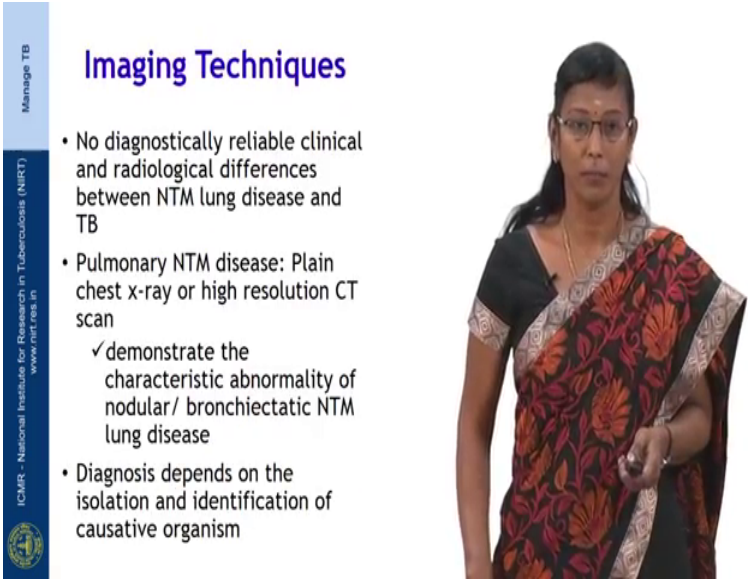


Manage TB
Dr. C. Padmapriyadarshini
National Institute for Research in Tuberculosis, Chennai

Lecture – 53
Non-tuberculous Mycobacteria: Diagnosis & Clinical management
Session 2

Hello welcome to session 2 of Non-tuberculous Mycobacteria, I am Dr. Padmapriya. And I will continue with the diagnosis and clinical management of NTM.

(Refer Slide Time: 00:19)

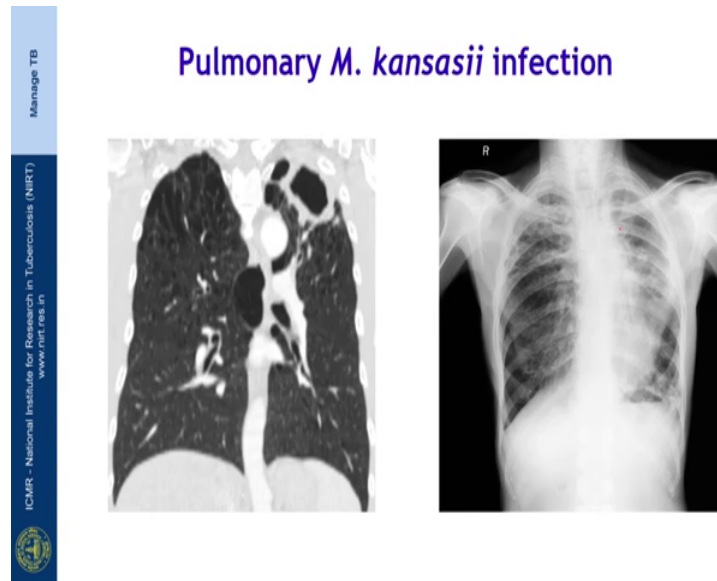


Imaging Techniques

- No diagnostically reliable clinical and radiological differences between NTM lung disease and TB
- Pulmonary NTM disease: Plain chest x-ray or high resolution CT scan
 - ✓ demonstrate the characteristic abnormality of nodular/ bronchiectatic NTM lung disease
- Diagnosis depends on the isolation and identification of causative organism

