for ATT.
- Diffusion weighted MRI is an alternative.
- Endoscopic or surgical interventions may be needed.

References:

1. Makharia GK, Srivastava S, Das P, Goswami P, Singh U, Tripathi M, et al. Clinical, endoscopic, and histological differentiations between Crohn's disease and intestinal tuberculosis. Am J Gastroenterol. 2010 Mar;105(3):642–51.

2. Sharma V, Soni H, Kumar-M P, Dawra S, Mishra S, Mandavdhare HS, et al. Diagnostic accuracy of the Xpert MTB/RIF assay for abdominal tuberculosis: a systematic review and meta-analysis. Expert Rev Anti Infect Ther. 2021 Feb;19(2):253–65.

3. Sharma R, Madhusudhan KS, Ahuja V. Intestinal tuberculosis versus crohn's disease: Clinical and radiological recommendations. Indian J Radiol Imaging. 2016;26(2):161–72.

4. Kedia S, Sharma R, Makharia G, Ahuja V, Desai D, Kandasamy D, et al. Indian guidelines on imaging of the small intestine in Crohn's disease: A joint Indian Society of Gastroenterology and Indian Radiology and Imaging Association consensus statement. Indian J Radiol Imaging. 2019;29(2):111–32.

5. Kedia S, Das P, Madhusudhan KS, Dattagupta S, Sharma R, Sahni P, et al. Differentiating Crohn's disease from intestinal tuberculosis. World J Gastroenterol. 2019 Jan 28;25(4):418–32.

6. Nayagam JS, Mullender C, Cosgrove C, Poullis A. Abdominal tuberculosis: Diagnosis and demographics, a 10-year retrospective review from a single centre. World J Clin Cases. 2016 Aug 16;4(8):207–12.

7. Kumar S, Bopanna S, Kedia S, Mouli P, Dhingra R, Padhan R, et al. Evaluation of Xpert MTB/RIF assay performance in the diagnosis of abdominal tuberculosis. Intest Res. 2017 Apr;15(2):187–94.
8. Shah S, Thomas V, Mathan M, Chacko A, Chandy G, Ramakrishna BS, et al. Colonoscopic study of 50 patients with colonic tuberculosis. Gut. 1992 Mar;33(3):347–51.

9. Rathi P, Gambhire P. Abdominal Tuberculosis. J Assoc Physicians India. 2016 Feb;64(2):38–47.
10. Pratap Mouli V, Munot K, Ananthakrishnan A, Kedia S, Addagalla S, Garg SK, et al. Endoscopic and clinical responses to anti-tubercular therapy can differentiate intestinal tuberculosis from Crohn's disease. Aliment Pharmacol Ther. 2017 Jan;45(1):27–36.

11. Jullien S, Jain S, Ryan H, Ahuja V. Six-month therapy for abdominal tuberculosis. Cochrane Database Syst Rev. 2016 Nov 1;11(11):CD012163.

12. Sonika U, Saha S, Kedia S, Dash NR, Pal S, Das P, et al. Predictive factors for malignancy in undiagnosed isolated small bowel strictures. Intest Res. 2017 Oct;15(4):518–23.

13. Bhansali SK. Abdominal tuberculosis. Experiences with 300 cases. Am J Gastroenterol. 1977 Apr;67(4):324–37.

5C. Hepatobiliary TB

5C.1 Introduction

Hepatobiliary tuberculosis is a rare manifestation of Mycobacterium tuberculosis infection and is usually secondary to tuberculosis of the lungs or gastrointestinal tract. The term hepatobiliary TB refers to either isolated hepatic, biliary, or hepatobiliary involvement with other organ system involvement. The manifestations of tuberculous liver involvement are nonspecific and pose significant diagnostic challenges.

5C.2 Epidemiology

Isolated hepatic involvement with TB is rare and is thought to be due to relative hypoxia of liver parenchyma. Tuberculous involvement of the liver, as a part of disseminated tuberculosis, is seen in up to 50–80 % of cases (1). Primary hepatobiliary TB is more uncommon still occurring in around 1% of patients with TB(2). In an Indian series, the majority of the patients were men and were younger than 40.

5C.3 Pathophysiology

The primary site of infection in hepatic TB is not always evident. Tuberculosis bacilli reach the liver via hematogenous dissemination or hepatoportal lymph vessels. In miliary TB, the common pathway of infection is via the hepatic artery, whereas in focal liver TB it is more commonly via the portal vein and gastrointestinal lymphatics.

Hepatobiliary TB can be classified based on clinicopathological presentation

- Miliary TB: Multiple miliary tubercles.
- Granulomatous hepatitis: Tuberculomas forming aggregates 1–4 cm.
- Nodular: Atypical heterogeneous abscess/solid pseudo-tumour. This can occur from the liquefaction of caseous necrosis or coalescing granulomas.
- Ductal: Focal/diffuse lesions affecting ducts.
- Nodal: Nodal mass/obstruction at the porta.

5C.4 Clinical presentation

The manifestations of hepatobiliary TB are nonspecific and resemble other diseases such as malignancies and infections with the most common symptoms being abdominal pain and jaundice, which is frequently accompanied by non-specific systemic symptoms like fever, weight loss, and anorexia. Rarely patients may present with upper GI bleed or melena (secondary to haemobilia) or palpable gallbladder mass. Respiratory symptoms are predominant in patients with miliary TB. It is often difficult to diagnose based on the non-specific clinical presentation, same was suggested by an Indian study, in which a preoperative diagnosis of TB was made in only 4 patients out of a total of 18(3). The symptom duration of the disease can vary from 2 weeks to 2 years.

The spectrum of presentation:

- Fever of unknown origin
- Hepatomegaly with or without space-occupying lesions
- Jaundice
- Abnormal LFTs (especially elevated alkaline phosphatase)
- Abnormal imaging (abscess, space-occupying lesions)

5C.5 Diagnosis

Diagnosis of hepatobiliary TB can be challenging due to variable symptomatology and therefore requires a high level of suspicion.

- Leukocyte count and CRP are often raised
- Liver Function Test (LFT)
  - TB affecting the liver parenchyma will be reflected in elevated transaminases as compared to alkaline phosphatase
  - Extrahepatic TB will cause an earlier rise in bilirubin due to obstruction
  - Progression to liver failure will cause alterations in bilirubin, INR, and albumin

Table 5C.1 Radiological features are non-specific and are of little help in diagnosis:

List of investigation	Micronodular type	Macronodular type	Others
USG	Small hypo-echoic nodules (miliary type)	Large hypoechoic mass like areas	Hepatomegaly, abscesses
CT	Multiple, small, low attenuation areas Acute: central enhancement Chronic: calcification	Single, large tumor-like mass	Diffuse hepatosplenomegaly
MRI	T1 iso-intense, T2 hyperintense areas with variable Gadolinium contrast enhancement (depending on the disease phase)		

5C.6 Histopathology and Microbiology

Due to nonspecific clinical and radiological features, definitive diagnosis depends on HPE and/or microbiology. Samples for the same can be taken by endoscopic US-guided biopsy, CT/US-guided percutaneous biopsy, and surgical biopsy. A liver biopsy for mycobacterial culture is the most specific diagnostic test for hepatic TB.

The characteristic HPE finding is the presence of caseating granuloma which is seen in up to 68% of the cases(4). However, several diseases, e.g. sarcoidosis and histoplasmosis, give rise to granulomas, it is therefore only suggestive and not pathognomonic for TB.

The various microbiological techniques that can aid in diagnosis are:-

- AFB can be demonstrated by Ziehl-Neelsen staining ranging from 0 to 45% of cases, which can be up to 75% in PLHIV(5)
- Mycobacterial cultures are positive in 0-43% of these cases(5)
  - NAAT have 88% sensitivity and 100% specificity for the detection of mycobacterial DNA on tissue specimens (6). In another series of 43 liver biopsies with granulomas, NAAT had a sensitivity of 53% and specificity of 96% (7).

5C.7 Treatment

ATT is the mainstay of treatment, but the duration of treatment is controversial with differences of opinion amongst various guideline bodies. Index TB guidelines endorse a standard 6 months therapy, which can be extended up to 1 year as per clinician discretion. Table 5C.2 The treatment regimen has to be modified according to the degree of liver dysfunction, as follows:

Child Turcotte Pugh score	Liver disease	Treatment recommended
Child's grade A cirrhosis CTP </=7	Stable MELD score <18	Regimens containing 2 hepatotoxic drugs (rather than the three in the standard regimen): Avoid Pyrazinamide • 9 months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented) • 2 months of isoniazid, rifampicin, streptomycin, and ethambutol, followed by 6 months of isoniazid, rifampicin, and ethambutol
Child's grade B cirrhosis or CTP 8-10	Advanced MELD score 18–25	Regimens containing only 1 potentially hepatotoxic drug: Rifampicin preferred over isoniazid, Pyrazinamide not to be used
Child's grade C cirrhosis or CTP >/=11	Very advanced MELD score >25	Regimens containing no potentially hepatotoxic drugs: 18-24 months therapy using a combination of Streptomycin/Amikacin/Kanamycin, Ethambutol, and levofloxacin, or other second-line oral drugs

Role of surgery

- Tuberculous abscesses may need surgical drainage
- TB causing biliary obstruction frequently requires initial decompression with endoscopic retrograde cholangio-pancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC)
- Biliary strictures may necessitate the placement of stents
- Biliary diversion surgery is an alternative treatment for extensive strictures

References:

1. Amarapurkar DN, Patel ND, Amarapurkar AD. Hepatobiliary tuberculosis in western India. Indian J Pathol Microbiol. 2008;51(2):175–81.

2. Kandasamy S, Govindarajalou R, Chakkalakkoombil SV, Penumadu P. Isolated hepatobiliary tuberculosis: a diagnostic challenge. BMJ Case Rep. 2018 Jun 6;2018:bcr2017223912.

3. Saluja SS, Ray S, Pal S, Kukeraja M, Srivastava DN, Sahni P, et al. Hepatobiliary and pancreatic tuberculosis: A two decade experience. BMC Surg. 2007 Jun 24;7(1):10.

4. Hickey AJ, Gounder L, Moosa MYS, Drain PK. A systematic review of hepatic tuberculosis with considerations in human immunodeficiency virus co-infection. BMC Infect Dis. 2015 May 6;15(1):209.

5. Evans RPT, Mourad MM, Dvorkin L, Bramhall SR. Hepatic and Intra-abdominal Tuberculosis: 2016 Update. Curr Infect Dis Rep. 2016 Oct 29;18(12):45.

6. Chaudhary P. Hepatobiliary tuberculosis. Ann Gastroenterol Q Publ Hell Soc Gastroenterol. 2014;27(3):207–11.

7. Diaz ML, Herrera T, Lopez-Vidal Y, Calva JJ, Hernandez R, Palacios GR, et al. Polymerase chain reaction for the detection of Mycobacterium tuberculosis DNA in tissue and assessment of its utility in the diagnosis of hepatic granulomas. J Lab Clin Med. 1996 Apr;127(4):359–63.

5D. Pancreatic Tuberculosis

5D.1 Introduction

Isolated pancreatic TB is a rare manifestation, often detected when screened for other malignancies. It usually occurs either as a part of miliary tuberculosis or due to spread from retroperitoneal lymph nodes.

Epidemiology

Pancreatic TB is observed more frequently in the fourth and fifth decades of life. The literature available on pancreatic tuberculosis is limited. Pancreatic involvement has been observed in 2.1-4.7% of patients with miliary tuberculosis (1). Risk factors for Pancreatic TB include those listed about abdominal TB in general, such as cirrhosis, HIV, diabetes mellitus, underlying malignancy, malnutrition, and immunosuppressive therapy. Clinical presentation remains vague such as epigastric pain, fever, jaundice, and weight loss, which could also point toward a malignancy.

5D.2 Pathophysiology

- Pancreatic involvement is rare because of the digestion of *Mycobacteria* by pancreatic enzymes and the synthesis of other anti-mycobacterial peptides.
- Mycobacteria may reach the pancreas via various routes:
  - Miliary or disseminated tuberculosis
  - Hematogenous dissemination from an occult site most commonly from the lungs
  - Direct spread from contiguous lymph nodes affected by tuberculosis
- Reactivation of a tuberculous focus in the pancreas may be induced by alcoholism, pancreatitis, steroid therapy or surgery.
- A toxic inflammatory insult of the pancreas may result in the following tuberculosis elsewhere in the body, in which case the organism may not be isolated from the pancreas.
- PLHIVs and other immunosuppressed people have a high likelihood of disseminated TB and it is wise to keep a differential of TB and other HIV-related opportunistic infections in this setting.

Differential Diagnosis for Pancreatic TB
- Gallstone disease: CBD stone
- Neoplastic :
  - Periampullary carcinoma
  - Carcinoma gallbladder
  - Lymphoma (on a background of HIV)

5D.3 Diagnosis

- Definitive diagnosis in this setting needs evaluation with imaging in the form of:
  - Ultrasound abdomen:
    - Pancreas appears heterogeneous and bulky.
    - Hypoechoic intrapancreatic collections may be seen with/without peripheral enhancement and fine internal echoes.

    - Pancreas visibility may be obscured by overlying bowel loops.
- CECT abdomen: more sensitive and preferred imaging modality
    - Most common presentation: focal involvement of the head of the pancreas.
    - Usually a focal lesion can be seen which can be cystic or solid.

Table 5D.1 Differential diagnosis based on imaging

Predominantly cystic components	Predominantly solid components
Mimickers: • Pancreatic cysts • Cystic neoplasms- cystadenoma • Chronic pancreatitis with pseudocyst • Pancreatic necrosis/abscess	When associated with dilated major pancreatic duct and lymph node enlargement, mimickers: • Adenocarcinoma • Lymphoma • Metastasis

- Calcifications may involve the pancreatic mass or duct in 50-70% of cases(2).
- Vascular invasion: occasionally seen in pancreatic TB, involving the portal vein, superior mesenteric vein, and hepatic artery misleading towards a malignancy.
- Pancreatic ductal dilatation is seen less frequently in pancreatic TB as compared to malignancy.
- Lymph node involvement or evidence of concurrent peritoneal, intestinal, or pulmonary lesions suggestive of tuberculous etiology aids in the diagnosis.

MRI and MRCP:

- Hypointense to isointense lesions on T1 weighted images, with heterogenous signal intensity on T2 weighted images.
- Gadolinium-enhanced T1 weighted: peripheral enhancement with areas of central necrosis or enhancement.
- May show dilated bilio-pancreatic ductal system.

Patterns of enhancement of the mass lesion, pancreatic ductal dilatation, intraparenchymal, ductal or mass calcification, and portal venous thrombosis can differentiate pancreatic TB from other causes.
Role of Endoscopic ultrasound:

- Endoscopic ultrasound (EUS) is used both for diagnostic imaging, with a better appreciation of the extent of the lesion, and to guide tissue sampling(FNA/biopsy)
- EUS-guided FNA has a slightly **smaller risk of seeding** and is technically better for small lesions
- EUS is available at very few centers and is practically not feasible, and is reserved for cases where no lesion is appreciated on USG or CECT, to take a closer look at the periampullary structure

5D.4 Medical Management (The Cornerstone Of Treatment)

- Pancreatic and hepato-biliary TB: decision to extend treatment beyond 6 months may be made on a case-to-case basis.
- **Referral:** Presumptive intestinal and presumptive peritoneal TB where the diagnosis is uncertain require referral to a gastroenterologist.
- **Follow-up:** Patients are assessed 2 months (end of IP) and 6 months after starting treatment

References:

1. Pancreatic Tuberculosis - an overview | ScienceDirect Topics [Internet]. [cited 2023 Jan 17]. Available from: https://www.sciencedirect.com/topics/medicine-and-dentistry/pancreatic-tuberculosis.

2. Dou Y, Liang Z. Pancreatic tuberculosis: A computed tomography imaging review of thirteen cases. Radiol Infect Dis. 2019 Mar 1;6(1):31–7.

6. Skeletal Tuberculosis

KEY POINTS:

- Skeletal tuberculosis is the 3rd most common form of Extrapulmonary Tuberculosis.
- Spinal tuberculosis should be suspected in individuals with persistent localized back or neck pain for more than four weeks.
- Contrast-enhanced MRI is the radiological investigation of choice in patients with suspected skeletal tuberculosis.
- Along with ATT, joint immobilization with braces/cast may be required for better outcomes.

6.1 Introduction

Skeletal TB is a common chronic infection of bones and marrow. It is the 3rd most common form of extra-pulmonary TB(Lymph Node>Pleural> Skeletal), and it is the most disabling form of TB. Skeletal TB can occur both in adults and children. These patients usually present late in the course of illness with neurological sequelae. Appendicular skeletal joints such as hip, knee, ankle, feet, shoulder, elbow, wrist and hand can also be affected by TB.

6.2 Epidemiology

Skeletal TB constitutes 1-2% of all cases of TB and 10% of extrapulmonary cases. Roughly 50% of skeletal TB involves the spinal column. (1)

6.3 Pathophysiology

Similar to other extrapulmonary TB infections, it is paucibacillary, and the spread is predominantly hematogenous, followed by the lymphatic or contiguous spread. The primary site of disease lies almost always in the lungs and rarely at other sites like genito-urinary sources.

Since the spine is a cancellous bone which is dense and vascular, it can act as a nidus for the hematogenous spread and thus is a common site for TB. Within the skeletal system, TB can affect bones, joints, and the synovial system. The damage to these structures is mediated via granuloma formation, caseous necrosis, hyperaemia induced osteopenia, and eventually leading to pathological fracture. (2)

SPINAL TB

Clinical features:

Presentation depends upon the duration of disease, site of disease (lower thoracic & upper lumbar region are most often involved while cervical spine involvement is especially dangerous) and integrity of the underlying bone. Pain (b ack pain or neck pain) is the earliest and most common symptom. While a sizable fraction of patients (with s pine TB) can present with a deformity such as kyphosis and even with neurological deficit (lower limb motor or sensory loss/ bowel and bladder incontinence and possibly respiratory paralysis), the progression is slow. The average duration of symptoms at the time of diagnosis is 3-4 months. Other constitutional symptoms like fever, loss of appetite and loss of weight can be seen at presentation in only half of patients.(3)

Cervical spinal TB should be considered an emergency as even though it is less common but can lead to severe neurologic complications like respiratory failure (due to phrenic nerve/upper spinal cord involvement) or airway compromise (dyspnea and stridor) due to a sizeable retropharyngeal abscess.

TB spine should be suspected in any case with a constellation of the following features:

- Persistent localized back or neck pain for more than four weeks.
- Spinal tenderness.
- Spinal cord compression with paraplegia or paraparesis, nerve root pain, or cauda equina syndrome.
- Spinal deformity, paraspinal muscle wasting and some degree of kyphosis.
- Fever and weight loss.
- Failure to thrive, night cries, inability to walk/cautious gait, and use of hands to support the head or trunk can be seen in children.

6.3.1 Classification:

Spinal TB is classified into four types based on location within the vertebrae:

- Paradiscal: most common variety, due arterial spread (disc and adjacent para-discal body is supplied by the same artery)
- Central: due to venous spread
- Anterior: subperiosteal spread
- Appendiceal or posterior: least common, structural instability of the spine

6.4 Diagnosis

Initial investigations advised in a presumptive case are blood investigations including CBC, LFT, KFT, FBS, PPBS, HbA1C, ESR, CRP, HIV serology, , imaging, microbiological workup and histopathology. X-ray of affected segments in AP and lateral views are helpful for further follow-up. A simultaneous chest X-ray for ruling out coexisting pulmonary TB should be obtained. In almost all cases, a microbiological diagnosis should be sought before treatment, even if radiological suspicion is high. Rarely, in a resource limited setting with appropriate setting with appropriate clinical background and suggestive imaging, the patient can be diagnosed as a case of spinal TB and treated.

6.4.1 Imaging:

Imaging is a cornerstone for diagnosis for spinal TB. MRI may be required in almost all suspected cases. Imaging in a suspected case must include cross sectional imaging, preferably contrast enhanced MRI (CE-MRI) > non contrast MRI. In the absence of an MRI facility, CECT may be used as an alternative for diagnosing such cases.

- Gadolinium contrast enhanced MRI (CE-MRI): It is the investigation of choice in appropriate settings (clinical + risk factors). Features seen on MRI:
    a. T1: hypointense marrow in adjacent vertebrae, T2: hyperintense marrow, disc, T1 contrast enhanced: marrow, sub-ligamentous, discal and dural enhancement suggestive of bone marrow edema. Surrounding peripheral enhancing collections with irregularity of vertebral bodies may be seen.

b. MRI may be considered earlier if any new symptoms appear or clinical deterioration occurs or there is progressive neurologic symptom worsening. MRI prior to treatment discontinuation at 12 months to assess healing is prudent. In some cases diagnosis can be nearly confirmed by typical findings of spinal TB on contrast enhanced MRI. (7)e

- X-rays: It has poor sensitivity (~15-30%), but can demonstrate the destruction of affected vertebrae, reduction of adjoining intervertebral space, involvement of multiple vertebral bodies and opacity reflecting paraspinal abscess. Additionally, it may identify bony deformities for follow up, such that if spinal TB is diagnosed by MRI or CT, one should perform an X-ray to establish a baseline for subsequent follow up visits. (1)

- CT scan: The CT scan in early stages of infection may show subtle bony erosions or osseous destruction. It can very well depict the vertebral body destruction and collapse, disk space narrowing, paraspinal soft tissue masses representing abscess formation, while the findings in later stages become evident if there is extensive osseous destruction, sequestrum formation, and marked heterotopic bone formation. (7)

- PET-CT scan: It is not available everywhere and is being used primarily as research modality of imaging. It may be utilised in follow up of skeletal TB patients where it may help in differentiating an ongoing active infection with destroyed bone architecture.

6.4.2 Sample:

Guided biopsy (CT guided or C arm guided) is the preferred procedure to access tissue for microbiological/histopathological diagnosis. CT or C-arm guided biopsy-> if inconclusive, may be followed by open biopsy to establish diagnosis. The obtained sample should be sent in all cases for bacterial culture, AFB staining, NAAT, mycobacterial culture, and histopathological examination.

If clinical and radiological features are highly compatible with the diagnosis of TB and if the site is not easily accessible, sampling may be avoided. However, in cases with clinico-radiological discordance, sampling must be attempted. Pus samples from soft tissue collections where feasible can be obtained as an alternate sample with comparable sensitivity.

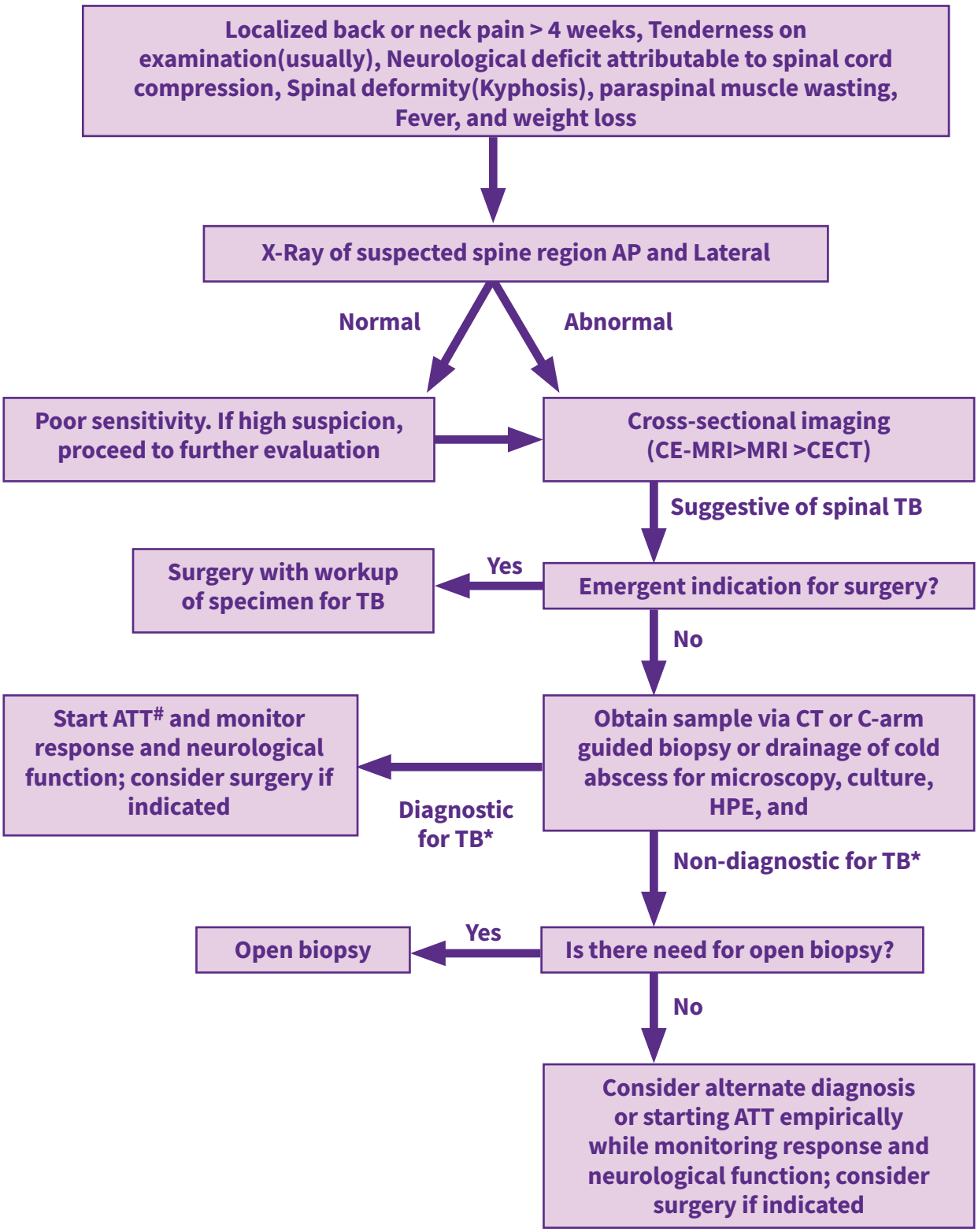
6.4.2 A. Microbiological Diagnosis:

Traditionally, tuberculosis of the spine is proven by culture or histopathology(HPE). The sensitivity of HPE (~90%) is highest among the commonly available methods, being higher than ZN/fluorescence stain or culture. The common findings on HPE are epithelioid cell granulomas (89.7%), caseating necrosis (82.8%), and lymphocytic infiltration (75.9%). (4) Among HPE proven spinal TB, culture positivity rates are ~50-55%. Nucleic acid amplification test (NAAT) is more frequently being applied in this field and have been suggested to have good accuracy: being slightly more sensitive than HPE (~92-95% vs 88%), much more sensitive than culture (~92-95% vs 55%) and with high specificity, PPV and NPV (>95%). (5) It also possesses a much shorter turnaround time (1-2 days vs. ~5-7 days for HPE OR 28-35 days for culture).

