MGM
Mahatma Gandhi Mission

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"Strength does not come from physical capacity. It comes from an indomitable will." – Mahatma Gandhi

MGM NEWS

TB Harega, Desh Jeetega

INSIDE THIS ISSUE

Mahatma Gandhi Mission Institute of Health Sciences (MGMIHS): An Innovation-Driven Health Sciences University Accredited with Grade 'A' by the National Assessment and Accreditation Council (NAAC), University Grants Commission.

MGMIHS, Navi Mumbai hosted a Symposium on Breakthroughs and New Challenges in Diagnosis and Management of Tuberculosis on 18-19 March, 2016. We were fortunate to have Dr. Deepak Sawant, Honorable Minister of Public Health and Family Welfare, Government of Maharashtra as the Chief Guest for this Symposium.

In his inaugural address, Dr. Deepak Sawant expressed immense pleasure to have been invited to participate in the symposium and interact with a galaxy of highly eminent scientists, clinicians and programme managers. He thanked the Vice Chancellor of MGMIHS Dr. Sudhir Kadam for taking initiative to organize the symposium on diagnosis and management of TB. "TB is a very major health problem for our state and also for the entire country, and we have accepted the challenge to make our country free of TB", he said. Some excerpts from the inaugural address of the Honorable Minister are summarized here:

The magnitude of the problem and the associated disease burden is very large. The decline in TB incidence has been slow, mortality remains high and the emergence of drug-resistant TB has become a major public health concern. Today we are also concerned about the increasing incidence of TB among children, in whom even the diagnosis of TB is very difficult. WHO has declared TB as a major global public health problem and has visualized it like an alarming situation necessitating more stringent measures to combat the disease. It is quite worrying to see number of multi-drug resistant TB cases increasing not only in Maharashtra but across India.

Dr. Deepak Sawant
Hon'ble Minister for Public Health and Family Welfare, Government of Maharashtra

RNTCP Center at MGMIHS

I welcome Shri. Kamal Kishor Kadam and Dr. Sudhir Kadam to join hands and work with the Government of Maharashtra in the TB Control programme for the entire state of Maharashtra. In this endeavor, my ministry will establish a RNTCP Center at MGM Medical Hospital and provide all necessary support for this purpose, announced the Hon'ble Minister.

PPP Proposal to Strengthen PHCs

Dr. Deepak Sawant in his address dwelled on the need for strengthening the PHCs in the State. He proposed to the Vice Chancellor Dr. Kadam to work with his ministry in providing quality healthcare services to the rural population. He proposed that the Ministry of Public Health and MGMIHS can agree on a memorandum of agreement and jointly work through public-private partnership mode. The minister opined that this will be mutually beneficial. On one hand the Government will offer better health services to the rural population and on the other hand MGMIHS will have greater access to PHCs to provide training to its medical students & serve the community.

Expansion of Jeevandayee Arogya Yojana

Hon'ble Minister lauded MGM Hospital for the wonderful work being done by offering emergency and trauma related services to accidental cases in Navi Mumbai area. He said, "We know, Mumbai-Pune Expressway is the most accident prone area and most of the accident cases are brought to MGM Hospital in Kamothe. Since this hospital has expertise for super specialty surgeries, we can provide all facilities under Rajiv Gandhi **Jeevandayee** Arogya **Yojana".** The Minister invited Dr Kadam to work with his department under public-private mode, and his Government was willing to sign an MOU in this regard. Hon'ble Minister also talked about expansion of scope and facilities under the Rajiv Gandhi **Jeevandayee** Arogya **Yojana** during next few months

Early diagnosis and management of TB are essential and are of highest priority for my government. It is also our priority to prevent further spread of TB. Dr. Sudhir Kadam in his address has rightly said, we must create awareness among masses, particularly the message that TB is curable, treatment is free, and taking medicines uninterruptedly is essential". In my view TB is an important health indicator of disease burden. It reflects the overall health status of the community. If we are successful in eradicating TB it would simultaneously help eradicate some of the associated diseases, to a greater extent.

The slogan "TB Harega Desh Jitega", has been coined by the Government of India. The awareness about eliminating TB from Indian soil is being spread by the legendry hero of Bollywood Shri. Amitabh Bachhan. The slogan is creating awareness all over the country.

I agree with the observations of Dr. Kadam that most of the affected people belong to poor economic class, but I would like to mention that a good percentage of rich and affluent class is also affected. The difference is they go to private doctors for diagnosis and treatment which is invariably not reported. Even we do not know whether those patients were provided with the right treatment and whether they had taken the medicine for the entire recommended course. Government of Maharashtra has taken number of initiatives under RNTCP programme to control TB. Efforts are being made to ensure that every TB patient gets the medicine through DOTS. Government of Maharashtra has installed around 49 GeneXpert machines all over the State to facilitate diagnosis of TB and MDR-TB. The objectives are quick diagnosis and to check the number of MDR-TB cases.

The Government of Maharashtra recognizes the need to involve private sector, including the medical colleges and deemed Universities, in the TB control programme. MGM medical colleges and hospitals have highly competent doctors, paramedical staff and facilities to diagnose and treat TB patients. Participation of MGM Hospitals and other private medical colleges, who have good network of doctors, paramedical staff and good laboratories, will expedite controlling the incidence of TB and providing care to TB patients. Government of Maharashtra will join hands with MGM Medical College in this noble work of saving a community so as to get rid of TB.

I also reiterate the need for thoracic surgeons who can operate on TB patients. I inform the audience that State of Maharashtra has only two thoracic surgeons who are doing surgeries since last so many years. MGM Medical College and Hospital should train thoracic surgeons. Medical Council of India should also look into the matter of increasing the number of thoracic surgeons. Now the Government of Maharashtra has started College of Physician and Surgeon courses. This will help us in a large number of doctors training in TB diagnosis and management and ready to work in rural areas of the State.

In his concluding remarks, Dr. Deepak Sawant expressed great satisfaction with the ongoing deliberations focused on expeditious development of point-of-care tests for screening and diagnosis of TB; strengthening of infection control measures; DOTS implementation; improve community awareness and utilization of DOTS through effective IEC; and develop comprehensive and feasible approaches to tackle HIV. He asked the Vice Chancellor to provide a detailed report of the meeting for his perusal and review by experts for appropriate action.

Honourable Chairman's Address

Mr. Kamalkishor N. Kadam
Chairman, MGMIHS Trust

I am thankful to MGM University for its efforts to provide quality education and affordable healthcare services. I may mention, 32 years back when this organization was established, the mission set in front of this organization was "to wipe every tear from every eye".

When independence was won, the freedom fighter Mahatma Gandhi was asked “the freedom is achieved what next?” The curiosity was to know whether the Father of the Nation Mahatma Gandhi was interested in power politics or had different agenda? The Mahatma said "my mission is to wipe every tear from the eyes of every Indian, that is my life mission".

To fulfill that mission of great leader and visionary, MGMIHS Trust was established in 1982 to provide quality education; affordable health care services; promote research and innovation; and serve the community. It is my humble request to the staff and students of this organization to keep the word of great man, it is not a power we seek but desired and zeal to serve the people. In the service of the people, we have to dedicate our lives to wipe every tear from every eye.

Wipe Every Tear From Every Eye

Mr. Kamalkishor N. Kadam, Chairman, MGMIHS Trust welcomed the Hon'ble Minister Dr. Deepak Sawant, all the dignitaries, distinguished delegates and students who had assembled to think of diagnosis of tuberculosis and how to eradicate the disease. He mentioned "at the time in 1947 India had got independence, the national average life expectancy for men was 32 years and for women 26 years. With the sustained efforts of last 68 years, in 2015 the life expectancy of a male had increased to 67 years and female 69 years. It was for the first time in history of our country that the life expectancy of a female was more than a male. This has been a gigantic task to increase the life expectancy from 32 to 67 years. We have eradicated plague, small fox, cholera and even polio. I compliment the contributions of Indian scientists, doctors, social workers, politicians, bureaucrats and all of you who have assembled today in reducing the disease burden in our country".

"Now we have to accept the challenge of making India free of TB by 2035, it is also not an easy talk, but through collective effort it is not difficult also, said Chairman Mr. Kadam.

To accomplish this goal, I request Hon'ble Minister to increase the share of government contribution in national, State and University spending. At present on world scenario, if we spend Rs. 1/- per capita on Indian population, Rs. 5/- is spent by China, Rs. 15/- by Russia and Rs. 145/- by America. Our spending is very meagre particularly on research in medicine and even an healthcare services. We will have to see that more funds are provided for national health services.

I may also mention that funds allocated for health and family welfare programme, as a percent of GDP of our country, are not only meager but public contribution is 67% and that of the government only 33%. The Government spending must increase to 50-60 percent, if the target of eradicating TB by 2035 is to be accomplished.

With this symposium, we have given a road map for challenges for diagnosing and treating TB. Even in the past, this organization has made highly significant contributions in this endeavor.

Dear Hon'ble Minister Sir, in a short period of six years this University has achieved Grade “A” from NAAC, and I may mention that only 10% of the institutions achieve this honour. This is not my credit, it is the result of hard work, dedication and commitment of entire staff including the doctors, paramedical staff, scientists, administrators and others working in this organization. All of them have worked ceaselessly and achieved this credit for this organization. While I thank all of you, I also expect better performance in the future.

Symposium Glimpses










Symposium Glimpses










Vice Chancellor's Voice

Dr. Sudhir N. Kadam
Vice Chancellor

We are deeply concerned about the high incidence of TB in our country. It is quite rampant and has reached epidemic proportions. In our country, about 22 lakh new cases of TB are diagnosed and two lakh people die of TB every year. The rapid emergence of drug resistant TB is yet another threat. The increasing incidence of TB among children and adolescents is also of major concern. Primarily it is a disease of the poor although even medical doctors have lost their lives because of TB. Treatment is expensive and long drawn.

In my view, TB Control Programme should be taken more vigorously as a national movement just like the recently launched Swachh Bharat Abhiyan. If each of our 420 government and private medical colleges take responsibility to eradicate TB from the districts in which they provide healthcare services, it will help in translating the vision of Government of India to have a TB-free country. We at MGM University share and support this vision to have a TB-free country through a holistic approach of offering quality diagnosis and treatment to all TB patients, in addition to providing infection-free environment and financial empowerment of community. Let us join hands to have a TB-free India.

Sincerely,

TB: Let Us Fight It Out

The following are the excerpts from the address of Dr. Sudhir Kadam, Vice Chancellor during the Symposium on Breakthroughs and New Challenges in Diagnosis and Management of Tuberculosis held at MGMIHS on 18-19 March 2016.

World Health Organization (WHO) estimates that in the world each year, 9.6 million people fall ill from TB and 1.5 million die. About 22% of these cases are in India. TB is also the leading cause of death among people living with HIV and AIDS and is responsible for approximately one quarter of all HIV-related deaths. Children and adolescents are also getting trapped. There is a growing resistant to available drugs, the number of drug resistant cases (MDR-TB) is increasing, and the treatment becomes more difficult, toxic and expensive.

There are reports suggesting that the projected numbers and incidence of TB are underreported due to diagnostic difficulties and poor reporting and recording systems. These are very worrying statistics. This public health problem is probably the world's largest tuberculosis epidemic.

The incidence of both TB and HIV diseases is the highest in the economically productive age groups between 15-54 years, poses significant threats not only to health but also to social and economic development in the region. WHO estimates that MDR-TB could cost the world $16.7 trillion by 2050.

We know that advances in diagnostics, availability of new drugs for treatment of TB, and good implementation of DOTS, have to some extent reduced the incidence of TB positive cases during the last ten years. There is also some decease in the “multi-drug resistant TB among newly-detected cases. It is estimated that globally 37 million lives were saved between 2000 and 2013 through effective diagnosis and treatment. Deaths from tuberculosis are preventable, however the death toll from the disease is still unacceptably high and efforts to combat it must be accelerated.

The new global strategy put forth by WHO of eliminating TB has given milestones of achieving 50% reduction in incidence and 75% reduction in mortality by 2025, and 90% reduction in incidence and 95% reduction in mortality by 2035. If these ambitious milestones are to be achieved in our country, we need more concerted effort, and perhaps we will need to revisit TB control strategies. Coverage and access to high-quality tuberculosis care to all those who are affected including the children, will need to be enhanced.

I will also like to mention that relying on treatment and drugs alone cannot beat TB, because TB is a condition strongly influenced by low nutrition, poverty, environmental factors, and rapid urbanization. As a result, large numbers of cases remain undiagnosed and unreported. These cases are of concern from the point of view of continuing disease transmission, risk of drug resistance and higher TB mortality. Therefore, it is essential that human suffering and socioeconomic burden associated with TB is also simultaneously reduced.

It necessitates engaging all care providers and stakeholders including public, voluntary, corporate and private providers through public-private mix approaches. It is essential to promote the use of international standards of TB care uniformly.

Editorial

Dr. Chander P. Puri
Pro Vice Chancellor

The delegates opined that drug-resistant TB is caused primarily by poor treatment practices, use of poor quality drugs and the failure to support patients' adherence to treatment. Treating drug-resistant TB is costly, toxic and very long.

They proposed expeditious development of point-of-care tests for screening and diagnosis of TB; strengthening of infection control measures; more effective implementation of DOTS including community awareness and utilization of DOTS.

The participants also emphasised the need for development of indigenous technologies which are cost effective and can be operationalised in rural settings.