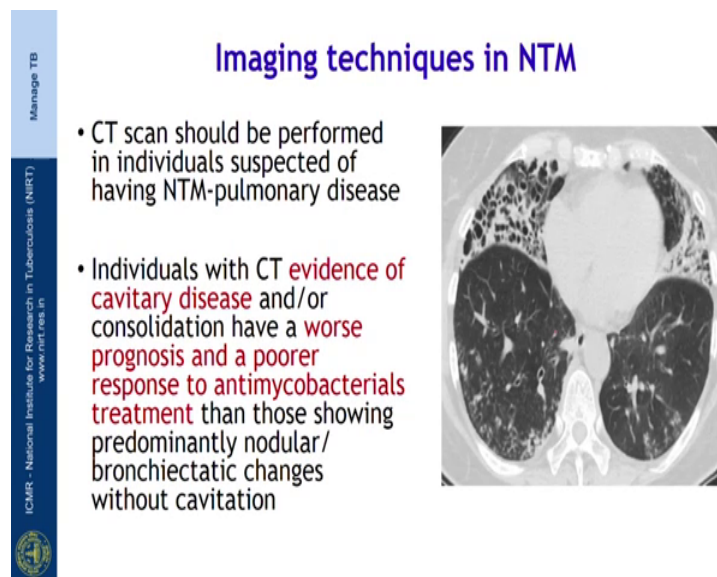
Imaging techniques there are no diagnostically reliable clinical and radiological differences between NTM lung disease and tuberculosis lung disease. Pulmonary NTM disease the plain chest x-ray, or high resolution CT scan will only demonstrate the abnormality, if it is either a nodular lesion or a bronchiectatic NTM lung disease or the presence of a cavitated lesion.

(Refer Slide Time: 00:49)



The final diagnosis depends upon isolation of the organism and identifying the species of the non-tuberculous mycobacteria. These are x-ray showing pulmonary *M. kansasii* as you can see the lesions are very similar to *M. tuberculosis* and is very difficult to identify or differentiate between on an x-ray and CT scan difference between pulmonary *M. kansasii* or pulmonary *M. tuberculosis*.

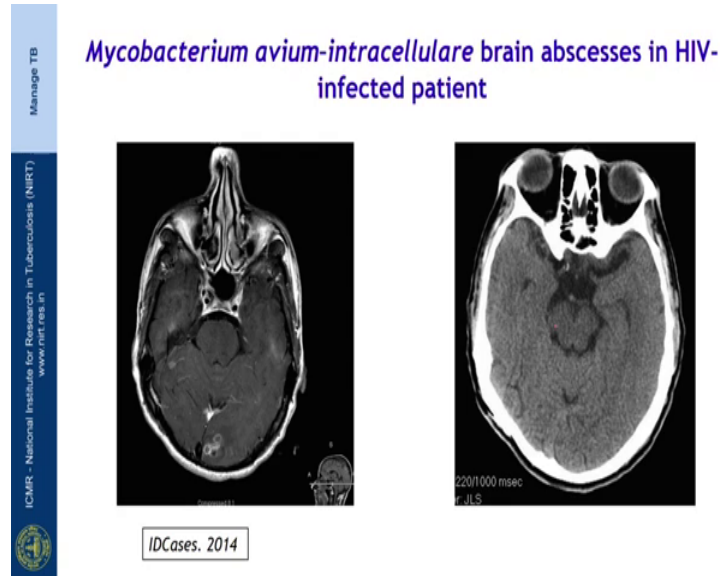
(Refer Slide Time: 01:07)



The imaging techniques in non-tuberculous mycobacteria does not vary much between the species also. Individuals with CT evidence of cavitary disease or consolidation they