Table 6.1 Summary of diagnostic investigations [1]

S. No	Investigation	Sensitivity	Specificity	Comment
1	Plain radiography	15%	NA	Changes prominent only after 30% of destruction
2	MRI	100%	80%	Considered gold standard imaging technique
3	CT	100%	NA	Fragmentary > osteolytic > subperiosteal > localized
4	ESR > 20 mm	60% to 90%	NA	Serial values show gradual drop after initiating treatment; second peak in case of reactivation
5	CRP	71%	NA	Reaches normal levels after 14 days of treatment
6	Ziehl-Neelsen technique	25% to 75%	99%	Ziehl-Neelsen technique-bright red bacilli; 10^4 to 10^5 bacilli/ml required
7	Culture	47%	100%	Lowenstein Jensen media, 6-8 weeks, requires 10^1 to 10^2 bacilli/ml (live bacilli). Liquid culture 2-4 weeks
8	GeneXpert MTB/RIF	82.9%	98%	Results <48 hours+ rifampicin resistance detection
9	Histopathology	53% to 81%	NA	Epithelioid cell granulomas, Langhans giant cells, caseous necrosis

Figure 6.1.Diagnostic Algorithm for Presumptive spinal TB case



*Clinico-radiological features along with either of positive NAAT, culture or histopathology suggestive of TB.

Start ATT if high clinical suspicion while awaiting results of the investigations. If NAAT -MTB/

Rif positive and sensitive to Rifampicin, or diagnosis based on ZN stain or histopathology- treat as drug-sensitive TB with 2(HRZE) and 10(HRE), which may be extended. If NAAT-MTB/Rif is resistant to rifampicin, treat it as MDR-TB.

6.5 Management

6.5.1 Drug Therapy:

The INDEX-TB guideline suggests the following drug therapy for drug-susceptible spinal TB:
Drugs: 2HRZE (Intensive phase) plus 10 HRE (Continuation phase)
Duration: 12 months (extendable to 18 months on case-by-case basis)

The available randomized controlled trials suggest that a shorter duration of therapy such as 6 or 9 months may be sufficient:

1. Compared 6-month, 9-month, and 18-month regimens in association with radical surgery and found similar clinical results with no recurrence or reactivation of tuberculosis. (9)
2. A study involving 3 centres with 6- and 9-month regimens of isoniazid plus Rifampicin found excellent response in terms of the proportion of patients achieving a favourable status by 5 years, most of whom had already achieved it by 3 years. (10)
3. A recent trial from India in patients with biopsy proven spinal-vertebral TB, 6 and 12 months of ATT give similar clinical outcomes at 24 months of completion of therapy. (11)

However, the quality of evidence is insufficient to conclude this change and larger double blind RCTs are required.

Referral:
All presumptive spinal TB cases should be referred and managed in specialist centers with the involvement of spinal orthopedic surgeons, microbiologists/infectious diseases specialist, and spinal radiologists, as well as physiotherapists and orthotists.

6.5.2 Surgery:

Large number of patients can present late in the disease course with severe neurological deficits. flaccid paraplegia, gross sensory deficit, prolonged weakness, bladder involvement and spinal cord signal changes demonstrated on MRI and surgery in these patients significantly improves outcomes (90% of patients with complete loss of power or severe dysfunction experienced improvement to mild-mod dysfunction (walking with or without support) at 3 months after surgery. (12)
Indications for spinal surgery are as follows:

1. In patients with neurological deficit
    a. Neural complications developing or **getting worse** or remaining stationary during the course of **non-operative treatment (3-4 weeks)**
    b. Paraplegia **of rapid onset**
    c. Severe neurological deficits
        i. flaccid paraplegia
        ii. Complete sensory/motor loss
        iii. Bowel or bladder incontinence
    d. Painful paraplegia in elderly patients
2. In absence of neurological deficit
    a. When diagnosis is uncertain and open biopsy is indicated
    b. Mechanical instability of spine

c. Suspected drug resistance
d. Spinal deformity – severe kyphotic deformity at presentation (example >60 degrees) or progressive kyphotic deformity
e. Mass effect - dysphagia/stridor
f. Cold abscess - not responsive to repeated aspiration with ATT

6.5.3 Complications and sequelae:

Sequelae of spinal TB include

1. Early onset paraplegia: Secondary to acute inflammation, good prognosis with treatment.
2. Late onset paraplegia: Reappearance of neural deficit after a disease-free period of at least 2 years in patients who completed ATT and achieved healed status. Occurs due to progression of deformity in healed patients, or a result of relapse of infection.
3. Deformity: **Kyphosis** is the most common deformity occurring due to collapse of vertebrae. Predominantly the anterior spine is involved. Deformities interfere with lung function. Surgical correction is required in most cases.
4. Cold abscess can be formed on either side of the spine, anteriorly or posteriorly. It can extend to involve loco-regional structures according to the level of spinal lesion. cold abscess may lead to pseudo-flexion deformity at the hip joint. In addition to ATT, it requires drainage (USG or CT guided). Extended drainage using a pigtail is better than a single time aspiration.

Table 6.2.Tuli and Kumar's Staging of Pott's Paraplegia

I	Patient unaware of neural deficit, physician detects plantar extensor and/or ankle clonus.	No support needed
II	Patient aware of deficit but manages to walk with support, clumsiness of gait.	Walks with support
III	Paralysis in extension, sensory deficit less than 50%	Unable to walk
IV	Paralysis in flexion/flaccid/sensory deficit more than 50%/sphincters involved.	Unable to walk, feel or control urine/stools

6.5.4 Follow Up:

Regular follow up of spinal TB patients is essential in order to take a timely call on surgical intervention. The protocolized follow up of spinal TB patients is as follows: (8)

1. Patients with neurological deficits require staging and grading of their deficit on each visit.
2. Patients without neurological deficit should be assessed weekly for neurological signs.
3. Repeat X-rays of the spine every 3 months.
4. Repeat CE-MRI
   a. After 6 months, if there is suspicion of poor treatment response (but is not required in most)
   b. At treatment completion (12 months) it would be prudent to assess healing before discontinuation of therapy.
   c. Findings of quiescent burnt out infection which do not warrant continuation of ATT such as bony/fibrous ankylosis or thin walled cysts without enhancement must be identified.
5. After completion of treatment, follow up every 6 months for at least 2 years.

6.6 Drug Resistance

Drug resistance is to be suspected in patients with spinal tuberculosis on ATT for 5 months or more showing:

1. Poor clinical and radiological response.
2. Appearance of a fresh lesion of osteoarticular tuberculosis
3. Deterioration of spinal deformity
4. Appearance of discharging sinus
5. Wound dehiscence of previously operated scar

Drug-resistant spinal TB

The largest studies till date report the prevalence of multidrug resistance in spinal TB to be between 16-30 % (30.7%, n= 249, Li L et al.; 16.2%, n= 686, Mohan K et al.; 30.3%, n=152, Xu Lan et al.). (13, 14, 15) The largest Indian study by Mohan et al. found widespread resistance to both isoniazid (15.4%) and Rifampicin (13.6%), followed by streptomycin (11.5%) and least resistance to second line injectables. Currently there is no data on management of drug resistant spinal TB and probably treatment similar to MDR pulmonary TB may be followed. (14)

6.7 Extra spinal skeletal TB

Bone and joints TB can affect people of all age groups, but some forms are common in children. Risk factors include previous TB infection, immunosuppression caused by conditions such as HIV, diabetes mellitus and chronic liver or kidney failure, among others; or by immunosuppressive drugs such as long-term corticosteroids. All patients should have specimens taken for microscopy and culture where possible before starting ATT. All extraspinal skeletal TB is to be treated with the same drugs and duration of therapy as spinal TB.

6.7.1 Hip Joint:

It represents 15% cases of skeletal TB (2nd most common site) and can affect any part of the joint- acetabulum, synovium, femoral epiphysis or metaphysis. (4) Usually there is associated contiguous spread to femur (greater trochanter) or pelvis bone involvement. If the upper end of the femur is involved (being entirely intracapsular), the joint is involved early in disease.

There are four stages of TB hip joint with their own clinical symptoms, examination and X-ray findings, as well as implications in surgical management:

1. Synovitis/Apparent lengthening
2. Early arthritis/Apparent shortening
3. Advanced arthritis/True shortening
4. Advanced arthritis with subluxation or dislocation

Diagnosis: Similar to spinal TB, X-ray is used as an initial screening tool but has poor sensitivity while MRI or CT are more sensitive in early stages to detect increased joint space and accumulation of fluid. USG guided synovial biopsy/aspiration is the definitive diagnosis in equivocal cases however in many cases microbiological diagnosis may not be possible.

Treatment: 12 months of ATT: 2HRZE/10HRE with analgesia and rest to the joint in above-knee skin traction or skeletal traction for around 4 weeks. In cases with synovitis and early arthritis, surgery is rarely required but synovectomy and joint debridement are indicated if the response to nonoperative

treatment is inadequate at 6 to 8 weeks.

However, in advanced arthritis, arthrolysis with joint debridement is applicable and if subluxation/ dislocation are present then excision arthroplasty (e.g., Girdlestone), arthrodesis or total hip replacement are indicated.

6.7.2 Knee Joint:

It represents 10% cases of skeletal TB (3rd most common site) with predominant synovial involvement. (4) The patients present with painful, swollen, tender joints which may be warm to touch, with limping and reduced range of motion and on examination, the joint feels boggy due to synovial thickening, with effusion. Treatment and surgical principles are similar to the hip joint.

6.7.3 Poncet's Arthritis/Tuberculous Rheumatism:

It is a rare presentation of Reactive arthritis due to extra-articular TB with just >200 cases reported till date. The disease is characterized by oligoarthritis without axial involvement, affecting the large joints like ankles (63%), knees (58%), wrists (29%), and elbows (23%) and is principally a diagnosis of exclusion. Resolves within weeks after ATT with no tendency to chronicity. (16)

6.7.4 Hand and wrist:

Can affect all age groups but children under five are more commonly affected. Pain and swollen joints are the common features. As the disease progresses, increasing effusions and synovial thickening causes boggy swelling with restricted range of motion. Systemic symptoms may not always be present. Advanced cases may present with wasting of the muscles of hand and forearm, deformity, enlargement of digits/metacarpals **(sausage finger/spina ventosa)**, discharging sinuses, cold abscess or compound palmar ganglion. Rarely, patients may present with carpal tunnel syndrome, or nail involvement. Ultrasound scan, CT or MRI may be used for describing extent of disease and to identify site of biopsy/ pus drainage. Along with ATT, immobilisation with plaster/brace may be required for 4 to 6 weeks of the affected joints. Surgical intervention may be required for nerve compression, impending bone collapse, joint debridement, drainage of large abscesses and correction of deformity in healed disease.

Other joints such as elbow, shoulder, ankle and foot may also be affected with TB. Rarely prosthetic joints are affected.

Reference:

1. Rajasekaran S, Soundararajan DCR, Shetty AP, Kanna RM. Spinal Tuberculosis: Current Concepts. Glob Spine J. 2018 Dec 1;8(4_suppl):96S-108S.

2. Fitzgerald DW, Sterling TR, Haas DW. 251 - Mycobacterium tuberculosis. In: Bennett JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases (Eighth Edition) [Internet]. Eighth Edition. Philadelphia: W.B. Saunders; 2015. p. 2787-2818.e5. Available from: https://www.sciencedirect.com/science/article/pii/B9781455748013002514

3. Raviglione MC. Tuberculosis. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo

J. eds. Harrison's Principles of Internal Medicine, 20e. McGraw Hill; 2018. Accessed December 18, 2022. https://accessmedicine.mhmedical.com/content.aspx?bookid=2129&sectionid=192023354

4. Tuli SM. Historical aspects of Pott's disease (spinal tuberculosis) management. Eur Spine J. 2013 Jun;22(Suppl 4):529–38.

5. Solanki AM, Basu S, Biswas A, Roy S, Banta A. Sensitivity and specificity of Gene Xpert in the diagnosis of spinal tuberculosis: A prospective controlled clinical study. Global Spine J [Internet]. 2020;10(5):553–8. Available from: http://dx.doi.org/10.1177/2192568219858310

6. Tuli SM. Tuberculosis of the skeletal system. JP Medical Ltd; 2016 Mar 30.

7. Rivas-Garcia A, Sarria-Estrada S, Torrents-Odin C, Casas-Gomila L, Franquet E. Imaging findings of Pott's disease. Eur Spine J. 2013 Jun;22(S4):567–78.

8. Sharma SK, Ryan H, Khaparde S, Sachdeva KS, Singh AD, Mohan A, et al. Index-TB Guidelines: Guidelines on extrapulmonary tuberculosis for India. Indian J Med Res. 2017 Apr;145(4):448–63.

9. Upadhyay SS, Saji MJ, Yau ACMC. Duration of Antituberculosis Chemotherapy in Conjunction With Radical Surgery in the Management of Spinal Tuberculosis: Spine. 1996 Aug;21(16):1898–903.

10. Darbyshire J. Five-year assessment of controlled trials of short-course chemotherapy regimens of 6, 9 or 18 months' duration for spinal tuberculosis in patients ambulatory from the start or undergoing radical surgery. Int Orthop. 1999 Jun;23(2):73–81.

11. Nene AM, Patil S, Kathare AP, Nagad P, Nene A, Kapadia F. Six versus 12 Months of Anti Tubercular Therapy in Patients With Biopsy Proven Spinal Tuberculosis: A Single Center, Open Labeled, Prospective Randomized Clinical Trial-A Pilot study. Spine (Phila Pa 1976). 2019 Jan 1;44(1):E1-E6.

12. Kiran NAS, Vaishya S, Kale SS, Sharma BS, Mahapatra AK. Surgical results in patients with tuberculosis of the spine and severe lower-extremity motor deficits: a retrospective study of 48 patients. Journal of Neurosurgery: Spine. 2007 Apr 1;6(4):320–6.

13. Li L, Zhang Z, Luo F, Xu J, Cheng P, Wu Z, et al. Management of drug-resistant spinal tuberculosis with a combination of surgery and individualised chemotherapy: a retrospective analysis of thirty-five patients. International Orthopaedics (SICOT). 2012 Feb;36(2):277–83.

14. Mohan K, Rawall S, Pawar UM, Sadani M, Nagad P, Nene A, et al. Drug resistance patterns in 111 cases of drug-resistant tuberculosis spine. Eur Spine J. 2013 Jun;22(Suppl 4):647–52.

15. Xu L, Jian-Zhong X, Xue-Mei L, Bao-Feng G. Drug Susceptibility Testing Guided Treatment for Drug-Resistant Spinal Tuberculosis: A Retrospective Analysis of 19 Patients. International Surgery. 2013 May 1;98(2):175–80.

16. Rueda JC, Crepy MF, Mantilla RD. Clinical features of Poncet's disease. From the description of 198 cases found in the literature. Clin Rheumatol. 2013 Jul;32(7):929–35.

7. Cutaneous Tuberculosis

Key Points

- Cutaneous tuberculosis is rare and thereby a high index of suspicion should be kept.
- Fever and other constitutional symptoms are usually absent in isolated cutaneous TB.
- Tissue sampling and histopathological examination is the mainstay for diagnosis.
- In scrofuloderma, FNAC from underlying lymph nodes/lesions increases the diagnostic yield.
- Re-evaluate the diagnosis if the patient fails to improve after 6 weeks of trial of ATT.

Introduction

Cutaneous tuberculosis is an ancient disease. Cutaneous TB lesions were described even before the discovery of *M. tuberculosis*. It is caused by *M. tuberculosis*, M. bovis and uncommonly with Bacilli Calmette-Guerin (BCG) vaccination. Isolated skin TB is rare and often coexists with other forms of tuberculosis. Unlike other forms of TB, constitutional symptoms are generally absent in isolated cutaneous TB. Lupus vulgaris and Scrofuloderma are the most common manifestations of cutaneous TB. (1)

It may not be a life-threatening disease, but it can cause profound distress to the patient due to discomfort and cosmetic disfigurement. It may take several months and multiple visits to several practitioners before a correct diagnosis is made, as it can mimic other skin disorders. The treatment is anti-tubercular therapy. If left untreated, it can result in disfigurement and scarring. (2)

Epidemiology

Extrapulmonary TB accounts for 15-20% of all TB cases. (1) Cutaneous TB is uncommon and accounts for 1.5% of all EPTB cases worldwide. (2) It is more commonly seen in children than that of adults.

In India, it accounts for 0.1-0.9% of total dermatology out patients. (3) Children contributed to 18-53% of total skin TB cases as reported from several studies, with the majority of affected belonging to the 10–14-year age group, with both sexes being affected equally. (3)

Pathophysiology

Cutaneous TB manifests in different ways and the clinical presentation is determined by the host immune response, route of inoculation, and previous sensitization of host to *M. tuberculosis*. Skin involvement may result from exogenous inoculation via tattooing, piercings, post-operatively, as seen in TB verrucosa cutis and tuberculous chancre. Infection may spread from an adjacent infective focus such as lymphadenitis, osteomyelitis causing scrofuloderma. Hematogenous spread can occur from a distant focus, as seen with lupus vulgaris, miliary skin TB. These can also present as hypersensitivity responses to a TB focus elsewhere in the body, the lesions commonly called tuberculids.

Table 7.1: Classification of Cutaneous Tuberculosis (4,5)

Basis	Classification	Examples
Based on load of pathogens	Multibacillary form	• Tuberculous chancre • Scrofuloderma • Acute miliary tuberculosis • Tuberculous gumma
	Paucibacillary form	• TB verrucosa cutis • Lupus vulgaris • Tuberculids
Based on route of Infection	Exogenous inoculation	• Tuberculous chancre • Tuberculosis verrucosa cutis
	Contiguous spread	• Scrofuloderma
	Hematogenous spread	• Lupus vulgaris • Tuberculous gumma • Acute miliary tuberculosis

The details of the clinically important presentations are discussed subsequently.

7.1 Lupus Vulgaris

7.1.1 Introduction:

Lupus vulgaris presents as slowly progressive skin lesions with nodular appearance, most often on the buttocks, trunk, extremities, head and neck especially around the nose and neck. It is the most common form of cutaneous TB. The lesions may lead to cosmetic disfigurement if left untreated.

7.1.2 Clinical Features:

Lupus vulgaris starts as a soft brownish red papule or nodule that gradually expands by involution in one area with expansion in another, gradually progressing over a period of many years to form a well-defined skin-coloured to erythematous plaque. The plaque is characterised by evidence of healing and atrophic scarring in some areas interspersed between areas of activity giving a wolf bitten appearance [Figure 1]. The lesions are usually located on the buttocks, thighs and occasionally on the face. Lesions involving the genitalia, nasal mucosa and auricular cartilage are rare but are associated with severe disfigurement.

The commonly encountered clinical variants include classic plaque or keratotic type, hypertrophic, ulcerative, atrophic and planar [Figure-2].

Although regional lymphadenopathy is not uncommon, in rare cases the lymph nodes may be involved due to intense tissue reaction.

Though lupus vulgaris is uncommon in the immunocompromised host, both solitary and disseminated lesions have been reported. The clinician must be aware that multiple forms of TB can occur concomitantly in such situations and the patient must be investigated and treated accordingly.

The diagnosis is made clinically, based on the morphology and on histopathology. However, these lesions have to be differentiated from deep fungal infections, sarcoidosis and discoid lupus erythematosus.

The lesions generally resolve with treatment. However, they may leave residual disfigurement and scarring. [figure 3,4]

Figure 7.1: Lupus vulgaris- Healing with areas of atrophy and scarring, extension with elevated, infiltrated border (Credits: Dr Ramam, Department of Dermatology, AIIMS, New Delhi)

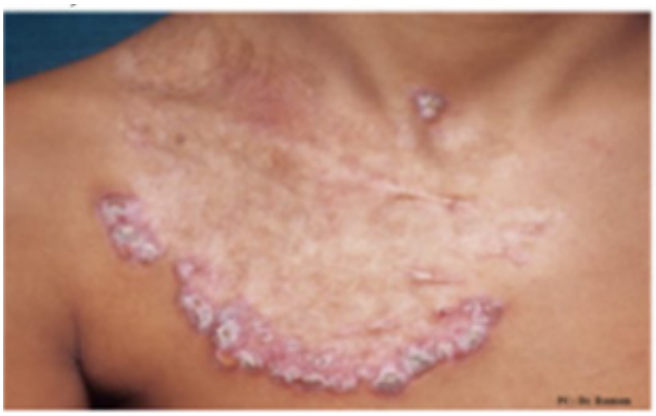


Figure 7.2: Lupus vulgaris: classic plaque or keratotic type (Credits: Dr Ramam, Department of Dermatology, AIIMS, New Delhi)

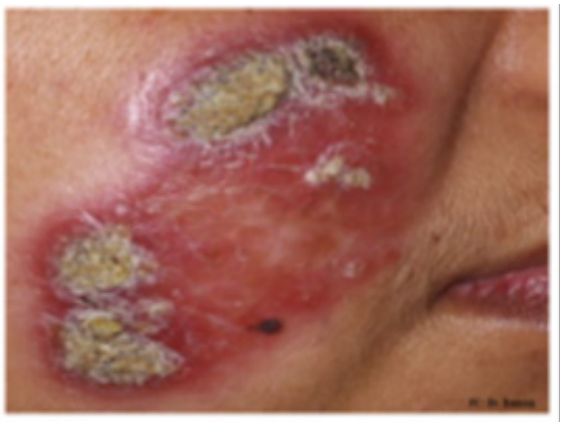


Figure 7.3: Lupus vulgaris: showing healing at one end (Credits: Dr Ramam, Department of Dermatology, AIIMS, New Delhi)

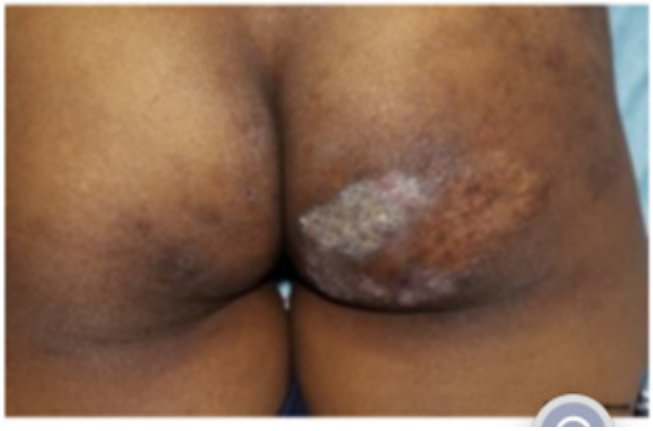
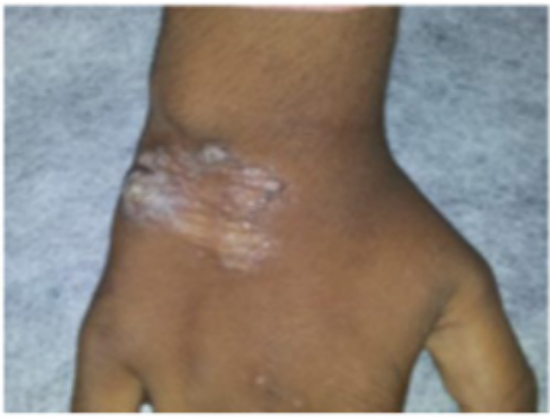


Figure 7.4: Lupus vulgaris: healing with areas of atrophy and scarring at one end with active edge at another end (Credits: Dr Ramam, Department of Dermatology, AIIMS, New Delhi)



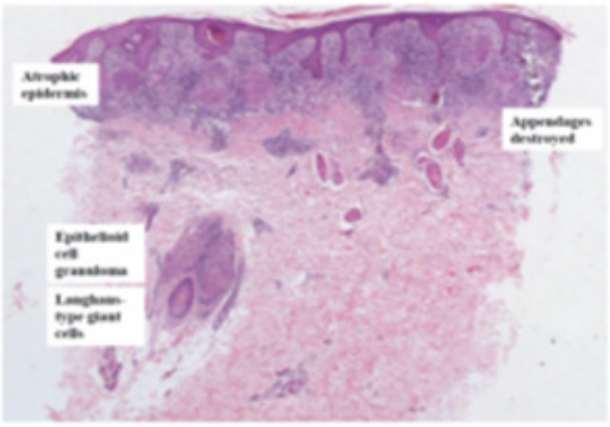
7.1.3 Histology:

The characteristic histological features of Lupus vulgaris are well formed granuloma without caseation. It is a paucibacillary disease and AFB are usually not seen. The epidermis may be atrophic or hypertrophic, with acanthosis, papillomatosis and pseudoepitheliomatous hyperplasia. The epidermal changes will vary based on the clinical presentation. Well defined tuberculoid granulomas composed of Langhans giant cells and mature epithelioid cells with a dense lymphocytic infiltrate and plasma cells located in the mid dermis are characteristic.

Caseation is rare and may occur within small foci of the granuloma. AFB are infrequently detected. A deep biopsy is highly recommended to visualize the entirety of the granuloma. Due to the paucibacillary state, the Zeil Nielsen stain has limited utility.

Histological differential diagnoses include sarcoidosis, tuberculoid leprosy, deep fungal infection, and foreign body reaction.

Figure 7.5: Histopathology of Lupus Vulgaris (Credits: Dr Ramam, Department of Dermatology, AIIMS, New Delhi)



7.2 Tuberculosis Verrucosa Cutis

7.2.1 Introduction:

Tuberculosis verrucosa cutis is a paucibacillary form of cutaneous tuberculosis that occurs in a sensitized host with high immunity against tuberculous bacilli. It is transmitted via direct inoculation, either by accidental superinfection or by autoinoculation. The most common areas of involvement are the exposed body surfaces such as dorsum of hands, knee, ankles and buttocks. If left untreated, skin lesions may persist for years, with some degree of spontaneous resolution.

7.2.2 Clinical Manifestation:

Tuberculosis verrucosa cutis is common in children in tropical countries, due to walking barefooted and adults with risk of occupational exposure. The lesion is usually single and painless. It occurs predominating on trauma prone areas such as fingers and toes. It starts as an erythematous papule surrounded by a purplish inflammatory halo which evolves to asymptomatic verrucous plaques, which can measure from 1 to 5 cm. These lesions tend to spread by peripheral extension leaving behind a central atrophied area. Rarely these lesions may ulcerate or may develop fissures. [Figure 6]

Additional clinical features are regional lymphadenopathy with lymphostasis and secondary bacterial infection leading to extensive and chronic involvement.

Such clinical presentation closely mimics tertiary syphilis, Majocchi's granuloma, chromoblastomycosis, verrucous epidermal nevus, hypertrophic lichen planus and hypertrophic variant of lupus vulgaris which are important differentials.

Figure 7.6: Tuberculosis verrucosa cutis:Hyperkeratotic, indurated warty plaques (Credits: Dr Ramam, Department of Dermatology, AIIMS, New Delhi)

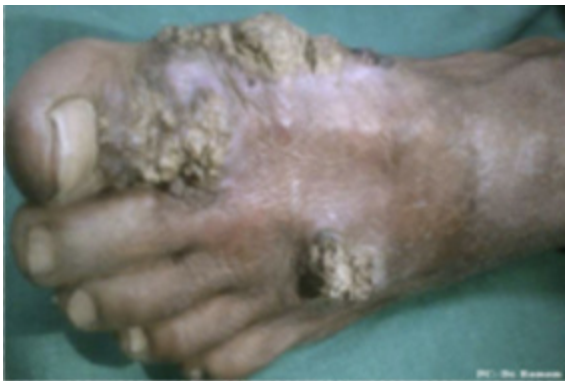
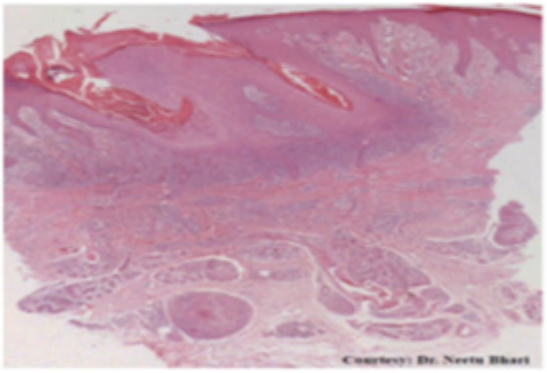


Figure 7.7: Tuberculosis verrucosa cutis(H&E, 40x): Pseudo-epitheliomatous hyperplasia and papillomatosis, Hyperkeratosis, Marked acanthosis with Frank tuberculoid granuloma may not be present (Credits: Dr Neetu Bhari, Department of Dermatology, AIIMS, New Delhi)



7.2.3 Histopathology:

Like Lupus vulgaris, Tuberculosis verrucosa cutis is a paucibacillary form of cutaneous TB hence, direct microscopic examination by ZN stain is of limited utility. Diagnosis is primarily based on clinical and histopathological correlation alongside evidence of high immunity to TB bacilli via IGRA or Mantoux test.

