South Indian Consensus on the

Diagnosis and Management of Genito-Urinary Tuberculosis

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History and Symptomatology

1. History of past infection or contact with a family member having Tuberculosis is important.
2. Symptoms are non-specific.
3. Chronic voiding symptoms like urgency not responding to conventional measures, recurrent or unresolved urinary tract infections, chronic epididymitis, repeated haematospermia should raise suspicion.
4. Constitutional symptoms such as fever, weight loss, night sweats may not always be present.
5. Urine analysis commonly shows acid pyuria and micro-haematuria in 50% of cases. 10% of patients present with gross haematuria; 20% of patients develop secondary coliform UTI.
6. Incidence of abnormalities in chest X-ray is about 75%.

Microbiological Diagnosis

1. Urine AFB smear – Atleast 3 early morning urine samples should be analysed. A bacterial load of 5000 organisms/ml is needed for positive smear.
2. In case of increased day/night urinary frequency, atleast 8 hours of collection of urine is required for AFB smear.
3. Sterile containers with specific inhibitors required for collection of samples.
4. Routine ZN staining has a sensitivity and specificity of 60-70% and 90-95% respectively.
5. Auramine/Rhodamine staining with fluorescent microscopy increases sensitivity by 10-15% as compared to ZN staining.
6. Smear positivity alone should not be considered as diagnostic of tuberculosis since chronic infections due to non-tubercular mycobacteria (NTM) is not uncommon and do not usually respond to the conventional ATT. In the absence of AFB culture or other molecular assays, there is high chance of branding a non-responder as non-compliant or resistant case of tuberculosis[i].

7. *M. smegmatis* is a rapid grower which produces a yellow pigment. M. tuberculosis is a slow grower and produces a buff/cream colour. *M. smegmatis* grows in Blood agar and MacConkey agar medium but not *M. tuberculosis*. Any mycobacteria grown in culture can be identified in 15 minutes using MPT64 card test (positive for *M. tuberculosis* complex). Clinical significance of *M. smegmatis* is questionable unless it has been repeatedly isolated and all other causes have been ruled out.

8. AFB culture by conventional LJ medium is still the gold standard and has a sensitivity and specificity of 80-85% and 98% respectively. The main drawback of this technique is that it requires 6-8 weeks for the results. Three types of media are used Egg based (LJ), Agar based (Middlebrook 7H10 or 7H11) or Liquid based (Middlebrook 7H9).
9. Radiometric culture methods give results in 2-3 wks and are equally sensitive (replaced by MGIT nowadays).

10. Mycobacterial Growth Indicator Tube (MGIT) uses Middlebrook 7H9 broth with oxygen sensitive fluorescent sensor at bottom. Positive signals are obtained in 10-12 days.

Immunologic Assays

1. Role of Mantoux skin test in Indian population is questionable. The issues in administering, interpretation in persons immunized with BCG and lower specificity in developing countries where prevalence of TB is higher have led to its questionable role.
2. Estimation of IgG and IgM antibodies has no role.
3. Interferon gamma assay has been found to be useful. The interferon (IFN)-γ assays are *in vitro* tests for quantifying the IFN-γ response to antigens representing *M. tuberculosis*, such as ESAT-6 or CFP-10. These antigens are not present in the BCG vaccine, but false-positive results can be caused by previous exposure to environmental mycobacteria. The IFN-γ release assay has a sensitivity of 84-95% and a specificity of 85-99%. Its validity in regions with high exposure like India needs further evaluation.