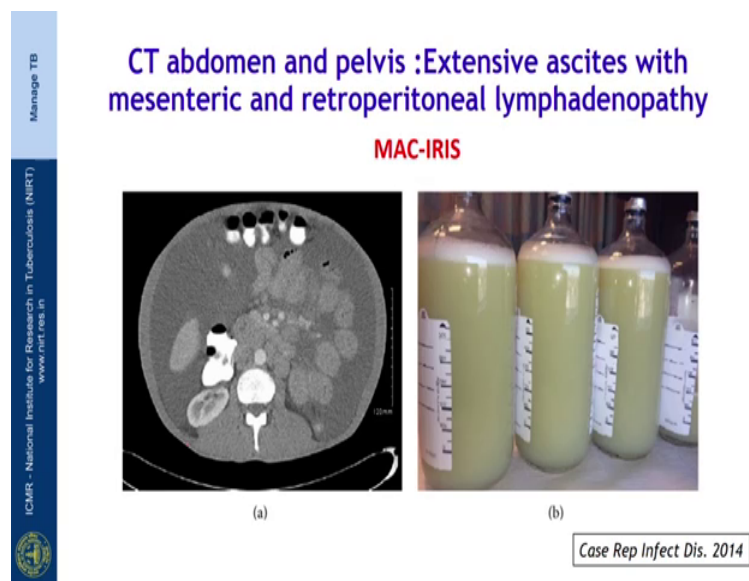
have a worst prognosis to treatment and a poorer response to antimicrobial treatment than those showing a nodular, or bronchiectatic changes without any cavity.

(Refer Slide Time: 01:30)



Now, these are few slide showing you various micro nontuberculous mycobacteria. This one shows you non mycobacterium avium intracellulare infecting the brain presenting in the form of brain abscess in a immunocompromised individual.

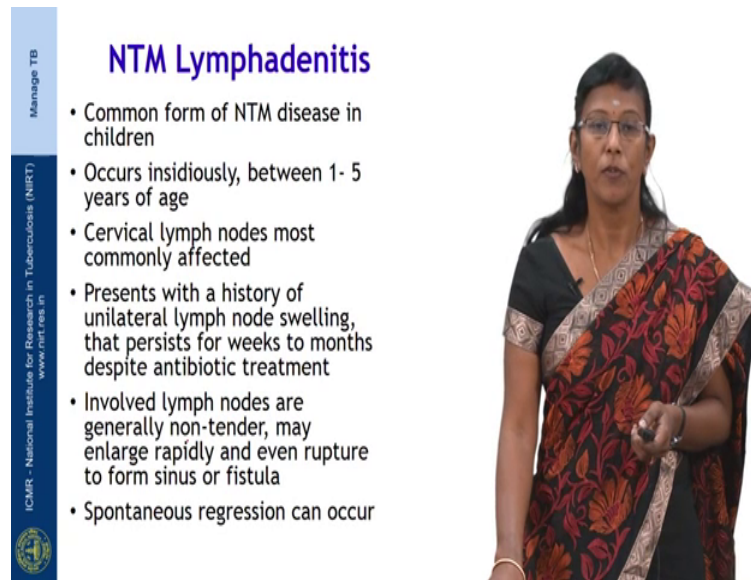
(Refer Slide Time: 01:47)



This is from a patient who has got nontuberculous mycobacterial infection of the abdomen presenting with the form of ascites and multiple lymph nodes of the abdomen.

This is also immunocompromised patient where he was started on treatment and subsequent to the start of treatment he ended up collecting ascites. When the ascites were stabbed this what was found purulent fluid from the abdomen and these grew non-tuberculous mycobacteria.

(Refer Slide Time: 02:17)




Manage TB

NTM Lymphadenitis

- Common form of NTM disease in children
- Occurs insidiously, between 1- 5 years of age
- Cervical lymph nodes most commonly affected
- Presents with a history of unilateral lymph node swelling, that persists for weeks to months despite antibiotic treatment
- Involved lymph nodes are generally non-tender, may enlarge rapidly and even rupture to form sinus or fistula
- Spontaneous regression can occur


ICMR - National Institute for Research in Tuberculosis (NIRT)
www.nirt.res.in



Another form presentation of nontuberculous mycobacteria is lymphadenitis this is one of the common form of NTM disease in children. It occurs insidiously between the age of 1 and 5 years among children, cervical node is most commonly affected though other groups of node can also be affected with nontuberculous mycobacteria.

We usually present with a history of unilateral lymph node swelling which persist 4 weeks and months and do not respond to antituberculosis treatment, or any other antibiotic treatment. The involve lymph nodes are non-tender, we can enlarge rapidly resulting in rupture and sinus formation spontaneous regression of these nodes have also been reported.