Histopathological feature comprises pseudoepitheliomatous hyperplasia with marked hyperkeratosis. Micro abscesses in the superficial dermis along with an inflammatory infiltrate comprising epithelioid and giant cells are also common findings however, a well-formed granuloma may not be always evident.

7.3 Scrofuloderma

Scrofuloderma is a multibacillary form of cutaneous TB representing the manifestation of endogenous TB due to M. tuberculosis and less commonly M. bovis. It is the most common type of cutaneous manifestation in children with the most common site of involvement being the chest, neck and axilla. It occurs due to direct extension from an adjacent tuberculous focus, most commonly an infected lymph node. If left untreated, they usually heal by scarring after many years.

7.3.1 Clinical Manifestation:

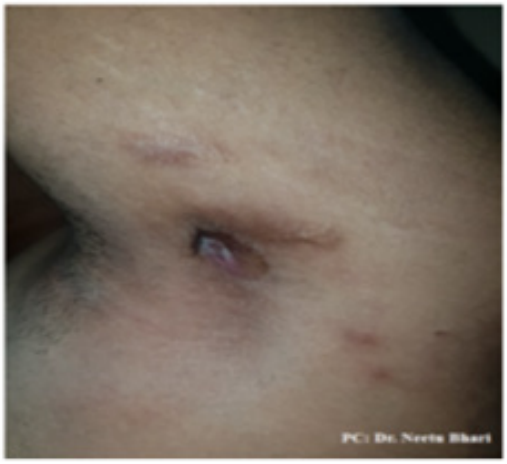
Scrofuloderma presents as a firm, painless subcutaneous reddish to brown nodule(s) overlying the tuberculous foci [Figure 8]. The most common area of involvement is the region of cervical lymph-node but there can be involvement of the axillary, inguinal, pre or post auricular, submandibular and epitrochlear lymph nodes as well. The Scrofuloderma nodules are slow growing lesions which can evolve into ulcers with formation of fistulous tract draining serous, purulent or caseous material. Lesions may sometimes be multiple, lying in a linear track due to underlying lymph node chain.

Diagnosis is usually clinical, with history of a pre-existing lesion and subsequent formation of the characteristic skin lesions and evidence of tuberculous bacilli in them. However, the lesions have to be differentiated from atypical mycobacterial infection, sporotrichosis, actinomycosis, nocardiosis, lymphogranuloma venereum, hidradenitis suppurativa and syphilitic gumma.

7.3.2 Histopathology

Diagnosis of scrofuloderma relies on identification of the TB bacilli by direct examination, culture or by histopathological examination of the skin lesions. Due to the multibacillary nature, AFB or culture is usually positive as compared to other forms of cutaneous TB. TB-PCR has low sensitivity but a high specificity.

Figure 7.8: Scrofuloderma (Credits: Dr Neetu Bhari, Department of Dermatology, AIIMS, New Delhi)



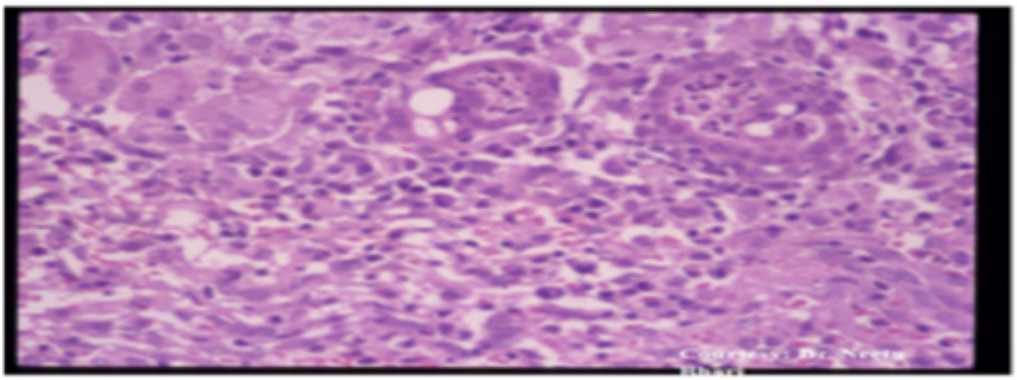
Histopathology is confirmatory which shows presence of tuberculous granulomatous inflammation comprising epithelioid cells, Langhans giant cells and lymphocytes. However, ZN stains for AFB are usually negative.

7.4 Management of cutaneous TB (All forms)

All clinically suspicious lesions for cutaneous TB should be treated with weight based Anti-Tubercular Therapy (table). The treatment is similar to that of pulmonary TB with Isoniazid, rifampicin, Pyrazinamide and Ethambutol as per NTEP weight bands. The duration of the therapy is 6 months with 2 months of intensive phase with HRZE and 4 months of continuation phase with HRE. After initiation of treatment, patients are to be followed up to look for evidence of clinical resolution.

The lesions generally resolve with treatment. However, some may leave residual disfigurement and scarring.

Figure 7.9: Histopathology of Scrofuloderma showing- mixed granulomatous inflammatory infiltrate composed of histiocyces, lymphocytes, epithelioid cells, langhans giant cells, neutrophils and plasma cells.
(Credits: Dr Neetu Bhari, Department of Dermatology, AIIMS, New Delhi)



Indication for treatment:
The following patients should be treated with Antitubercular drugs:

- Patients with positive culture of Mtb or microscopy for Acid Fast Bacilli from skin biopsy.
- Patients with histology suggestive of cutaneous tuberculosis.
- Suspicious skin lesions with negative microscopy and culture, but strongly positive Mantoux Test.

7.5 Approach to Cutaneous TB

The following flow-chart represents the algorithm for diagnosis and management of Cutaneous Tuberculosis.

When to suspect Cutaneous TB

- Ulcer or discharging sinuses over sites of lymph nodes, bones and joints
- Persistent, asymptomatic raised reddish/reddish-brown skin lesion with scarring
- Persistent large warty skin lesion of duration > 6 months

Always remember

- Fever and other constitutional symptoms are generally absent in isolated cutaneous TB
- To ask for past history of tuberculosis
- To elicit the exposure to known or suspected tuberculosis cases and to look for other sites of dissemination

Investigations

- Routine investigations: Complete blood counts, liver/kidney function tests, ESR, Mantoux Test, chest radiograph
- Skin Biopsy {taken from active edge for Histopathological examination (if compatible with TB, mainstay of diagnosis), Microbiological tests GeneXpert, AFB stain and culture (poor sensitivity)}

Treatment

- 6 months of ATT; 2HRZE followed by 4HRE
- First Follow up at 4-6 weeks, subsequently every 6-8 weeks to look for resolution

References:

1. Sharma SK, Ryan H, Khaparde S, Sachdeva KS, Singh AD, Mohan A, Sarin R, Paramasivan CN, Kumar P, Nischal N, Khatiwada S, Garner P, Tharyan P. Index-TB guidelines: Guidelines on extrapulmonary tuberculosis for India. Indian J Med Res. 2017 Apr;145(4):448-463. doi: 10.4103/ijmr.IJMR_1950_16. PMID: 28862176; PMCID: PMC5663158.

2. Ministry of Health & Family Welfare-Government of India. Index TB Guideline : Guidelines on extra-pulmonary tuberculosis for India [Internet]. Index-TB Guidelines :: Ministry of Health and Family Welfare. 2016 [cited 2022Dec17]. Available from: https://tbcindia.gov.in/showfile.php?lid=3245.

3. Singal A, Kaur I, Jakhar D, Pandhi D, Grover C, Gandhi V. Clinicoepidemiological characteristics of cutaneous tuberculosis in 1458 Indian patients: a retrospective analytical study from a tertiary care center. Int J Dermatol. 2022 Aug;61(8):1012-1022. doi: 10.1111/ijd.16267. Epub 2022 May 17. PMID: 35583803.

4. Barbagallo J, Tager P, Ingleton R, Hirsch RJ, Weinberg JM. Cutaneous tuberculosis: diagnosis and treatment. Am J Clin Dermatol. 2002;3(5):319-28. doi: 10.2165/00128071-200203050-00004. PMID: 12069638.

5. Lai-Cheong JE, Perez A, Tang V, Martinez A, Hill V, Menagé Hdu P. Cutaneous manifestations of tuberculosis. Clin Exp Dermatol. 2007 Jul;32(4):461-6. doi: 10.1111/j.1365-2230.2007.02352.x. Epub 2007 Mar 21. PMID: 17376216.

8. Otorhinolaryngeal Tuberculosis

KEY POINTS

- The common forms of extra-nodal ENT TB include laryngeal, sinonasal, oropharyngeal, para/retropharyngeal TB, salivary gland TB, thyroid gland TB, TB otitis media and TB mastoiditis.
- Laryngeal TB is highly infectious and needs appropriate precautions.
- Tissue sampling is key to diagnosis.
  ATT regimen is similar to other forms of EPTB given for a total duration of 6-12 months, with a longer duration preferred in cases of bony involvement.

8.1 Introduction

Among the extrapulmonary manifestations of tuberculosis (TB), ear, nose and throat manifestations are mainly in the form of cervical lymphadenopathy, otitis media, laryngitis, pharyngitis and nasal TB. Nasopharyngeal TB is the most common extranodal ENT site. TB of the oral cavity is uncommon. tuberculous tonsillitis may be suspected with bilateral symmetric enlargement of tonsils associated with cervical lymphadenopathy. Vocal cords are mainly affected in the laryngeal form.

Early initiation of anti-tubercular therapy after ruling out other systemic involvement remains the cornerstone of treatment. Although ENT presentation of TB is rare but high degree of suspicion should be kept in cases of chronic ear discharges, chronic lymphadenopathy, hoarseness and nasal masses with blood stained discharges.

8.2 Epidemiology

In a recent review of all head and neck tuberculosis cases published from 1990-2017,
Cervical lymph node TB is seen in 87.9% of cases, laryngeal TB in 8.7% and other ENT sites 3.4%. Extra-nodal head and neck tuberculosis constitute <1% of all EPTB cases. (1)

8.3 Pathophysiology

Most ENT tuberculosis sites are seeded hematogenously from a primary pulmonary focus. Clinical manifestations develop usually after a latent period followed by reactivation of these latent foci. In the pre-chemotherapy era, laryngeal tuberculosis occurred in more than a third of patients dying of pulmonary TB by direct contiguous spread. There may be simultaneous involvement of multiple ENT sites due to further contiguous spread

8.4 Clinical Presentation

Common forms of extra-nodal ENT tuberculosis are -

- Laryngeal TB (Most common)

- TB Otitis Media/TB Mastoiditis
- Sinonasal TB
- Oropharyngeal TB
- Deep neck cold abscess (retro/parapharyngeal)
- Salivary glands
- Thyroid gland

8.4.1 Laryngeal TB:

8.4.1 A. History:
Hoarseness is the most common symptom. Other symptoms include chronic productive cough, dysphagia/odynophagia (usually due to perichondritis around arytenoid cartilages), and stridor. It may mimic non-specific laryngitis.

8.4.1 B. Examination:
Indirect laryngoscopy/fiberoptic laryngoscopy shows diffuse erythema/oedema, granulomatous/ polypoidal/exophytic/ulcerative lesions of the vocal cords, the moth-eaten appearance of vocal cords and pale granulations. It may be associated with similar lesions of epiglottis, pharynx, tonsils and mouth as well as middle ear involvement.
The most important differential diagnosis of laryngeal TB is carcinoma larynx, which can only be differentiated by histopathology.

8.4.2 TB otitis media/mastoiditis:
It is a very rare presentation of EPTB and it is commonly misdiagnosed even by experienced practitioners. Patients may give a history of successful treatment attempts,including surgery (mastoidectomy). Half of the cases have no other evidence of present or past TB. It mimics chronic suppurative otitis media.

8.4.2 A. History:
1. Painless chronic ear discharge (despite antibiotics use)
2. Early severe hearing loss

8.4.2.B. Complications:
1. Facial nerve palsy,
2. Mastoid bone necrosis

Examination by otoscopy:
1. Multiple tympanic membrane perforations is characteristic
2. Exuberant, pale granulation tissue may be seen

8.4.3 Sinonasal TB
History: Sinonasal TB may simulate Granulomatosis with Polyangiitis. They can present with a history of persistent nasal discharge (despite antibiotics use), nasal obstruction, epistaxis and headache.
Examination: Abundant polypoid or avascular pale granulation tissue will be seen.

8.4.4 Oropharyngeal TB:
History: Reveals dysphagia, odynophagia, dyspnea and/or drooling of saliva.

Examination: There may be significant edema of the oropharyngeal region (palate and uvula) which may extend to epiglottis ("Turban epiglottitis").

8.4.5 Deep Neck Cold Abscess:

It may be retropharyngeal or parapharyngeal abscess. Most cases are bacterial - usually acute,secondary to infection of surrounding structures. Tuberculous abscesses are rare, chronic, and secondary to TB of the cervical spine, petrous apex or the lung.

History: fever, dysphagia, neck pain/stiffness, stridor
Laryngoscopy: shows minimal signs of inflammation, localized swelling of pharyngeal wall

8.5 Diagnosis

- Routine investigations: CBC, ESR, LFT, KFT, HIV, Mantoux test
- Thorough ENT review:
  - Rhinoscopy/otoscopy/laryngoscopy
  - Pure tone audiometry (if indicated)
- Imaging modalities:
  - CT of PNS/temporal bone/head/cervical spine (as indicated) with contrast for ENT involvement
  - Chest radiograph for evidence of concurrent pulmonary TB
- Definitive diagnosis can only be established with tissue sampling (punch biopsy is preferred to FNAC. Tissue sample to be sent for (in descending order of priority):
  - TB (saline) – NAAT, AFB staining, MGIT culture followed by LPA
  - Histopathology (formalin)
  - Fungus (saline) – KOH stain and fungal culture
  - Bacteria (saline) – Gram stain and bacterial culture

8.6 Management

- In the real world scenario, microbiological evidence is rare as disease is often paucibacillary. Histopathology showing necrotizing granulomas may be the only attainable evidence. The decision to treat is based on a composite picture of clinical/imaging/laboratory features. Response to treatment is retrospective evidence of a diagnosis in case the initial diagnosis was uncertain.
- Anti-tubercular therapy: 2HRZE + 4-10 HRE. Total duration: 6-12months. Longer duration preferred in bony involvement as in TB Otitis Media, osteomyelitis of nasal bones/petrous apex/ anterior skull base/cervical spine etc. Treatment may be stopped after completion of entire duration of treatment and resolution of all signs and symptoms.
- If no adequate response by 2 months, suspect and investigate for drug-resistant TB.
- No role of steroids.
- Unlike other EPTB, laryngeal TB is highly infectious and needs appropriate precautions.
- Aspiration of large abscesses in case of impending complications, preferably ultrasound guided to avoid procedure related complication.

8.7 Complications

- Drug related complications

- Primarily vestibulotoxic – Streptomycin
- Primarily ototoxic – Kanamycin, Amikacin
- Pure tone audiometry is investigation of choice
- In resource limited setting, screen with Rinne/Weber tests
- In case of lack of a suitable alternative drug, the risk of further hearing loss versus risk and benefit of adding drugs from DR-TBregimen should be weighed.

8.8 Conclusion

Extra-nodal head and neck TB is a rare and underdiagnosed presentation of EPTB. A high index of suspicion is needed for its diagnosis. Tissue sampling should be done in all suspected cases.

8.9 Diagnostic Algorithm

SUSPECTED TB OTITIS MEDIA
Chronic painless otorrhea, early hearing loss/facial nerve palsy/mastoid bone necrosis
Multiple tympanic membrane perforations, pale exuberant granulation tissue

SUSPECTED LARYGEAL TB
Chronic hoarseness, productive cough, dysphagia/odynophagia, stridor
Vocal cords showing ulcerative/nodular/polypoidal lesions, edema, erythema, moth-eaten appearance with distorted architecture

SUSPECTED SINONASAL/OROPHARYNGEAL /DEEP NECK TB ABSCESS
Nasal discharge/obstruction, epistaxis, dysphagia/odynophagia, drooling of saliva
Polypoidal granulation tissue, edema of uvula/palate/epiglottis, deep neck abscess

Any past history of tuberculosis?
Any exposure to known or suspected tuberculosis cases?

Routine investigations: Complete blood counts, liver/kidney function tests, ESR, CRP, HIV, Mantoux Test, chest radiograph
Complete ENT review: Rhinoscopy + otoscopy + laryngoscopy followed by tissue sampling (preferably PUNCH BIOPSY), pure tone audiometry (if indicated), CT PNS/temporal bone/head/cervical spine with contrast (as indicated)
Processing of tissue sample: NAAT/AFB staining/MGIT culture, Histopathology, other relevant cultures (fungal/bacterial)

Evaluation for alternate causes through histopathology and appropriate cultures

Malignancy (LARYNX)
Chronic suppurative otitis media & cholesteatoma (EAR)
Granulomatosis with polyangiitis (NOSE)
Non-Tuberculous mycobacteria
Fungi – Aspergillus, Candida, Rhinosporidium, Histoplasma
Infiltrative disorders – Amyloidosis, Sarcoidosis

Decision to treat on basis of clinical picture, imaging and laboratory tests

References:

1. Qian X, Albers AE, Nguyen DTM, Dong Y, Zhang Y, Schreiber F, et al. Head and neck tuberculosis: Literature review and meta-analysis. Tuberculosis. 2019 May 1;116:S78–88.

2. Index TB Guidelines, 2016

9. Ocular Tuberculosis

KEY POINTS

- Ocular Tuberculosis can cause moderate-severe visual impairment.
- Posterior uveitis is the most common presentation.
- It needs to be differentiated from other causes of granulomatous-uveitis such as sarcoidosis.
- Always rule out systemic involvement.
- Medical therapy with weight based antitubercular drugs.
- Surgery is indicated for management of complications.

9.1 Introduction

Mycobacterium tuberculosis is an obligate aerobe which primarily involves the choroid in the eye, it being an area of high oxygen tension.

Ocular TB is described as an infection by MTB affecting any part of the eye (intraocular, superficial or surrounding the eye), with or without systemic involvement. It has a wide spectrum of presentation making it difficult to diagnose. The most common manifestation is the inflammation of the uveal tract due to high blood supply.

The treatment involves early initiation of anti-tubercular therapy as it is known to cause severe visual impairment. Surgery is indicated for management of complications of uveitis.

9.2 Epidemiology

Among various aetiologies in patients presenting with uveitis, the incidence of tuberculosis has been reported at 10.1% in north India (1), but prevalence in south India is around 22.5% (2). The prevalence of Ocular TB in uveitis cases ranges from 5-10% in endemic areas (3). Ocular TB can cause moderate to severe visual impairment in up to 40% of affected eyes. (4) About 1.39% of Pulmonary TB (n=1005) patients in South India had concomitant Ocular TB (5).

9.3 Pathogenesis

Primary ocular TB is rare. Most cases of ocular TB are secondary due to hematogenous spread from tuberculosis elsewhere in the body. Posterior uveitis is the most common presentation of intraocular TB. TB bacilli, being an obligate aerobe, will tend to localise in tissues with high regional oxygen tension. Ocular TB is usually paucibacillary.

9.4 Clinical Manifestations

The common presentations of ocular TB are choroid tubercle, choroidal tuberculoma and granulomatous uveitis. Less common presentations include subretinal abscess, recurrent non-granulomatous uveitis, scleritis, eyelid granuloma, etc.
A person with ocular TB may present with red eye, blurred vision, photophobia, eye pain, floaters or

flashing lights (photopsia).

9.5 Differential Diagnosis

The most common differential diagnosis to be considered is sarcoidosis. Others include ocular malignancy and syphilis.

9.6 Investigations

Investigations in a suspected case of ocular tuberculosis should include tests to accurately identify the ocular pathology and to identify/rule out coexisting tuberculosis of other organs of the body. A chest X-ray is needed to identify coexisting pulmonary tuberculosis and if the clinical suspicion is high, a contrast-enhanced CT (CECT) of the thorax must be done. An ultrasound or CECT of the abdomen will help identify peritoneal or intra-abdominal lymph node tuberculosis. If any neck lymph nodes are present, an FNAC or biopsy should be done. An HIV test should be done in all cases of ocular TB.

Several ocular diagnostic modalities are available which help in characterising the type of involvement in ocular TB. These include slit-lamp microscopy, Optical Coherence Tomography (OCT) and Fundus Fluorescein Angiography (FFA).

9.6.1 Optical Coherence Tomography (OCT):

OCT helps in assessing the morphological details of mass, its location- whether choroidal/subretinal/retinal, associated changes at the level of retinal pigment epithelium and secondary complications like choroidal neovascularization. However, it is not an essential first-line investigation.

9.6.2 Fundus Fluorescein Angiography (FFA):

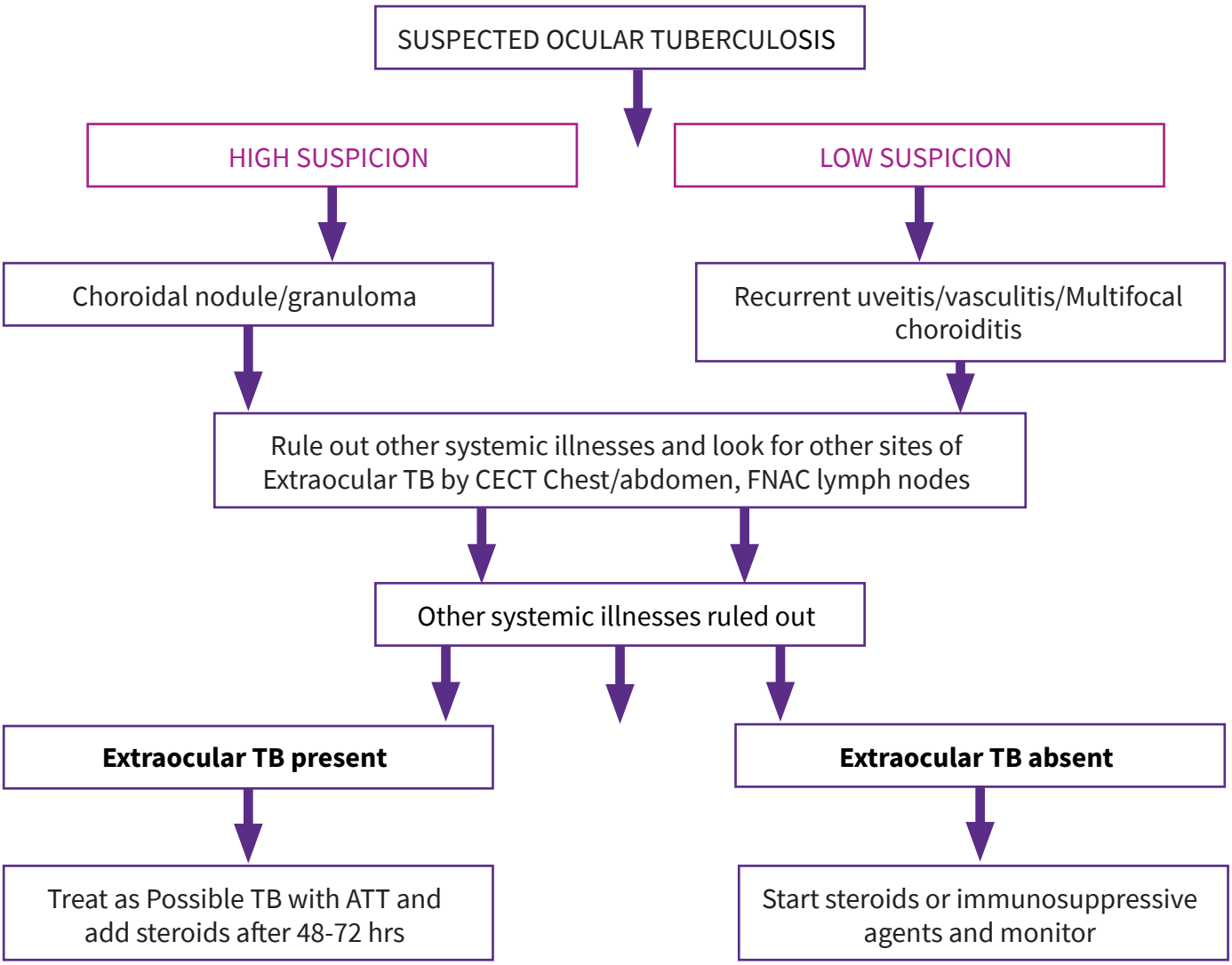
FFA helps to study the circulation of the retina and choroid using photographs taken after intravenous injection of fluorescein. It can help in assessment of vascularity of mass, associated vasculitis, macular and disc oedema. It is also not an essential first line investigation.

9.7 Management

The total duration of treatment is a minimum of 6 months which can be extended up to 9 months. Careful follow-up is to be done and frequency of follow up should be as per the treating physician's discretion. Among the ATT drugs, ethambutol and linezolid can produce optic neuritis as adverse effects.

Paramacular and optic nerve head TB requires treatment with ATT together with systemic corticosteroids (oral prednisolone 1 mg/kg/day) followed by tapering doses depending on the clinical response. Development of neovascularization warrants photocoagulation of the retina. Indications for surgery include management of complications of retinal vasculitis such as vitreous haemorrhage, tractional or combined retinal detachment, epiretinal membrane, etc. as well as complications of uveitis such as cataract and glaucoma.