They emphasised evidence-based decision making and need to support scientists involved in TB research for development of more effective drugs; improved drug delivery systems; vaccine development; development of simple cost-effective point-of-care tests for screening and diagnosis of TB, epidemiology, and operational research. They also emphasised the need to foster partnership with private health sector, and medical schools to ensure that every single TB case in the community is diagnosed and cured of TB.

TB Control Programme

The Mission - A world free of TB, zero deaths, zero disease, and zero suffering due to Tuberculosis after 2035.

MGMIHS had organised a Symposium on Breakthroughs and New Challenges in the Diagnosis and Management of Tuberculosis, on 18-19 March 2016, Navi Mumbai. Over 200 distinguished clinicians, scientists, policy makers and programme managers from various institutions in the country had met to brainstorm on diagnosis and management of tuberculosis, and suggest strategies and action plan to combat the disease burden. Several participants projected their research findings and clinical experiences in control and management of TB.

The symposium was inaugurated by Hon'ble Dr. Deepak Sawant, Minister for Public Health and Family Welfare, Government of Maharashtra. Chairman of MGMIHS Trust Shri. Kamalkishor N. Kadam had presided over the function. Dr. Sunil Khaparde, Deputy Director General Health Services, Government of India; Dr. Sudhir Kadam, Vice Chancellor, MGMIHS; Dr. Satish Pawar, Director Health Services, Government of Maharashtra were some of the other dignitaries who had joined the inaugural function.

The issues discussed related to: control of spread of TB infection, how to accelerate decline in incidence, how to reduce TB deaths, how to contain MDR TB, quicker diagnosis of all possible TB cases including MDRTB cases, and more effective treatment and standard of care.

A Panel Discussion had debated on: TB Control in India: Have we done enough? Some of the broader issues which were discussed included are: the statistics of disease incidence realistic or underestimated; necessity to screen for latent TB in HIV patients and periodic screening for active disease; possible speed breakers in accomplishing the target of 2035, unmet needs for programme implementation; mobilization of public private partnership; and do we have enough financial resources to make the TB Control Programme a success. Some of the observations and suggestions during the meeting are given below:

Tuberculosis is quite rampant and has reached epidemic proportions and is a major public health problem for our country. Increasing numbers of multidrug resistant TB and extensively resistant TB cases is also a concern. In fact the increase in MDRTB is a serious barrier to TB control program. TB among children and adolescents is yet another problem, where both diagnosis and management are difficult.

The delegates recognized that the Government was making unstinting efforts to control TB in the face of a heavy burden of disease. They noted that national TB control programmes had made much progress with DOTS expansion, making these services accessible to a large percentage of the population, while continuing to maintain excellent overall treatment success rates. Case detection rates had also increased appreciably during the last few years.

The delegates also opined that to accomplish the task of eliminating TB in next 20 years is not so easy. The general views were that the ongoing TB control programmes need to be strengthened and more vigorously followed and progress monitored periodically. They proposed that the strategies should curtail the epidemic rather than merely treating those who are infected and have the disease today.

Treatment of Pulmonary TB: Surgeon's Perspective

Dr. Shibban Kaul, *MS, MCh, FIACS*
Pro Vice Chancellor, and Head, CVTS

Antitubercular Drugs Discovery Impact

After discovery of 2 potent antitubercular drugs viz Streptomycin and INH in 1945 and 1953, respectively and advancement in anaesthetic techniques, critical care and imaging modalities, surgery was frequently performed to help in curing residual disease and its complications. Procedures performed were Resections (Lobectomy, Segmentectomy, Pneumonectomy) and Decortication (for Empyema). In 1966, Rifampicin was introduced. It was highly effective. So role of surgery became less in management of uncomplicated pulmonary TB. However its role in managing complications became prominent. During next 2-3 decades, two unfortunate events which unfolded are Drug resistance TB and HIV, making management of pulmonary TB difficult.

Principles of Surgery in Pulmonary TB

- Careful pre-op assessment of cardio-pulmonary reserve prior to resection;
- Improvement of nutritional status;
- Postural drainage to make affected lobe/lung as dry as possible prior to surgery;
- Bronchoscopy;
- Sputum culture & AST;
- At least 2 weeks of anti-tubercular therapy prior to surgery;
- One-lung anesthesia.

Role of Surgery in Pulmonary Tuberculosis

Evolution of Surgery in Pulmonary TB

Hippocrates is reported to have advocated drainage of Tubercular Empyema in 400 BC. In 1744, Hastings & Stork reported 'Cavernostomy' in which they laid open and drained cavities in tuberculosis patients. Robert Koch discovered M Tuberculosis in 1982 but no drugs were known which could kill the organism. Surgery was the only 'effective' therapy.

Surgery consisted of collapse therapy. Rationale of this procedure was to let the diseased part of lung to collapse so that it could heal with rest. Besides, it was thought to cut off oxygen supply to the organism which is an obligatory aerobe. It was achieved in following ways: (i) Induced Pneumothorax, in which air was introduced into Pleural cavity to collapse the lung; (ii) Induced Pneumoperitoneum in which air was introduced into peritoneal cavity so that dome of diaphragm rises and collapses the lung; (iii) Phrenic Nerve Crush, to paralyze one dome of the diaphragm; (iv) Extrapleural Pneumolysis: Extrapleural space was created between apex and chest wall, and this space was filled with foreign material (paraffin lumps, air refills, saline bags etc.); and (v) Thoracoplasty: A number of ribs are excised so that chest wall muscles fall onto the underlying lung which collapses. This procedure (Standard Thoracoplasty) produced chest wall deformity. Another procedure to avoid deformity called Plombage Thoracoplasty was introduced in which ribs were not excised. Instead 'plombs' were introduced underneath the ribs, after dissecting the soft tissues off the ribs.

Current Indications for surgery in Pulmonary TB

We can discuss these under following headings: In Drug Sensitive Tuberculosis; In MDR and XDR TB; In NTM (Non Tubercular Mycobacterial) Lung Infections; For ruling out malignancy; and For complications of previous surgeries

Drug Sensitive Pulmonary TB: Uncomplicated drug sensitive pulmonary TB can be treated by drugs alone. Complications, which are listed below, may need surgery; Branchostenosis due to endo-brochial tuberculosis; Mediastinal cold abscesses; Massive haemoptysis (>600 mls in 24 hrs); Broncho pleural fistula (BPF); Chronic empyema with trapped lung; Bronchiectasis with persistent symptoms; Destroyed lung with symptoms; Aspergilloma; and 'Open-Negative Cavity' >2cm in a young person even if asymptomatic.

Surgical procedures carried out are Resections (Segmentectomy, Lobectomy, Pneumonectomy) for residual disease, Decortication for chronic empyema with trapped lung and specialized procedures for non healing BPF's.

MDR and XDR TB: Surgery is used as an adjunct to second line drugs to reduce mycobacterial load by resecting enough radiologically visible diseased lung with the hope that drugs will be able to eliminate remaining reduced bacterial burden and promote healing. Surgery can reduce cost of treatment in resource-poor countries because 2nd line / 3rd line drugs are prohibitively expensive. Surgery will have to be carried out in complications arising out of MDR/XDR-TB, as in drug sensitive TB.

NTM Lung Infections: These usually do not respond to antibiotics and may be extremely virulent. Surgery offers the only possible hope of cure, in conjunction with antibiotics.

Ruling out Malignancy: Open biopsy / Excision biopsy should never be delayed in any mass lesion of lungs/pleura like coin lesions, intra-cavitary masses, pleural nodules etc. Biopsies should be done even in confirmed TB cases because TB and malignancy may co-exist (which is not as rare an occurrence as might be presumed).

For Complications of past surgeries: Postoperative BPF's, due to breakdown of a bronchial stump post-resection will need surgery. Patients having undergone Plombage Thoracoplasties earlier have been reported to come with Sinuses in the chest wall which extrude the 'Plomb' material (paraffin chunks, plastic spheres etc.). They may need surgical treatment.

Symposium on Breakthroughs and New Challenges in Diagnosis and Management of Tuberculosis

18-19 March, 2016, MGMIHS, Navi Mumbai, India.

Chief Patrons

Dr. Soumya Swaminathan
Secretary to the Government of India
Department of Health Research, and
Director General, Indian Council of Medical Research

Dr. Sudhir N. Kadam
Vice Chancellor
MGM Institute of Health Sciences

SYMPOSIUM ABSTRACTS

Role of FIND in Augmenting the Diagnostic Efforts of National TB Control Programme: Future Prospects

C.N. Paramasivan
Senior Scientific Advisor, FIND India

FIND has supported better access to new diagnostics in India through implementation, quality assurance and lab strengthening work under the guidance of CTD along with the help and support provided by WHO and other partners. Ever since FIND was established in India in 2007, it has contributed significantly towards augmenting the diagnostic capacity of TB and multi drug resistant tuberculosis (MDR-TB).

Evidence gathered at multiple sites in 2008 from the demonstration studies of LED FM, LPA and LC & DST eventually led to the incorporation of these technologies within the national TB diagnostic algorithm. Subsequently, with a view to bridge the gap in patient-care for an early and accurate detection of drug resistant TB, the EXPAND TB project was initiated with FIND as the key implementing partner. The project primarily supported the procurement of key technology equipment, test kits, consumables and HR capacity-building through national trainings. Accordingly in India, the project led to the establishment of 43 LPA and 37 Liquid Culture & DST and 38 CBNAAT laboratories.

FIND on behalf of EXPAND TB also established the International Center for Excellence in Laboratory Training (ICELT) at the National Tuberculosis Institute (NTI) in Bangalore in 2010. Through 41 national level trainings conducted to date, more than 400 lab personnel have been trained on various WHO-approved MDR-TB diagnostic technologies. In the year 2011, the GFATM project was initiated and FIND was identified as the implementing partner of CTD for TB laboratory strengthening activities.

The project was focussed on upgradation of lab infrastructure, HR support and on-site training of laboratory staff on newer technologies. FIND has been engaged in the implementation of these activities including provisioning of HR support stationed on-site at various identified laboratories. The GFATM project complemented the EXPAND TB initiative, providing additional equipment, on-site training and technical support to ensure the sustainability of the outcomes.

In 2011 with USAID/WHO funding, FIND under the guidance of CTD and WHO carried out CBNAAT (XPert) feasibility and impact assessment study at 18 laboratories at the lower levels of the health system. Another 14 X-pert laboratories were established in 2012 under the EXPAND TB project. The outcomes of this study provided vital evidence for the planning and further roll-out of X-pert within the national TB programme.

FIND, in consultation with RNTCP and with funding support from USAID and CDC, has been implementing from February 2014 a novel paediatric TB diagnostic initiative in 4 cities of India with a specific focus on Public Private Mix. Till the end of 2015, more than 30 000 paediatric suspects have been tested resulting in the diagnosis of >2300 TB (7.6%) patients with 264 (11.3%) of them being Rif-resistant.

In line with the national priority of augmenting the SL DST capacity within the NTP Genotype MTBDRsl® (ver. 2.0) validation study was initiated recently at five study sites and is expected to be completed by September 2016.This will provide evidence on resistance to fluoroquinolones and second line injectable and to collect in-country evidence on its utility in programmatic setting.

The impact of FIND-implemented projects in India has been substantive. The increase in the number of tests from 7,500 in 2010 to 795,376 by 2015 resulted in a high number of MDR-TB cases diagnosed, which went from 740 cases in 2010 to 83,000 cases cumulatively by 2015. The TB diagnostic capacities will be further augmented by adding 15 more Liquid Culture and DST labs which are being planned under GFATM NFM grant. This funding will also help in establishing the state-of-art genome sequencing facilities alongside facilitating C-DST labs for NABL accreditation. On the whole it is a gratifying experience for FIND to assist the National TB Control Programme of India in its mission towards fulfilling universal access and DST guided treatment across the country as early as possible.

Tools for TB Diagnosis

Ameeta Joshi

Associate Professor and In-Charge TB Diagnostic Center,
Grant Medical College & Sir JJ Group of Hospitals, Mumbai

Inadequate tools and weak systems for laboratory based diagnosis of active TB have contributed to under-diagnosis of disease, leading to individual morbidity and mortality and to continued transmission, over-diagnosis of diseases, leading to unnecessary treatment with attendant consequences to the patient and inappropriate resource utilization by the health care program and delayed diagnosis of drug resistance leading to acquisition of additional resistance and to morbidity and transmission

The main objectives for tuberculosis (TB) control program in any country is to rapidly diagnose patients with active TB and treat them correctly and to have rapid diagnostic methods, with high sensitivity and specificity to diagnose diseased patients at the beginning of the symptoms for an adequate treatment prescription.

The laboratory diagnostic tools available for TB are microscopy, culture, molecular techniques, histopathology and imaging. Smear microscopy though inexpensive, simple and relatively easy to perform has the disadvantage of low sensitivity. Light Emission Diode (LED) fluorescent microscope because of its high-quality optics, robustness, battery operation and affordable price may gradually replace conventional microscopy in the public health sector of resource-limited countries.

Although a combination of solid and liquid media is currently the gold standard for the primary isolation of mycobacteria, a few modern, rapid methods are also available like micro colony detection on solid media (including the rapid slide culture technique), septi-check AFB method, microscopic observation of broth culture (MODS), the BACTEC 460 radiometric system, BACTEC MGIT 960 system (Becton Dickinson), MB/Bac T system (Organon Teknika), and the ESP II culture system.

Molecular tests are used for diagnosing the presence of MTB directly from the specimen, identification of mycobacterial species and also for identification of drug resistance – especially rapid detection of Multidrug TB (MDR TB) and XDR TB. The two main tests that are being used in the National TB program are Line probe assays (LPA) and the Gene Xpert.