(Refer Slide Time: 02:53)



Manage TB

NTM Lymphadenitis

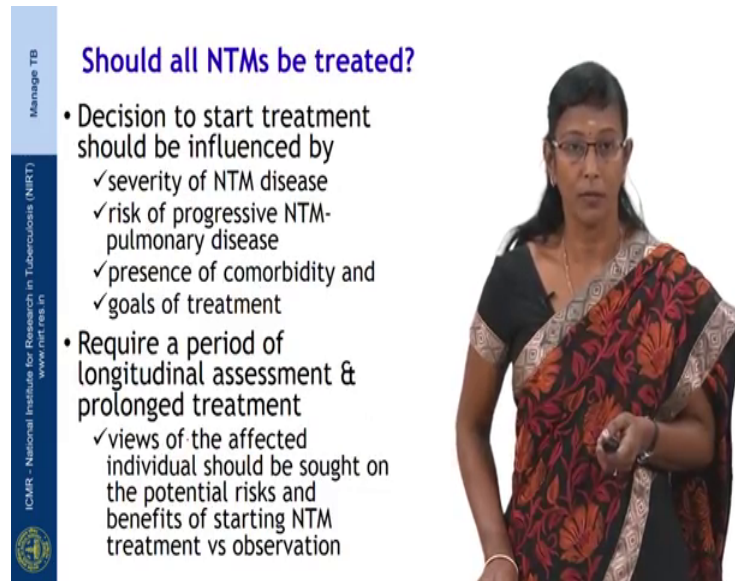
- Superficial cervical lymphadenitis : caused by *M. avium complex*, *M. Scrofulaceum*, *M. ulcerans* or *M. malmoeense* though *M.tb* is still a more common cause of lymphadenitis
- Unlike TB lymphadenitis, there is typically no history of exposure to TB, screening tuberculin skin tests are usually negative and chest radiograph is normal
- Histopathology is a useful method to diagnose *MAC* infections of the lymph nodes especially when it is confirmed with an in situ method like antigen detection or gene probe

ICMR - National Institute for Research in Tuberculosis (NIRT)
www.nirt.res.in

Since, the superficial cervical lymphadenitis is the usual mode of presentation of NTM lymphadenopathy. They can be the discharge can be taken up for biopsy and culture and many of them grow *M avium complex*, *M scrofulaceum*, or *M ulcerans* have also been identified. Now, one thing that we also remember is *M tuberculosis* still the common cause of lymphadenitis in TB endemic countries.

The difference here would be unlike TB lymphadenitis there is typically no history of exposure to tuberculosis the screening tuberculin skin test or the TST test are usually negative and the chest x-ray may be normal in such cases. Histopathology is a useful method to diagnose *MAC* infection as the lymph nodes confirm the presence of *MAC* can be confirmed with antigen detection or the gene probes in the lymph nodes.

(Refer Slide Time: 03:43)




Manage TB

ICMR - National Institute for Research in Tuberculosis (NIRT)
www.nirt.res.in

Should all NTMs be treated?

- Decision to start treatment should be influenced by
 - ✓ severity of NTM disease
 - ✓ risk of progressive NTM-pulmonary disease
 - ✓ presence of comorbidity and
 - ✓ goals of treatment
- Require a period of longitudinal assessment & prolonged treatment
 - ✓ views of the affected individual should be sought on the potential risks and benefits of starting NTM treatment vs observation



Now, moving on to treatment should all NTM cases be treated the decision to start treatment should be influenced by severity of the disease, the risk of progression of NTM pulmonary disease as well as the presence of comorbidity and the goals of treatment.

Now, why are we so particular about the severity or the risk of progression is? The duration of treatment for NTM is long drawn. It is something very close to MDR treatment, the infected patient has to continue treatment for a longer period of time with potentially toxic drugs and they need frequent monitoring as well as follow up.

(Refer Slide Time: 04:19)



Manage TB

ICMR - National Institute for Research in Tuberculosis (NIRT)
www.nirt.res.in

When should NTM be treated?