Figure 9.1 Workflow Chart



Fundus images courtesy: Dr. Rohan Chawla, Rajendra Prasad center, All india Institute of medical sciences, New Delhi

Image 9.2: Fundus showing tuberculous choroidal

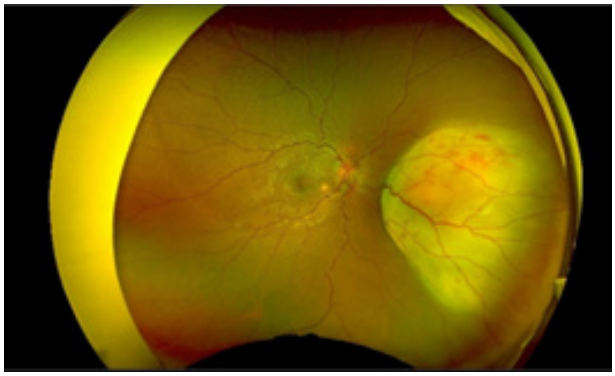


Image 9.3: Fundus at 3 months of ATT granuloma

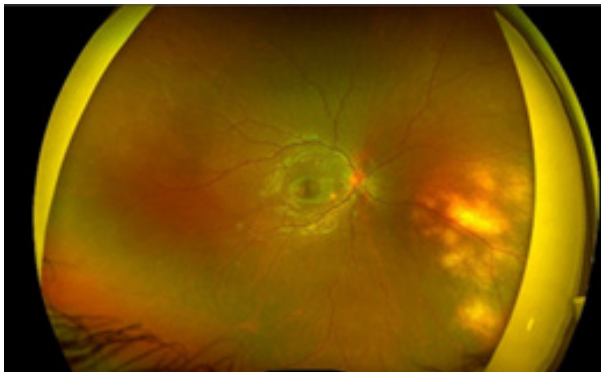


Image 9.4: Fundus images showing Multifocal peripapillary choroiditis with multiple subretinal abscess/granulomas and multiple subretinal abscesses in both eyes

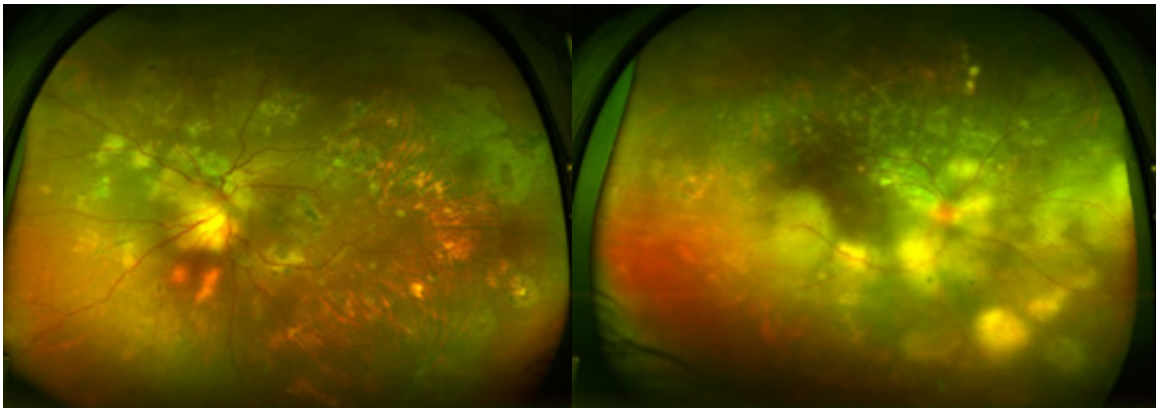


Image 9.5: Fundus photo after 1 month of ATT (left & right)

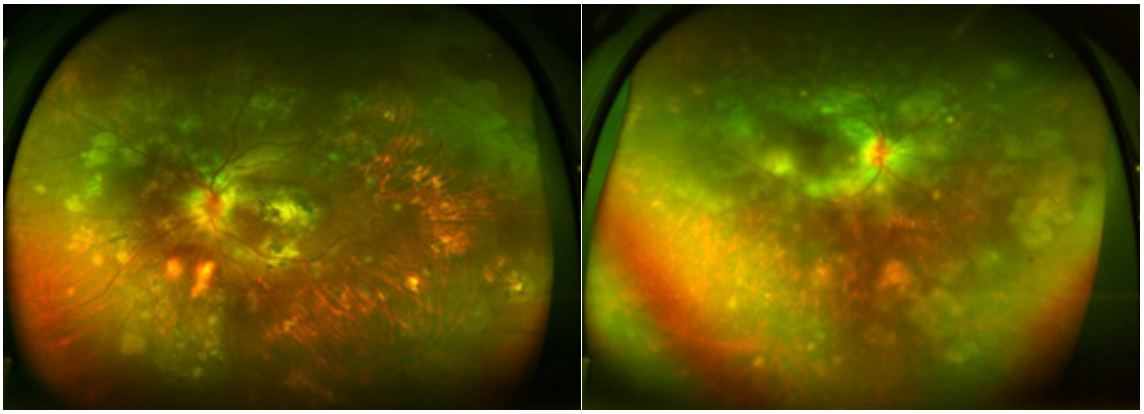
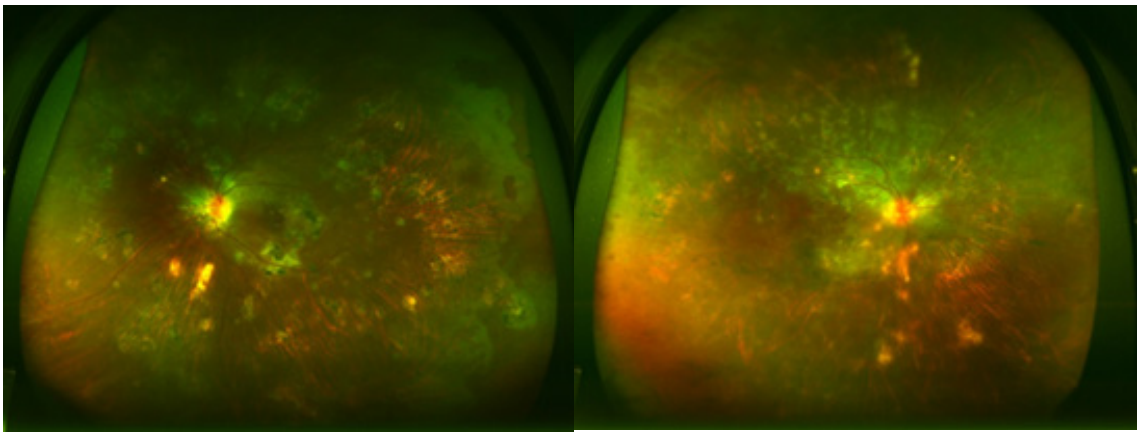


Image 9.6: Fundus photo after 3 months of ATT (left & right)



References:

1. Singh R, Gupta V, Gupta A. Pattern of uveitis in a referral eye clinic in north India. Indian J Ophthalmol. 2004 Jun;52(2):121–5.

2. Biswas J, Kharel (Sitaula) R, Multani P. Changing uveitis patterns in South India - Comparison between two decades. Indian J Ophthalmol. 2018 Apr;66(4):524–7.

3. Kumar A, Priyanka, Maheshwari M. Recent Changes in Tuberculosis Guidelines: What's New for Ocular Tuberculosis. Trends Ophthalmol Open Access J. 2019 Feb 1;2(1):1–4.

4. Index TB Guidelines-Guidelines on extra-pulmonary tuberculosis for India 2016.

5. Biswas J, Badrinath SS. Ocular morbidity in patients with active systemic tuberculosis. Int Ophthalmol. 1995 1996;19(5):293–8.

10. Urinary Tuberculosis

KEY POINTS:

- Urinary tuberculosis is a form of extra-pulmonary tuberculosis
- Occurs more commonly in adult males (males: females 2:1)
- The estimated prevalence of urogenital tuberculosis in India is approximately 4% [2] of all patients of extrapulmonary tuberculosis
- Diagnosis is made by history, clinical examination and Urine routine (sterile pyuria), Urine GeneXpert, Urine For MGIT and Culture on LJ media, USG KUB and Urography /CECT in advanced disease.
- Medical management with ATT is the mainstay of therapy with reconstruction surgery for ureteral strictures and constricted bladder.

10.1 Introduction

Tuberculosis of the urogenital tract was first described in literature by Wildbolz in 1937. Urogenital tuberculosis has been classified into three broad categories, viz, urinary tuberculosis, female genital tuberculosis and male genital tuberculosis. Urinary tuberculosis refers to tuberculous involvement of the kidneys, ureters, bladder and/ or urethra. Female genital tuberculosis involves uterus, fallopian tubes, ovaries, vulva and/ or vagina, whereas, male genital tuberculosis encompasses tuberculous involvement of the epididymis, prostate, testes and/or penis.

10.2 Epidemiology

Urogenital tuberculosis mostly affects adults with male to female ratio of 2:1[1]. In the developed countries, 2%-10%[1] of patients with pulmonary tuberculosis have associated urogenital tuberculosis. In developing countries the association is much higher. It has been observed in several studies that 15%-20% of pulmonary tuberculosis patients have concomitant urogenital tuberculosis. The estimated prevalence of urogenital tuberculosis in India is approximately 4% of all patients of extrapulmonary tuberculosis.

10.3 Pathophysiology

Urinary tuberculosis occurs as a result of hematogenous spread from a pulmonary focus. Tubercle bacilli are seeded in the renal cortex to form cortical granulomas. They may remain dormant for years. When these foci get activated during diminished host immunity, they spread to renal medulla to cause papillitis. Papillary necrosis in the renal medulla causes cavitary changes. It may progress to pyelonephritis or pyonephrosis. tuberculous involvement of the renal pelvis leads to the subsequent involvement of the ureters and the lower urinary tract. Strictures and dilatations of the ureters are common in end-stage urinary tuberculosis. Lower urinary tract disease manifests with granulomas and fibrosis of the urinary bladder [3][4].

10.4 Clinical features

The average latent period between pulmonary infection and the development of clinical urogenital tuberculosis is 22 years (1-46 years). Urinary tuberculosis is mostly asymptomatic till the ureter and/or bladder is involved. [6].Urinary tuberculosis is suspected when patients present with the following symptoms for 2 weeks or more with no response with antibiotics for 3-7 days:

- Lower urinary tract symptoms like dysuria, increased frequency, nocturia etc.
- Hematuria
- Flank pain

Systemic systems like fever, weight loss, night sweat are present in approximately 20%[2] of patients. Immunocompromised patients and the patients with tuberculosis at other sites are at higher risk to develop urinary tuberculosis. On clinical examination, there might be suprapubic pain. Renal angle tenderness is present in case of pyelonephritis.[5]

10.5 Diagnosis

The diagnosis of urinary tuberculosis is difficult due to the lower sensitivity of the tests. It requires early clinical suspicion to diagnose and treat it early to prevent long term complications in the form of irreversible damage to the urinary tract and the subsequent development of end-stage renal disease [2].

The following investigations are indicated for all suspected cases of urinary tuberculosis:

- Urine R/M, C/S: concurrent bacterial infection with coliforms in ~30% cases
- Urine for NAAT
- Urine AFB: ZN staining
- Urine C/S for TB: Liquid MGIT
- USG KUB: to identify any lesions in the urinary tract/kidney
- CBC with ESR, Liver Function Tests, Renal Function Tests
- Chest X-ray: for evidence of pulmonary focus
- HIV (ICTC): higher association with EPTB

10.5.1 Sample collection:

- **Urine Collection Routine Microscopy And Culture:** Early morning mid-stream urine sample is the most preferred sample. Urine to be collected in a sterile, leak-proof container and to be sent to the laboratory within four hours of collection.

- **Urine Collection For Mycobacterial Analysis:** A glass bottle (e.g., saline bottle) to be boiled in water for 20 mins. Morning urine sample (whole urine passed in morning) to be collected in the glass bottle and transported to the laboratory within four hours of collection. Patients are instructed to void before retiring to bed on the previous night of the urine collection. The first morning, entire urine specimens to be collected in the sterile container. Three such urine samples to be sent to the laboratory for examination. Urine from a catheter bag, less than 40ml of urine and 24 hours pooled urine specimens are unacceptable samples for mycobacterial analysis. Collected specimens should be transported to the laboratory without any delay. Refrigeration of the samples are required if it is not transported to the laboratory within 4 hours of collection. Freezing of the samples decreases the diagnostic yield [6].

10.5.2 Investigations:

10.5.2 A. Microbiological tests:

Urine Routine Microscopy And Culture: Pus cells (90%-100%), RBCs (50%-60%) and degenerated epithelial cells are commonly seen in urine microscopy of the patients with urinary tuberculosis. Cultures for aerobic bacteria are positive in 30% of cases of urinary tuberculosis due to concurrent infections of the urinary tract [5].

Urine NAAT: It is a rapid test for the molecular detection of *Mycobacterium tuberculosis* in urine along with the detection of rifampicin resistance. It has shown good quality preliminary evidence with a pooled sensitivity 0.87 and specificity 0.91. It is to be remembered that a negative test does not rule out urinary tuberculosis [1].

Urine Culture For *Mycobacterium tuberculosis:* The preferred culture system is the MGIT automated culture system which has a shorter turn-around time of four weeks. Conventional culture methods using LJ media have a longer turn-around time of six to eight weeks. They can be used when MGIT is not available. The overall sensitivity of culture to diagnose urinary tuberculosis varies from 10.7%-80% in different studies [8][9].

Ziehl Neelsen (ZN) Staining: It has very low sensitivity for urinary tuberculosis. Acid alcohol (3% HCl in 95% ethyl alcohol) is preferred to H2SO4 as a decolouriser for genitourinary samples to avoid confusion with *Mycobacterium smegmatis* (colonizer).

10.5.2 B. Radiology:

Ultrasonography of the urinary tract is the initial imaging of choice. When USG is grossly abnormal or there is high clinical suspicion despite a normal USG, the following investigations to be considered:

- Intravenous urography and/or cystography
- CECT with CT urography
- Cystourethroscopy with or without biopsy (may be considered)
- MR Urography (only in special cases e.g., patients with deranged KFT)

Ultrasonography of the kidneys, ureters and bladder: The following are the common ultrasonographic findings in urinary tuberculosis.

- Early disease:
  - Small focal cortical lesions +/-calcifications
- Progressive disease:
  - Papillary destruction
  - Distorted parenchyma
  - Hydronephrosis (usually asymmetric) [Fig10.1&2]
  - Mucosal thickening +/- ureter /bladder involvement
  - Small, fibrotic thick-walled bladder
  - Pyonephrosis
- End stage disease:
  - Small shrunken kidney, paper thin cortex, dystrophic calcification

Intravenous Urography: It helps to detect the earliest changes. IV urography is cheap and widely available. Changes include parenchymal scars, moth eaten calyces, irregular calyces and phantom calyx. Lower tract involvement can cause ureteral strictures and contracted bladder. [Fig 10.3&4].

CECT with CT Urography: Apart from the findings of IV urography, it provides other supportive findings like lymph node status, involvement of bowel etc. which aid in the further management of the patients. The following are the findings in accordance with the stage of the disease:

- Early disease:
  - Papillary necrosis
- Progressive disease:
  - Multifocal ureteral strictures
  - Generalized or focal hydronephrosis, perinephric abscess
  - Poorly enhancing renal parenchyma (direct involvement or hydronephrosis) [Fig. 10.7]
  - Ureteric dilatation with or without wall thickening
  - Bladder wall thickening, contracted bladder [Fig 10.6]
- End stage disease:
  - Progressive hydronephrosis with very thin renal cortex
  - dystrophic calcification of kidney [Fig 10.5], putty kidney

Cystourethroscopy With Or Without Biopsy: This procedure is used when other tests are inconclusive/malignancy needs to be ruled out. It allows direct visualization and targeted biopsy from vesicoureteral junction or from other suspected areas, if any. All the specimens are to be sent in two parts; specimens in formalin will be used for histopathology and the specimens in normal saline will be subjected to GeneXpert, culture and ZN staining for *Mycobacterium tuberculosis.*

10.6 Management

The aim of the management of urinary tuberculosis is to achieve cure, to prevent long term sequelae and to restore functionality of the kidneys and the urogenital tract, wherever possible. Anti-tubercular therapy (ATT) daily regimen to be given for 6 months in the following regimen:

- Isoniazid + Rifampicin + Pyrazinamide + Ethambutol (HRZE): 2 months (Intensive phase)
- Isoniazid + Rifampicin + Ethambutol (HRE): 4 months (Continuation Phase)

All patients should be referred to higher centers, if renal function is deranged. Urology consultation should be sought in case of urinary tract abnormalities. Reconstruction surgeries are indicated for ureteric strictures and reduced bladder capacity.

10.7 Complications And Follow Up

The major complications of urinary tuberculosis is the progression to end-stage renal disease. Other possible complications are the development of hypertension and secondary amyloidosis.

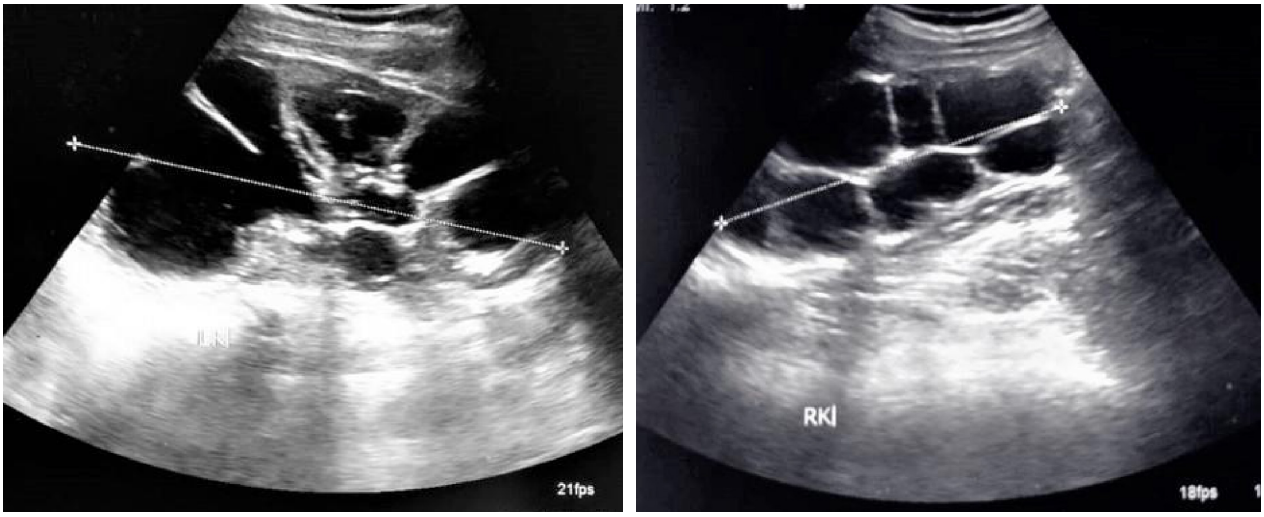
All patients with urinary tuberculosis will be followed up after 4 weeks after treatment initiation. The following parameters will be monitored during the follow-up visits:

- Improvement in urinary symptoms
- Resolution of systemic symptoms
- Improvement in renal function
- Repeat urine mycobacterial C/S (if positive at the time of diagnosis)
- A repeat ultrasonography KUB to be performed after 4-6 weeks of ATT. To refer to urology, if the USG comes abnormal.
- Repeat urine mycobacterial C/S should be done at 2 months and 6 months.

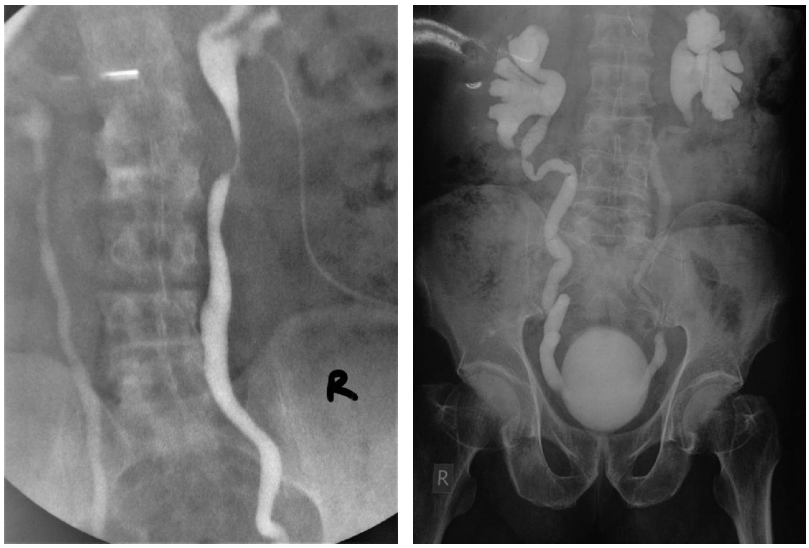
10.8 Conclusion

Urinary Tract Tuberculosis still remains an important differential for sterile pyuria. Delay in presentation with poor sensitivity of microbiological tests poses a challenge in diagnosing this entity. If not diagnosed and managed actively, it can lead to poor outcomes including end stage renal disease. The need for early surgical intervention to relieve obstruction is an important part of the management along with effective antitubercular therapy.

Figures 10.1&2: Gross hydronephrosis with non-dilated renal pelvis on USG
Courtesy: Dr.Ankit Mittal, Senior Resident DM Infectious Diseases

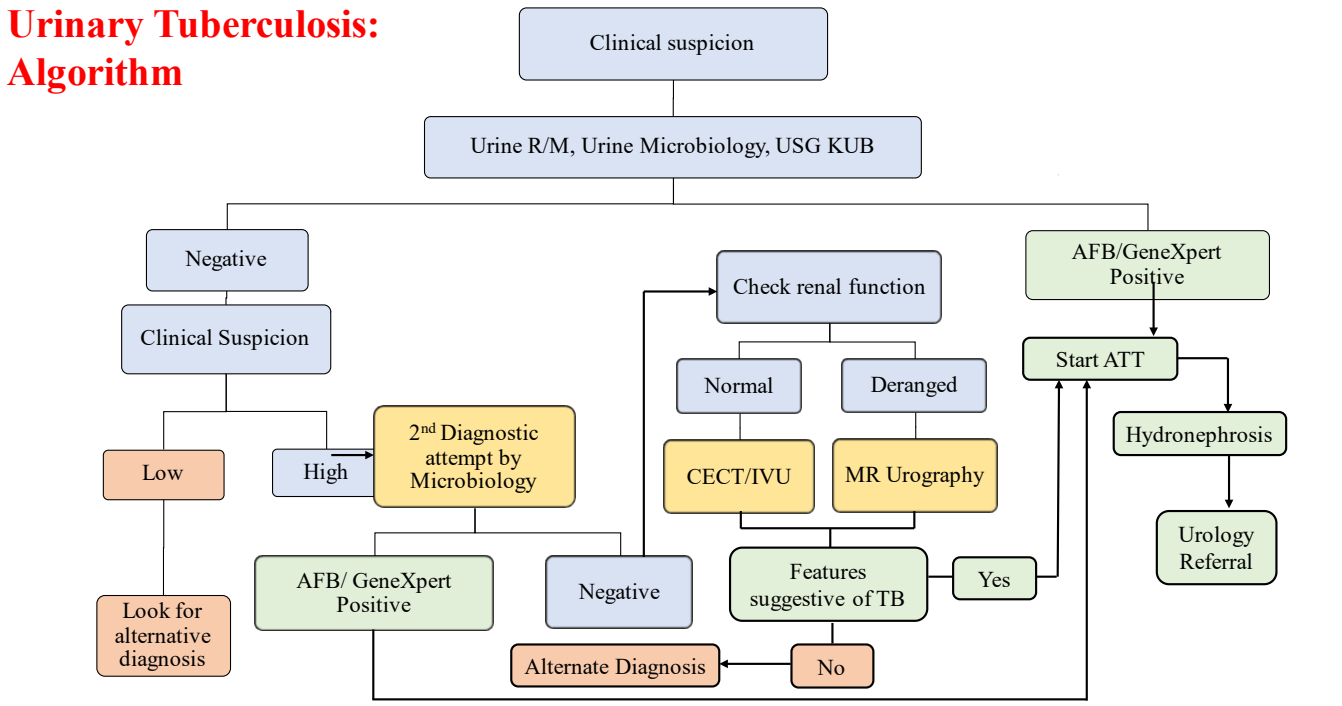


Figures 10.3&4: IVP films showing ureteral stricture, bilateral gross hydronephrosis & contracted bladder.
Courtesy: Dr.Prabhjot, Associate professor, urology, AIIMS New Delhi



Figures 10.5,6&7: Calcification of left Kidney with pelvicalyceal dilation ;Contracted (Thimble) Bladder; Rt Hydronephrosis with thickened ureter
Courtesy: Dr.Prabhjot, Associate professor, urology, AIIMS New Delhi

Figure 10.8. Diagnostic Algorithm of Urinary Tuberculosis



Adopted from: Kapoor et al. Clinical presentation and diagnostic approach in cases of genitourinary tuberculosis. Indian Journal of Urology. 2008

References

1. Altez-Fernandez et al, Diagnostic accuracy of NAATs in urine for genitourinary tuberculosis: a systematic review and meta-analysis. BMC Infectious Diseases, 2017

2. Index TB guidelines: Guidelines on extra-pulmonary TB in India. 2016

3. Daher et al. Review: Renal Tuberculosis in the Modern Era. American Journal of Tropical Medicine. 2013

4. Viswesaranet al. Tuberculosis of the Urinary Tract

5. Figueiredoet al. Epidemiology of Urogenital Tuberculosis worldwide. International Journal of Urology. 2008

6. Kulchavenyaet al. Urogenital tuberculosis: Definitions and classification. Therapeutic advances in infectious disease. 2014

7. Yadavet al. Genital tuberculosis: current status of diagnosis and management. Translational Urology and Andrology. 2017

8. Mousaet al, Rapid diagnosis of genitourinary tuberculosis by polymerase chain reaction and non-radioactive DNA hybridization. J Urol2000.

9. Hemal et al, Polymerase chain reaction in clinically suspected genitourinary tuberculosis: comparison with intravenous urography, bladder biopsy, and urine acid fast bacilli culture. Urology 2000

10A Male Genital Tuberculosis

KEY POINTS:

- Male Genital Tuberculosis (MGTB) is defined as a patient with scrotal pain or swelling for 2 weeks or more not responding to a 7-to-14-day course of antibiotics.
- In India, Urogenital Tuberculosis (UGTB)constitutes 4% cases of EPTB (1) (may be an underestimate). In > 50% cases [1], both urinary and genital organs are involved.
- Men of all age groups can present with the symptoms classically non responsive to antibiotics such as scrotal swelling, discharging scrotal sinuses and pelvic pain.
- In case there is a suspicious mass, a CE MRI of the Pelvis may be warranted, or a CECT pelvis. Biopsy of Testicular mass is avoided.

Medical management with ATT is the mainstay of therapy with reconstruction surgery for strictures and fistulae

10A.1 Introduction

Tuberculosis of the urogenital tract was first described in literature by Wildbolz in 1937. Urogenital tuberculosis has been classified into three broad categories, viz, urinary tuberculosis, female genital tuberculosis and male genital tuberculosis. Urinary tuberculosis refers to tuberculous involvement of the kidneys, ureters, bladder and/ or urethra. Female genital tuberculosis involves uterus, fallopian tubes, ovaries, vulva and/ or vagina, whereas, male genital tuberculosis encompasses tuberculous involvement of the epididymis, prostate, testes and/ or penis.

A presumptive case of MGTB is defined as a patient with scrotal pain or swelling for 2 weeks or more not responding to a 7-to-14-day course of antibiotics, or presenting with discharging sinuses in the scrotum. Rarely, patients have systemic symptoms of fever, weight loss and night sweats. MGTB presents with nonspecific symptoms and laboratory findings, with only about 36% cases being culture positive.

10A.2 Epidemiology

In developed countries, urogenital TB occurs in 2% to 10% of cases of pulmonary TB. In developing countries, 15% to 20% cases of pulmonary TB have concurrent urogenital TB. In India, UGTB constitutes 4% cases of EPTB (may be an underestimate).In > 50% cases, both urinary and genital organs are involved. Isolated involvement of genital organs is reported in about 5-30% of the cases of GUTB. (2)

10A.3 Pathophysiology

The most common route of spread is hematogenous, from a primary pulmonary focus to the epididymis as it is highly vascular and the prostate followed by contiguous, canalicular or urinary spread to testes, seminal vesicles, urethra and penis. Isolated testicular involvement is uncommon due to the presence of blood testis barrier, hence malignancy should be ruled out if testes is involved in isolation. (3)

10A.4 Clinical Features

Men of all age groups can present with the symptoms classically non responsive to antibiotics such as scrotal swelling, being the most common, exclusively or along with scrotal pain, discharging scrotal sinuses, pelvic pain, increased urinary frequency, nocturia, dysuria, hematuria, hematospermia and infertility which is seen in about 10% of the cases (3). Systemic symptoms may/may not be present. On Examination the common findings include an enlarged, hard epididymis which can be tender or nontender. A thickened, beaded vas deferens may be present with prostatic indurations or nodules on Digital Rectal Exam. A non tender testicular mass, perineal or scrotal fistula may be present. Hydrocele, inguinal lymphadenopathy are however rare findings. (3)

10A.5 Diagnosis

For anyone suspected to have TB of any site, a chest X-ray to look for a primary focus and a HIV test is mandatory. In case of suspected Genital TB. A coexisting urinary tract TB should be investigated for as an abnormal urine Routine examination is seen in up to 90% cases. Urine samples sent for genexpert, AFB staining and mycobacterial culture help to rule out a coexisting Urinary Tract Tuberculosis. An Ultrasound KUB and the scrotum needs to be done in adjunct to microbiological investigations as therapy can be instituted on radiological evidence alone.