No laboratory test whether phenotypic, molecular or immunologic is 100% full proof. Molecular detection of resistance depends ultimately on the presence of the resistance-conferring mutation, the organism may use alternate mechanisms of resistance; or mutations may appear which the test kit may not be able to detect as it was not designed to detect it; for which one will have to fall back on the phenotypic methods which are slow & subject to contamination. Combination of multiple tests that include smear using fluorescence microscopy, liquid culture methods and molecular detection to rapidly distinguish M. tuberculosis from NTM is necessary to provide reliable and accurate results for patient care.

Tuberculosis Biomarker Discovery Work at ICGEB

Ranjan Nanda
Group Leader, Translational Health Group,
International Center for Genetic Engineering and Biotechnology New Delhi

Early tuberculosis diagnosis is key to initiate anti-tuberculosis therapeutic intervention and reduce tuberculosis-associated mortality. Infection induces inflammation and these factors alter host metabolic homeostasis to its favour and impact basic host pathophysiology. In this talk, I will discuss about some results on deregulated phenylalanine-tyrosine metabolism in tuberculosis patients as observed from a urine metabolomics study. And how urine metabolites isolated from tuberculosis patients could be useful to predict the acetylation status and to identity novel intermediates of anti-tuberculosis drugs. Our team also works on exhaled breath based biomarker studies of pulmonary tuberculosis patients and some findings of this project will also be discussed in this meeting.

Breath–based Point–of–Care Test for Diagnosis of Pulmonary TB

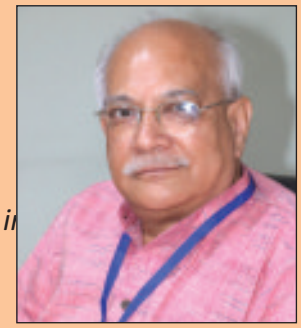
Swomitra Mohanty
Assistant Professor, University of Utah, Chemical Engineering

There is a real need for advanced sensing technology to address significant health disparities in resource limited environments. Diseases such as Tuberculosis (TB), affect over 9 million people a year world-wide, with another estimated 3 million being missed because of the lack of low cost tools to help manage the disease and reach patients in rural settings. In order to address this problem a good understanding of the medical, and socio-economic ecosystems present in a particular community are important.

Disease-specific volatile organic compounds (VOCs) from human breath are considered volatile biomarkers for diagnostics and have the potential to be utilized in non-invasive rapid testing at the point of care (POC). Several diseases have associated volatile biomarkers such as lung cancer, breast cancer, diabetes, and TB.TB is of particular interest as few highly sensitive and specific POC test is available for low resource settings at a low cost.

This research presents a label-free method of sensing using a TiO2 nanotube based nanomaterial developed to detect volatile biomarkers associated with TB (from the breath of patients). In this work self-aligning TiO2 nanotubes were fabricated using anodization methods and functionalized with cobalt for specific binding to the volatile biomarkers.TiO2 nanotubes have large surface area and conductivity making it suitable for electronic detection. This talk will discuss the development of a point of care tuberculosis screening technology based on breath, and how the design, deployment and application is being driven by the end-user (physicians and healthcare professionals).

TB Confirm Test: A Rapid Test for the Confirmation of M. Tuberculosis



Vijay K. Chaudhary

Professor of Biochemistry, University of Delhi South Campus, and Centre for Innovation in Infectious Disease Research, Education and Training, University of Delhi, New Delhi 110021.

In present practice for TB detection, the sample from a suspected patient of Tuberculosis (TB) is subjected to culture on solid or in liquid medium. The presence of M. tuberculosis in the growing culture needs to be confirmed by a battery of tests including Ziehl Neelsen staining for Acid Fast bacilli (AFB) followed by either slow biochemical tests or instrument-intensive expensive molecular tests.

TBConfirm test or other similar rapid tests simplify this identification without requiring any instrumentation. TBConfirm is a gold-nanoparticle-based immunochromatography test for detection of two proteins secreted specifically by Mycobacterium tuberculosis. As per WHO recommendation for resource-constrained countries using liquid culturing, the confirmation for presence of M. tuberculosis should be done by rapid tests in contrast to existing expensive molecular tests. Since treatment and management is different for tuberculous (M. tuberculosis) and non-tuberculous (NTM) mycobacterial infection patients, the confirmed identification of M. tuberculosis is important. Three existing rapid tests (Capilia TB; SD BIOLINE TB Ag MPT64 and BD MGITTM TBC Id) employ detection of only one protein, MPT64 (Rv1980c) and reportedly miss up to 3% clinical samples.

TBConfirm test in addition to MPT64 antigen includes another M. tuberculosis specific protein (viz. MtbAg/MTcAg) and is therefore expected to detect even those M. tuberculosis samples that are missed by existing kits due to absence of MPT64 protein. For TBConfirm test, a drop of culture is placed in the sample loading area of the device followed by three drops of buffer and after 15-20 minutes appearance of reddish-purple bands at T1 for MtbAg and at T2 for MPT64 confirms that the culture contains M. tuberculosis. The TBConfirm test has been evaluated at many centers for efficacy and was found to have near 100% sensitivity and 100% specificity.

The TB Confirm test is the result of generous funding by Department of Biotechnology, Government of India to UDSC, and expert testing by laboratories of Dr. Sarman Singh and Dr. Camilla Rodrigues.

Design and Development of TB Detection System

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India carries one third of the global burden of tuberculosis (TB) worldwide. WHO plans to eradicate TB globally by year 2035. To achieve this target we have to scan very large population. The conventional diagnosis method, microscopy lacks sensitivity, whereas, Culture based diagnosis takes very long time. Delayed diagnosis may cause wide spread transmission of this airborne disease. To plug this gap a novel method has been conceived, wherein micro-nanotechnology has been efficiently deployed to develop a quick & sensitive TB detection system.

"Development of Quick TB Detection Sensor using Nanotechnology" is taken up in "Collaborative Project Mode" involving BARC, MGM Institute, IIT, Delhi and BITS, Goa. Extra mural funding in two phases has been provided by BRNS. In first phase a joint patent shared by BARC, MGMIHS and BITS, Goa has been field. This TB Detection sensor

works on the principle of Nucleic acid hybridization reaction between nanoparticles tagged modified synthetic single strand probe and oligonucleotides obtained from clinical samples. The detection is based on laser based fluorescent detection system. The preliminary prototype device has been developed and tested. The patent field and published, covers the Bio-Chip micro-nano-engineered device based on nuclear hybridization reaction. The detection was carried out using fluorescence microscope. This being expensive, needs regular power supply and skilled operators hence cannot be deployed in remote rural environment. To address this issue a small standalone Detection system has been designed and developed in close collaboration with RRCAT, Indore. A rudimentary Laser based fluorescence detection system has been developed and tested.

Presently engineering design optimization of the Bio-Chip, Biochemical Process optimization & standardization and technology development of laser fluorescence Detection system is in hand. This will be followed by comprehensive clinical Trials and conformance in line with regulatory requirements.

Evaluation of Point-of-Care Testing for Rapid, Simple and Cost-effective Detection of Mycobacterium Tuberculosis

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In high-incidence countries, like India TB control relies on passive case finding among individuals self-presenting to health care facilities, followed by either diagnosis based on clinical symptoms or laboratory diagnosis using sputum smear microscopy. Serial sputum specimens are required. For many patients, the costs of repeated visits to health care facilities are prohibitive, and patient dropout is a significant problem. There are few opportunities for the training of staff and little staff capacity to handle high-volume workloads.

Thus, there is a critical need for new, sensitive, easy, and rapid point-of-care diagnostics and also for investments in laboratory infrastructure, quality assurance programs, and well-trained staff Currently, TB culture laboratories in resource-poor countries often lack adequate infrastructure and have inadequate or outdated equipment and poor biosafety measures, with a scarcity of human and financial resources.

Current diagnostic strategies must be improved by both initial existing TB diagnostic capacity and integrating effective and rapid diagnostic technologies close to or at the point of care (POC) for patients. In the absence of appropriate POC diagnostic tests, laboratory capacity building is essential for ensuring an effective TB response.

In present study, we had standardized and evaluated TrueNAT, RT micro PCR, mobile device, a chip based assay for rapid detection of MTB in PTB cases EPTB cases and for Rifampicin resistance detection. TrueNAT MTB is not POC but it is near to POC: One Step Closer. Utilization of molecular methods in routine for diagnosing in developing country like India depends on factors like high cost, rapid and accessibility of skilled personnel to perform the test. The TrueNAT MTB test evaluated in this study had a TTP of approximately one hour, enabling rapid detection of MTB DNA. The optimized sputum processing protocol ensured that PCR inhibitors were removed from the isolated DNA.

Lyophilized master mix on chip eliminated the need to wait for reagents to thaw and false positive results due to reagent contamination. The disposable, self-contained chip, designed to be a single-use consumable eliminated the possibility of carryover between specimens. The lightweight, portable nature of the devices makes them deployable in peripheral laboratories. The True NAT MTB test was found to have sensitivity of 98.9% as compared to Xpert. Liquid culture had an average time to positivity of 25 days, and the TrueNAT MTB test had a TTP of approximately 1 hour.

Developing and Scaling up TB Lab Infrastructure: Current Understanding and Challenges

Tarak Shah
Medical Officer, FIND India

T A high-quality laboratory system that uses modern diagnostics is a prerequisite for early, rapid and accurate detection of TB. Diagnosis of drug resistance remains a particular challenge for laboratory systems in many low- and middle-income countries. Only 19% of the 310 000 cases of multidrug-resistant TB (MDR-TB) are estimated to exist among patients with pulmonary TB received a laboratory-confirmed diagnosis of their disease and were notified in 2011 (Global TB control Report 2012). With increasing threat of MDR and XDR TB and the availability of modern rapid TB diagnostics, a lot of attention and resources were provided by national and international agencies in the last 4-5 years to strengthen the laboratory systems for uptake of these technologies.

In India, RNTCP in collaboration with FIND as implementing partner and other stakeholders like WHO under EXPAND TB and Global Fund projects planned to scale up lab infrastructure for diagnosis of MDR TB. A total of 46 LPA and 40 LC and 38 GeneXpert labs were established and supported for service delivery. More than 820,000 MDR TB suspects have been tested and more than 72000 MDR TB cases have been diagnosed in the last five years under these projects (2011-15).

Developing and scaling up TB Lab infrastructure is a systematic process involving doing a lab assessment followed by upgrading lab infrastructure, procurement and supply of equipment and consumables, training manpower, undergoing proficiency testing and certification process to service delivery. Considerable experience has been generated in scaling up Lab infrastructure and systems. Many challenges have been overcome in the process though new ones continue to emerge as the RNTCP move towards sustenance and maintenance of the existing TB C&DST labs and further scale up new labs as its diagnostic needs increase in pursuit of universal access to diagnosis and treatment.

Diagnosis of Pulmonary TB: Clinical and Radiological

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Tuberculosis can manifest differently in different individuals. Exposure to M.tuberculosis bacilli by an individual can be of no consequences to various manifestations with infection to disease. Clinical tuberculosis has been defined by Center for Disease Control, USA and American Thoracic Society based on the history of exposure to and/or infection with the bacilli into the following categories: No TB exposure: Not infected; TB exposure: No evidence of infection; TB infection: No disease; TB: Clinically active; TB: Not clinically active; TB suspect.

Infection to disease is dependent on many risk factors and a complex interaction between the host and parasite besides a number of risk factors playing a major role. The risk of developing tuberculosis is shown in Table below.

Risk of developing tuberculosis

Risk Factor	Estimated increased risk(Compared with persons with no risk factors)
AIDS	170
HIV Infection	113
Kidney transplant	37
Silicosis	30
Chronic renal failure	10-25
Imunocompromised	4-16
Infection within past 2 years	15
Chest X-ray consistent with prior TB	2-14
Age <5 and >60	2-5
Diabetes mellitus	2-4

Clinical tuberculosis can present as: Congenital tuberculosis; Primary tuberculosis; Miliary tuberculosis; Post-primary tuberculosis.

Primary Tuberculosis

In the majority of cases the primary infection is symptomless, and is passed off unnoticed. The only indication is a Mantoux conversion. A proportion will experience a short febrile illness. Only a small minority with severe infection or low host resistance will manifest with features of being unwell with anorexia, fretfulness, and failure to gain weight. After the initiation of infection, TB may take 8 to 10 weeks to manifest as a disease. The primary symptoms that develop due to an active TB infection are- tiredness or weakness, weight loss, fever, and night sweats. As lungs are the major organs to be affected, worsened symptoms such as- coughing, chest pain, coughing up of sputum and shortness of breath may also appear.Cough and wheeze may be present because of compression of bronchial wall due to enlarged lymph nodes.

(a) *Pneumonia/collapse*

Dense homogenous radiologic shadows may be present in children due to enlarged lymph nodes compressing the bronchus. These may either be segmental or lobar. The right middle lobe is most commonly affected, because the right middle lobe bronchus is surrounded by a chain of lymph nodes at its origin and gets compressed easily (*middle lobe syndrome*).

(b) *Erythema Nodosum (EN)*

(c) *Phlyctenular Conjunctivitis*

(d) *Pleural effusion*

(e) *Other manifestations*

Broncholiths or bronchiectasis may rarely be seen as complications.