- Factors frequently associated with progressive NTM pulmonary disease -
 - Patient-related
 - ✓ severe symptoms
 - ✓ low BMI
 - ✓ lung cavitation and comorbidity
 - Mycobacterial factors
 - ✓ smear positivity
 - ✓ two or more positive mycobacterial cultures of the same organism
 - ✓ and particular mycobacterial species



The factors that frequently associate with progressive NTM pulmonary disease are both patient related as well as the bug related. Among the patient patients with severe symptoms, low body mass index, somebody with a lung cavitation on a imaging techniques and the presence of comorbidity warrant treatment. Among the mycobacterial factors smear positivity presence of two or more positive cultures of the same organisms warrant treatment of this disease.

(Refer Slide Time: 04:47)

Treatment schedule for common NTMs

Species	Treatment Regimen	Dosage	Alt regimen/ follow-up
Mycobacterium avium complex	Clarithromycin 7.5 mg/kg (max 500 mg) BD + Rifampicin 10 mg/kg (max 600 mg) OD + Ethambutol 15 mg/kg (max 1.5 gm) OD orally	Daily for minimum 18 months or until culture negative for 12 months	Azithromycin 10 mg/kg (max 500 mg) orally instead of clarithromycin or rifabutin** (15-300 mg) instead of rifampicin
Mycobacterium abscessus	Clarithromycin 7.5 mg/kg (max 500 mg) BD + Amikacin IV 30 mg/kg OD + Cefoxitin (max 12 gm/day) or imipenem	Three weeks intensive phase followed by prolonged continuation phase Surgical resection	Full blood count and Hepatic and renal function must be done before treatment. Hepatic and Renal function tests every 12 weeks
Mycobacterium kansasii	Isoniazid 5 mg/kg (max 300 mg) + Rifampicin 10 mg/kg (max 600 mg) + Ethambutol 15 mg/kg (max 1.5 gm) OD orally	Daily till 12 months of negative sputum cultures	Clarithromycin, Rifabutin and Ethambutol can be used as alternate regimen
Mycobacterium fortuitum	Clarithromycin + Doxycycline + TMP-SFX or levofloxacin	Daily till 12 months of negative sputum cultures	Avoid Minocycline, Doxycycline, Tigecycline in children less than 12 years

We have we have a British thoracic guideline on NTM recently released in November 2017, and the treatment schedule is very clearly explained and this is taken from that. I have I have kind of given the most commonly seen NTM species and causing various kinds of disease. M avium the corner stone with the treatment is clarithromycin 500 milligram twice daily along with rifampicin ethambutol.

The dosage has to be continued for at least 18 months or until 12 months after culture negativity. In case we find resistance to either clarithromycin or rifampicin alternate regimens can be given in terms of azithromycin, or with rifabutin instead of rifampicin. The treatment for M abscessus again is clarithromycin along with an injectable aminoglycoside and cefoxitin if available.


Now if patients complain about injectables, in 3 weeks of intensive phase is when injectable is given in this regimen for everyday for a period of 3 weeks and then it can be continued as a continuation phase without an injectable. Mycobacterium kansasii consist

of treatment consist of isoniazid, rifampicin, and ethambutol treatment to given every day for a period of 12 months after they become culture negative.

One thing to remember here is M kansasii we are seeing increasing number of resistant M kansasii resistant as same both the isoniazid as well as to rifampicin. In those cases we should look for alternate therapy for this patients. The alternate regimen includes clarithromycin or rifabutin and also ciprofloxacin, or any of the fluoroquinolones.