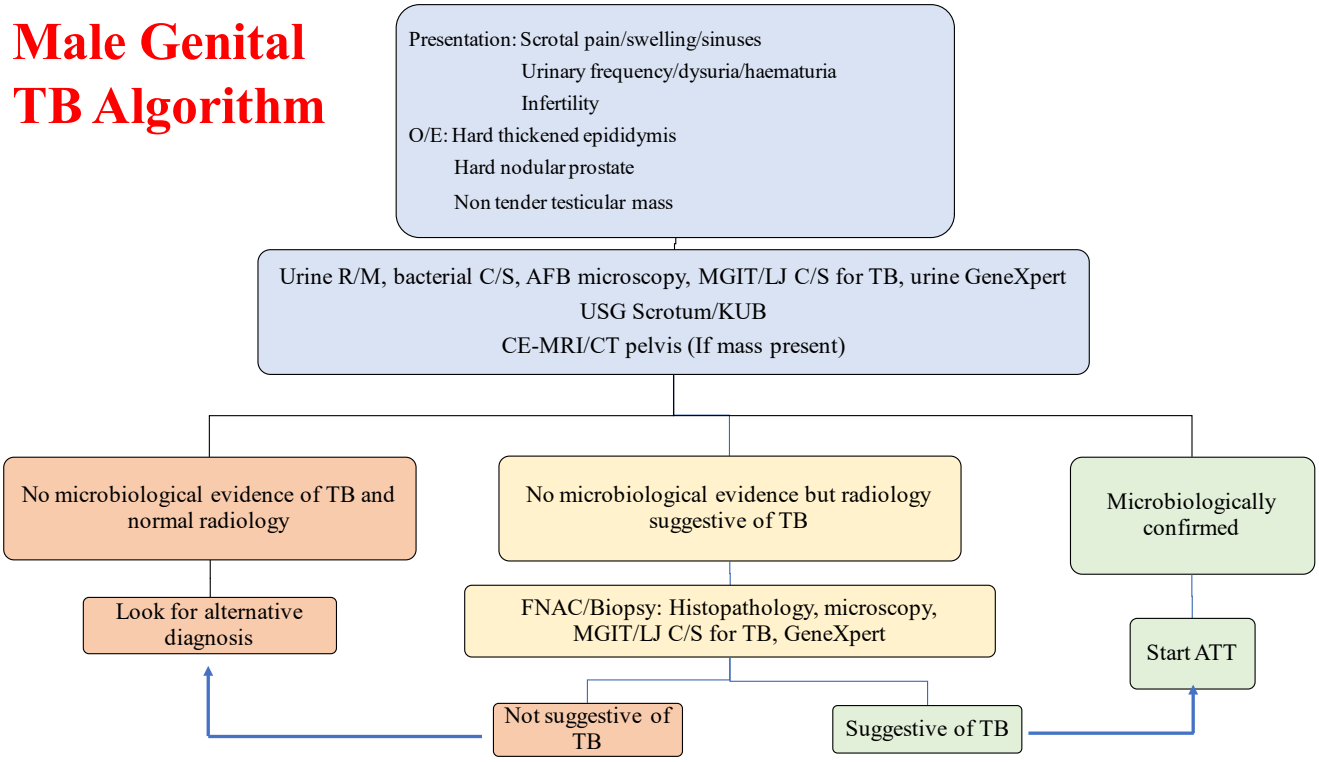
For suspected cases of isolated genital Tb, analysis of expressed prostatic secretions (EPS), post massage urine and ejaculate for mycobacterium by microscopy, culture and PCR may be helpful. EPS can be collected using either the standard four glass test or the modified 3 glass test that is proposed to have lesser contamination of urine samples with prostatic secretions. At least 3 but 5 or more samples should be collected and plated within 40 min of collection. But the search of Mycobacterium in semen or EPS samples by these methods is often futile even in diagnosed cases of genital TB or may be incidentally positive in clinically asymptomatic men undergoing infertility analysis. All other obtainable body fluid specimens from possible sites of infection, such as pus from epididymal or prostatic abscess and discharge from penile lesion or perineal or scrotal sinuses, must be subjected to smear, culture and possibly PCR for detection of bacilli.(4).In case there is a suspicious mass, a CEMRI of the Pelvis may be warranted, or a CECT pelvis (subject to Renal function). The mass, if involving the epididymis, can be sampled (Biopsy/FNAC) carefully. Send the samples for histopathology in Formalin, and in saline for Genxpert, AFB staining and Culture with drug sensitivity testing. Avoid sampling the testis due to possible seeding of an occult malignancy of the testis which is a close differential of testicular TB.

10A.6 Management

Anti-Tubercular Therapy (ATT), Weight based Daily Regimen consisting of Isoniazid/Rifampicin/ Pyrazinamide/Ethambutol (H/R/Z/E) for 2 months during the intensive phase followed by H/R/E for 4 months, during the Continuation Phase is the standard of treatment. For drug resistance TB refer to programmatic guidelines for management and follow up (Guidelines for Programmatic Management of Drug Resistant TB) Aspiration of abscesses should be done with utmost care, against gravity to prevent fistula formation.

Surgical intervention may be required in cases where sequelae such as strictures and fistulae are seen.

Figure 10A.1 .Diagnostic Algorithm for Male Genital Tuberculosis



10A.7 Complications And Follow Up

Patients on treatment are followed up after 8 weeks to assess response. There can be improvement in constitutional symptoms if present initially. However, resolution of infertility may not be seen and this does not indicate failure of therapy. Long term sequelae include complications like infertility, sexual dysfunction, scrotal and perineal fistulas and strictures.

10A.8 Conclusion

Male Genital TB is still underdiagnosed and often undertreated in India. It warrants a high degree of suspicion and timely investigations and treatment initiation to prevent long term sequelae. A thorough evaluation of the urinary tract and other systemic sites is also mandated.

References

1. Yadav S, Singh P, Hemal A, Kumar R. Genital tuberculosis: current status of diagnosis and management. Transl Androl Urol. 2017 Apr;6(2):222–33.

2. Index-TB Guidelines.pdf [Internet]. [cited 2021 Jul 11]. Available from: https://tbcindia.gov.in/WriteReadData/l892s/5585665076Index-TB%20Guidelines.pdf.

3. Kulchavenya E, Kim C-S, Bulanova O, Zhukova I. Male genital tuberculosis: epidemiology and diagnostic. World J Urol. 2012 Feb;30(1):15–21.

4. Kumar R. Reproductive tract tuberculosis and male infertility. Indian J Urol IJU J Urol Soc India. 2008;24(3):392–5.

10B Female Genital Tuberculosis

KEY POINTS:

- Female genital tuberculosis is a form of extra-pulmonary tuberculosis.
- Occurs more commonly in pre-menopausal women.
- Under/delayed diagnosis of this condition is common, leading to significant morbidity in the form of infertility and chronic menstrual dysfunction.
- Diagnosis is made by history, clinical examination and endometrial aspirate testing for AFB, Mtb culture, NAAT and histopathology aided by endoscopy.
- Medical management with ATT is the mainstay of therapy with surgery having a limited role in certain cases.

10B.1 Introduction

Female Genital tract Tuberculosis (FGTB) is an important form of extra-pulmonary tuberculosis associated with significant morbidity. Incidence of FGTB varies from 0.69% (Australia) to 19% (India) [1]. It is more common in pre-menopausal women and they often present with infertility and menstrual dysfunction. Mainstay of management is anti-tubercular therapy with surgical intervention necessary in only a few special scenarios. Despite adequate therapy, fertility outcomes may be poor, re-emphasizing the importance of early diagnosis and treatment of these patients.

10B.2 Pathogenesis

Female genital tract tuberculosis is generally secondary to pulmonary involvement with hematogenous spread. It may also spread by lymphatic route or by direct spread from abdominal TB. FGTB may even develop after sexual intercourse with a man with tuberculosis of the penis or epididymis, although this is rare. FGTB is more common in pre-menopausal women. The reason for this may be that the endometrium in post-menopausal women is atrophic, which provides a poor milieu for mycobacterial growth.

FGTB affects the following parts [1] [refer Figures 10B.1, 10B.2 &10B.3]:

- **Fallopian tubes** in 90-100% cases: lesions include endosalpingitis, exosalpingitis, interstitial salpingitis or salpingitis isthmica nodosa.
- **Uterine endometrium** in 50-80% cases: lesions include ulcers, synechiae and adhesions.
- **Ovaries** in 20-30% cases: lesions include ulcers, synechiae and adhesions.
- **Cervix** in 5-15% cases: lesions include polypoidal growth and ulceration.
- **Vulva and vagina,** rarely, in 1% cases: Lesions include growth, ulceration and fistulas.

10B.3 Presentation

Genital Tuberculosis may be asymptomatic in around 10% of cases(1). Enquiry must be made about a past history of pulmonary TB or family history of TB. A common scenario is a young female patient, caring for her family member affected with TB, secondarily getting infected by TB herself. Hence, a thorough history is of utmost importance.

Patients could present with fever and constitutional symptoms such as malaise, anorexia and weight loss. However, these symptoms may not be seen in all patients. The most common form of presentation is with infertility (either primary or secondary). Around 11% of women (1) present with infertility alone and need to be evaluated for other causes as well. Patients also frequently present with menstrual disturbances which may be long standing and also varied in their manifestations. Heavy menstrual bleeding can be an early symptom. Patients can present with dysmenorrhea, Puberty menorrhagia or Postmenopausal bleeding. Complaints of Oligomenorrhoea, Hypomenorrhoea and Amenorrhoea can also be seen.

Some of these patients may also complain of chronic abdominal/pelvic pain and a mass may be palpable on clinical examination. While some patients may complain of vaginal discharge of varying duration and quality, a few patients may also present with urinary disturbances such as incontinence.

10B.4 On Examination

General examination
- Fever
- Lymphadenopathy

Abdominal examination
- Mass abdomen (vague or definite)
- Ascites
- Doughy feel of abdomen

Vaginal examination
- Uterine enlargement (Pyometra)
- Adnexal masses and induration
- Tubo-ovarian mass
- Fullness and tenderness in pouch of Douglas

10B.5 Laboratory Investigations

- CXR: In all patients, to look for coexisting Pulmonary TB.
- HIV Testing: In all patients, since there is a strong association noted between HIV and EPTB
- USG pelvis: In all patients, to look for anatomic changes.
- Urine Pregnancy Test, where relevant, to rule out pregnancy as the cause of symptoms
- Endometrial aspirate: For all patients

It is to be taken preferably during the luteal phase of Menstrual Cycle.
Endometrial biopsy/curettage may be considered in selected patients.

The following samples are to be subjected to saline for:

(a) WHO approved NAAT – [Sensitivity ~ 35-46%; Specificity- 100%] [2,3]
(b) Microscopy (Fluorescent/ZN staining) (refer Fig 10B.4)
(c) Culture (MGIT/LJ) and drug sensitivity

- A positive Xpert is confirmatory but a negative test does not always rule out TB [2,3]

Sample in formalin for: Histopathological examination (HPE)

- Menstrual blood may also be tested (in case of unmarried women).
- Hysterosalpingogram: Involves injecting a dye into the genital tract to visualise the same. HSG may be normal in patients with TB. In case of active discharge, HSG is contraindicated to prevent further spread of disease cranially (refer Fig 10B.5).
- CE MRI/CECT pelvis: indicated when a tubo-ovarian (TO) mass is present. It can help guide intervention for selected patients. CE MRI is superior to CT for characterization of lesions.
- FDG-PET: Not routinely recommended. It is helpful to differentiate between persistent mass due to active TB or Fibrotic mass.
- Laparoscopy and FNAC/Biopsy: Indicated when other less invasive tests are less conclusive, and/or malignancy is also suspected. Laparoscopy allows pelvic organ visualization and specimen collection from otherwise inaccessible sites (refer Figures 10B.6 & 10B.7).

Specimens should be subject to:

a) Histopathology (sample in formalin)
b) WHO approved NAAT
c) TB culture (MGIT/LJ) and DST
d) Microscopy by Fluorescent/ZN stain

} Sample in saline

As per Index TB guidelines, 2016 [4] (Index-TB Guidelines: Guidelines on extrapulmonary tuberculosis), the diagnosis of FGTB should be made based on any one of:

- Laparoscopic appearance typical for FGTB (tubercles, caseation or beaded tubes).
- Any gynaecological specimen positive for AFB on microscopy, GeneXpert or positive for *M. tuberculosis* on culture.
- Any gynaecological specimen with findings consistent with FGTB on histopathological examination.

10B.6 Treatment

As per the Index TB guidelines, 2016[4]:

- All cases must be treated with ATT: HRZE (2 months) + HRE (4 months).
- All FGTB patients require assessment by a gynecologist to make the diagnosis and treat complications.
- ATT in women presenting with infertility alone should only be started following assessment by a specialist.
- Uncomplicated cases can be managed in secondary care centers. However, MDR cases, persistent tubo-ovarian (TO) masses and cases requiring surgical care need to be referred to higher centers.
- **Surgical Management:**

Surgery is not part of primary treatment in FGTB. It is performed rarely and may be associated with significant morbidity. However, it may be needed for large, residual tubo-ovarian abscesses, in the form of drainage of persistent pelvic or tubo-ovarian abscess, despite medical treatment.

More severely affected cases may necessitate the removal of the uterus, both tubes and ovaries for persistent disease, tubercles, pyosalpinx, tubo-ovarian mass, and non-healing ulcers.

10B.7 Follow Up

Assess response to treatment at completion of 6 months of ATT by USG pelvis. Persistent tubo-ovarian masses merit evaluation to rule out drug resistance by FNAC. Drug resistant cases must be referred to higher centers. Overall fertility outcome is poor in FGTB. It must be noted that infertility may be a permanent consequence of FGTB and does not indicate treatment failure or re-infection. It does not warrant repeated courses of ATT.

Laparoscopy may be advisable in selected patients for assessing the prognosis and fertility outcome:

- If tubes, ovaries and uterus are normal, spontaneous conception or ovulation induction can be tried.
- If fallopian tubes are still not patent following treatment, one can go for In-Vitro Fertilization and Embryo Transfer.
- If ovaries are normal but tubes and uterus are damaged, one may go for surrogacy.
- If both ovaries are destroyed by the disease process, or endometrium is involved, then adoption is advised.

10B.8 Challenges in management

- Late diagnosis
- Infertility may be a permanent consequence

10B.9 Summary

- FGTB causes gynecological symptoms such as infertility, menstrual dysfunction and chronic pelvic pain
- Diagnosis is made by history, clinical examination and endometrial aspirate for AFB, culture, PCR and histopathology aided by endoscopy
- Fertility outcome is poor in FGTB, but In-Vitro Fertilization (IVF) can be performed for tubal blockage with normal endometrium with a good outcome

Figures: (All images- courtesy Dr JB Sharma, Professor Department of Obstetrics and Gynecology, AIIMS, New Delhi)

Figure 10B.1: Laparoscopic view: hydrosalpinx with beaded tubes

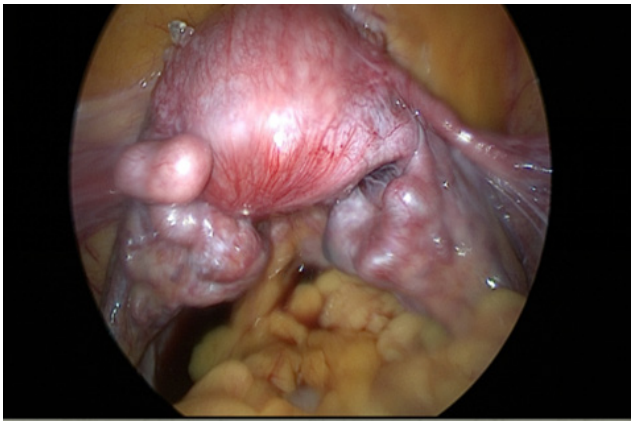
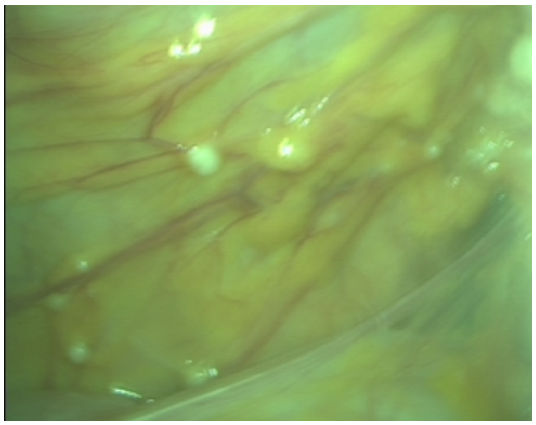


Figure 10B.2: Laparoscopic view: caseous nodules on peritoneum.



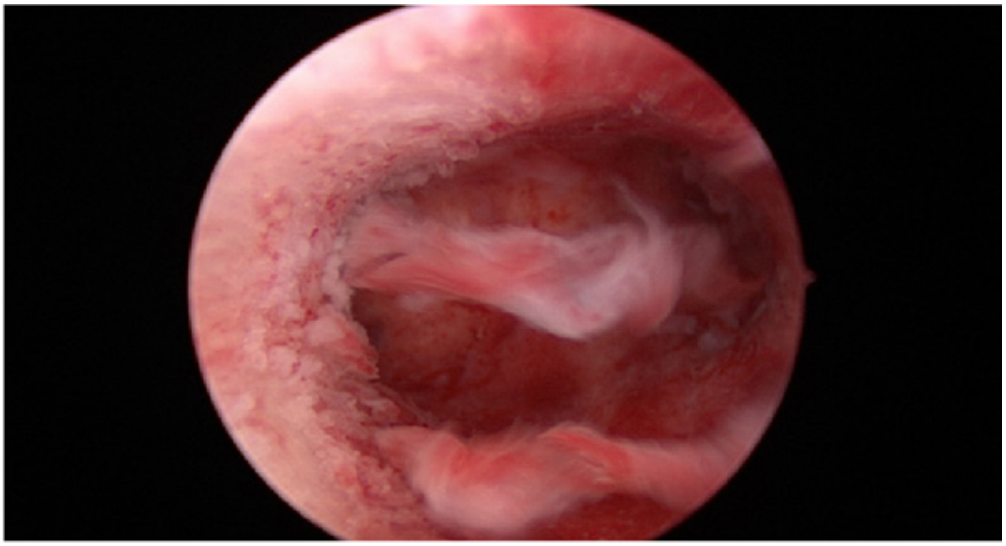


Figure 10B.3: Hysteroscopic view: intrauterine adhesions in FGTB.

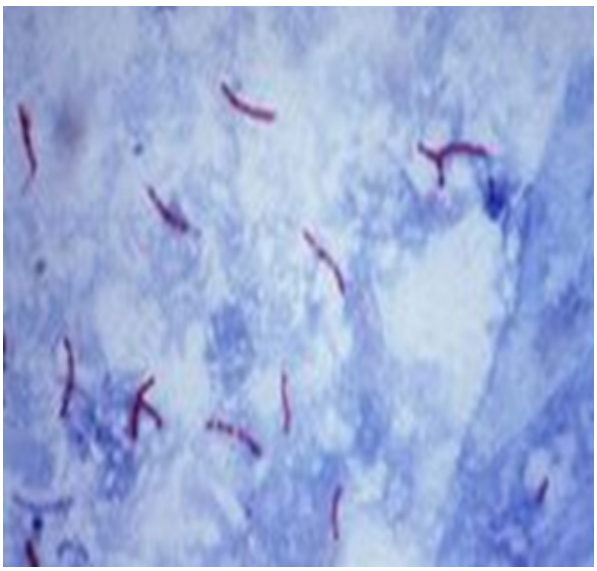


Figure 10B.4: AFB in Endometrial Aspirate

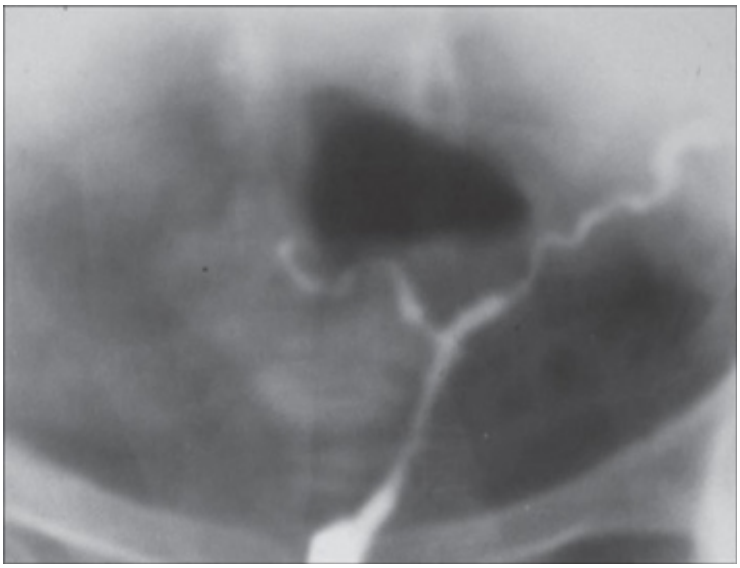


Figure 10B.5: Hysterosalpingography image showing 'Dried Branch' fallopian tube in bilateral tubal involvement

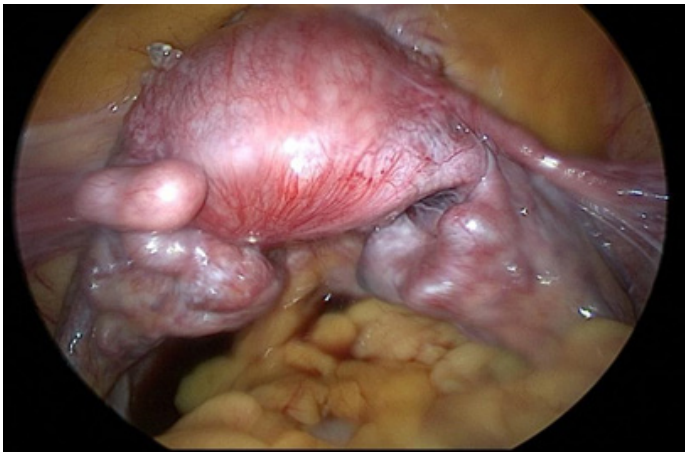


Figure 10B.6: Hydrosalpinx with Beaded Tubes

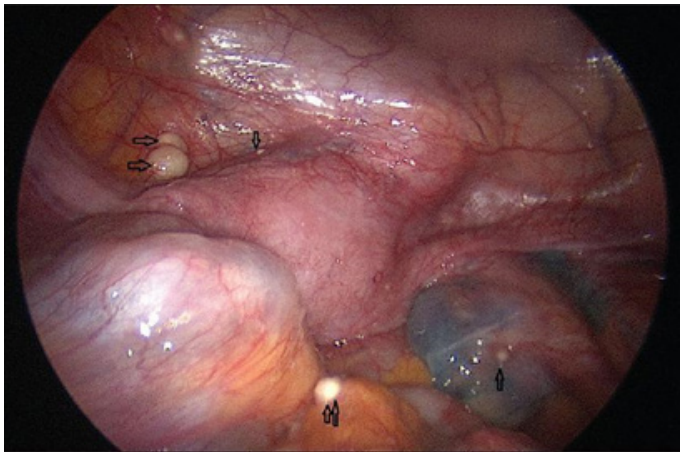
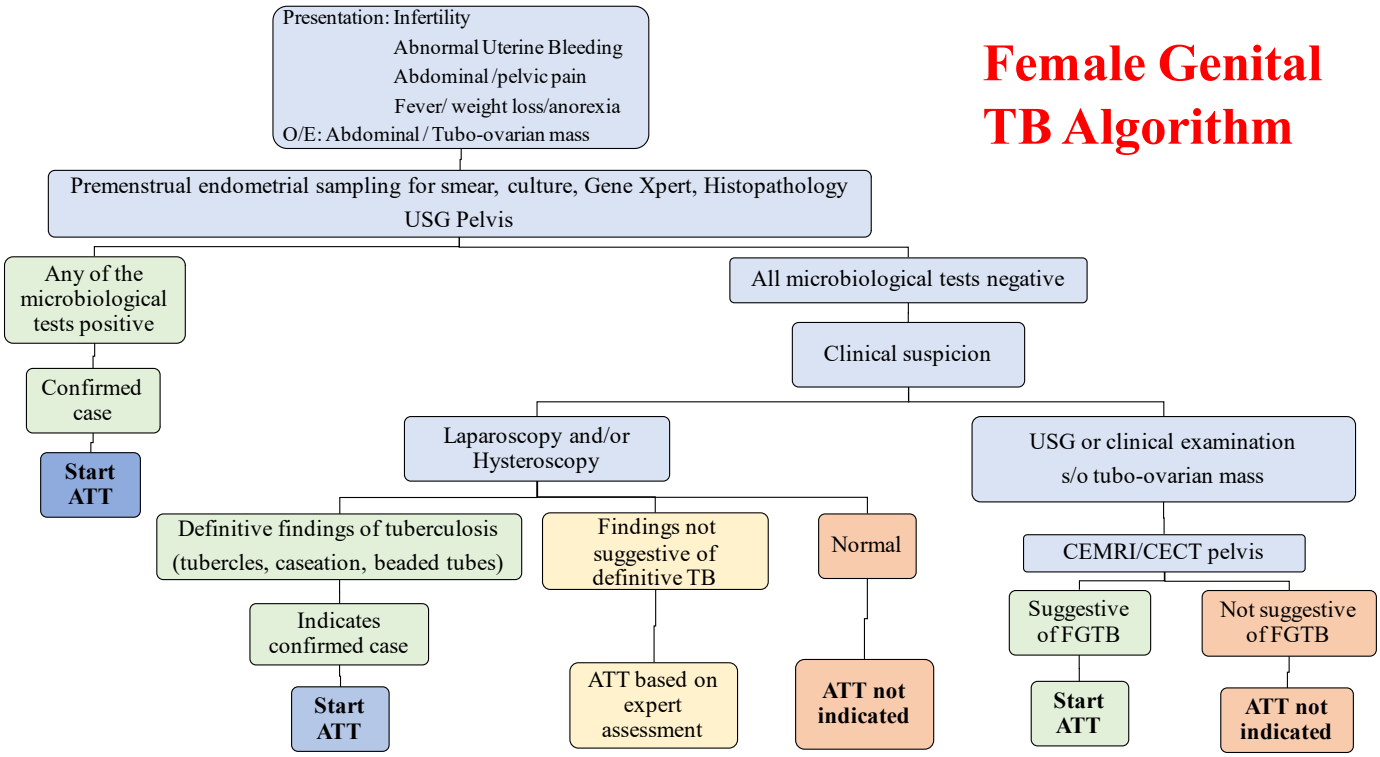


Figure 10B.7: Laparoscopic findings of tubercles (single arrow) on uterus, fallopian tubes, and caseous nodules (double arrow)

Figure 10B.8: Diagnostic Algorithm for Female Genital Tuberculosis



References

(1) Sharma J B et al. Female genital tuberculosis: Revisited. Indian Journal of Medical Research. 2018.