Miliary Tuberculosis (32-35)

Post-primary Tuberculosis

Post-primary tuberculosis is the most important type of clinical tuberculosis, because it is much frequent and smear-positive sputum is the main source of infection responsible for the propagation and persistence of the disease in the community. The infected individual usually remains asymptomatic and can be diagnosed only with a positive tuberculin test reaction. Tuberculosis is more common in particular socio-economic situations such as crowded living conditions, recent immigrations from high prevalence countries (for developed countries where this is one of the important factors), substance abuse, close contacts like household contacts, prisons, institutional residences, slum dwellers, residents of shelter homes etc.

Classically, the onset of symptoms occurs over weeks to months. General symptoms like tiredness, malaise, weight loss, anorexia, and weakness are very common and reported by majority of patients. Fever with night sweats, is a classical symptom of tuberculosis, and more common in patients with more advanced form of the disease. Prolonged undiagnosed fever (PUO, pyrexia of unknown origin) is one of the common presentations of tuberculosis. Fever is present in up to 60% of patients, which disappears rapidly within 1–2 weeks with therapy. Most important symptom related to respiratory system includes cough.

Many National Tuberculosis Control Programs insist that any patient having cough, which persists for more than 2–3 weeks, should have a chest X-ray and sputum examination for acid-fast bacilli. In such cases, the diagnosis of TB will be in around 12–15% of cases. Sputum may be mucoid, purulent, or blood-stained. Hemoptysis is a classical symptom of pulmonary tuberculosis and may vary from mere blood staining of the sputum to massive amount of bleeding. Chest pain is common and may vary from a dull ache or tightness to pleuritic pain, but distinctly different from that due to lung cancer. Elderly patients (>65 years) with TB are more likely to present with non-specific complaints and atypical radiographic appearance. They usually have a lower body weight, less hemoptysis, and more non-specific symptoms.

Various cytokines are thought to be responsible for the clinical manifestations of tuberculosis. Fever is a part of the acute-phase reaction to immune challenge and is complex coordinated and can be diagnosed only with a positive tuberculin test reaction. Tuberculosis is more common in particular socio-economic situations such as crowded living conditions, recent immigrations from high prevalence countries (for developed countries where this is one of the important factors), substance abuse, close contacts like household contacts, prisons, institutional residence, etc.

Fever might be initiated by an endogenous substance secreted during inflammation (endogenous pyrogen) rather than due to direct effect of the mycobacteria. The pyrogenic cytokines include interleukin-1 β, IL-6, TNF-α and interferons of which IL-6 has least pyrogenic action. Though the mechanisms of weight loss are not well known, but cachectin and TNF are thought to be responsible, particularly, the latter which induces catabolic response. Pleuritis and pleural effusion are thought to be due to TNF-alpha and IFN-gamma. Tuberculosis can also produce features like ARDS. Lipoarabinomannan, a component of mycobacterial cell wall acts in a similar fashion to that of lipopolysaccharide in Gram-negative sepsis to activate macrophages to release various cytokines in the causation of lung injury.

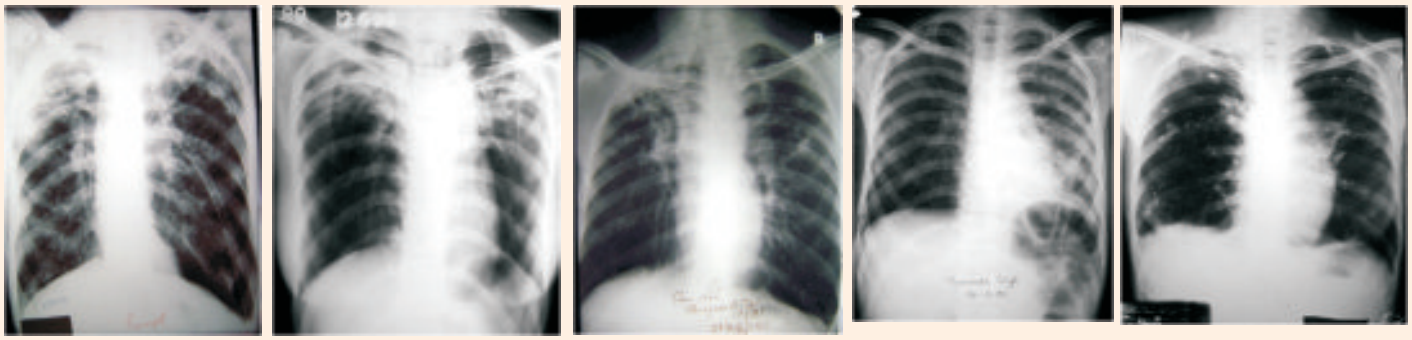
There may be no physical signs in pulmonary tuberculosis even with relatively advanced disease. However, fever, anemia, and cachexia will be present. Advanced cases may show finger clubbing. The earliest chest sign is a post-tussive crepitation in the upper lobes or apices. With advanced disease, fibrosis with cavity is the most common finding in post-primary tuberculosis. The findings are most often bilateral. There may be signs of consolidation also when the presentation is like pneumonia. Loss of lung volume in chronic cases is very common with shifting of mediastinum to the same side. Clinical findings of collapse are not the findings of tuberculosis except in very young individuals where the node may compress a lobe. Occasionally, bronchostenosis may produce collapse. Localized wheezes are heard sometimes as a result of associated chronic bronchitis or rarely, due to tubercular bronchostenosis. Associated findings of pleural disease in the form of pleural effusion or pleural thickening may also be present. Fibrothorax may be present in more advanced and chronic cases. Empyema or bronchopleural fistula is other clinical finding. Post-tubercular bronchiectasis is another sequel of tuberculosis and therefore findings of bronchiectasis are not uncommon observations. Examination of the respiratory system is very important and findings of a cavity with fibrosis in association with history will strongly point toward tuberculosis as the underlying cause particularly in countries with high prevalence of the disease. The differential diagnosis of pulmonary tuberculosis includes pneumonia, bronchogenic carcinoma, lung abscess, bacterial bronchiectasis, and pulmonary infection, which can be differentiated by their specific clinical findings.

Radiology of Tuberculosis

Radiologic features of tuberculosis can almost mimic to any other form of respiratory disease. However some generalizations can be made. A normal chest X-ray almost always excludes post-primary tuberculosis except under two conditions: (i) when there is an observer error and a small radiologic lesion is often missed; and (ii) localized post-primary endobronchial tuberculosis may produce positive sputum, but normal chest X-ray. There are certain characteristic appearances which strongly suggest tuberculosis (but not exclusively due to tuberculosis) and they are: opacities in the upper zones, patchy or nodular opacities, presence of one or more cavities, presence of calcification, bilateral opacities particularly in the upper zones, and persistent shadows for weeks. Post-primary tuberculosis most commonly involves the apical and posterior segments of the upper lobes and the superior segments of the lower lobes. Some of the typical post-primary tuberculosis as seen on radiology are depicted below. Certain radiologic appearances suggest activity: a cavity, unless there has been previous effective treatment (INH cavities are usually inactive); soft shadows; and shadows which extend on serial X-rays.

CT appearances of pulmonary tuberculosis include nodular opacities, consolidation, and consolidation with associated lossof volume (38). The diabetics and immunocompromised subjects will have a non-segmental distribution and multiple small cavitations within any given lesion. Unusual localizations are also possible. Further, centrilobular lesions (nodules or branching linear structures 2–4 mm in diameter) are most common findings. Most of these lesions disappear within 5 months of treatment. CT can also differentiate between old fibrotic and recent activation of tuberculosis. Lesions in and around the small airways appear to be the most characteristic CT features of early active tuberculosis and may be a reliable criterion for disease activity (39).

Classically, post-primary pulmonary tuberculosis is located predominantly in the upper lobes. However, it is not uncommon to find TB in the lower lung fields. Lower lung field is defined as the area on the postero-anterior chest radiograph that extends below an imaginary horizontal line traced across the hilum including the parahilar region. Prevalence of lower lung field varies between o.003 to 15.8% of all cases of pulmonary TB. The condition is more common in patients receiving corticosteroids, patients with diabetes mellitus, hepatic or renal disease, pregnancy, scoliosis and kyphoscoliosis.



Complications of Tuberculosis

The complications of pulmonary tuberculosis can be l**ocal such as:** Hemoptysis, Tubercular bronchiectasis, Fungal ball or, aspergilloma, Tubercular endobronchitis and tracheitis, Spontaneous pneumothorax, Scar carcinoma, Disseminated calcification of the lungs, Obstructive airway diseases, Secondary pyogenic infections, Empyema, Hyper-reactivity of the airways, Respiratory disability with pulmonary function impairment.

These can also be general such as: Secondary amyloidosis, Respiratory failure and Pulmonary hypertension or cor pulmonale.

Strategies to Link TB and Other Disease Control Programmes

Alaka Deshpande
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The history of tuberculosis is at least as old as mankind. Known since time immemorial, TB has been a phenomenal foe to mankind. A third of world's TB burden exists in India. Conservative estimates reveal that there is one death every minute due to TB. In the absence of efficacious vaccine, the efforts to control Tuberculosis are failing, especially due to HIV pandemic, rising incidence of diabetes, and increasing use of immunosuppressive drugs in various conditions.

Dysfunction of cell-mediated immunity is the basis of pathogenesis of tubercular disease. Present era is seeing increased longevity, epidemic proportions of T2DM, rising incidence of auto-immune diseases, increasing use of immune-suppressants, transplant recipients and finally HIV/AIDS cases----all vulnerable to tuberculosis. Time has come that linkages need to be developed between all these conditions of immune–compromise, immune-suppression, immunodeficiency and tuberculosis.

HIV/AIDS and TB are partners in crime! Both are characterised by dysfunction of CMI, long latency and both together have devastating effects. National AIDS control programme and National TB control programme have developed the linkages. Every TB case is tested for HIV and vice-versa. However the detection of HIV is much easier using a simple blood test. TB involving various organs cannot be detected by a single test making its detection difficult and expensive. Radiography of chest is limited only for detection or for ruling out of pulmonary TB but it cannot help in cases of Ex-PTB.

Although a Govt. Programme for NCD is recently launched; the linkages need to be developed. In case of diabetic case the pretherapy work-up should include X-ray chest as well as abdominal sonography. The same may be repeated once a year during follow up.

The linkages need to be developed as presence of TB in these conditions has repercussions on treatment modalities too. Finally, one needs to explore the feasibility and role of TB chemoprophylaxis in a country like India. A simple blood test but diagnosis of both pulmonary and Ex-PTB is not so easy. Prompt and accurate diagnosis of TB will help in initiating Anti-TB treatment immediately.

Latent Tuberculosis Infection in Children

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Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens without evidence of clinically manifested active TB. There are basic differences in the pathophysiology and clinical presentation of TB in children which make diagnosis more challenging than in adults and definitions of latent infection and disease are less clear cut. Following exposure and infection several factors appear to influence the balance of risk between latent TB infection (LTBI) or progression to active disease, including age and nutritional, vaccination and immune status. This risk is greatest for infants and children under 2 years of age. Active surveillance data from the prechemotherapy era suggest the majority of children developed radiological abnormalities following infection, including 60-80% of children under 2 years; however <10% of these were notified, suggesting disease was controlled by the host immune response in most cases.. Most disease occurred in the first year following infection. Thus because disease in young children reflects recent infection, rather than secondary reactivation, the paediatric disease burden potentially provides a useful measure of current transmission within a community, including multi-drug resistant (MDR) and extensively drug resistant (XDR) strains. Untreated LTBI provides the seeds of the epidemic for the next generation.

LTBI, in children as in adults, lacks a diagnostic gold standard. The diagnosis is usually pursued after a documented household exposure, or to evaluate if chemoprophylactic therapy is indicated in the context of immunosuppression. In this setting, pre-existing MTB specific host immune responses are measured to confirm previous infection. IGRA and TST are the available tools at present for diagnosis of latent TB. Longitudinal studies assessing their positive predictive value for the development of active TB are required in both TB-endemic and low-incidence countries, as the continued exposure in TB endemic settings might yield very different results, compared to the “one-off” exposure more typically encountered in non-endemic countries.

Global efforts are being done for early diagnosis and prediction of progress of disease. These are aimed to 1) Detect presence of active antigenic material from mycobacterium 2) Develop cost effective test to find out presence of active mycobacterium in person and progression.3) prevent unnecessary use of anti tubercular drugs. During infection, mycobacterium accumulates intracellular lipid loaded inclusion bodies. Mycobacterial lipids and lipolytic enzymes are thought to play important role during dormancy and reactivation. Lipolytic enzymes have recently emerged as key factors in lipid metabolism during dormancy and/or exit of the non-replicating growth phase, a prerequisite step of TB reactivation. (8, 9, 10). Specific antibodies against lipolytic enzymes may be induced at different stages of the infection process. Mycobacterium possesses at least seven genes related to lipase and cutinase family. Mycobacterium tuberculosis differentially expresses genes of various lipolytic enzymes which could be used for differentiation of activity and progression of tuberculosis.

Recent Advances in the Diagnosis of Drug Resistant Tuberculosis

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Tuberculosis is global health problem, especially after AIDS epidemic. India is having largest pool of drug resistant tuberculosis. The most important concern is its early diagnosis and drug resistance. The conventional methods of diagnosis and drug resistance detection are cumbersome, takes several weeks and lack reproducibility. Therefore in recent years several molecular methods such as conventional monoplex and multiplex polymerase chain reactions, real time PCR assays, Line probe assay and XpertMTB/RIF have been made commercially available.

The MTBDR*plus* line probe assay (LPA) and XpertMTB/RIF have been endorsed by World Health Organization and both these tests can be used for detecting Tuberculosis as well as for drug resistant detection in *Mycobacterium tuberculosis*. However, there is no clarity regarding the superiority of one over the other. Improved diagnostics are required for the detection of *Mycobacterium tuberculosis (Mtb)*, infection especially in the patients with smear-negative disease.

