Management and Treatment of TB Disease and Latent TB Infection

TB 101 Web-based Workshop

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Objectives

- Describe the basic principles for the medical management of TB cases
- Describe the basic principles for the medical management of latent TB infection (LTBI)
- Identify the recommended 4-drug regimen for initial treatment of TB disease and why a multi-drug regimen is used
- Describe common side effects of TB medication
- Describe a timeline of TB treatment

Objectives (2)

- Define “directly observed therapy” (DOT)
- Identify risk factors for non-adherence to a TB treatment regimen and strategies to improve adherence rates
- Identify strategies to keep field workers safe
- Describe strategies for working effectively with private providers
- Describe why confidentiality is essential in TB case management

Treatment of TB Disease

- Goals for treatment of TB disease:
  - To cure the individual patient (personal health)
  - To minimize the transmission of *Mycobacterium tuberculosis (M. tb)* to others (protection of the public's health)

TB Disease

- Millions of TB organisms are present
- Must kill all organisms to have lasting cure
- Multiple drugs to which the TB organism is sensitive must be used initially and to prevent the emergence of drug resistance during treatment

Short Course Treatment

- Treatment has gone from several years to 6 months and now less in some instances
- Isoniazid and rifampin are required to shorten the length of treatment
- Without them, treatment can turn into many more months to years
- DOT is critical to prevent loss of isoniazid and rifampin to resistance due to non-compliance

DOT

- Standard of care for TB treatment
- Every dose should be observed by a healthcare worker
- Who is at risk for non-adherence?
- Every person can be at risk
- Treatment is long and boring
- Patients feel better when taking treatment on their own and then are prone to quit

Principles of TB Treatment

- Every dose is observed
- Multiple drugs are used for treatment
- Count doses and not months of treatment
- Treatment must be closely monitored by nurse for symptoms and side effects
- There can be deaths from little or no monitoring of patients on TB treatment

First-line Drugs

- Most effective anti-TB drugs and used before all others
- Exception: in the presence of known or suspected drug resistance
  - Known: drug susceptibilities known
  - Suspected: known exposure to certain drug resistance patterns and/or coming from areas where certain drug resistance patterns exist

First-line Drugs (2)

- Isoniazid (INH)
- Rifampin (RIF)
- Ethambutol (EMB)
- Pyrazinamide (PZA)

Second-line Drugs

- Many older drugs; still effective
- Not as effective as first-line drugs
- Mostly used in the presence of drug resistance or intolerance to first-line drugs
- Length of treatment is increased when these drugs are used
- We'll mention names of these drugs but will not go into detail today

Second-line Drugs (2)

- Levofloxacin
- Streptomycin (SM)
- Para-amino salicylic acid (PAS)
- Ethionamide (ETH)
- Cycloserine (CYS)
- Kanamycin (KM)
- Capreomycin (CM)

Second-line Drugs (3)

- Used in the treatment of drug resistance
- Multidrug-resistant (MDR) TB
  - Defined as when TB organisms are resistant to both INH and RIF
  - Decreases the chance of a cure from 95% to 50%
  - If the patient is not put on DOT, they can become an untreatable case

Adverse Events of First-line TB Drugs

- Side effects
- Toxicities

Patient Safety in TB Treatment

- Important that the patient's health be carefully monitored during treatment
- Baseline bio-chemical monitoring and then if adverse events develop:
  - Baseline and monthly clinical monitoring for symptoms of TB and adverse events is mandatory; never optional
  - Report to physician if side effects are persistent or toxicities occur

Patient Safety in TB Treatment (2)

- Chart all of patient's other medications and note potential for drug interactions
- Use DOT visits as opportunities to monitor patient tolerance and progress to cure
- Monitor weight baseline at least monthly for all patients, especially children
- Don't forget that as patient gains weight, dosages may need to be changed
- Report all abnormalities to physician

Side Effects of TB Drugs

- Unpleasant, but mild reactions
- No long lasting health effects
- Does not usually require changes in therapy
- Gas, bloating, mild nausea
- Discoloration of body fluids
- Irritability
- Insomnia
- Photosensitivity

TB Drug Toxicities

- More severe than side effects
- May be life threatening
- May require changes in dosage or discontinuation of the drug(s)
- May require additional treatment or hospitalization

TB Drug Toxicities (2)