(Refer Slide Time: 06:29)

Species	Treatment
Mycobacterium terrae	Optimal therapy not established. Suggested use of a macrolide + ethambutol or other agent based on susceptibility test
Mycobacterium chelonae	Optimal therapy not established. Suggested regimen include clarithromycin with a second agent based on in-vitro susceptibility test till 12 months of negative cultures
Mycobacterium scrofulaceum	Susceptibility data is lacking and standard treatment regimen still controversial



The slide is titled "Treatment schedule for common NTMs" and is presented in a table format. The table has two columns: "Species" and "Treatment". The rows correspond to Mycobacterium terrae, Mycobacterium chelonae, and Mycobacterium scrofulaceum. The slide is part of a presentation from the National Institute for Research in Tuberculosis (NIRT), as indicated by the logo and text on the left side of the slide.


The guidelines also gives treatment for mycobacterium terrae, mycobacterium chelonae, and the scrofulaceum. Most important thing to remember here the treatment does not end with the patient becoming culture negative. Treatment has to continue for 12 months after the patient becomes culture negative to the species.

(Refer Slide Time: 06:47)

Manage TB

Follow-up of NTM patients


- Sputum samples for mycobacterial culture
 - ✓ every 4-12 weeks during treatment and
 - ✓ for 12 months after completing treatment to assess the microbiological response
- If there is doubt about persisting NTM infection despite negative sputum cultures, a CT-directed bronchial wash to assess microbiological response to treatment



Since, these patients are taking treatment for more than 12 months they have to be followed up regular intervals for two important points, one is look for toxicity of these drugs, second to see for the sputum culture conversion. The sputum samples for mycobacterial culture during follow up period has to be con taken every 4 to 12 weeks for 12 months after completing treatment to assess for the microbiological response

At any time period if there is a doubt about persisting NTM infection though the sputum smear and cultures become negative, a CT directed bronchial wash can be done to assess for the microbiological response to treatment.

(Refer Slide Time: 07:24)



Drug adverse event monitoring

- **Aminoglycosides** : Auditory, vestibular and renal side effects
- **Ethambutol** : Ocular toxicity, particularly with daily dosing
 - Ethambutol excretion is reduced in patients with renal dysfunction
- **Azithromycin** : Gastrointestinal side effects, tinnitus and hearing loss (particularly with higher doses in elderly patients)


ICMR - National Institute for Research in Tuberculosis (NIRT)
www.nirt.res.in

Manage TB

Now, moving on to drug adverse event monitoring the three commonly used drugs include aminoglycosides, ethambutol, azithromycin, besides rifampicin, and isoniazid auditory and vestibular. Monitoring has to be done frequently when a patient is on aminoglycoside group of drugs, ocular toxicity should be monitored when someone is getting ethambutol for beyond 6 months and these drugs have to be given every day for almost 12 months of culture negativity.

Hence periodic ocular testing as well as audiometry testing is mandatory for these patients on a long drawn course of ethambutol, or dollar aminoglycoside. The group of azithromycins including clarithromycin can cause gastrointestinal disturbances mainly in the form of severe abdominal aches and pancreatitis. As a GI side effect has to be monitored frequently at least once in 3 months for the entire period of treatment.

(Refer Slide Time: 08:20)



Manage TB

Drug adverse event management


- When aminoglycosides are administered serum levels and serum creatinine must be monitored
- Audiometry should be considered before starting aminoglycosides and intermittently during treatment
- Patients should be informed to stop aminoglycoside treatment immediately and to inform if they develop tinnitus, vestibular disturbance or hearing loss

ICMR - National Institute for Research in Tuberculosis (NIRT)
www.nirt.res.in

We also have to monitor the serum levels for aminoglycoside if feasible if not at least look for serum urea, and creatinine during the follow up period when a patient is an aminoglycoside containing regimen. Patient can also be informed to stop aminoglycoside in the presence of tinnitus, or vertigo and inform to the medical officer immediately to look and then patient can be followed up for further investigations.

Visual acuity both in the form of color vision as well as any distance vision has to be monitored frequently. Serum ether module levels can also be monitored in case of suspected drug toxicity.