The rapid detection of pathogen specific antibodies in human sera have played crucial role in the diagnosis and control of various infectious diseases. However, for the diagnosis of tuberculosis (TB) several antigens have been tried but most have failed. Because of poor sensitivity and specificity, the existing serology based commercialised tests have been banned and future discoveries were encouraged by World Health Organization.

Recently our work has demonstrated the production of five novel recombinant antigens and their sero-diagnostic efficacy in tuberculosis. The respective five genes were cloned, proteins expressed, purified and the recombinant antigens were used for this study. Their sensitivity and specificity was measured using dot-blot and enzyme linked immuno-sorbent assay (ELISA) on bacteriologically confirmed TB patients and controls (non-TB and healthy individuals). Area under curve (AUC) values of the selected antigens were between 0.88 and 0.99 for these antigens. More interestingly, three recombinant antigens were able to discriminate between drug susceptible-TB and multidrug resistant (MDR-TB) (p_{rss1}=0.008, p_{rss4}=<0.001 and p_{rss5}=<0.001). Therefore, we concluded that these recombinant antigens could be used for the serological diagnosis of active TB and to predict drug resistance development in the causative *Mtb*.

Programmatic Management of Drug Resistant TB

Sandeep Bharaswadkar
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WHO RNTCP Technical Support Network
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Drug resistant TB has emerged as significant public health problem in India. Estimated number of MDR TB patients in India in 2015 is estimated to be 71 thousand as per Global TB report 2015 published by World Health Organization. Government of Maharashtra has taken proactive steps to control tuberculosis as well as drug resistant TB through Revised National TB Control Programme. Following are some of the achievements of RNTCP Maharashtra in PMDT:

Maharashtra has been one of the first states in the country to initiative Programmatic Management of Drug Resistant TB in the country in 2007. 10 C&DST labs are established in all parts of Maharashtra. 48 Gene X-pert labs are available for sensitive and sophisticated diagnosis of Tuberculosis. All diagnostic technologies are available for diagnosis of drug resistant TB in Maharashtra. Solid C&DST, Liquid C&DST, LPA, Gene xpert, 2nd line DST are some of the techniques available in the state. 16 DR TB Centres are established in Maharashtra for pre-treatment evaluation and initiation of treatment of MDR TB. In order to ensure decentralized initiation of treatment of MDR TB, Maharashtra has established District DR TB centres at 9 locations in Maharashtra.

Maharashtra has been one of the first states to initiate baseline 2nd line DST for all MDR TB patients. It helps detecting resistance early and appropriate modified treatment may be initiated due to this intervention. Every year around 30000 MDR TB suspects are tested for MDR TB and more than 5500 MDR TB patients are put on treatment every year. More than 600 XDR TB patients are taking treatment in the state. Success rate of around 50% is seen in the state, country and most of the other countries. Programme has recognized the need of newer tools, interventions to improve outcome of MDR TB. In this regard, Novel Anti TB drug called Bedaquiline and Delaminide are being introduced in the programme. It is quiet heartening that 1 of the six sites where Bedaquiline will be introduced is KEM Hospital Mumbai.

State looks forward to expand Bedaquiline initiative based on experience. Management of adverse drug reaction is an important activity that may promote compliance hence programme has undertaken steps like training and supervision to address the same.

Maharashtra has proposed for Universal DST and DST guided treatment. State intends to implement it in near future under the guidance of Central TB Division Government of India. Apart from MDR TB suspect, programme has started screening HIV positive TB suspect, Extra pulmonary TB suspects and paediatric Tb suspects for TB and drug resistant TB through Gene X-pert.

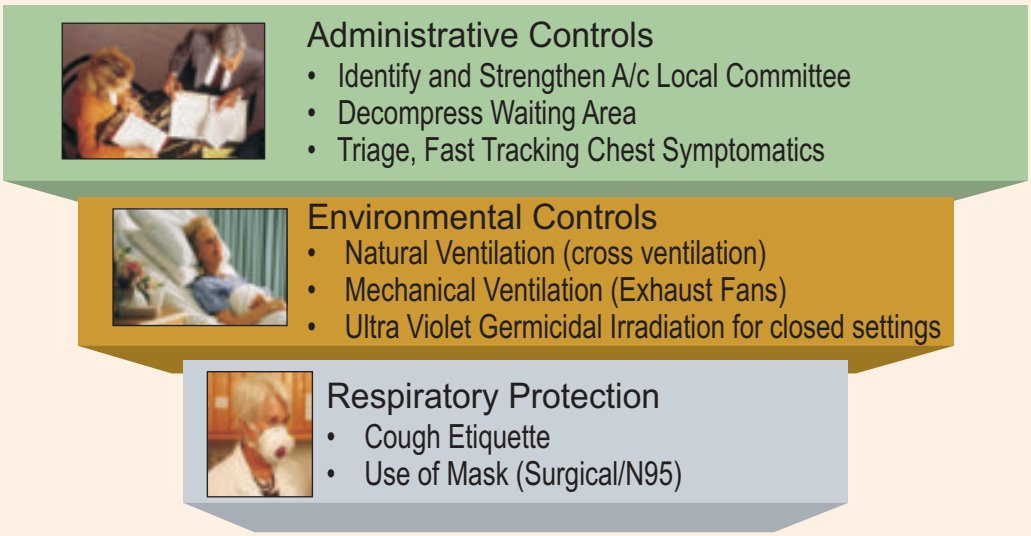
I am quite confident that we will achieve our dream of universal access of TB care. Till then let us denote to make most of the opportunity. Slogan of World TB day 2016 is apt to present need i.e. “Unite to End TB”.

Airborne Infection Control

Amit B. Karad
Medical Consultant, WHO NTCP TSN Mumbai

Tuberculosis is caused by M. tuberculosis. Invisible M. tuberculosis droplets are formed when a person with TB in the lung or larynx coughs, sneezes, laughs or speaks. Droplet formation can also occur in laboratories, autopsy rooms or during procedures like bronchoscopy. Small droplets (aerosols) laden with bacilli can be suspended in air for a long time while bigger droplets drop to the floor quite quickly. Infection occurs when a susceptible person inhales one or more droplets containing mycobacteria, which then lodge in the alveoli of the lungs. Once in the lungs the bacilli may then spread all over the body. TB disease may develop soon after infection with TB bacilli. In most persons however, an immune response generated within 2-10 weeks after infection limits further multiplication and spread of the TB bacilli.

Guidelines on Airborne Infection Control in Healthcare & other settings, 2010 have been prepared and widely disseminated by Central TB Division. Objective of these guidelines is to provide up-to-date information about recommended methods of reducing the risk of airborne infections in health care facilities. Set of activities listed below provide the managerial framework for the implementation of TB infection control in health-care facilities, congregate settings and households under Revised National TB Control Programme. Following are fundamental recommendations under AIC guidelines.



Heartiest Congratulations

Dr. Syed Abdus Sami, Professor Emirates and former Professor and Head Department of Forensic Medicine, MGM Medical College, Aurangabad has been awarded with the prestigious Fellowship of Indian Academy of Forensic Medicine in recognition of contributions and services in the field of Forensic Medicine and Toxicology by Governing Council of IAFM.

MGMIHS has signed MoU with IKP Knowledge Park to pursue a research project "Evaluate a Point-of-Care test for diagnosis of tuberculosis". Dr. P V Potdar and Dr. Samir Pachpute are the Principal Investigators of the project.

MGMIHS has signed a MoU with University of Utah and NanoSynth Materials and Sensors, USA to pursue a project "Non-Invasive TB Triage and Patient Mapping Platform Using Breath via Low-cost TiO2 Nanotube Sensor". Dr. P V Potdar and Dr. Samir Pachpute are the Principal Investigators of the Project.

Design Development of Micro-Nano-Biosensor & Detection System for Quick Diagnosis of TB

Yogesh Patil, Girish Pai, Mansee Thakur, D. S. Joshi and V. K. Suri

Department of Medical Biotechnology

MGMIHS Central Research Laboratory, MGM Institute of Health Science

Kamothe, Navi Mumbai

New technologies for the early detection of tuberculosis (TB) are urgently needed. There is need to develop a detection system which would be affordable, portable and easy to operate. These attributes would facilitate its deployment for clinical application on large scale in the country in both rural and urban settings.

Method based on nucleic acid hybridization reaction between probes that can recognize TB specific complementary sequences from clinical samples. Florescence based detection is based on hybridization reaction between nanoparticle tagged synthetic single stranded probe and oligonucleotides obtained from the clinical sample.

Hybridization reaction is carried out in a novel micro-trench confirmation with probe DNA along with special fluorescence dye highly specific to the double stranded DNA molecules. The HRM fluorescent dyes have been developed to interact specifically and only with double stranded regions of DNA. The detection of such positive hybridization reaction can thus be monitored by laser based fluorescent detection system. In our work carried out so far we have optimized the length and sequences of oligonucleotides that can be used for such devices. We have also tested various fluorochromes for optimizing the intensity of signal.

To test this hypothesis, 10 clinical suspected samples and 20 normal healthy volunteers. The resulting spectra could be used to differentiate TB positivity from normal healthy control. The studied with the resulting sensitivity, specificity, and positive predictive value of 100%, 97%, and 94%, respectively. These results, although preliminary in nature, suggest that laser-induced fluorescence detector can be used in diagnosis of MTB.

Present day classical system of diagnosis need expensive equipment, skilled operators, reliable electric supply and controlled environment, hence are available only in tertiary health care centers. This device will consist of battery operated portable system, hence can be used in primary and secondary healthcare centers. The device will give accessibility of diagnosis of TB in remote and inaccessible area.

Study of Serum Adenosine Deaminase and Globulin in Diagnosis of Extra-Pulmonary Tuberculosis and Pulmonary Smear Negative Tuberculosis

V.K. Shah, Z.G. Badade, K. More & P.V. Potdar

Department of Biochemistry, Department of Respiratory Medicine

MGM Medical College, Navi Mumbai

Extrapulmonary TB (EPTB), Pulmonary Smear Negative TB (SNPTB), Adenosine Deaminase (ADA), Globulin. Tuberculosis is a highly prevalent chronic infectious disease caused by Mycobacterium tuberculosis. The year 2015 is a turning point moment in the battle against tuberculosis (TB). It marks the deadline for global TB targets from the 'Stop TB Strategy to the End TB Strategy'.

In 2014, 9.6 million people are estimated to have fallen ill with TB worldwide, however, 5.2 million incidents of pulmonary TB patients reported globally in 2014. Only 3.0 million (58%) smear positive were bacteriologically confirmed, 42% were not bacteriological, which were diagnosed clinically. ADA is measured in diagnosis and differential diagnosis of TB. ADA assay in various body fluids had established its usefulness in the laboratory diagnosis of extrapulmonary TB and Pulmonary Smear Negative Tuberculosis.

To evaluate the diagnostic value of serum ADA activity, ESR, platelet and serum globulin in extrapulmonary tuberculosis, pulmonary smear negative tuberculosis and to compare it with control.

Total 120 volunteers were enrolled in the study after obtaining informed written consent. They were divided into 3 groups. Group I includes 40 healthy Individuals; Group II 40 patients diagnosed with EPTB and Group III 40 patients diagnosed with SNPTB. Serum ADA was estimated by modified GIUSTI method and ESR by Wintrobe method.

Serum ADA levels were significantly increased ($p<0.001$) in extrapulmonary TB (27.81 ± 7.034 U/L), SNPTB (35.12 ± 12.1 U/L) and as compared to control (14.603 ± 4.69 U/L) with cut-off value 20 U/L. ESR and Platelets were also significantly increased ($p<0.001$) as compared to control. Serum globulins levels were significantly increased ($p<0.001$) in extrapulmonary TB (3.035± 0.562g/dl), SNPTB (3.111± 0.639 U/L) as compared to control (2.783± 0.472g/dl).

Serum ADA is increased significantly in study groups as compared to control group, it helps in rapid and accurate diagnosis of EPTB and pulmonary smear negative tuberculosis. It can be included in routine diagnosis and prognosis of tuberculosis.

Development of Rapid Molecular Detection Method for Multidrug Resistance Mycobacterium Tuberculosis By Using Biprobe Real Time PCR Assay

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The emergence of multi drug resistant Mycobacterium tuberculosis (MDR MTB), i.e. resistant to both isoniazid and rifampicin, is an increasing threat to tuberculosis control program. Susceptibility testing of MTB isolates for MDR by phenotypic Culture method requires a minimum of 14 days for a clinical isolates. Molecular methods can be used to reduce this diagnosis time to 1-2 hr significantly if they are used. The current study is based on biprobe assay utilizing Real Time PCR technology for detection of Rifampicin Mutation. Assay developed to detect rifampicin resistance-associated gene mutations in the Mycobacterium tuberculosis rpoB gene. Mutation specific Florescent labelled Probes were used to genotype point mutations in rpo B codon 531,526,516,511 that associates with resistance to rifampicin. After performing about 50 clinical isolates biprobe based Real Time PCR assay indicate greater than 90% sensitivity and specificity when compared with gold standard Culture-based technique. The total turnaround time of assay is 1-1.5hr after DNA isolation. This method provides a rapid and sensitive assay for diagnosis of MDR MTB and offers several advantages over phenotypic method. The Biprobe RT PCR assay described here represents an alternative method for rapid screening for rifampicin resistance in Mycobacterium tuberculosis isolates.