(2) Kulshrestha et al. International Journal of Gynecology and Obstetrics 113 (2011) 229-234.

(3) Sharma et al. European Journal of Obstetrics & Gynecology and Reproductive Biology 207 (2016) 235–246.

(4) Index TB guidelines, 2016.

11. Tuberculosis Diagnostics

KEY POINTS:

- It is highly recommended to obtain microbiological evidence of the presence of tuberculosis for diagnosis in all cases of extra-pulmonary tuberculosis.
- NAAT is a rapid test used for molecular diagnosis as well as rifampicin sensitivity.
- The automated MGIT 960 liquid culture system has a relatively shorter turn-around time than solid culture.
- Susceptibility testing using LPA/DST is performed from culture positive for *M. tuberculosis*.
- ZN staining or fluorescent microscopy is invaluable in resource-limited settings.

11.1. Introduction:

Tuberculosis can involve almost all anatomical locations of the human body. Various clinical specimens, based on the anatomical sites, can be collected for microbiological analysis when extrapulmonary TB (EPTB) is suspected. Based on site and mode of specimen collection and the extent of unavoidable contamination occurring during the collection procedure, EPTB specimens can be broadly divided into two groups:

- **Sterile Specimens:** These samples should be collected aseptically to render those free from other microorganisms e.g., sterile body fluids like pleural fluid, lymph node aspirates etc. All samples for microbiological diagnosis should be collected in a sterile container and transported to the laboratory as soon as possible, at the most within 7 days.
- **Non-sterile Specimens:** Specimens cannot be collected aseptically as those are contaminated by normal flora during collection e.g., urine, pus etc.

The microbiological diagnosis of extrapulmonary tuberculosis (EPTB) is often challenging largely due to paucibacillary nature.Microbiological evidence in the diagnosis of tuberculosis should always be considered to confirm the diagnosis as well as to obtain information related to drug resistance. The demonstration of acid-fast bacilli by Ziehl Neelsen (ZN) staining is an inexpensive and widely available technique but it lacks sensitivity in extrapulmonary samples due to low bacilli load. Culture is considered to be the gold standard for diagnosis. Liquid culture systems like MGIT (mycobacteria growth indicator tube) are preferred over conventional culture (LJ media) techniques due to higher sensitivity and shorter turn-around time (6 weeks vs 8 weeks in LJ media). A positive culture also provides an ideal platform to perform susceptibility testing by first-line and second-line line probe assay (LPA). NAAT has been demonstrated to be a highly useful molecular test in EPTB as it has a very short turnaround time (2 hours) and it can be performed from almost all specimens collected. NAAT also provides valuable information on rifampicin resistance. Therefore, efforts must be made to obtain microbiological evidence of tuberculosis to confirm the diagnosis and to decide on the appropriate antitubercular drugs regimen.

11.2.Specimens For EPTB:

- **Pleural Tuberculosis:** Pleural fluid, pleural biopsy.
  1) **Pleural Fluid:** Pleural fluid is aspirated by pleurocentesis and should be transferred into

a sterile wide-mouth container and to be transported to the laboratory within 2 hours for microbiological analysis. At least 5ml of pleural fluid is to be sent. As individual sensitivity of all three testing modalities (ZN stain, NAAT and MGIT culture) is very less, efforts should be made to perform all three of them for better sensitivity.

2) **Pleural Biopsy:** Pleural biopsy with thoracoscopy is the diagnostic test of choice for pleural tuberculosis. Biopsy specimens can be collected by percutaneous, thoracoscopic or surgical thoracotomy approach. These samples should be sent to the laboratory in sterile normal saline within a sterile container for microbiological analysis.

- **Central Nervous System Tuberculosis:** Cerebrospinal fluid (CSF). At least 5-10ml of CSF should be collected for adults, 2-3ml for children, in a sterile container under aseptic precautions.

- **Gastrointestinal Tuberculosis:** Biopsy samples (USG or CT or colonoscopy guided), open biopsy.
- **Skeletal tuberculosis:** Guided biopsy (CT guided or C arm guided), open biopsy. They are the most preferred samples to access tissue for microbiological diagnosis. If the CT or C-arm guided biopsy is inconclusive, it may be followed by an open biopsy to obtain samples.

- **Cutaneous Tuberculosis:** Skin biopsy

- **Ocular Tuberculosis:**
  1) **Vitreous Humour/Aqueous Humour:** The diagnostic accuracy of various PCR-based tests is highly variable. However, they are often the only specific tests available that may identify ocular TB. Further evidence is needed to determine the selection of a specific test.
  2) **Intra-ocular Biopsy Specimen:** This is a highly invasive sampling technique and carries the risk of exacerbating visual loss. However, in rare cases, it may be the only way to clinch a diagnosis of ocular TB. If the culture is positive, first-line LPA must be done.

- **Otorhinolaryngologic Tuberculosis:**
  1. **Incisional Or Punch Biopsy**Preferred method for diagnosis of ENT lesions from the affected site.
  2. **Fine Needle Aspiration Cytology (FNAC):** Especially in case of lymph node involvement or abscess formation.

- **Hepatobiliary Tuberculosis:** For microbiological tests are obtained by biopsy techniques which include endoscopic USG-guided biopsy, CT/USG-guided percutaneous biopsy and surgical biopsy.

- **Urinary Tuberculosis:**
  1. Urine
  2. Cystourethroscopy with or without biopsy (may be considered).
  3. Urine collection routine microscopy and culture: Early morning mid-stream urine sample is the most preferred sample. Urine is to be collected in a sterile, leak-proof container and to be sent to the laboratory within four hours of collection. Morning urine sample (whole urine passed in the morning) to be collected in the glass bottle and transported to the laboratory within four hours of collection. Patients are instructed to avoid before retiring to bed on the previous night of the urine collection. The first morning, entire urine specimens to be collected in the sterile container. Three such urine samples to be sent to the laboratory for examination. Urine from a catheter bag, less than 40ml of

urine and 24 hours pooled urine specimens are unacceptable samples for mycobacterial analysis. Collected specimens should be transported to the laboratory without any delay. Refrigeration of the samples are required if it is not transported to the laboratory within 4 hours of collection. Freezing of the samples decreases the diagnostic yield.

- **Male Genital Tuberculosis:** For anyone suspected to have TB of any site a chest X ray to look for a primary focus and a HIV test is mandatory. In case of suspected Genital TB. A coexisting urinary tract TB should be investigated for as an abnormal urine Routine examination is seen in up to 90% cases. Urine samples sent for NAAT, direct microscopy and mycobacterial culture helps to rule out a coexisting urinary tract tuberculosis.
    1. **Expressed Prostatic Secretions (EPS) Or Post Massage Urine And Ejaculate:** EPS can be collected using either the standard four glass test or the modified 3 glass test that is proposed to have lesser contamination of urine samples with prostatic secretions. At least 3 but 5 or more samples should be collected and plated within 40 min of collection. But the search of Mycobacterium spp in semen or EPS samples by these methods is often futile even in diagnosed cases of genital TB. It may be incidentally positive in clinically asymptomatic men undergoing infertility analysis, pus from epididymal or prostatic abscess and discharge from penile lesion or perineal or scrotal sinuses.
    2. **FNAC/biopsy** from epididymis can be obtained under radiological guidance.

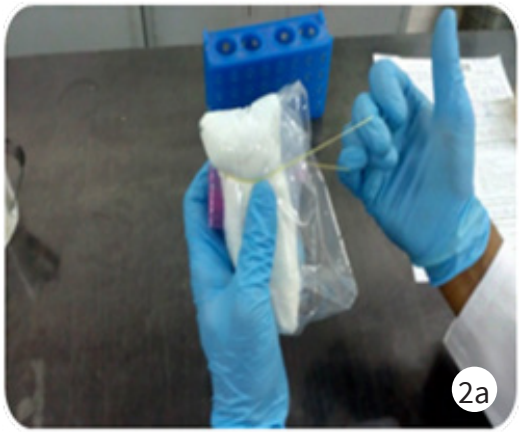
- **Female genital tuberculosis:**
    1. **Endometrial Aspirate:**
        - To be collected for all patients (preferably in the luteal phase of the menstrual cycle)
    2. **Endometrial Biopsy/Curettage:**
        - It may be considered in selected patients.
        - Menstrual blood is to be used in the case of unmarried women, though diagnostic results may be inferior.
    3. **Lymph Node Tuberculosis:**
        - Lymph node FNAC, Lymph node biopsy
        - cTBNA: Helpful in resource limited settings (EBUS not available).
        - EBUS-TBNA: Both the radiological characteristics of nodes and sampling can be done. Many mediastinal lymph nodes stations can be sampled. Right lower paratracheal and sub carinal lymph nodes can be sampled easily.

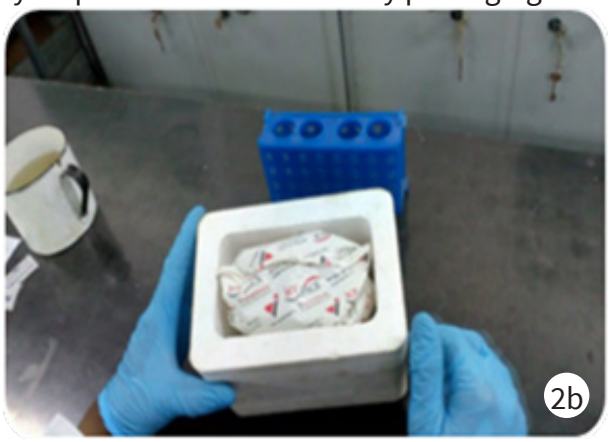
To diagnose EPTB two important steps need to be taken care (A) sample collection and transportation (B) appropriate test for diagnosis. A diagnostic algorithm as per NTEP guideline has been attached in annexure III.

A. EPTB sample collection and transportation: Extra Pulmonary specimens will need to be transported in cool boxes which maintain temperatures below 20oC for specimens to be compatible for solid, liquid culture systems as well as molecular methods. Maximum time for transportation in a cool chain should be 5 days from time of collection.Triple packaging system should be utilised for transportation. For further detail refer click to this link "Guidelines for Programmatic Management of Drug Resistant TB".

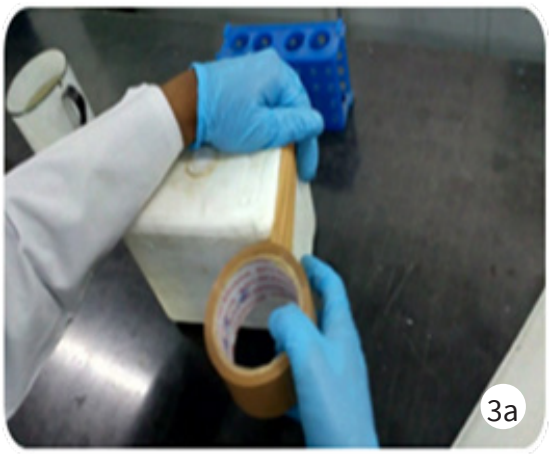
- The triple layer packaging contains the following:
Primary Container: A watertight, leak-proof, unbreakable tube containing the specimen. The tube is packaged with enough absorbent material to absorb all fluid in case of breakage or leakage.

Secondary Packaging. A watertight, leak-proof packaging to enclose and protect the primary container. Several primary containers may be placed in one secondary packaging





Outer Packaging. Secondary packaging is placed in rigid outer packaging to protect the contents from physical damage during transport. Gel packs to maintain temperature along with suitable absorbent/cushioning material is also placed inside.



11.4. Diagnostic tests for Microbiological Confirmation of EPTB:

11.4.1. Molecular (Genotypic) Testing: Nucleic acid amplification tests (NAATs) assays rely on the amplification of a targeted genetic region of the *Mycobacterium tuberculosis Mycobacterium tuberculosis* (M. tb) complex, typically by Polymerase Chain Reaction (PCR). Molecular tests can detect TB and resistance to key anti-TB drugs, such as rifampicin (R) and isoniazid (H), fluoroquinolones (FQ) and second-line injectable drugs (SLID) more quickly than Culture and Drug Susceptibility Tests (C&DST).

11.4.2. Rapid Molecular Tests:
Upfront NAAT is offered to all presumptive EPTB patients as per the NTEP programmatic guidelines. The following are the NTEP-approved NAAT tests:

11.4.1.a. CBNAAT MTB/RIF is a cartridge-based Nucleic Acid Amplification Test (NAAT) (CBNAAT) for the simultaneous detection of TB and Rifampicin Resistance (RRTB). It detects DNA sequences specific for the M. tb complex and mutations in the RNA polymerase related to drug resistance TB. Results are obtained from unprocessed sputum samples in 90 minutes, with minimal biohazard and minimal technical training required to operate.

11.4.1.b. TrueNat (Chip-based): TrueNat MTB and TrueNat MTB-Rif Dx are chip-based, micro real-time Polymerase Chain Reaction-based (PCR) NAAT for TB and rifampicin resistance detection, respectively. Resistance to rifampicin is detected by doing a second Reverse transcription polymerase chain reaction (RTPCR). For further detail, click on this link https://tbcindia.gov.in.

11.4.1.c. Line Probe Assay (LPA) uses PCR and reverse hybridisation methods to detect gene mutations associated with drug resistance. This is currently the only WHO and NTEP recommended rapid test to detect additional drug resistance in MDR-EPTB and XDR-EPTB patients. The First Line-LPA (FLLPA) detects M.tb and the presence of resistance to R and H. A second Line-LPA is available for testing for resistance to Levofloxacin (Lfx), Moxifloxacin (Mfx), Amikacin (Am), Capreomycin (Cm), and Kanamycin (Km).

11.4.2. Direct Microscopy:
- Ziehl-Neelsen (ZN) staining
- Fluorescent staining

Microscopy using ZN staining is a simple, cheap and quick valuable method for detecting acid-fast bacilli in smears prepared from various clinical samples. ZN staining is of limited diagnostic value (0-40%). It requires more than 10^5 to 10^6 bacteria/ml samples to detect acid-fast bacilli (AFB). Therefore, most of the EPTB samples are usually paucibacillary. Furthermore, ZN staining usually cannot differentiate non-tuberculous mycobacteria from Mycobacterium tuberculosis.

11.4.3. Culture: The culture of *M. tuberculosis* on the Lowenstein Jensen (LJ) medium has been replaced by automated liquid culture systems as the turnaround time is shorter and has a better yield than the LJ medium. The most preferred liquid culture system is MGIT (Mycobacteria Growth Indicator Tube) 960, which is an automated liquid culture system. MGIT 960 system provides higher sensitivity in terms of the growth of mycobacteria along with a shorter turnaround time. MGIT liquid culture system contains an oxygen quencher for detecting fluorescence inside the culture tubes. Whenever there is a growth inside the tube, microorganisms utilise the oxygen in the quencher, leading to fluorescence. MGIT liquid culture system can be used for culture and drug susceptibility testing for all extrapulmonary and pulmonary specimens. There is a considerable contamination rate in the MGIT tube cultures; thus,

an LJ culture is always performed in parallel as a backup.

Drug Susceptibility Test:

1. Phenotypic Drug susceptibility test (DST): DST on BACTEC MGIT 960 – an Automated Liquid Culture System. It can be used to test both the pulmonary & EP specimens for sensitivity to:
   - First-line drugs: Isoniazid (H); Rifampicin (R)and Pyrazinamide (z).
   - Second-line drugs: Levofloxacin (Lfx), Moxifloxacin (Mfx), Amikacin (Am), Capreomycin (Cm), Streptomycin (S), Kanamycin (Km), P-Aminosalicylic Acid (PAS)and Linezolid (Lzd).

2. Molecular (Genotypic) DST: Along with the diagnosis of TB/EPTB, both CBNAAT (one step, simultaneously) and TrueNat (second RTPCR) also detect rifampicin resistance.

11.5.1. Preservative Used For Transportation of Extra Pulmonary Specimens:

1. **Body Fluids:** (spinal, pleural, pericardial, synovial, ascitic, bone-marrow) should be aseptically collected in a sterile container by the physician using aspiration techniques or surgical procedures. Specimens should be transported to the laboratory as quickly as possible.
2. **Pleural Fluid:** Considered a suboptimal specimen as tubercle bacilli are mainly in the pleural wall and not within the fluid. The minimum volume for pleural fluid required for processing for culture is 20–50ml. The fluid is collected using pleural tap or thoracocentesis.
3. **Pericardial Fluid:** Should be collected using ultra sonogram.
4. **Blood:** As a specimen for isolating *M. tuberculosis* should be generally discouraged for the low diagnostic yield and high possibility of contamination with respect to the technique required for its culture. However, if there are specific indications when a physician suspects disseminated TB in a HIV infected patient, blood can be collected provided, the culture systems for recovery of mycobacteria is available in that laboratory (BacTAlert, MB Bact or MycolyticF medium on BACTEC 9050 systems).
5. **Tissues:** The aseptically collected tissues are placed by the physician in sterile containers preferably without fixatives or preservatives. If the specimen is to be shipped, it should be protected from drying by adding sterile saline or ideally in selective Kirchner's liquid medium and maintaining a temperature of 4- 15oC. Specimens should be transported to the laboratory as quickly as possible.
6. **Swabs:** Swabs are always sub optimal specimens and not recommended because of risk of infection for specimen collector. They may be useful in children and patients who cannot produce sputum or may swallow it. A sterile absorbent cotton swab should be used for collection. The best time for the collection is early morning before food and drinks are taken. The swab should be placed in a screw capped container containing normal (0.9%) saline to prevent drying. Swabs except for laryngeal swabs or from discharging sinus should be avoided.
7. **Urine:** Among specimens expected to be contaminated, urine is the most common. To minimize excessive contamination of urine specimens, special instructions for collecting urine with adequate cleansing of external genitalia to prevent contamination by commensals should be given. Early morning sample should be collected in 500ml screw capped sterile containers. Once received in the laboratory, urine must be immediately processed or centrifuged and the pellet refrigerated for further processing. As excretion of tubercle bacilli in urine is intermittent, three early morning specimens must be collected on different days.
8. **Bronchial Secretions:** Other respiratory specimens that can be submitted to the laboratory for mycobacteria culture are bronchial secretions (minimum volume: 2- 5ml) and bronchial alveolar lavage (BAL) (minimum volume of 20 – 50ml). Trans-bronchial and other biopsies should be collected under sterile conditions and placed in 0.5-1.0ml of sterile normal (0.9%) saline to

prevent drying during transportation to the laboratory.

9. **Gastric Lavage:** In children, who rarely produce sputum, the aspiration of the early morning (gastric content) may be used for TB diagnosis. This is done as an inpatient procedure. This should be transported immediately to the lab and processed (nor more than 4 hours) to prevent the killing action of the acid content in the gastric lavage on the tubercle bacilli. In the event of delay, the sample can be neutralised using 1-2ml of sterile 10 % sodium bicarbonate solution depending on the volume of gastric aspirate. Trisodium phosphate at a final concentration of 25% can be used but it may affect the viability of tubercle bacilli with prolonged storage.

Note:

- Samples for culture should never be collected in formalin.
- If histopathological examination is required, two samples should be collected.
- No preservative should be used for any extra-pulmonary specimen for culture. Necessary instructions are to be given to the concerned staff for sending the biopsy specimen in normal saline for culture and NOT IN FORMALIN as it will kill the bacilli.
- Extra pulmonary specimens should never be collected or transported in cetylpyridinium chloride (CPC).

Table 11.1. Type of Specimens, Volume Needed For Test And Storage

Sr. No	Sample Type Sample	Volume
1	Bronchoalveolar Lavage (BAL)	5-10ml
2	Pleural Fluid, Peritoneal Fluid	5-10ml
3	Cerebrospinal Fluid (CSF)	0.5ml
4	Pus, abscess	0.5ml
5	Lymphnode Aspirate	0.5ml
6	Tissue, Biopsy Samples	100mg approx

11.5.2. Transportation Of Extra Pulmonary Specimens:

As for pulmonary samples, extra pulmonary specimens will need to be transported in cold chain which maintain temperatures below 20°C for specimens to be compatible for solid, liquid culture systems as well as molecular methods. Triple packing system should be utilised for transportation. (https://tbcindia.gov.in/showfile.php?lid=3590).

When **sending out** specimens or when **receiving them**, check that:

- Request forms are located separately from the specimen containers.
- Containers are labelled not on the cap but on the wall of the container.
- Each transport box has an accompanying list which identifies the specimens and the patients; the information on the specimen containers should correspond to that on the accompanying list.
- Accompanying list contains the necessary data for each patient.
- Date of dispatch and particulars of the health centre are on the accompanying list.

11.5.3. Specimens And Request Forms:

All specimen transported to the laboratory must be accompanied by the request form for C & DST in hard and soft copy formats (See C & DST request form). For quality control reasons, the tests must be performed only upon written request of authorized persons and oral requests without follow up written instructions should not be entertained. It is also important that specimen request forms are kept separate from the specimens themselves. Forms that have been contaminated by specimens should be sterilized by autoclaving. If mistakes in filling request forms and labelling of specimens are found, reject specimens and do not register them. Document the arrival of specimens in the laboratory and note any delays in delivery in the remarks column of the specimen register and on the report form, particularly for negative/contaminated results. The packaging material should be decontaminated using autoclaved before discarding.

11.5.4. Steps And Precaution For Registration Of Sample:

11.5.4.1. Steps After Receiving Of Incoming Specimens:

For safety and work-flow reasons, a separate/dedicated area to be designated for sample collection and delivery boxes should be opened using all the applicable biosafety procedures inside the lab. To minimize risk of infection, the following procedures should be applied:

1. The specimen package received should be opened only in a biosafety cabinet which may be located in a small area within the reception or in the culture room.
2. Before opening the packet, inspect the delivery box for signs of leakage; if there is gross leakage evident, discard the box by autoclaving or burning; do not try to open and retrieve any specimen.

3. If on gross inspection there is no leakage, disinfect the outside of the delivery box using cotton wool or paper towels saturated with a suitable disinfectant (5% phenol).
4. Open carefully and check for cracked or broken specimen containers or leakage within the packaged container. If there is minimal leakage without any gross loss of specimen, they may be processed with an asterix that leakage was noted on receipt. (This will assist in identifying reasons for contamination used in lab performance indicators). In case of gross leakage, with only very little sample being available, accept the sample and process after carefully making a note of the same – as extrapulmonary specimens are precious and repeat collection may not be possible.
5. Check labelling of specimens with individual identification numbers and correspondence with numbers on the accompanying list or Clinical information forms (CIF) that are accompanying the specimens.
6. Disinfect the inside of the delivery box, wash hands after handling specimen containers.
7. Autoclave the packaging material before discarding.
8. Assign a unique lab serial number to each patient.
9. Evaluate the quality of specimens and make a note as to volume (in case of fluids), leakage, blood mixed, etc. Always register the incoming specimen in the laboratory register; each specimen receives a serial number that should be used to label every test for the specimen. Other data that should be reported on the laboratory register are: the date of the receipt of the specimen, patients name, age, sex and address, the name of the referring health centre, the reason for DST. The signature (with the name in capitals) of the person requesting the examination should always be present.

Fresh specimens must either be processed immediately as per sample procedure outlined in section on Sample processing protocol or stored frozen at -20° C. Frozen samples must be brought to room temperature before starting sample processing.

Note: Frozen specimens should not be subjected to more than 3 freeze/thaw cycles as this can lead to erroneous results.

Operational aspects of handling EPTB samples for diagnosis of TB:

- The integrated TB diagnostic and treatment algorithm (2021) PMDT - Central TB Division is designed to segregate patients based on NAAT results as RR detected or RR not detected and offer DST guided treatment. As soon as NAAT results are available, the report must be updated in Ni-kshay.
- For patients with NAAT result as MTB detected (irrespective of R status) the second specimen will by reflex be transported in cool chain from the NAAT facility to the C&DST laboratory. In rare circumstances, if the second specimen is used at the NAAT facility itself to repeat the test, a fresh specimen will be collected from the patient and transported in cool chain to the concerned C&DST laboratory.
- However, this will not always be possible for Extra Pulmonary TB specimens. All fluid EP samples can be processed in NAAT in the periphery. However, EP TB samples such as tissue biopsy and lymph nodes require homogenization, which is to be performed in a TB containment facility available at NRL, IRL, C& DST labs.
- High volume samples such as gastric aspirate/lavage may need to be concentrated by bio-safe centrifugation for obtaining valid results in laboratory tests including NAAT.
- Processing BAL, plural fluid and peritoneal fluid in Truenat requires bio-safe centrifugation which is available only at the laboratories with TB containment facilities but no attempt should be made

to perform aerosol generating procedures such as centrifugation and homogenization in the peripheral labs.

- Precious samples such as FNAC and CSF although can be processed at the peripheral NAAT, may be escalated to laboratories with TB containment facility (if volumes are very low) for testing by multiple methods.
- CSF must be processed as quickly as possible after collection; therefore, the laboratory must preferably be pre-intimated.
- Samples must not be collected in formalin EXCEPT for histopathology examination.

11.6. Decontamination Of Extrapulmonary TB Samples

Most of the extra pulmonary specimens are paucibacillary in nature. Hence, they require milder decontamination.

11.6.1. Sample Processing Procedure:

Sample Processing For NAAT
The NAAT can be used directly for CSF specimens and homogenised extra-pulmonary samples (lymph node biopsies and other tissues) or on decontaminated specimens if culture is performed concurrently. Whenever possible, specimens should be transported and stored at 2 to 8°C prior to processing.

11.6.1.A Lymph Nodes And Other Tissues Processing For (NAAT Only):

1. Cut the tissue sample into small pieces in a sterile mortar (or homogenizer/tissue grinder) using a clean, sterile pair of forceps and scissors.
2. Add approximately 2ml of sterile phosphate buffer (PBS).
3. Grind tissue/PBS-solution with a mortar and pestle (or homogenizer/tissue grinder) until a homogeneous suspension is obtained.
4. Transfer approximately 0.7ml of homogenized tissue sample to a sterile conical, screw-capped tube using a transfer pipette.
   Note: Avoid transferring any clumps of tissue which have not been properly homogenized.
5. Add a double volume of NAAT Sample Reagent (1.4ml) to 0.7ml of homogenized tissue using a transfer pipette.
6. Vigorously shake 10 to 20 times or vortex for at least 10 seconds.
7. Incubate for 10 minutes at room temperature, and again shake the specimen vigorously 10 to 20 times or vortex for at least 10 seconds.
8. Incubate the sample at room temperature for an additional 5 minutes.
9. Using a fresh transfer pipette, transfer 2ml of the processed sample to the NAAT
10. Load the cartridge into the NAAT instrument as per manufacturer's instructions.

11.6.1.B. 11.6.1.B. Lymph Nodes And Other Tissues (Non-Sterile Collections –NAAT And Culture):

1. Cut the tissue sample into small pieces in a sterile mortar (or homogenizer/tissue grinder) using a clean, sterile pair of forceps and scissors.
2. Add approximately 2ml of sterile phosphate buffer (PBS)
3. Grind tissue/PBS-solution with a mortar and pestle (or homogenizer/tissue grinder) until a homogeneous suspension is obtained.
4. Use a sterile transfer pipette to add the suspension into a 50ml conical tube.
5. Add an equal volume of 4% NaOH and tighten the screw-cap.
6. Vortex thoroughly to homogenise the suspension.
7. Stand for 15 minutes at room temperature.