(Refer Slide Time: 08:53)



Manage TB

Role of Surgery in NTM-PD

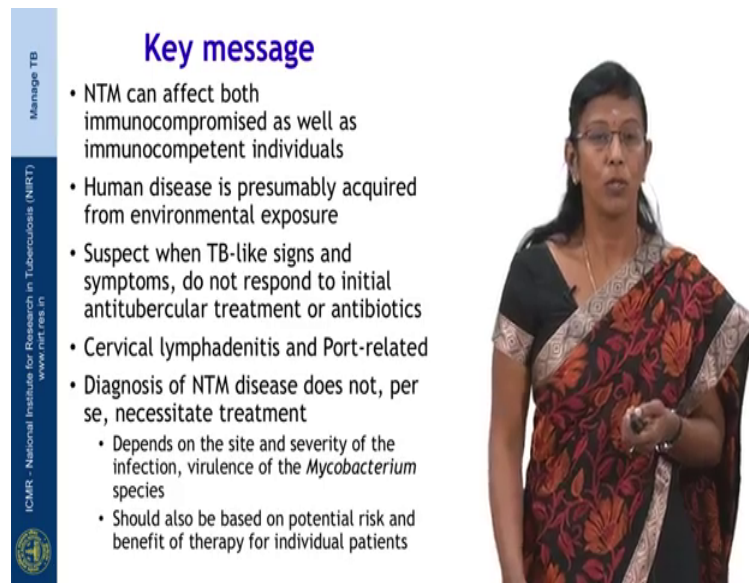
- Should be considered at the time of diagnosis and revisited in individuals who develop refractory disease
- Indicated in individuals with localised areas of severe disease
- Individuals with NTM-pulmonary disease should be established on antibiotic treatment prior to lung resection surgery and should continue treatment for 12 months after culture conversion
- Following resection of a solitary NTM nodule in an individual with no other features of NTM-pulmonary disease, antibiotic treatment is not usually required

ICMR - National Institute for Research in Tuberculosis (NIRT)
www.nirt.res.in

Is there a role of surgery in NTM pulmonary disease? Yes, surgery should be considered at the time of diagnosis and again revisit when the patient becomes refractory to treatment after 6 months of appropriate regimen.

It is usually indicated in individuals with localized areas of severe disease, individuals with NTM pulmonary disease should be established on antibiotic treatment prior to lung resection. They should also continue the same treatment for 12 months after culture conversion. In case the patient continues to have smear positivity and you are waiting for the culture results the antibiotic to be continued even in the post surgical period.

(Refer Slide Time: 09:35)



The slide features a vertical blue bar on the left with the text 'Manage TB' at the top, 'ICMR - National Institute for Research in Tuberculosis (NIRT)' in the middle, and the website 'www.nirt.res.in' at the bottom. The main title 'Key message' is in blue. The content is a bulleted list of points regarding NTM disease. To the right of the text is a photograph of a woman wearing a black and red floral saree, holding a small object in her hand.

Key message

- NTM can affect both immunocompromised as well as immunocompetent individuals
- Human disease is presumably acquired from environmental exposure
- Suspect when TB-like signs and symptoms, do not respond to initial antitubercular treatment or antibiotics
- Cervical lymphadenitis and Port-related
- Diagnosis of NTM disease does not, per se, necessitate treatment
 - Depends on the site and severity of the infection, virulence of the *Mycobacterium* species
 - Should also be based on potential risk and benefit of therapy for individual patients

ah So, we to end our session on NTM pulmonary disease as well as other NTM disease the key messages from this lecture we would like to inform that NTM can affect both immunocompromised as well as immunocompetent individuals. Human disease is specifically acquired from the environmental exposure, suspect NTM disease when TB like signs and symptoms do not respond to initial antitubercular treatment or antibiotics.

Cervical lymphadenitis and port related NTM disease are being more frequently seen and have to be suspected when they do not respond to the regular treatment. Diagnosis of NTM disease is laboratory based it does not per se necessitate treatment.

The treatment of NTM disease depends upon the site, the severity of the infection as well as the virulence of the organism. Hence, identification of the speeches of mycobacterium is the cornerstone for the management of NTM disease, and once identified treat the species appropriately with the given regimen with this we come to the end of NTM session.

Thank you.