Circulating MicroRNAs as a Biomarker in Tuberculosis

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Tuberculosis (TB) caused by Mycobacterium tuberculosis remains a global health challenge and is one of the leading causes of death worldwide. New biomarkers that support rapid and accurate TB diagnosis, and are able to recognize early treatment failures as well as cure are urgently needed. MicroRNAs (miRNAs) are small non-coding RNAs that have recently come into prominence as promising diagnostic and prognostic biomarkers. They have been isolated from a number of tissues and body fluids and have been extensively studied and reviewed in both health and disease.

This study explores the application of miRNAs as biomarkers in pulmonary tuberculosis. The panel of 4 MicroRNA was examined in 30 TB patients, 18 MDR patients and 30 control samples. Using real-time quantitative reverse transcriptase

polymerase chain reaction (qRT-PCR) kit, we investigated the expression of selected miRNAs. These miRNAs were chosen based on miRNAs previously reported in the literature to be regulated in the setting of TB, other infections or known to be important in immune function. miRNA expression levels were compared to those in 30 healthy controls. MicroRNA expression levels from serum samples were analyzed for their ability to detect and differentiate active pulmonary tuberculosis from healthy subjects. From the four miRNAs selected for the validation study, two were differentially regulated in newly diagnosed pulmonary TB subjects. miR-16 and miR-155 were significantly altered in the setting of tuberculosis infection, while miR-29 and miR-125 were not altered.

Following the TB patients over the course of treatment, this study observed that miR-16 which was significantly elevated in TB patients before the commencement of therapy returned to levels similar from healthy subjects following the therapy, whereas the levels of miR-155, which were up regulated after the course of therapy. The expression of the miR-16 and miR-155 was down regulated in the MDR population compared to control population, while miR-29 and miR-125 were not altered. Given that serum miRNA expression levels were clearly modulated by M. tuberculosis infection the capacity of M. tuberculosis to modulate miRNA expression.

These findings suggest that miRNA may be able to act as an early biomarker to disease diagnosis/predict treatment failure. Based on the findings from this work, miR-16 and miR-155 were demonstrated great promise in their role as a potential biomarker for TB diagnostics. Further work is needed to better understand the function of these miRNAs in the biology of TB, and to better explore external factors that may alter their expression.

Recent Diagnosis in Rapid Identification of Mycobacterium Tuberculosis

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Mycobacterium tuberculosis is the most pathogenic bacteria worldwide, which causes tuberculosis in immune-competent as well as immunocompromised individuals. Patients suffering from tuberculosis need urgent diagnosis & prognosis. The available conventional bacteriological culture method is time consuming hence there is a need for rapid diagnosis.

The aim and objective of the study was to compare conventional method & recent diagnostic method for TB.

All the samples that were received for AFB culture were included in the study. Preliminary identification was done performing ZN staining. The conventional method & the rapid diagnostic method for TB (TB-PCR, Line Probe assay) were done and the data were analyzed. In rapid diagnostic method results were obtained within 24-48 hours, whereas in conventional method results were obtained after 1 week or more. Rapid diagnostic method was found to be least time consuming & more reliable method as compared to conventional culture method.

Mycobacterium avium Complex in Diarrheal Stool of HIV Seropositive Patient- A Case Report

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HIV infection leading to AIDS and opportunistic infections are major cause of morbidity and mortality in the patients. Amongst the opportunistic infections, tuberculosis accounts for the maximum cases followed by candidiasis and diarrhoea. There is a wide variety of protozoal, viral and bacterial organisms as diarrheal pathogens. Stool samples are usually tested for opportunistic parasitic infections if the patient is HIV seropositive. However Mycobacterium avium complex (MAC) is also a major cause of diarrhoea in AIDS patients.

Here we present a case of a HIV seropositive patient belonging to paediatric age group who was suspected to have parasitic diarrhoea. The CD 4 count was 25. The smear stained by Modified ZN stain revealed presence of Acid Fast Bacilli. The case was further investigated for the source of AFB whether secondary to pulmonary or otherwise. The Gene Xpert report for pulmonary tuberculosis was negative. Hence the sample was cultured and the growth revealed presence of Mycobacterium avium Complex. Hence diarrheal cases in HIV seropositive patients with CD 4 counts < 100 need to be evaluated for the presence of Mycobacterium avium complex.

Socioeconomic Conditions Contributing to Multi Drug Resistant and Extremely Drug Resistant Tuberculosis

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Tuberculosis is also known as a social disease. Overcrowding, malnutrition, poverty, and unhygienic living conditions especially in urban slums form a very conducive environment for spread of this airborne infection. Being diagnosed with drug resistant TB also has an impact on the social environment of the patient. To study socio economic conditions contributing to MDR/XDR Tuberculosis. To study impact of drug resistant TB on the social environ of the patient. 26 patients diagnosed as MDR (23) or XDR (3) tuberculosis coming to tertiary care Hospital were subjected to a detailed questionnaire regarding the socio economic background and the following results were obtained.

The results show: 84% of the Patients lost their employment after being diagnosed as MDR/XDR tuberculosis. Out of which 76% of the patients belonged to the productive age group of 18 to 35. Also 4 children dropped out of school. 46% of the patients who lived in temporary shanties and houses with shared bathrooms and toilets contributing to overcrowding with very poor sanitation. These structures had poor cross ventilation.25% out of these patients lived near the industrial areas with polluted neighbourhood. 42% patients had primary MDR.1 patient had primary XDR. 63% Of Primary MDR/ XDR patients had History of contact to patients suffering from Tuberculosis. 20 % of the MDR/XDR patients taking proper treatment expired. One patient was evicted from her husband's house due to the disease. 25 % reported feeling depressed after contracting the disease.36% patients felt the social stigma and felt isolated in the community.

In brief, the study suggests drug resistant tuberculosis is more common in low income groups; poor quality housing and unhygienic living conditions were common; 84% lost their source of income due to illness, this included youth in productive age group; and more than 1/3rd of the patients perceived social stigma and isolation.

Tuberculosis Mastitis Of Breast: A Study of 10 Patients

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The objective of this study is to present our experience with isolated tuberculous mastitis patients over the last 2 years. Tuberculosis is the most widespread and persistent human infection in the world. The infection can involve any organ and mimic other illness, hence it is called the great mimicker. Tuberculosis of the breast is an uncommon presentation of tuberculosis, even in countries where the incidence of pulmonary and extrapulmonary tuberculosis is high. Tuberculous mastitis (TM) is a rare extrapulmonary presentation of tuberculosis accounting for less than 1% of all diseases of the breast in the industrialized world. Incidence of this disease is higher in countries endemic for tuberculosis, like the Indian subcontinent, where it may be as high as 4%.

Ten multiparous women with isolated tuberculosis of breasts. All patients presented with lump in breast. None had any nipple discharge, 2 had discharge from the lesion (lump), one had palpable axillary lymph node on the same side, all diagnoses were confirmed histopathologically, all treated with wide local excision, and one patient had a recurrence and is being treated. All referred to DOTS for ATT.

The incidence of tuberculosis mastitis is low. However, it is to be suspected in young multiparous women with breast lump in whom malignancy has been ruled out. Wide local excision along with antituberculous drugs shows high efficacy with minimal recurrence.

Evidence of Tuberculosis and Drug Susceptibility Testing Among Patients Attending to Tertiary Care Hospital in Navi Mumbai

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The converging epidemics of tuberculosis pose one of the greatest public health challenges of our time. Rapid diagnosis of TB is essential in view of its infectious nature, high burden of cases and emergence of drug resistance. The purposes of this recent study was to evaluate the feasibility of implementing various methods for diagnosis of tuberculosis like microscopic smear, line probe assay and MGIT culture method and to detect MDR TB directly from sputum specimen. This study involved microscopy (Zeihl-Neelson staining), Line probe assay (reverse hybridisation) and MGIT culture method of 100 non repetitive sputum sample from clinically suspected pulmonary tuberculosis cases. Among the total samples processed (n=100), 15(15%) were positive for smear while Line probe assay and MGIT culture showed 23(23%) and 25(25%) positive cases respectively. By comparing microscopy and line probe assay with the culture, culture is more sensitive but it is time consuming (1 week to 15 days). The sensitivity of microscopy is only 15% and line probe assay and MGIT showed 23% and 25% sensitivity respectively. However, in line probe assay, the result were obtained within 8 to 10 hours.

Ileal Ureter for Pan-Ureteral Stricture of Tubercular Origin

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A 20 year old male patient residing at Mumbai presented with c/o haematuria, dysuria, anorexia & repeated UTI since 1.5 years & left PCN in situ since 1 year resulting into college drop out. Patient was a diagnosed case of GUTB on bladder biopsy and had completed 9 months of AKT. No past h/o pulmonary kochs. On investigations- Hb- 13, TLC- 12,700, ESR- 20, creat- 1.3, Urine routine - 18-20 pus cells & 2-3 rbc's. Urine for AFB was negative & Mantoux test was positive. Chest X-ray - normal, USG s/o left side moderate hydroureteronephrosis with cystitis. CT-IVU was s/o beaded appearance of left ureter p/o pan ureteral stricture with delayed excretion from left kidney with hydronephrosis. PCNO gram - complete cut off at PUJ. DIURETIC DTPA scan showed moderately impaired function of 36% & GFR of 23 in left kidney & obstructed drainage pattern. URODYNAMIC STUDY- normal compliance & capacity of bladder. So, in view of salvageable kidney and pan ureteral stricture, ileal ureter was done. Post-operatively patient was symptom free along with good renal function & excretion on IVP.

It is a devasting disease with dreaded complications because of both disease & treatment. Genitourinary tuberculosis (GUTB) is the second most common extrapulmonary tuberculosis(TB) after tubercular lymphadenitis. 8-15% of tubercular patients suffer from GU TB. Commonest age of presentation is 4th decade and commonest organ involved is kidney. Ureteric stricture resulting in obstructive uropathy can lead to renal function loss. Review literature states that

management of ureteral stricture of tubercular origin poses both a diagnostic dilemma as well as taxes the surgical skills of the reconstructive surgeon. (Ordorica R, Wiegand LR, Webster JC et-al. Ureteral replacement and only repair with reconfigured intestinal segments. J. Urol. 2014;191 (5): 1301-6.doi:10.1016/j.juro.2013.11.027 ; Cordonnier JJ, Nicolai CH. An evaluation of the use of an isolated segment of ileum as a means of urinary diversion. J. Urol. 1998;83: 834-8.

Breast Mass with Lung Cavity: Is it Tuberculosis?

Aleena Mariam Mathew, Girija Nair, Abhay Uppe, Akanksha Das and Jayalakshmi TK

A 35 year old diabetic female presented with fever for 1 month,cough for 10 days and right sided breast abscess for 10 days. Incission and drainage of breast abscess done ,its FNAC was suggestive of fibro fatty and fibromuscular mastopathy and AFB smear negative.Despite of this patient was started on AKT under private for 18 months as tuberculosis is common cause of breast abscess in diabetic.Later patient underwent an excision biopsy and the biopsy reported fibro-fatty and fibro-muscular stroma showed scattered nodules with sheets of round to oval cells with abundant eosiniphilic cytoplasm and vesicular folded and grooved nucleus----morphology suggestive of langerhans cell histiocytosis with positive CD1A.

An Xray showed Bilateral cavities with thin walls-?bronchiectasis; HRCT Chest s/o bilateral cavities and left lower lobe thin walled cysts; Biopsy of breast mass suggestive of LCH; Patient then underwent a bronchoscopy with TransBronchial Lung Biopsy -The HP of the sample was features suggestive of langerhans cell histiocytosis; and Patient had completed 5 cycles of vinblastin and oral steroids.

Common causes of breast abscess are staphylococcal abscess,fibroadenoma,fibrocystic lung disease,TB and malignancy. Cavities in lung:TB,Invasive lung disease,malignancies,occupational lung disease and are conditions like LCH and Lymphangioleiomyomatosis (LAM). LCH is a disease of abnormal clonal proliferation of a unique type of cell in the monocyte-macrophage cell line known as the Langerhans cell, occurs predominantly in young smokers, with an incidence peak at 20-40 yrs of age. Types are: Eosinophilic Granuloma {unifocal}(80%), Hand-Schuller-Christian disease {multifocal unisystem}(15-20%), Letterer-Siwe disease {multifocal multisystem}(>10%). In this case our patient was diagnosed as LCH in biopsy:The IHC report on microscopy- the sample cores contained an almost exclusive population of mononuclear cells with an abundant eosinophilic cytoplasm. The mononuclear cells display an immunopositivity for CD1/S100 protein and focal immunoreactivity for CD68.

This case is presented to stress that breast lump and cavities in lung are not usually tuberculosis and long term therapy of AKT should not be encouraged with out AFB smear .

DIAGNOSIS AND MANAGEMENT OF PAEDIATRIC TB

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The global annual incidence of tuberculosis is 9.6 million to which India contributes 2.2 million cases. Continued detection of childhood TB to the tune of half a million cases per year indicates ongoing transmission at a higher rate in India, coupled with problems of malnutrition, HIV, poverty, illiteracy, lack of awareness, poor detection rate, non-compliance, apathy, so on and so forth. TB in children is often extra-pulmonary unlike adults. The subtle symptoms and signs, variable presentations make it difficult to diagnose at grass root level in the community due to lack of experience among general practitioners, besides poor facilities for early detection and treatment. The whole gamut of childhood tuberculosis –clinical, diagnostic and therapeutic aspects have been updatedin this review.