8. Fill the tube to within 2 cm of the top (e.g., to the 50ml mark on the tube) with PBS.
9. Centrifuge at 3000g for 15 minutes.
10. Carefully pour off the supernatant through a funnel into a discard can containing 5% phenol or other mycobacterial disinfectant.
11. Re-suspend the deposit in approximately 1-2ml PBS.
12. Use another sterile transfer pipette to inoculate deposit into liquid media and/or onto two slopes of egg-based medium labelled with the sample ID number.
13. Label a NAAT cartridge with the sample ID.
14. Using a transfer pipette, transfer approximately 0.7ml of homogenized tissue sample to a conical, screw-capped tube for the NAAT.
    Note: Avoid transferring any clumps of tissue which have not been properly homogenized.
15. Using another transfer pipette, add a double volume of NAAT Sample Reagent (1.4ml) to 0.7ml of homogenized tissue.
16. Vigorously shake 10 to 20 times or vortex for at least 10 seconds.
17. Incubate for 10 minutes at room temperature, and again shake the specimen vigorously 10 to 20 times or vortex for at least 10 seconds.
18. Incubate the sample at room temperature for an additional 5 minutes.
19. Using a fresh transfer pipette, transfer 2ml of the processed sample to the NAAT
20. Load the cartridge into the GeneXpert instrument as per manufacturer's instructions.

11.6.1.C. Lymph Nodes And Other Tissues (Sterile Collection –NAAT And Culture):

1. Cut the tissue sample into small pieces in a sterile mortar (or homogenizer/tissue grinder) using a clean, sterile pair of forceps and scissors.
2. Add approximately 2ml of sterile phosphate buffer (PBS).
3. Grind tissue/PBS-solution with a mortar and pestle (or homogenizer/tissue grinder) until a homogeneous suspension is obtained and adjust to a final volume of approximately 2ml with PBS.
4. Transfer the suspension with a sterile transfer pipette to a 50ml conical tube.
5. Use another transfer pipette to inoculate suspension into liquid media and/or onto two slopes of egg-based medium labelled with the sample ID number.
6. Label an NAAT cartridge with the sample ID.
7. Transfer approximately 0.7ml of homogenized tissue sample to a conical, screw-capped tube for the NAAT using a transfer pipette.
   Note: Avoid transferring any clumps of tissue which have not been properly homogenized.
8. Transfer a double volume of NAAT Sample Reagent (1.4ml) to 0.7ml of homogenized tissue using a transfer pipette.
9. Vigorously shake 10 to 20 times or vortex for at least 10 seconds.
10. Incubate for 10 minutes at room temperature, and again shake the specimen vigorously 10 to 20 times or vortex for at least 10 seconds.
11. Incubate the sample at room temperature for an additional 5 minutes.
12. Using a fresh transfer pipette, transfer 2ml of the processed sample to the NAAT
13. Load the cartridge into the NAAT instrument as per manufacturer's instructions.

11.6.2. CSF:

The preferred processing method for CSF in Xpert MTB/RIF depends on the volume of sample available for testing.

Note: Blood stained and xanthochromic CSF samples may cause false negative Xpert MTB/RIF results.

1. Transfer all of the sample to a conical centrifuge tube and concentrate sample at 3000g for 15 minutes.
2. Carefully pour off the supernatant through a funnel into a discard can containing 5% phenol or other mycobacterial disinfectant.
   Note: Decanting concentrated CSF should be performed within a BSC.
3. Re-suspend the deposit to a final volume of 2ml with NAAT sample reagent.
4. Label an NAAT cartridge with the sample ID.
5. Using a fresh transfer pipette, transfer 2ml of the concentrated CSF sample to the NAAT cartridge.
6. Load the cartridge into the NAAT instrument as per manufacturer's instructions.

1-5ml Of CSF (Including Blood-Stained Or Xanthochromic Samples)

1. Add an equal volume of the CSF to the sample reagent.
2. Add 2ml of the sample mixture directly to the NAAT.
3. Load the cartridge into the NAAT instrument as per manufacturer's instructions.

0.1-1ml Of CSF

1. Re-suspend the CSF to a final volume of 2ml with NAAT sample reagent.
2. Add 2ml of the sample mixture directly to the NAAT cartridge.
3. Load the cartridge into the NAAT instrument as per manufacturer's instructions.

11.7.1. Sample Processing And Testing By Truenat Testing:

Truenat™ MTB requires purified nucleic acids from pulmonary and EPTB specimen that are extracted using the Trueprep AUTO Universal Cartridge Based Sample,Prep Device and Trueprep AUTO Universal Cartridge Based Sample Prep Kit, Samples must be liquefied and pre-treated using the Trueprep AUTO MTB sample Pre-treatment pack provided, as per protocol below, before proceeding for extraction.

For non- sputum samples:

11.7.1.A. Protocol For BAL, Pleural Fluid, Peritoneal Fluid:

1. Take appropriate volume (Refer Table 11.1.) of the sample in a tube.
2. Spin at 4000x g for 5 minutes.
3. Discard the supernatant until 500µl remains at the bottom and then add 2 drops of Liquefaction buffer to the sample.
4. Transfer all the entire contents to Lysis Buffer tube from Trueprep AUTO MTB Sample Pre-treatment pack and leave it for 5 minutes.

11.7.1.B. Protocol For Pus, Abscess, Lymph Node Aspirate And CSF:

1. Take the appropriate volume (Refer Table 11.1) of the sample in a tube.
2. Add 2 drops of Liquefaction buffer to the sample.
3. Transfer all the contents to Lysis Buffer tube from Trueprep AUTO MTB Sample Pre-treatment pack and leave it for 5 minutes.

11.7.1.C. Protocol For Tissue/Biopsy Samples:

1. Tissue samples must first be homogenized by using 100µl Lysis Buffer using micro pestle.
2. Collect homogenized sample and add 2 drops of Liquefaction buffer.
3. Transfer liquefied sample to Lysis buffer tube from Trueprep AUTO MTB Sample Pre-treatment pack and leave it for 5 minutes.

Note: If un-dissolved tissue remains, transfer only the clear fluid to Cartridge ® provided in the Trueprep AUTO Universal Cartridge Based Sample Prep Kit.

Sample Storage And Transportation: Sample Pre-treatment decontaminates the specimen and makes it ready for extraction. Sample in this form is stable for 3 days at up to 40°C and 1 week at 30°C .

Nucleic acid extraction: Follow Extraction procedure (Section-13) of Trueprep AUTO Universal Cartridge Based Sample Prep Kit package insert(Refer to the User Manual of Trueprep AUTO Universal Cartridge Based and Sample Prep Device and the package insert of Trueprep AUTO Universal Cartridge Based Sample Prep Kit for details). Dispose off the lysis buffer tube, and transfer pipette after use, as per the section on **"Disposal and Destruction"**.

11.8. Culture By Solid Culture Methods

When using solid culture for primary isolation of tubercle bacilli from these specimens, it is preferable to use multiple media including one liquid medium made selective by the use of specific antibiotics that inhibit the growth of other microorganisms.

Standard Operating Procedures for MGIT 960 may be followed to process for culture and DST (MGIT Manual 2006). Culture is the preferred method in NTEP for both culture and DST.

The media include, LJ, LJ with sodium pyruvate (LJ–P) and selective liquid Kirchner's medium (SK). Sodium pyruvate facilitates the growth of M. bovis. Antibiotics incorporated in the liquid medium include polymixinB, amphotericin B, carbenicillin and trimethoprim (PACT) and vancomycin.

11.8.1. Preparation Of Solid media:

11.8.1.a. Lowenstein-Jensen Medium With Sodium Pyruvate:

Lowenstein-Jensen (LJ) medium is enriched with 0.5% sodium pyruvate. In the preparation of the mineral salt solution, glycerol is omitted and 8.0g sodium pyruvate is added for every 600ml. This is added to 1 litre of egg fluid, mixed well and distributed.

SELECTIVE KIRCHNER'S MEDIUM (For culture of extra-pulmonary specimens)

Disodium hydrogen phosphate, Na2HPO4.12H2O, A.R.	19.0 g (7.5g of anhydrous salt)
Potassium dihydrogen phosphate, KH2PO4, A.R.	2.0 g
Magnesium sulphate, MgSO4.7H2O, A.R.	0.6 g
Sodium citrate	2.5 g
L-asparagine	5.0 g
Casein hydrolysate (Bactocasitone)	0.5 g
Glycerol	20.0ml
Phenol Red, 0.4% solution	3.0ml
Distilled water, to	1 litre
Check pH to	6.9 – 7.2

Autoclave at 15 lbs/15 minutes Then add aseptically the following:

Polymyxin B (20,000 units)	31mg
Carbenicillin	100mg
Trimethoprim	10mg
Amphotericin B, solubilised	10mg

Dissolve the above in 5ml sterile distilled water before addition
Also, add sterile calf serum 100ml

Mix the above carefully and distribute, under sterile conditions, in 10ml amounts. Check sterility by overnight incubation at 37°C and store in cold chain.

11.8.1.a. Processing Of CSF And Pericardial Fluid Smear:

1. Label a clean dry slide with the lab number and place the slide and the sample container inside the cabinet.
2. Mix well and aseptically remove one loopful of the fluid and place in the centre of the slide; close the container and allow the drop to air-dry.
3. Place one more drop of the CSF on the same spot and let dry.
4. Place the third drop after processing the sample as below:

Culture of CSF is done in two steps:

1. Direct inoculation in media.
2. Inoculation after decontamination.

Direct

1. Place one loopful of CSF on to one slope each of LJ and LJ-P.
2. Add 0.2ml of CSF in to one bottle containing SK medium.
3. Label the set as 'A'.

Decontamination

1. Add 1ml of 5% H_2SO_4 to CSF.
2. Mix well and let stand for 15 minutes.
3. Fill the container with sterile distilled water and centrifuge at 3000xg for 15 minutes.
4. Aspirate the supernatant carefully without disturbing the deposit or discard carefully in to a disinfectant bin containing 5% phenol or any other mycobactericidal solution.
5. Inoculate one slope each of LJ and LJ-P with one loopful of deposit for each slope.
6. Transfer the remaining deposit in to one bottle of SK.
7. Label the set as 'B' 8. Incubate both set A and B at 37°C.

11.8.1.b. Processing Of Bronchial Alveolar Lavage (BAL) For Culture:

1. Make a direct smear.
2. Process using 5% H_2SO_4 as in CSF.
3. Inoculate two slopes each of LJ and LJ-P with one loopful of deposit using 5mm twisted wire loop.
4. Transfer the remaining deposit in to one bottle of SK.
5. Incubate the slopes and SK medium at 37°C

11.8.1.c. Processing Of Gastric Lavage For Culture:

1. Gastric Lavage should be processed immediately upon arrival in the lab to prevent the killing action of the gastric pH (due to HCl) on the tubercle bacilli.
2. Make a direct smear and process by modified Petroff's method.
3. Place one drop of the final pellet on the direct smear.
4. Inoculate two slopes each of LJ and LJ-P with one loopful of deposit for each slope.
5. Transfer the remaining deposit in to one bottle of SK.
6. Incubate the slopes and SK medium at 37°C.

11.8.1.d. Processing Of Tissue /Biopsy For Culture

1. Ideally, biopsy specimens should be collected and transported in SK medium.
2. Carefully place the tissue inside a sterile petriplate inside the BSC.
3. Using sterile scissors and forceps, cut the tissue in to tiny pieces.
4. Transfer to a sterile tissue grinding tube – add a little water to the petriplate to facilitate transferring.
5. Add sterile distilled water to the tube (not more than 5ml).
6. Homogenise using a sterile Teflon grinding rod using a foot operated tissue grinder.
7. Make a direct smear from the homogenate.
8. Centrifuge the homogenate at 3000xg for 15 minutes.
9. Decant the supernatant carefully in to the disinfectant bath.
10. To the deposit add 1ml of sterile distilled water.
11. Add one drop to the direct smear, air dry, fix and stain.
12. To the remaining pellet, add 1ml of 5% H_2SO_4.
13. Proceed as for CSF.
14. Inoculate two slopes each of LJ and LJ-P with one loopful of deposit for each slope.
15. Transfer the remaining deposit in to one bottle of SK.
16. Incubate the slopes and SK medium at 37°C, along with the SK medium used for transporting.

11.8.1.e. Processing Of Fine Needle Biopsy Specimen For Culture:

1. Fine needle specimens should be collected and transported only in SK medium or any other liquid medium.
2. The medium is incubated as such at 37°C, since only a very tiny piece of the tissue is obtained as Sample If the sample is received without SK.
1. Add the contents of two SK medium bottles to the specimen.
2. Shake vigorously and let stand for 10 minutes.
3. Divide the medium in to two aliquots and incubate both at 37°C

11.8.1.f. Processing of Pus for Culture

1. Make a direct smear, air dry, fix and stain.
2. If the pus is thick or purulent, process by modified Petroff's method using 4% NaOH.
3. Inoculate two slopes each of LJ and LJ-P with one loopful of deposit for each slope.
4. Transfer the remaining deposit in to one bottle of SK.
5. Incubate the slopes and SK medium at 37°C.
6. If the pus is thin or dilute, proceed with decontamination using 5% H_2SO_4.
7. Inoculate two slopes each of LJ and LJ-P with one loopful of deposit for each slope.
8. Transfer the remaining deposit in to one bottle of SK.

11.8.1.g. Processing Of Urine /Ascitic Fluid For Culture:

1. Distribute the entire specimen in to 20 or 40ml volumes in Universal containers /Falcon tubes inside a BSC
2. Centrifuge at 3000 x g for 15 minutes.

Process The Supernatant And Deposit Independently As Follows:

Supernatant:

3. Aspirate carefully 1ml of the top layer from each tube and pool.
4. Process by 5% H_2SO_4 as for CSF.

5. Transfer 1ml of the final supernatant on to two bottles of SK each – Label the set as DSS (Decontaminated Supernatant Supernatant).
6. Decant the supernatant carefully in to the disinfectant bath.
7. From the deposit transfer about 0.2ml and the remaining in to 2 bottles of SK respectively – Label as DSD (Decontaminated Supernatant Deposit) Deposit:
8. Pool all the deposit in to one tube.
9. Process using 5% H_2SO_4 as for CSF.
10. Inoculate two slopes each of LJ and LJ-P with one loopful of deposit for each slope.
11. Transfer the remaining deposit in to one bottle of SK.

11.8.1.h. Processing Of Swabs:

If two swabs are available, use one for smear and one for culture; if only one is available do only culture.

1. Immerse the swab in 5ml of 4% H_2SO_4 for 1 minute.
2. Transfer the swab to another tube containing 5ml of 4% NaOH.
3. Directly inoculate two slopes each of LJ, LJ-P.
4. Transfer the swab finally to a tube containing SK medium.
5. Incubate all tubes at 37°C.

Culture Reading

1. Read all cultures used for isolating *M. tuberculosis* from extrapulmonary specimens every week for up to 8 weeks using the same methodology used for pulmonary samples.
2. If the solid media show typical growth report immediately after confirmation.
3. Read SK medium up to 6 weeks.
4. MTB appears as whitish granular or flaky growth that settles down at the bottom.
5. If the SK medium shows growth or contamination (in the form of turbidity) within 6 weeks, decontaminate as sputum by modified Petroff's method and inoculate deposit on LJ medium alone and read up to 8 weeks.
6. Even if the SK medium shows no growth within 6 weeks, proceed with decontamination using modified Petroff's method and inoculate deposit on LJ medium alone and read up to 8 weeks.
7. If LJ shows typical MTB growth within 8 weeks, report immediately after confirmation.
8. Report as negative only after LJ completes 8 weeks (a total of 14 weeks).

11.8.2. Processing Of Extra Pulmonary Samples For MGIT960:

Isolation of *M. tuberculosis* by MGIT system requires the final inoculum to be in an ideal condition that will not interfere with the fluorescence.

11.8.2.a. Pus And Other Muco-Purulent Specimens:

1. Thick pus of volume >10ml is decontaminated using the NALC-NaOH method as sputum
2. If the volume is < 10ml, either aliquot and process only 10ml by NALC-NaOH method or concentrate the initial volume by centrifugation for 15-20 minutes and resuspend the pellet in 5ml of sterile distilled water. If the pus is too thick, add about 50-100mg of NALC powder; mix well and decontaminate using NaOH. Resuspend the final pellet in buffer to reduce the pH
3. If the pus is not thick, decontaminate using 2-4% NaOH. The concentration of NaOH can be changed based on the expected level of contamination in the specimen which depends on the site of collection.

11.8.2.b. Gastric Aspirates:

1. Distribute the volume in smaller aliquots and centrifuge the tubes at 3000xg.

2. Pool the deposits, add 5ml distilled water and decontaminate it using NALC-NaOH or 2-4% NaOH.

11.8.2.c. Bronchial Washings:

1. Process using NALC-NaOH like sputum.
2. If the specimen is >10ml in volume, process the whole specimen.

11.8.2.d. Laryngeal Swabs:

1. Transfer the swab into a sterile centrifuge tube and add 2ml sterile water.
2. Add 2ml of NaOH-NALC solution and mix well in a vortex mixer.
3. Let stand for 15 minutes. Remove the swab with forceps, squeezing the liquid out of the swab and discarding it.
4. Fill the tube with phosphate buffer and mix.
5. Centrifuge at 3000xg for 15-20 minutes.
6. Discard the supernatant fluid and resuspend the sediment in 1-2ml sterile buffer. Use this suspension for smear and culture.

11.8.2.e. Tissue:

1. Homogenize the tissue in a tissue grinder with a small quantity of sterile saline or water (2-4ml).
2. Decontaminate the homogenized specimen using NALC-NaOH procedure as in sputum.
3. Resuspend the sediment with phosphate buffer.
4. If the tissue grinder is not available, use a mortar and pestle.
5. Tissue may also be placed in a Petri dish with sterile water (2-4ml) and be torn apart with the help of two sterile needles.

11.8.2.f. Urine Isolation of mycobacteria from urine specimens using MGIT has not been validated:

1. Aliquot the entire volume in several centrifuge tubes.
2. Concentrate the specimen by centrifugation for at least 20-25 minutes.
3. Resuspend the pellet in each tube with 1-2ml of sterile water and pool together/
4. Decontaminate using 4% NaOH as for sputum.

11.8.2.g. Other Body Fluids (CSF, Synovial Fluid And Pleural Fluid) As These Fluids Are Collected Usually Under Aseptic Conditions, They Require Only Milder Decontamination:

1. If the specimen volume is more than 10ml, concentrate by centrifugation at about 3000x g for 15-20 minutes
2. Liquefy thick or mucoid specimens prior to centrifugation by adding NALC powder (50-100).
3. Resuspend the sediment in about 5ml of saline.
4. Mix and decontaminate as for sputum.

- Blood Isolation of mycobacteria from blood specimens by MGIT 960 has not been evaluated thoroughly.

Table 11.2. Sensitivity and specificity of microbiological tests in extrapulmonary TB specimens

Extrapulmonary Samples	ZN Staining		Culture (MGIT/LJ)	NAAT	
	Sensitivity	Specificity	Sensitivity	Sensitivity	Specificity
Cerebrospinal fluid	12.5%-69%		25-70%	71%	97%
Lymph node	~50%	>90%		82%	96%
Pleural fluid	Very low		12-30%	50%	99%
Synovial fluid				97%	64%
Bone biopsy	25-75%	99%	50-55%	92-95%	95-98%
Liver biopsy	0-45%		0-43%	88%	100%
Intestinal biopsy	2.7-37.5%		~50%	32%	100%
Urine	very low		10.7-80%	87%	91%

Table.11.3. Comparison between the sensitivity and specificity of NAAT in extrapulmonary TB

Extrapulmonary Samples	NAAT		NAAT (Xpert Ultra)		Rifampicin resistance	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Cerebrospinal fluid	71%	97%	89%	91%	97%-100%	99%-100%
Lymph node	82%	96%	70%	100%		
Pleural fluid	50%	99%	75 %	87%		

References:

1. Kohli M, Schiller I, Dendukuri N, Yao M, Dheda K, Denkinger CM, Schumacher SG, Steingart KR. Xpert MTB/RIF Ultra and Xpert MTB/RIF assays for extrapulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database of Systematic Reviews 2021, Issue 1.

2. Purohit M, Mustafa T. Laboratory Diagnosis of Extra-pulmonary Tuberculosis (EPTB) in Resource-constrained Setting: State of the Art, Challenges and the Need. J Clin Diagn Res.2015 Apr;9(4):EE01-6.

3. Singhal R, Myneedu VP. Microscopy as a diagnostic tool in pulmonary tuberculosis.International Journal of Mycobacteriology. 2015 Mar;4(1):1-6.

4. Gerardo Alvarez-Uria, Jose M. Azcona, Manoranjan Midde, Praveen K. Naik, Srinivasulu Reddy, Raghuprakash Reddy, "Rapid Diagnosis of Pulmonary and Extrapulmonary Tuberculosis in HIV-Infected Patients. Comparison of LED Fluorescent Microscopy and the GeneXpert MTB/RIF Assay in a District Hospital in India", Tuberculosis Research and Treatment, vol. 2012, Article ID 932862, 4 pages, 2012.

5. Lee JY. Diagnosis and treatment of extrapulmonary tuberculosis. Tuberculosis and

6. Respiratory Diseases. 2015 Apr;78(2):47-55.

7. Gopalaswamy R, Dusthackeer VNA, Kannayan S, Subbian S. ExtrapulmonaryTuberculosis—An Update on the Diagnosis, Treatment and Drug Resistance. Journal of Respiration. 2021; 1(2):141-164.

8. Molecular assays intended as initial tests for the diagnosis of pulmonary and extrapulmonary TB and rifampicin resistance in adults and children: rapid communication. Policy update.Geneva: World Health Organization; 2020.

9. Altez-Fernandez, C., Ortiz, V., Mirzazadeh, M. et al. Diagnostic accuracy of nucleic acid amplification tests (NAATs) in urine for genitourinary tuberculosis: a systematic review and meta-analysis. BMC Infect Dis 17, 390 (2017).

12. Treatment Of Drug-Susceptible extrapulmonary Tuberculosis

12.1. Introduction

Commonly the treatment of extra-pulmonary tuberculosis is with the combination therapy of first line agents active against the *Mycobacterium tuberculosis*, but mainly differs from the pulmonary tuberculosis in terms of duration of therapy required for different sites of EPTB.

Table 1: Treatment duration of medical therapy in extrapulmonary Tuberculosis.

Site of Disease	Initial Regimen (IP + CP)	Duration
Ocular TB	(2)HRZE + (4-7)HRE	6-9 Months
CNS TB	(2)HRZ+E/S + (10)HRE	6-12 Months
Tuberculous Otitis Media	(2)HRZE + (7)HRE	9 Months
Ear, Nose and Throat TB (Others)	(2)HRZE + (4-7)HRE	6-9 Months
Lymph node TB	(2)HRZE + (4-7)HRE	6-9 Months
Pleural TB	(2)HRZE + (4)HRE	6 Months
Pericardial TB	(2)HRZE + (4)HRE	6 Months
*Hepatobiliary TB	(2)HRZE+(4-7)HRE	6-9 Months
Intestinal TB	(2)HRZE + (4)HRE	6 Months
Urinary TB	(2)HRZE + (4)HRE	6 Months
Genital TB (Male or Female)	(2)HRZE + (4)HRE	6 Months
Spinal TB	(2)HRZE + (10-16)HRE	12-18 Months
Bone and Joint TB (others)	(2)HRZE + (10)HRE	12 Months
Cutaneous TB	(2)HRZE + (4)HRE	6 Months

H – Isoniazid, R – Rifampicin, Z – Pyrazinamide, E – Ethambutol, S – Streptomycin, Amikacin
*Treatment may be modified according to stage of Liver Disease. Refer below

12.2.Treatment Of Drug Susceptible EPTB

Treatment consists of combination therapy starting with 4 first line agents - Rifampicin (R), Isoniazid (H), Pyrazinamide (Z) and Ethambutol (E). Anti-Tubercular therapy should be administered as a daily regimen of fixed dose combination of these drugs based on the weight band.

Table 12.2. Weight bands for FDC in adults

Weight Band (Kg)	No. of FDC tablets	
	#IP – 4FDC (HRZE) 75/150/400/275 (mg)	CP – 3FDC (HRE) 75/150/275 (mg)
25 – 34	2	2
35 – 49	3	3
50 – 64	4	4
65 – 75	5	5
>75*	6	6

*can be given 5 tablets/day if they do not tolerate the revised doses.
#FDC: Fixed Dose Combination tablets containing 3(3FDC) or 4(4FDC) drug combination

If anytime during the treatment, the patient gains or loses 5 kg or more of weight and crosses the weight band, the dosage should be changed accordingly.

12.3. Drugs For First-Line Therapy

12.3.A. Rifampin: Is a semisynthetic compound, derived from Rifamycin. It inhibits DNA dependent RNA polymerase and has bactericidal action. It has a sterilizing effect on both intracellular and extracellular organisms. It is rapidly absorbed from the gut and distributed throughout the cellular tissues. It undergoes significant entero-hepatic circulation before being metabolised by deacetylation in the liver. Resistance develops rapidly if used as monotherapy. Rifampicin should be preferably taken in an empty stomach as food decreases absorption however intolerability is reduced if taken with food.

Contraindication: Similar to Isoniazid, hypersensitivity and active hepatitis are the contraindications for Rifampicin use.

Precautions: Anaemia, thrombocytopenia and renal dysfunction may occur as part of immunological response to Rifampicin, especially if Rifampicin is restarted after a prolonged lapse. In such situations drugs should be withdrawn and never re-challenged. Patients with pre-existing liver dysfunction should be closely monitored. Patients should be warned about reddish/orange discolouration of body fluids (urine, etc.) due to the drug. It is safe for use during pregnancy. Vitamin K should be given to infants born to mothers taking Rifampicin as it increases the chances of postnatal haemorrhage.

Adverse Effects: Abdominal pain, nausea and vomiting are the most commonly documented adverse effects. Pruritus with or without rash is also documented. Exfoliative dermatitis is particularly seen in patients with HIV co-infection. Mild to moderate rise in transaminases and bilirubin is common and does not require intervention. Dose related hepatotoxicity usually with doses exceeding 600mg/day is a life threatening event and the drug should be promptly discontinued.

Drug Interaction: Rifampicin being an enzyme inducer decreases serum concentration of drugs metabolised in the liver, warranting higher doses of such drugs.

12.3.B. Isoniazid: Isoniazid is a bactericidal agent affecting rapidly dividing tubercular bacilli. It acts by inhibiting mycolic acid synthesis, a cell wall component of Mycobacteria. It is a pro-drug activated inside tubercular bacilli by the bacterial KatG enzyme. It is rapidly absorbed and distributed in all tissues. Half-life of Isoniazid is dependent on whether the patient is a fast acetylator or slow one.

Known hypersensitivity and active hepatitis are the contraindications for use of Isoniazid.

Precautions: Patients with pre-existing liver disease should be closely monitored clinically and with liver function tests. Patients should be supplemented with pyridoxine 10mg daily while receiving Isoniazid for prevention of peripheral neuropathy. For treatment of established neuropathy, the dose should be 50mg to 75mg per day.