Molecular Techniques

1. NAAT- PCR methods have sensitivity of 70-100% and specificity of 80-100%. PCR assays may target either DNA or rRNA and these could be based on conventional DNA based PCR, nested PCR and RT-PCR. There has been concern about false positive reports due to contamination. The problem of false positivity can be substantially reduced by proper laboratory design, strict discipline about collection and processing of specimens, handling of reagents and use of certain blocking agents. Application of in-situ PCR approach eliminates doubts about contamination. It is also a good tool to detect drug resistance.
2. Molecular diagnostic techniques for TB are rapidly evolving and show great promise. Extrapulmonary samples are being validated on PCR machines, such as those based onGeneXpert® platform. Xpert®MTB/RIF is an automated nucleic amplification assay

for the simultaneous detection of tuberculosis and rifampicin resistance and has demonstrated 100% sensitivity on urine samples. This assay is beneficial, is a self-contained cartridge-based test, does not require intensive training to use, can give a result in less than two hours and was shown to correctly identify 97.6% of rifampicin-resistant bacilli in sputum samples. The role of this test in the diagnosis of EPTB, and of GUTB in particular, requires further evaluation.

Histological Diagnosis

Presence of granuloma with caseation is the hallmark of TB in a biopsy specimen.

Radiological Studies

1. IVU- High dose IVU is the standard procedure. Dynamic cystography may be helpful in distinguishing the refluxing megaureter from obstructive.
2. Radionuclide studies are helpful in determining the differential renal function and drainage pattern from the collecting systems.

3. RGP- The current recommended indications are
    a. To assess stricture length in the ureter
    b. To obtain isolated samples of urine from the kidney

    If RGP is not feasible, antegrade pylography may be done for delineating the anatomy and urine sampling

Cystoscopy and Biopsy

Cystoscopy and Biopsy should be performed under general anaesthesia (with muscle relaxants) in a gentle manner. Bladder biopsy is indicated in presence of tubercles or ulcers and should be avoided in acute cystitis phase.

Criteria for Definitive Diagnosis[ii]

One major and/or two minor criteria are required for definitive diagnosis of Tuberculosis.

Major Criteria

a) Granulomatous lesion in biopsy specimen

b) AFB in urine or tissue(smear or culture)

c) Positive PCR

Minor Criteria

a) IVU/CT/MRI findings suggestive of GUTB

b) Haematuria

c) Raised ESR

d) Pulmonary changes of old Kochs

Medical Management

First chance is the best to cure the disease (100%) and in preventing the emergence of resistance. Treatment of multidrug resistant tuberculosis is 100 times more expensive and often highly toxic.

Short course chemotherapy for 6 months is sufficient which includes 2 months of initial intense treatment phase with 4 drugs followed by 4 months of continuation treatment phase with 2 drugs. Areas of calcification, poor function, severe scarring and obstruction, fistula formation may require additional procedures and prolongations of treatment. In cases where isoniazid or rifampin cannot be used, treatment is continued for 12-18 months. If second line treatment is to be offered, treatment is recommended for 18-24 months. Surgery or steroid therapy by itself is no indication to prolong ATT.

ATT is to be taken on empty stomach since food, antacids containing aluminum and magnesium and prokinetics reduces the absorption of the medicines significantly. If it cannot be tolerated, the medication may be taken 2 hours after breakfast or 2-3 hours after dinner.

Use of steroids: recommended in severe bladder symptoms and involvement of tubular structures like ureter, fallopian tube, vas and spermatic cord. 4-6 weeks of high dose of prednisone (at least 20mg thrice daily) is recommended since rifampicin reduces the bioavailability and effectiveness of steroids by 66%.

Indications for prolonged therapy

a. immunocompromised patient

b. Coexistent HIV/AIDS

Special situations

1. Pregnancy: add pyridoxine; avoid streptomycin. Isoniazid, rifampicin, ethambutol and pyrazinamide are safe.
2. Renal failure: modify the dosage of isoniazid, ethambutol and streptomycin according to eGFR.
3. Diabetes Mellitus: attain tight glycemic control; add pyridoxine.

4. Post-renal transplant on cyclosporine: avoid rifampin since cyclosporine clearance is augmented.

5. HIV positive: Short course therapy is indicated in asymptomatic serology positive patients. Usually good response but relapse is more common.

   Prolonged course of treatment may be required in late stages and with other immune-compromised conditions.
6. Seriously ill patients with suspected TB: use of specific empiric anti-tuberculosis [SEATT] therapy with isoniazid, ethambutol, pyrazinamide can be used as a method of therapeutic diagnosis and treatment of seriously ill and febrile patients with clinical and radiological suspicion of TB in the absence of bacteriological or histological proof. Fever is used as guide for response to therapy. Rifampicin is added when fever settles.