Key words:

Pediatric tuberculosis, Latent TB, Extra-pulmonary TB, Mantoux test, Gastric aspirate, AFB, GeneXpert, AKT, HIV

Introduction:

Confronted with an alarming situation, the WHO declared TB as global emergency (1993). 1/3rd of world's population are infected with My.TB, with an annualburdenof 5,30,000 children which is 6% of the global burden. 74,000 children died from TB in 2012, excluding HIV. TB in children always points to the recent transmission, not controlled as yet. Diagnosis of one child TB indicates 10 times adults cases in community – a tip of the ice-berg. Under-5 children are the most vulnerable group. Most conventional tests are of low specificity and low +ve predictive value. Still we have inadequate commitments towards the problem, wantingin services, poor detection and management commitments and an over-reliance on BCG, a false sense of security. Epidemiological investigations are of prime importance to establish the at risk children as clinical diagnosis often delayed, compounded with late attention to symptoms in children. Low sensitivity of microscopy, slower process of culture and sensitivity, non-specific shadows in chest X'Ray and imprecise tuberculin skin testing compound the problem[1].

Symptoms:

Fever, loss of appetite, weight loss, night sweats, cachexia are known features of wasting diseases like tuberculosis. Diagnostic criteria for Pediatric TB: **Specimen (Sputum / Gastric / Nasopharyngeal aspirate) positive for AFB or culture; or 2 or more of the following:** (a) Contact history, (b) Cough for more than 2 weeks, (c) Weight loss more than 5% within last 3 months, (d) Reactive Mx, (e) Radiographic finding compatible with TB and (f) response to AKT (Indicated by improvement in weight by >10% in 2 months and decrease in symptoms). The triad of +veMx, suggestive CxR, h/o contact are most predictive[2]. Specific focus on paediatric TB diagnosis should include all attempts to isolate AFB from GA / sputum / BAL / NPA. The Tuberculin Skin Testing (Mantoux test) to be done using 2 TU and considered positive with induration 10 mm or more after 72 hours. There is no role for sero-diagnosis as well as non-validated in-house PCR.

Bacteriology:

In one study, Induced sputum among under 12 children with 3% saline nebulisation, 8 were found AFB positive out of 29. To obtain gastric aspirate, a feeding tube is left in situ overnight; gastric contents aspirated in morning while child still asleep without disturbing him/her. Yield 75% AFB positivity. Other body fluids, aspirates: Yield less than 50%. BAL In 36 children: 43%. ZN stain: AFB +ve confirmatory, Culture takes 6-8 weeks, BACTEC-MGIT960, fluorescence sequencing 3-14 days whereas GeneXpert in 2-3 days. [3]

X'Ray:

Varieties of pictures are seen. One study revealed mediastinal lymphadenopathy (27%), adenopathy and consolidation (23%), consolidation, collapse, segmental hyperinflation (17%), miliary TB (11%), cavitary lesions and pleural effusion (10% each). Primary TB as initial infection commonly seen in children. Also collapse and consolidation.Re-activation or secondary TB usually seen in adults.

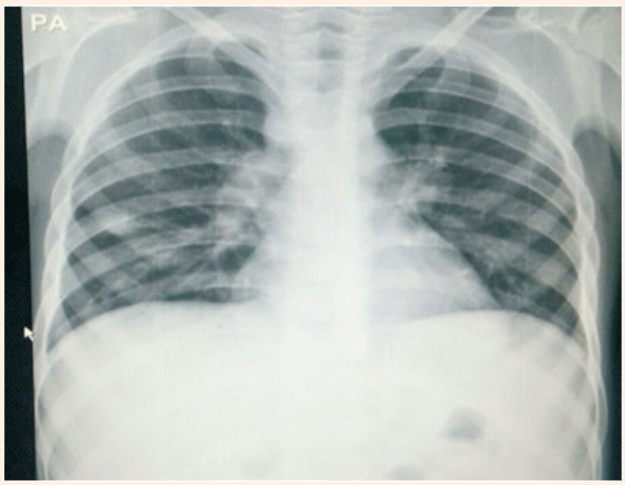

**Fig. 1. Primary complex.
Heavy hilar and para-tracheal shadows, prominent B-V markings extending towards periphery.**

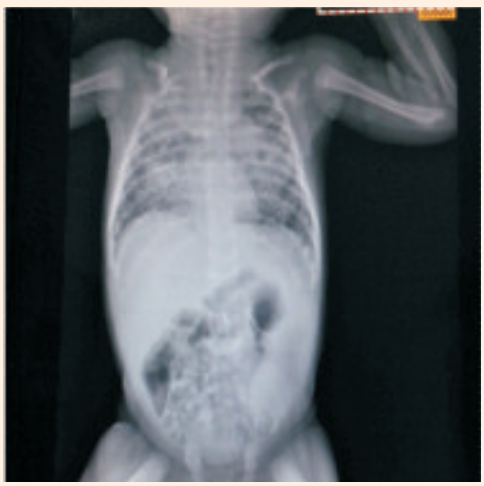

Fig. 2. Miliary & disseminated TB in one month old infant. Lung parenchyma show multiple modularity and interstitial infiltations. Hepato-splenomegaly, dilatation of bowel loops evident. Mother open case of plum TB.

Extra-pulmonary TB

Tuberculosis can involve any system. In children, extra-pulmonary TB constitutes to the tune of 60 to 80 percent. The scenario is fast changing with advent of HIV/AIDS. The presenting symptomatology would vary depending upon the system involved.

Abdominal TB

Besides constitutional symptoms, presenting symptoms are variable, often non-specific. While weight loss, nausea, vomiting, diarrhoeapredominate in paediatricseries, cases of intestinal obstruction, acute pain abdomen mostly reported to surgical facilities [4].

Table.1. Symptomatology in abdominal tuberculosis [5].

Symptoms	Number	Percentage
Fever	8	18
Weight loss	38	83
Pain abdomen	42	92
Nausea / vomoting	10	22
Bowel disturbances	34	75
Constipation / obstipation	16	35
Diarrhoea	4	9
Constipation alt diarrhoea	14	31
Fullness after food	12	26
Abdominal distension	12	26
Borborygmi	10	22

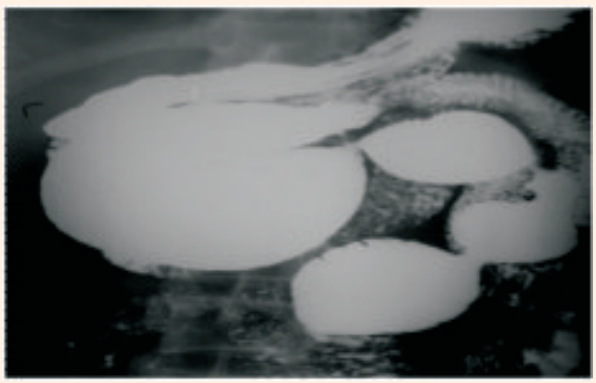

Fig. 3. Duodenum and proximal Jejunum show Multiple strictures and dilatations

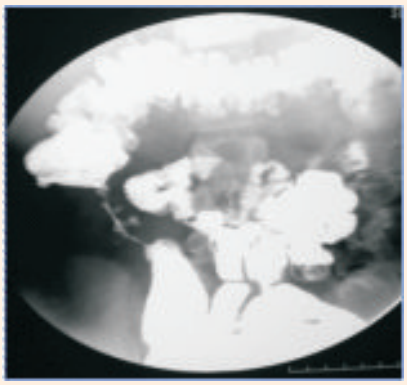

Fig. 4. Ilio-caecal TB showing pulled-up and deformed Caecum, concentric narrowing of terminal ileum and oedematous mucosal folds of ascending colon

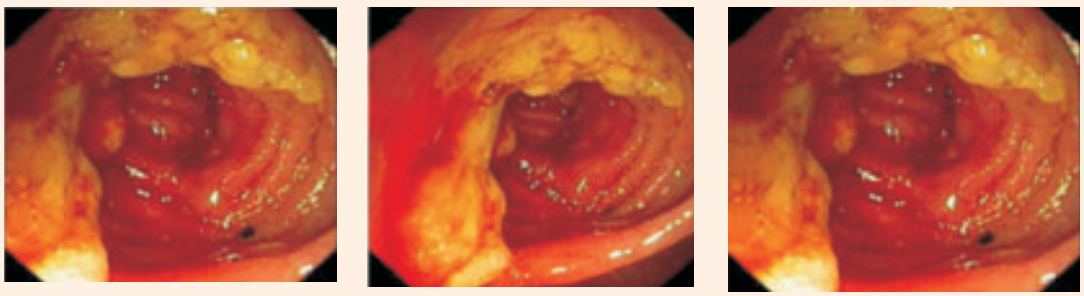

Fig. 5. Ulcero-hypertrophic circumferencial lesions on colonoscopy

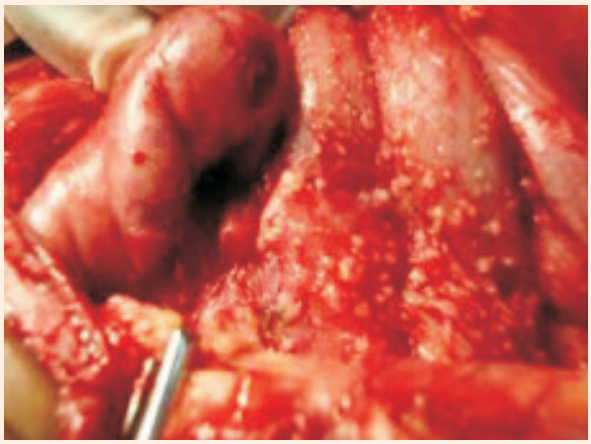

Fig. 6. Multiple tubercles studded on the surface of visceral peritoneumcovering bowel loops.

Tuberculous Meningitis:

Symptoms:

Headache, Anorexia, Nausea, Vomiting, Restlessness, irritability, altered sensorium Fever, myalgia, tachypnoea, tachycardia, Photo-phobia, neck-rigidity, Stupor, coma, seizures, back-pain.

Seizures: (Focal or generalized) Due to cerebritis, tuberculoma, meningitis, hydrocephalus, infarction, vasculitis, electrolyte imbalance. Seizure which are difficult to control, often associated with bad prognosis.

Signs:

A. Signs of Meningeal irritation: Nuchal rigidity, Kerning's sign (Flexion of hip at 90^0 with subsequent pain on extension of leg), Brudzinski sign (Involuntary flexion of knees, Hip follows flexion of Neck while supine). These signs may not be evident in infants.
B. Signs of increased ICT and hydrocephalus:Irritability, Headache, Vomiting, Bulging A.F., Widening of cranial sutures, sunset sign, Occulomotors and abducents palsy, Hypertension and bradycardia, Apnoea or hyperventilation, STUPOR, COMA, Papilledmasuggest chronic process, SOL e.g. - brain abscess / sub-dural effusion. Optic atrophy may be encountered.
C. CranialNerveInvolvement (III, IV, VI, VII): Due to focal inflammation, vasculitis and raised ICT (False localising signs).
D. Focal neurological deficit
E. Miscellaneous manifestations: Altered Mental Status and decreased sensorium due to raised ICT, cerebritis or hypoxia, Lethargy, irritability, stupor, coma are bad prognosis factors. Photophobia, cranial nerve involvement, bulging fontanels, suture separation, UMN signs are common.

CSF - Pressure increased
- Cloudy, cob-web formation
- Cells increased, usually > 10 – 500 / HPF (Lymphos)
- Proteins > 40 mg % (Significantly high, can be 100 to 5,000)
- Sugar< 40 mg % (Range 36 – 56)
- Gram Stain, C /S, AFB, GeneXpert

CT / MRI: May reveal ring enhanced lesions suggestive of tuberculoma, ventricular dilatations, basal exudates. Vasculitis, cerebritis and infarction.

Latent tuberculosis:

After inhalation, most children remain asymptomatic, do not develop active disease, but LTBI;Mx+ve. In-vitro tests measure IFN-y response to T-cell stimulation by My TB Antigens: Protein 10, Antigen target-6. At risk for active TB (1/3rd of world population). Who among deserve treatment? How to decide?Important considerations for treatment of LTB on merit are the risk factors for progression to active TB:

1. Age < 5 years, infected recently (<2 most vulnerable). Have higher risk for progression. Untreated infants with LTBI have 40% chance of developing active tuberculosis.
2. Riskof progression decrease through childhood until adulthood when increases again.
3. Infants and children likely to have life threatening TBM, disseminated disease
4. Children have more years at risk to develop disease than adults.

5. Adolescents and young adults, immunecompromised, HIV, Malnutrition, associated CRF, DM, Silicosis andMx conversion within last 1-2 years.

Tuberculin test:

My. TB PPD, 1, 2, 5 TU; intradermal, marked. Read after 72 hrs for induration (mm) horizontally. Interpretation:

- 5 mm +ve in recent contact / HIV / abnCxR
- 10 mm in infants / drug addicts / health workers
- 15 mm in all other, even without any risk factor.

Same interpretation if has had BCG [6].

BCG test is no longer used for diagnosis of TB. In-vitro assessment of gamma-interferonproduction or testing for CMI may replace Mx test in future.

IGRA:

Preferred in BCG recipients, more than 5 years:

1. T-SPOT.TB measures number of lymphocyte / monocytes producing IFN-y
2. QuantiFERON-TB measures whole blood IFN-y. Do not contain Agn of My. Bovis& My Avium from Environment. Hence Higher specificity as compared to Mx TST.
3. Only one patient encounter Vs. twice with Mx (Mx preferred in < 5 year olds)

Indications for undertaking advanced tests:

1. For diagnosis of PTB :Xpert MTB/RIF should be used as an initial test for suspected cases and MDR TB with HIV (Depending on resources).
2. For diagnosis of extra-PTB: Xpert MTB/RIF be preferred to conventional microscopy & CSF culture in suspected TBM. Xpert/RIF as an alternative test for non-respiratory specimen (LN, tissue diagnosis).