Adverse Effects: Generally, well tolerated at the recommended doses. Occasionally cutaneous and systemic hypersensitivity occurs during the first week of therapy. Peripheral neuropathy rarely occurs while on pyridoxine supplements. Other neurological manifestations include optic neuritis, toxic psychosis and seizures, which manifest in the latter part of treatment. Symptomatic hepatitis is a serious adverse event which usually promptly resolves on stopping Isoniazid. Mild asymptomatic rise in hepatic enzymes are commonly observed, which subside spontaneously and do not need discontinuation of treatment. Isoniazid is not shown to be toxic in pregnancy. Drug induced lupus, pellagra, anaemia and arthralgia are other less common adverse effects of Isoniazid.

Drug Interaction: Isoniazid is an enzyme inhibitor with significant drug-drug interactions.

12.3.C. Pyrazinamide: Pyrazinamide is a synthetic analogue of nicotinamide with weak bactericidal action on Mycobacterium tuberculosis. Exact mechanism of action is not known. it may inhibit fatty acid synthetase I enzyme of *M. tuberculosis*. It has a sterilizing effect on bacteria in acidic environments inside macrophages and in areas of acute inflammation, so mostly useful during intensive phase of therapy. Oral absorption is good with rapid penetration into all tissues. It is metabolised in the liver and metabolites are excreted in urine.

Contraindication: Pyrazinamide is contraindicated in patients with active hepatitis, porphyria and in those with known hypersensitivity.

Precautions: Pyrazinamide causes fluctuations in blood glucose concentrations, diabetics should be closely monitored. Arthralgia is a common side effect with elevated uric acid levels. May worsen or precipitate gouty arthritis. Pyrazinamide should be discontinued if arthritis does not respond to management with NSAIDs.
Pyrazinamide is generally considered safe during pregnancy.

Adverse Effects: Gastrointestinal intolerance is common. Mild elevation in transaminases is a usual finding. Serious hepatotoxicity is rare. Sideroblastic anemia and photosensitive dermatitis are rare side effects.

12.3.D. Ethambutol: Ethambutol is a congener of 1, 2 ethane diamine and has bacteriostatic action against Mycobacterium tuberculosis. It is also effective against non-tuberculous mycobacteria. Though the mechanism of action is not clearly understood, it is believed to act by inhibiting arabinosyl transferase enzymes. It is rapidly absorbed from the gastrointestinal tract. It is partly metabolised by the liver and some parts are excreted unchanged in urine.

Contraindication: Ethambutol is contra-indicated in patients with known hypersensitivity and optic neuritis of any cause. Dose modification is required in renal impairment.

Precautions: It should be discontinued at the earliest symptom of impaired vision or deranged

perception of colours. Ocular examination is advised before starting and during treatment with ethambutol. Dose modification is required in case of renal dysfunction.
*Ethambutol is considered safe in pregnancy.

Adverse effects: Dose dependent optic neuritis may diminish visual acuity and impair colour vision. Early changes of visual impairment are reversible. Signs of peripheral neuritis may manifest in legs. Arthralgia, cutaneous rash and hepatotoxicity are rare adverse effects.

12.4. Special Population

12.4.1. Patients With Chronic Kidney Disease:

Many patients with Chronic Kidney Disease (CKD) may need to be initiated on anti-tubercular therapy (ATT), in such cases, care should be taken while giving aminoglycoside drugs. Reduced creatinine clearance can lead to accumulation of some drugs leading to toxicity. Some of the drugs may be filtered out during hemodialysis causing decreased serum concentrations and under dosing.

Table 3. Recommended dose for patients with CKD

Drug*	Recommended dose in patients with creatinine clearance <30ml/min
Rifampicin	No adjustment in dose required
Isoniazid	No adjustment in dose required
Pyrazinamide	Recommended dose given three times per week (NOT DAILY)
Ethambutol	Recommended dose given three times per week (NOT DAILY)
Streptomycin	12-15 mg/kg per dose two or three times per week (NOT DAILY)

* Administer the drugs after the dialysis session on the day of haemodialysis.

12.4.2. Patients With Chronic Liver Disease:

Patients with a past history of acute hepatitis or jaundice do not require changes to standard first-line treatment. In patients with co-existent acute hepatitis and a non-life-threatening EPTB, ATT can be deferred until liver function tests normalize. If EPTB is life threatening, e.g., CNS-TB, select an ATT regimen containing least hepatotoxic drugs.

The number of hepatotoxic drugs used in this setting should depend on the severity of liver disease. Hepatotoxic drugs used in the first line therapy are - Pyrazinamide (Z), Isoniazid (H) and Rifampicin (R). Rarely, fluoroquinolones can also cause hepatitis. (1)

Table 4. Recommended dose for patients with CLD

CLD Status	Regimen	Treatment recommended
Child A / MELD score <18	Regimens containing 2 hepatotoxic drugs (rather than the three in the standard regimen)	• (9) HRE (until or unless isoniazid susceptibility is documented) • (2) HRE(S/L) + (6) HRE • (6-9) RZE
Child B / MELD 18–25	Regimens containing 1 hepatotoxic drug	• (2) RES + (10) RE • (9-12) RLE+/- S
Child C / MELD score >25	Regimens containing no hepatotoxic drugs:	(18-24) SLE

S – Streptomycin /Amikacin, L – Levofloxacin

12.4.3. Patients Who Are Pregnant Or Breastfeeding:

In pregnant females, all cases on EPTB can be given Rifampicin, Isoniazid, Pyrazinamide and Ethambutol. Aminoglycosides are to be avoided during the pregnancy period due to its teratogenicity and toxicity to the developing ear.

Some of the drugs can be secreted in breast milk. But breastfeeding need not be stopped and the drugs can be continued in the mother as these drugs seldom attain toxic levels in breast milk. Mother can safely breastfeed the child.

12.4.4. Patients With Co-Infection – HIV:

The two diseases - HIV and TB are well known to be interlinked. The chance of EPTB and Disseminated TB increases in people having HIV infection. All EPTB patients are to be screened for presence of HIV infection and all patients with HIV infection should be screened for presence of Tuberculosis. People with HIV and TB infection have a high risk for Immune Reconstitution Inflammatory Syndrome (IRIS) and which can rarely be life-threatening. These patients should be started on Anti-Tubercular Therapy first and followed by a delay before the start of Antiretroviral Treatment to decrease the risk of developing IRIS in these patients.

12.5. Managment for Drug Resistance- EPTB

Management of DR-TB case is a complex process and requires a perfect blend of clinical and programmatic interventions. Compared to drug-susceptible TB (DS-TB) treatment, DR-TB treatment require a longer course of duration which include higher drug dose burden and higher toxicity profile, resulting in lower treatment adherence and poorer treatment outcomes, including loss to follow and even deaths. Decentralized management of DR-TB includes availability of NAAT for diagnosis and the pre-treatment evaluation carried out at treatment initiation which is valid for one month from date of result, furthermore, the patient can be re-initiated on a subsequent regimen based on this. DR-TBC for treatment in each district is crucial for provision of early and prompt services. As per estimation of number of MDR/RR-TB cases in India is 124 000 (9.1/lakh population) (2) .For presumptive EPTB patients mandatory bacteriological confirmation and drug susceptibility testing samples are required e.g., gastric aspirate, induced sputum, bronchoscopic lavage, lymph node aspiration, CSF, tissue biopsies are needed for NAAT or LPA and culture and drug susceptibility testing. This may even imply referral to a higher centre to facilitate invasive testing for few difficult specimens (CSF, tissue biopsy and

thoracoscopy guided pleural biopsy). Diagnosis of DR-TB in the absence of bacteriological confirmation must be thoroughly reviewed as it may often be undetectable. In a presumptive DR-EPTB patient, if there is no bacteriological confirmation, bacteriologically negative clinically diagnosed probable DR-EPTB can be considered after ruling out alternative diagnosis. Drug resistance EPTB treatment regimen includes shorter oral Bedaquiline-containing MDR/RR-TB regimen and longer oral M/XDR-TB regimen which are to be initiated from DDR-TBC, preferably ambulatory and H mono/poly DR-TB treatment to be initiated at HF level.

As per India TB report 2022 , 48,232 MDR/RR-TB patients were diagnosed and 43,380 (90%), were put on treatment, 8455 Pre-XDR-TB, 376 XDR-TB and 13724 H mono/poly patients were diagnosed and out of which 7562 (89%), 333 (89%) and 12008 (87%) were put on treatment respectively.(3) and based on treatment regimen, total of 1939 patients were initiated on a shorter oral Bdq-containing MDR/RR-TB regimen, 23,889 on longer M/XDR-TB regimen, and 25,235 patients were initiated on the shorter injection-containing MDR-TB regimen.

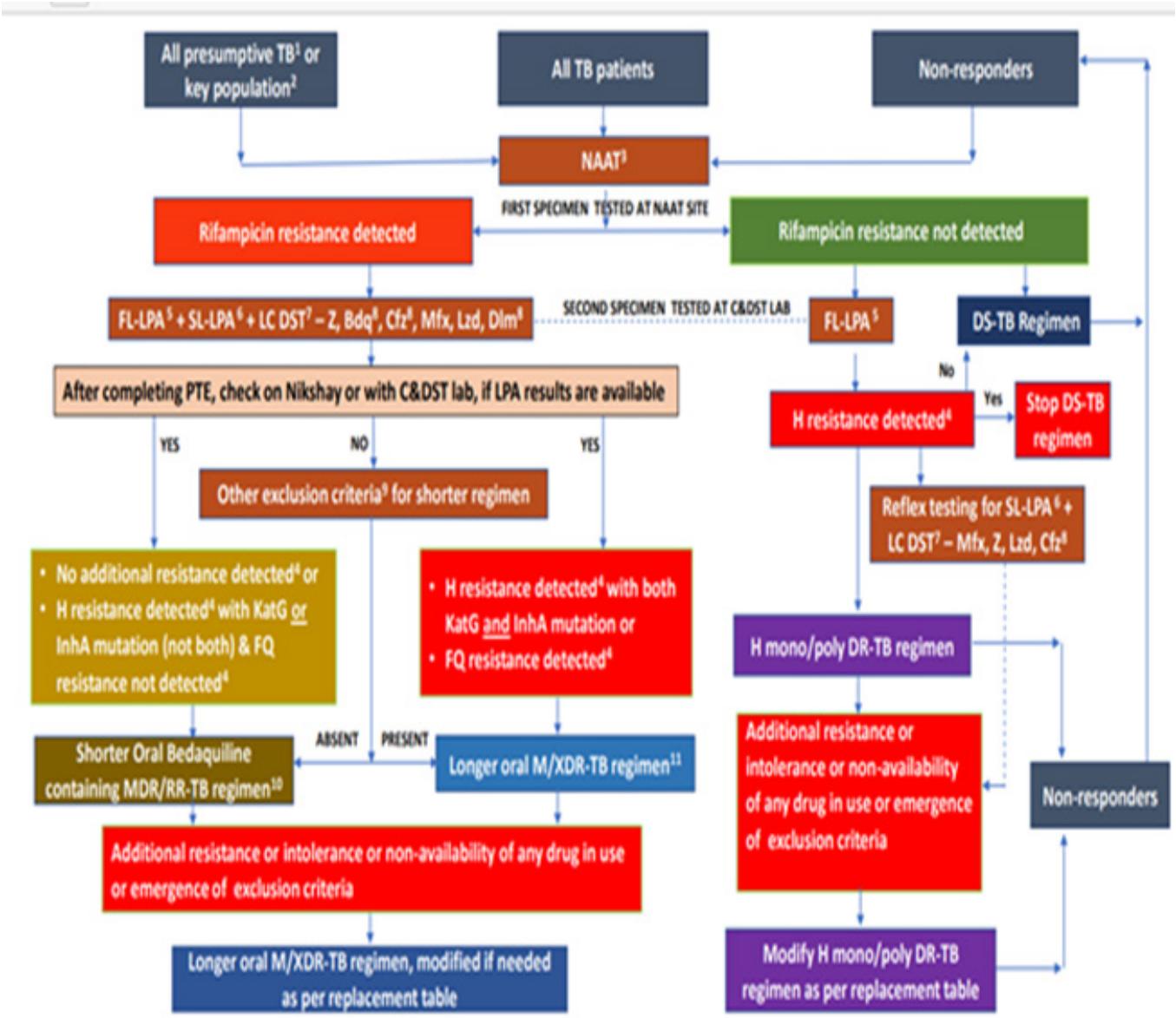
To overcome challenges related with Drug resistance tuberculosis treatment cascade model was developed which include diagnosis, retreatment evaluation, initiation of treatment, counselling, follow up, adverse events. All patients attending public or private health facilities should receive diagnosis and management services free of cost.

12.6. Diagnostic Approach For DR-EPTB

All EPTB specimens for diagnosis need to be collected in aseptic manner and collection and transportation of specimens have been described in the diagnostic chapter.

- In case of Presumptive DR-EPTB, two to three samples are collected for diagnosis and sent to NAAT facility, one specimen will be used for the test. If TB is detected (R resistant detected or not detected), the other specimen is packaged and transported in a cool box through courier or speed post to the linked C&DST laboratory. If there is likely to be a delay in transporting the specimens, these should be stored in a refrigerator at the peripheral TB detection centre/HF with biosafety precautions. At the C&DST lab, smear positive specimen would be subjected to FL and/or SL LPA and further for LC DST as per the diagnostic algorithm. Smear negative specimen will be inoculated in liquid culture and the isolate obtained subjected to LPA. Discordance in RR results between NAAT & FL-LPA to be resolved with a repeat NAAT at C&DST lab and microbiologists will provide the final decision. Integrated diagnostic and treatment algorithm for drug resistant tuberculosis has been attached below.

- To treat DRTB either PTB or EPTB , a treatment cascade model is available which include pre-treatment evaluation, counselling of patients, selection and initiation of appropriate regimen ,monitoring of patient for adverse events ,follow up of patient for adherence and final outcome of treatment cascade.



Integrated diagostic and treatment algorithm for drug resistant tuberculosis

- **Shorter Oral Bedaquiline-Containing MDR/RR-TB Regimen:** The regimen consists of Bedaquiline (Bdq), Levofloxacin (Lfx), Clofazimine (Cfz), Pyrizinamide (Pyz), Ethambutol (E), Ethionamide (Eth) for an initial phase of 4 months that may be extended up to 6 months and a continuation phase of 5 months, giving a total duration of 9-11 months. Bdq is used for a duration of 6 months, but to initiate this regimen all patients need to fulfill eligibility criteria which has been mentioned in PMDT guideline,2021 (Guidelines for Programmatic Management of Drug Resistant TB)(4). After initiation of treatment, follow up will be done which include clinical follow up and bacteriological follow up at the interval of 2, 4, 6 and end of the treatment months. Apart from follow up medical monitoring of patients for adverse events needs to be done and counselling of patient and his/her family members should be done for treatment adherence is also very important.

- **Longer Oral M/XDR-TB Regimen:** In India the experts concurred to start with all 5 drugs of Levofloxacin (Lfx), Bedaquiline (Bdq), Linezolid (Lzd), Clofazimine (Cfz) and Cycloserine (Cs) and continue with 4 drugs in the latter part of the regimen (beyond 6-8 months) if the patient can tolerate the drugs. Although standardization in the design of longer regimens is possible, in many cases, the modification of the composition and duration of a regimen to make it individualized could enhance regimen effectiveness or safety (or both) based on clinicians expertise. Longer oral M/XDR-TB regimen is of 18-20 months with no separate Intensive phase(IP) or Continuation Phase (CP). Once treatment is initiated all patients need to be followed up for their treatment outcome and treatment adherence. For further detail click to this link Guidelines for Programmatic Management of Drug Resistant TB

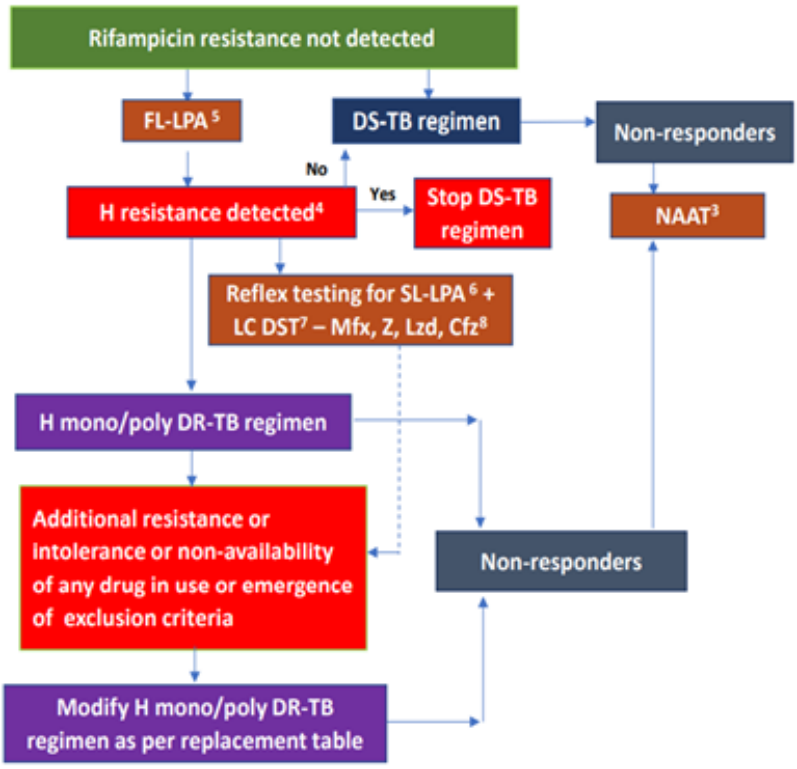


Figure 4.5 Treatment algorithm for H mono/poly drug resistant tuberculosis

- **H Mono/Poly DR-TB Regimen:** The diagnosis for H mono/poly DR-TB patients need to be ruled out among key population which includes (PLHIV, children, EPTB, smear -ve/NA with X-ray suggestive of TB, contact of DR-TB patient, other vulnerable groups) and treatment is initiated based on diagnostic result, in case if Isoniazid (H) resistance is not detected, the patient will be continued on DS TB regimen and monitored for response to treatment. If Isoniazid (H) resistance is detected on FL-LPA, then LPA deposit must be subjected to SL-LPA and LC&DST to Mfx, Z, Lzd, Cfz* and the test result must simultaneously be uploaded. Based on that regimen consist of Lfx R E Z for duration of 6 to 9 months with no IP & CP but pre-treatment evaluation of patient is needed at first and then treatment is initiated. All patients who have initiated the treatment need to be monitored for adverse events and serious adverse events. However all patients need to be followed up for treatment adherence, treatment outcome and post treatment follow up are done .For further detail click to this link Guidelines for Programmatic Management of Drug Resistant TB.

- All those patients who seek care from private health care facilities for DR-TB treatment, for those patients all private health facilities need to be linked with the NTEP programme because few newer drug containing regimens like Bdq, Dlm etc. are only available under the NTEP supply chain.

- NTEP recognizes the fact that although free quality diagnostic, treatment and patient support services are available in the public health sector, a significant number of patients are seeking health services from the large unorganized private health sector. Reaching out to these patients is important, especially to deliver essential public health services to prevent the spread of disease, emergence of drug-resistance, to support TB patients on treatment and address comorbidities which adversely affect treatment outcomes.

- Additionally, health-care seeking is also guided by the willingness on part of the patient as well as the provider. A TB patient seeking care in the private sector may come in the purview of NTEP through notification or referral. PMDT services including latest recommended treatment regimens and new drugs like bedaquiline, Delamanid or any other in future, would be available from NTEP and can be provided to the patient seeking services in the private/other sector.

- All patients will be followed up for treatment outcome and also for post treatment to know any recurrence and treatment failure cases.

*Note: For further information regarding Programmatic clinical management of DR-TB cases including detail about drug ,eligibility criteria for regimen ,adverse events ,management of adverse events ,replacement of drug, follow up ,modification of Regimen as per special situation refer to Guidelines on PMDT which can be accessed through Guidelines for Programmatic Management of Drug Resistant TB.

References :

1. Dhiman RK, Saraswat VA, Rajekar H, Reddy C, Chawla YK. A guide to the management of tuberculosis in patients with chronic liver disease. J Clin Exp Hepatol. 2012 Sep;2(3):260-70. doi: 10.1016/j.jceh.2012.07.007. Epub 2012 Sep 21. PMID: 25755442; PMCID: PMC3940527.

2. INDEX-TB GUIDELINES: Guidelines on extrapulmonary tuberculosis for India. Central TB Division, Ministry of Health and Family Welfare, Government of India; 2016.

3. INDIA TB REPORT 2022: Coming Together to End TB Altogether. Ministry of Health and Family Welfare, Government of India; 2022.

4. Guideline for Programmatic Management of Drug Resistance TB in India; Central TB Division, Ministry of Health and Family Welfare, Government of India; 2021.

Section 3

Standard Treatment Workflow

Please refer to the accompanying supplementary booklet on Standard Treatment Workflows

Standard Treatment Workflow for Management of Adult Lymph Node Tuberculosis.
Standard Treatment Workflow for Management of Adult Pleural Tuberculosis.
Standard Treatment Workflow for Management of Adult Pericardial Tuberculosis
Standard Treatment Workflow for Management of Adult Tuberculous Meningitis
Standard Treatment Workflow for Management of Abdominal Tuberculosis
Standard Treatment Workflow for Management of Adult Musculoskeletal Tuberculosis
Standard Treatment Workflow for Management of Adult Skin Tuberculosis
Standard Treatment Workflow for Management of Adult Intraocular Tuberculosis
Standard Treatment Workflow for Management of Adult Genitourinary Tuberculosis
Standard Treatment Workflow for Management of Adult Female Genital Tuberculosis
Standard Treatment Workflow for Microbiological work-up for EPTB
Standard Treatment Workflow for Anti-Tubercular Therapy related Hepatitis
Standard Treatment Workflow for Drug Sensitive TB Treatment
Standard Treatment Workflow for Paediatric Abdominal TB
Standard Treatment Workflow for Paediatric Intrathoracic TB
Standard Treatment Workflow for Paediatric Lymph Node TB
Standard Treatment Workflow for Paediatric Osteoarticular TB
Standard Treatment Workflow for Paediatric Tuberculous Meningitis

Section 4

Annexures

Health Establishment Registration Form

(for TB Notification)

1	Name of Health Establishment	
2.	Sector	☐ Public ☐ Private/NGO
3.	Type of Health Establishment	☐Laboratory ☐ Private Practitioner /clinic (single) ☐Hospital / Clinic / Nursing Home (multi)
4	MCI/Hospital/Clinical Registration Number	
5.	Authorized Contact Person	
6.	Designation of Contact Person	
7.	Email	
8.	Land Line Number (with STD Code)	
9.	Mobile Number	
10.	Complete Address	
11.	PIN Code	

For Office Use

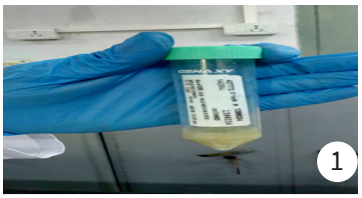
Registration Form Received on	
Mode of Receipt	E Mail / Post / By Hand /Fax
Verified By	
Verified On	
HEID Allocated	
State	
District	
Tuberculosis Unit	

9

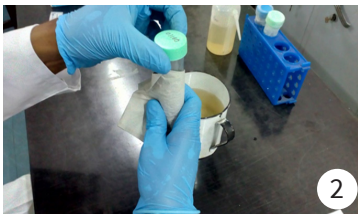
Form for Registration (https://tbcindia.gov.in/showfile.php?lid=3139)

Annexures 2: Standard operating procedure for specimen packaging (triple layer packaging)

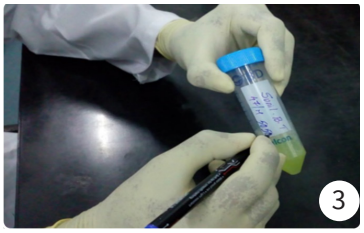
Step 1. Make sure that the specimen collection tube is tightly closed after the sample has been collected from the patient.



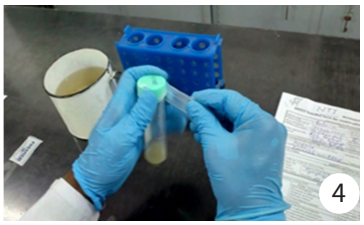
Step 2. Wipe the outer surface of the 50ml conical tube with 5% phenol followed by absorbent tissues and allow it to air dry.



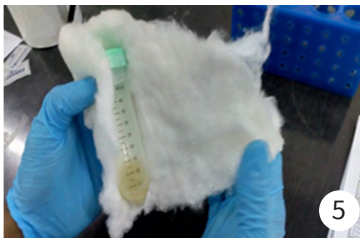
Step 3. Write the patient details on the opaque area (white area) of the specimen collection tube using a permanent marker pen, clearly in capital letters.



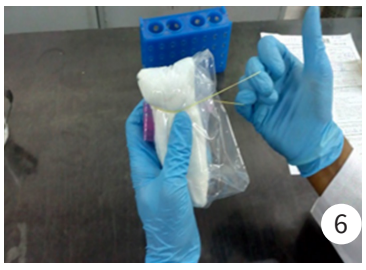
Step 4. Cut the parafilm strip, wrap one of the strips at the joint between the cap and the neck of the specimen collection tube such that a secure seal is formed. (primary receptacle/package)



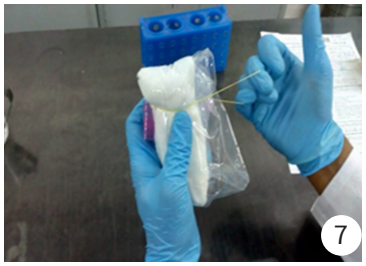
Step 5. Open the absorbent cotton roll and spread out on the work bench; separate the cotton into two equal layers. Roll the specimen collection tube containing the sample tightly in the absorbent cotton such that the tube is covered completely.



Step 6. Put this roll containing the specimen collection tube into the ziplock pouch. Roll the whole into a tight bundle, ensuring that there is no air in the pouch. This bundle should be secured with the rubber bands. (secondary receptacle/ package)

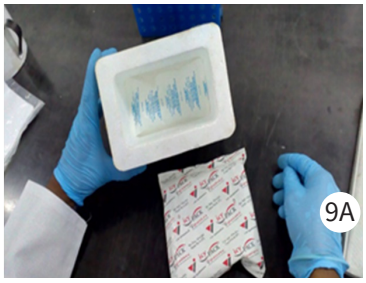


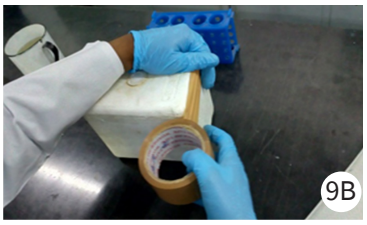
Step 7. Repeat Steps 5-7 for the second sample of the patient.



Step 8. Insert the Test Request form printed from Nikshay in to the zip lock pouch after ensuring that the details on the form and the sample tubes match, with the writing facing outside (details visible though the package). Seal the ziplock on the pouch.

Step 9. Place the cooled gel packs into the thermocol box, place the sample tubes packed in zip lock pouches on the frozen gel packs (frozen for 48 hrs at -40°C) and also keep the pouch containing the Test Request form printed from Nikshay on top. Stick the BIOHAZARD sign over the lid and "To and From" stickers on the exterior of the thermocol box or box used to pack the specimen. Close the lid of the box and wrap tightly with brown duct tape. (Tertiary receptacle/package)





Step 10. Complete the 'From' and 'To' addresses on the stickers, using a permanent marker pen.

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