7. In case of MDR TB, 4 drug therapy selected on basis of sensitivity, to be given for 18-24 months.

Follow Up Protocol When On ATT

Follow up is required to monitor the toxicity of ATT and development of complications. ATT cannot prevent or cure persistent residual lesions, paradoxical worsening or complications developing from immunological or mechanical reasons. Monitoring for hepatic toxicity, drug interactions and visual and auditory complications are done in the standard way as recommended for ATT for tuberculosis at any site. Blood test for LFT, Hb, platelet count, ESR, RFT, serum electrolytes and calcium is done at 1, 2, 4 and 6 months and as necessary as the condition demands thereafter. Monitoring is tailored according to the structural and functional involvement of the genital and urinary organs affected. Since healing is a prolonged process, ongoing fibrotic changes may be expected to occur for long even after completion of ATT and such changes may lead to mechanical complications like infundibular and ureteral strictures, secondary PUJ and VUJ obstructions, reducing bladder capacity, urethral strictures, tubal and vassal obstructions etc. Ultrasonography, IVU, RGU, cystoscopy and RGP, nephrostograms and radionuclide renal scans may be obtained as appropriate till the structural abnormality that has occurred is found to have stabilized which may take several months to years even after completing ATT.

The response to therapy is monitored clinically. Fever may take a few weeks to settle. Worsening of fever may be indicator or drug sensitivity when all drugs have to be stopped forthwith and to resume the medication one by one to identify the offending medication and thereby to modify the treatment protocol. Urine AFB smear and culture and PCR may be obtained at 2 months, after the completion of the initial intensive regimen of therapy. If positive, second line therapy is to be considered.

Follow up is also necessary to ensure the compliance with the ATT. After completion of ATT patient needs to be on yearly follow-up, atleast for initial few years to detect development of late complications.

Surgical Management

1. Indications for Stenting

Maintain drainage during medical therapy.

After surgery, to facilitate healing

After dilatation of ureteral strictures

Stents are retained if inserted sufficiently long to stabilize strictures which may take a year or two or more. RGP may be obtained without or with ureteroscopy to study the progression of stricture. Appropriate surgical intervention may be considered for non-resolving strictures. If stent is decided to be removed, follow up may be done with ultrasonography, IVU or DTPA or MAG3 renal scintigraphy in 1-3 months to ensure that restructuring is not developing.

2. Indications for Percutaneous Nephrostomy

Inability to place a stent especially in ureteral strictures

Infundibular stenosis with calyceal dilatation

3.Indications for Nephrectomy

Nonfunctioning kidney with or without calcification

Extensive disease involving whole kidney

Hypertension due to tuberculous nephropathy

Co-existing renal carcinoma

Surgical intervention should be planned after atleast 4-6 weeks of completion of chemotherapy.

It should be noted that nephrectomy in the setting of TB is not an easy task.

Nearly 50% of the tuberculous nephrectomy specimens harbor active TB inspite of adequate chemotherapy.

4.Indications for Partial Nephrectomy

Localised polar lesion with calcification, not responding to 6 weeks of intensive chemotherapy.

Area of calcification gradually increasing in size.

5.Abscess Drainage

This should be restricted to percutaneous drainage by PCN or aspiration.

6.Indications of Epididymectomy

Caseating abscess not responding to ATT

Firm swelling in the epididymis increasing in size in-spite of ATT

7.Management of Ureteral Strictures

Uretero-vesical junction strictures are more common and may require ureteral reimplantation if strictures fail to resolve with chemotherapy and DJ stenting.

PUJ strictures may need pyeloplasty in cases not responding to conservative measures like stenting and dilatation.

Complex cases may need reconstruction on a per case basis.

8.Bladder Reconstruction

Augmentation cystoplasty may be required in cases of thimble bladder.

Suggested Reading

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