Rational approach in children:

1. Liquid BACTEC-MGIT960 C/S and molecular based My.TB NAAT for early diagnosis
2. Combined AFB + Culture, clinical exam; algorithm based approach reliable.
3. High index of suspicion in the appropriate clinical setting is the key

Management:

Certain important definitions on treatment out-come must be understood :

1. Cured: Bact +ve at initiation, proved to be smere / culture – ve in last month of treatment
2. Treatment completed: Completed treatment but My.TBpositivity report in last monthN/A
3. Treatment failure: Positive for My. TB for 5 months on therapy.
4. Lost to follow-up: Did not receive ATT or has interruption for 2 months or more.
5. Drug resistant (Mono): To at least 1st line drug
6. Poly-resistance: To > 2 drugs other than INH, RIF
7. MDR TB: Resistant to INH and RIF
8. XDR TB: Resistant to any one of fluoroquinolone, one 2nd line injectable and INH, RIF
9. Primary drug resistance: Resistance in patient who never took ATT in past
10. Acquired resistance: in view of previous treatment, may be infection with resistant TB

Drug therapy[1] according to Categories (2013):

I. New case (Smere +ve / -ve PTB / extra-pulmonary):= 6 months therapy
   Intensive phase : 2 $H_3R_3Z_3E_3$ = 2 months
   Maintenance phase : 4 H_3R_3 = 4 months

II. Re-treatment (Relapse, fail to respond or lost to follow-up) for 8 months
   Intensive phase: 2 $H_3R_3Z_3E_3S_3$ + 1 $H_3R_3Z_3E$ = 3 months
   Maintenance phase: 5 $H_3R_3E_3$ = 5 months

Daily dosing preferred in paediatricpractice which is also being tried in 5 states under RNTCP.

Intermittent therapy in maintenance phase in HIV uninfected and under DOTS (Supervised). Daily dosing advocated for initial 2 weeks (Nelson)

DOTS regimen is not preferred for seriously sick, TBM, HIV, GI, hepatitis. Supervised daily dosing in hospital. WHO recommends daily regimen in areas of high HIV prevalence (More than 5% among adults; and more than 1% among pregnt ladies).

If persistent symptoms and signs, extend intensive phase by 1 month and maintenance by 3 months. Also in disseminated TB, CNS, LN, bone TB. Conventionally, the Clinicians' Choice have been: TBM, LN: 1 Yr, Bone 1 ½ year. There are certain difficulties peculiar to children.TB in them isgenerally pauci-bacillary in nature. Higher proportion isof extra-pulmonary.Training of doctors and staff in specimen collection from children remains wanting. Pediatric formulations, particularly liquid preparations and appropriate dosage forms (Being resolved) are not available under DOTS. Notification, treatment with due attention and seriousness by family and practitioners with standard regimen are important.

Chemoprophylaxis:

Serves 2 goals: reduce reservoir, protect young from active disease.

INH prophylaxis - 9 months reduce risk by 90% (6 months by 26-90%; 3, 6,12 months by 31,63, 93%) (Cochrane DB systrev.2000(2) Z:CD001363). RNTCP recommends INH 10mg / Kg OD for 6 months (For 9 months in US)

Indications: Symptomatic children below 6 months, babies with sputum +ve contacts (Irrespective of Mx); First rule out active TB.

All HIV +ve who were exposed to sputum +ve TB case; or having Mx> 5mm

Mx +ve children on immunosuppression and Neonate born to sputum AFB +ve mother.

Managing Drug induced hepatitis:

Indicated by appetiteloss, nausea, vomiting, icterus. May result in acute liver failure (ALF) in 2-39% cases. Rule out other causes of ALF.Out of 5, three drugs (INH, RIF, RBN, PZM) induce liver enzymes.ALT > 1.5 times rise is usual; Upto 3 times of upper limit of normal rangedoesn't warrant discontinuing AKT. Withheld only if ALT rise > 5 times of ULN. In severe disease (TBM, miliary): SM, OFL, EMB. LFT every 3rd day. If ALT < 3 times of ULN, restart AKT.Start Rifampicin at low dose, increase after 3 days. Add INH, dose subsequently hiked.$S_2E_2H_2$+ $E_{10}H_{10}$ if RIF induced hepatotoxicity. $E_9R_9Z_9$ in case INH induced hepatotoxicity.H_9R_9 if PZM not used in initial induction phase

Newer Anti-TB drugs:

Most are in Ph-III / IV clinical trials. Expected to be more potent, reduce duration, inhibit new targets to be suitable for MDR TB; must be compatible with existing AKT and ART drugs, having no antagonism.Exploring newer uses of existing anti-micobials :Fluoroquinolones, Rifamycins, Riminophenazines, Clofazimines, meropenem /imipenem + Clavunate combinations, Oxazolidinones(PA 824), SQ 109, Sutezolid (PNU 100480). Approved for use: (Both included in WHO essential drug list, 2015)

1. Bedaquiniline (Diarylquinolinederivative). Being provided by RNTCP to XDR TB on close monitoring and on limited trial basis. 2. Dalamanid (OPC 67683)

Conclusion:

After Small-pox and polio, the world aims at eradicating tuberculosis by 2035. It is a herculean task no doubt, although not impossible. It's success depends on intensive and sustained case detection, besides cent percent drug compliance at all levels to stamp out the reservoir of infection. Chest physicians usually manage TB patients. Their availability is scarce. Physicians and general practitioners usually avoid handling TB cases for obvious reasons, taking excuses like lack of training and logistics. The childhood TB, mostly extra-pulmonary and LTB, are handled by pediatricians. Their number and presence are very limited in rural India, looking at 42% of our population being children. Hence intensive campaign is required not only to train all our medical students, interns and general practitioners, but also initiate a mass movement at the grass root level, the way we could involve our school and college teachers, students, village panchayats, Government officials, Armed Forces in case of Polio for ensuring success. Training modules need to be developed on priority for expeditious implementation on voluntary and PPP mode in addition to concerted efforts at Government establishments and all medical colleges. Otherwise the 'Stop TB by 2035' is likely to remain as a distant dream.

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Smarting Telemedicine

The renewed Information and Communication boom has triggered the wide-spread proliferation of smart, wireless, versatile and affordable devices and applications. Just like the mobile phone revolution in India, we may also perhaps see a wave of application of telemedicine in India.Here are some trending aspects of telemedicine to ponder and track:

In-bound & Out-bound devices (such as smart-phones) that can be enabled to carry structured data such as patient details, records and reports. Thus, on the one hand it is now easier to share readily saving time, money and efforts related to in-bound and out-bound documentation. On the other hand, it also means that this data is vulnerable to virus/loss/theft, etc. that the infrastructure has to be equipped to manage well.

Monitoring Patients Remotely. Just as patients and doctors can access information from anywhere through mobile and wi-fi networks, monitoring of patients too will become all pervasive.

Rural Telemedicine via Video. Experts can now reach out live over video (and audio) to our rural population and extend their expert advice, just as the rural population can seek centralized guidance on crop and weather patterns.

Editor Requests and Credits

The newsletter, "MGM NEWS" is published quarterly. The staff and students of the MGM Institute of Health Sciences and its associated colleges and departments are invited to send their contributions and/or suggestions for consideration of publication in the next issue.

I also take this opportunity to express gratitude to Mr. Sunil Tatkar, Founder and Managing Partner, Valurevolution™ for his valuable contributions, including creative thinking, editing and artwork, for the MGM NEWS.

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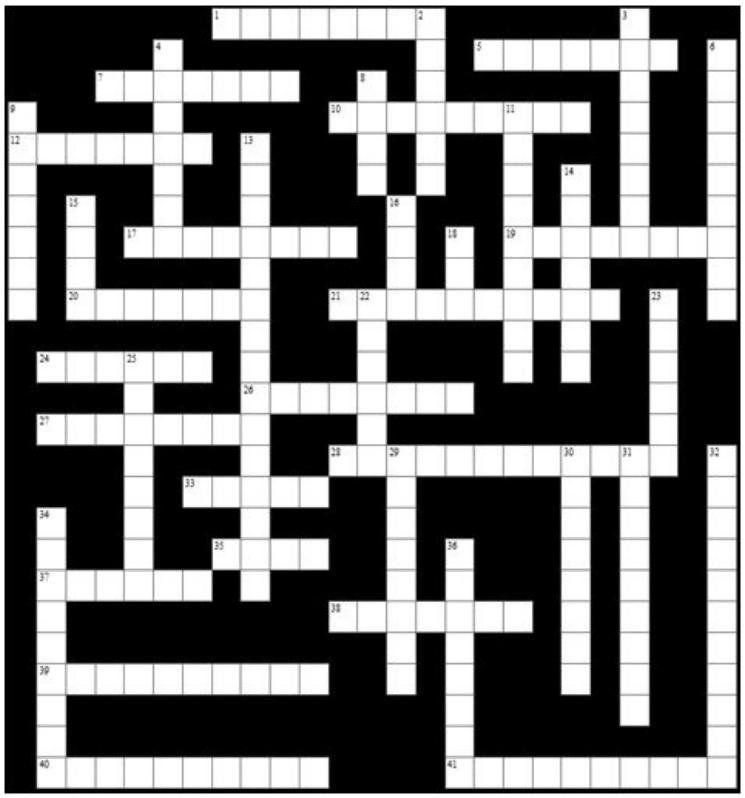
Medico Crossword



CLUES ACROSS
1. Side effect of too much drinking
2. Tetanus
3. Teeth grinding
10. Natural Cold Remedy
12. Mosquitoes transmit it
17. Transient _____ attack
19. Breast Tissue Infection
20. Parasite that causes diarrhoea
21. Robin Williams played this MD (two words)
24. Neil Patrick Harris character
26. Testicular inflammation,
27. Varicella-zoster reactivation
28. Infection of the heart
33. Dr._____, Medicine Woman
35. You can judge it on a scale of 0 to 10, 37. Sores in the stomach, 38. Egg-free flu vaccine 39. Brain injury, 40. Vocal cord inflammation, 41. No menstrual period

CLUES DOWN
2. Deadly disease caused by wild animal bite, 3. Mucocutaneous lumph node syndrome
4. They can make shoes uncomfortable, 6. Curvature of the spine,
8. It forms over a cut, 9. Loss of memory, 11. Most commonly reported STD,
13. Soap opera set in Port Charles (Two words), 14. Endothelin receptor antagonist for PAH,
15. Society of Ob/Gyns (Abbreviation), 16. St. John's_____
18. Cialis indication (Abbreviation), 22. Insomnia medicine
23. Renal Calculi, 25. Body tissue death
29. Flaky scalp symptom, 30. SGLT2 inhibitor
31. Study of the iris, 32. Rapid heartbeat
34. Visit the home of a patient, 36. Skin cancer

Laughter Medicine

Nurse! Quickly get your smart phone, connect to the net on our wifi, go to onlifesurgery.com, get to the "Surgeon's Priority Help section", click on "Are you totally lost Surgeon?" and let me know what it says...(pause)...
Why do you look so shocked Sister? Hurry up! We got a few more surgeries to be done on-line after we *finish this one off*!!

"Stop TB" Strategy to "End TB" Strategy

Dr Sunil D Khaparde
Deputy Director General (Leprosy and TB)
Ministry of Health and Family Welfare
Government of India

Dr Sunil D Khaparde, presenting the key note address, mentioned that TB is an age-old menace that has a devastating impact not only on individuals but also on families, communities and overall development of the nation. TB affects people more in their most productive years of life, driving families into poverty. In-turn poverty and related conditions including congregate settings like Slums, prisons and vulnerable conditions like malnourishment, stress amongst migrants further fuel the transmission of TB.

He stated that though MDG targets for incidence, prevalence and mortality have been achieved but it is not enough. Huge burden of deaths and suffering still remains in India, etimated 22 lakh incidence of TB cases in 2014, with 2.2 lakh deaths.

He revealed India's future strategy and said "we have to now move towards new era of SDG and from "STOP TB Strategy" to "END TB Strategy". Everyone with TB should have access to the innovative tools and services including rapid diagnosis, treatment and care. This is a matter of social justice, fundamental to our goal of universal health coverage. Given the prevalence of drug-resistant tuberculosis, ensuring high quality and complete care will also benefit global health security". The program started with passive case finding strategy, then intensified efforts and now moving towards to more aggressive case finding strategies.

“RNTCP has initiated use of various ICT (information Communication Technology) enabled treatment adherence mechanism including 99DOTS which is based on missed call, mobile based Active compliance including Video DOT, and smart pill box .” He also mentioned about Bedaquiline, a new anti-TB drug available in more than 40 years. He said “Program is introducing BDQ under RNTCP through Conditional Access Program starting with 6 sites. This will provide access to the needy at the same time prevent inadvertent use leading to drug resistance.”

He stated that nearly half of TB patients are treated by private sector in India, private sector shares equal responsibility in controlling TB and plays a major role for preventing the spread of disease. Hence RNTCP has constantly endeavored to engage all care providers to move towards universal access.

He emphasized the importance of STCI in the fight against TB. He said “The STCI is a true guide for all care providers including private to ensure the principles to be adhere to for diagnosing and treating TB patients including the Public Health Responsibility.” He ended his keynote address talking about the future strategies and a firm belief that “TB Harega Desh Jeetega”.