- Significant gastrointestinal (GI) upset (stomach)
- Hepatotoxicity (Hepatitis–liver)
- Dermatologic and hypersensitivity reactions (skin)
- Ophthalmic toxicity (eye)
- Renal toxicity (kidney)
- Musculoskeletal adverse events (muscles and joints)
- Hematological significant changes (blood)

TB Drug Interactions

- Increase or decrease the actions of TB drugs or other drugs
- To find complete listing of drug interactions: go into your web-browser and type in “TB drug interactions”

Immune-suppressive Actions

- Rheumatoid Arthritis (RA) medications
- Be aware of these reactions of newer RA drugs
- Can cause relapse of old inadequately treated TB disease and/or possible rapid progression from TB infection to TB disease
- Very serious, possibly fatal complications
- Flag charts of patients who are taking these and other immune-suppressive drugs while on TB treatment for disease or LTBI

Isoniazid (INH)

- Bacteriocidal (kills TB organisms)
- Helps other TB drugs penetrate the organism's waxy covering
- Only works on *M. tb*
- Penetrates spinal fluid (TB meningitis)
- Penetrates caseous material (cavities)
- Metabolized in liver (implications for close monitoring in infection and disease)

INH Side Effects

- GI upset
- Rash (very common)
- Liver toxicity (can be life-threatening)
- Peripheral neuropathy (tingling in extremities–give vitamin B-6 to prevent)
- Mild central nervous system (CNS) toxicity

INH Drug Interactions

- Phenytoin (dilantin and other anti-convulsants)
- Theophylline
- Warfarin (coumadin)
- Cycloserine
- Benzodiazepines (CNS depressants) alium, Xanax, Ativan, Restoril, Librium, and others

Rifampin (RIF)

- Bacteriocidal
- Inhibits growth of *M. tb*
- Can be used on other organisms
  - *Mycobacterium* other than TB (MOTTs), Nontuberculous Mycobacteria (NTM)
  - Staph, Legionella, Meningococcal Meningitis, Methicillin-resistant *Staphylococcus Aureus* (MRSA)

RIF Side Effects

- GI, anorexia, diarrhea
- Rash, itching
- Arthralgias, myalgias
- Liver toxicity
- Thrombocytopenia (decreased platelets with petechiae), most serious

RIF Other Characteristics

- Enters other body fluids
- Colors urine, tears are orange
- May discolor some contact lenses
- Does not enter CNS

RIF Drug Interactions

- HIV protease inhibitors (give rifabutin, instead of RIF)
- Phenytoin (dilantin)
- Methadone
- Oral contraceptives that are estrogen-based (offer additional method or another method)
- Oral anti-coagulants
- Oral hypoglycemic agents

Pyrazinamide (PZA)

- Bacteriocidal
- Only used for treatment of TB
- Works well in the cell and on slow growing organisms

PZA Adverse Events

- Rash, photosensitive dermatitis
- Elevated uric acid with joint pain (gout)
- Hepatotoxicity
- Hyperuricemia

Ethambutol (EMB)

- Bacteriostatic and bacteriocidal (both stuns and kills TB organisms)
- Interferes with the cells growth
- Used for *Mycobacterium other than TB*

EMB Adverse Events

- Optic neuritis
- Red/green color discrimination
- Decreased visual acuity
- Note: also interacts with aluminum salts as in some antacids

Streptomycin (SM)

- Only drug contraindicated in pregnancy
- Causes 8th nerve damage (deafness) in fetus
- Can cause deafness and vestibular damage (balance)
- Nephrotoxicity (kidney)

Basic TB Drug Regimen

- Four drugs initially for all patients
  - INH, RIF, PZA, EMB for two months daily, then
  - INH and RIF for four months twice weekly (biw)
  - Daily doses can now be given five days per week
  - DOT mandatory for compliance with therapy

Counting Doses

- Patient must ingest prescribed number of doses within a given time period
- Do not count **months** of treatment
- Only count **doses** observed by DOT
- All doses missed must be made up or treatment is not complete
- Look to ATS/CDC documents for required doses and timeframe according to the chosen regimen

Remember This: Important Rule in Treatment of TB Disease

- If patient is failing treatment, **never** add just one drug to a failing regimen—causes resistance to develop
- Signs of treatment failure
  - Failure to convert sputum
  - Worsening chest x-ray
  - Failure of patient to improve clinically (*i.e.,* fever, cough night sweats, anorexia, malaise, weight loss)

Who is at Risk for Non-adherence?

- Persons at **most** risk for non-adherence and treatment failure are those that have demonstrated:
  - Previous failure to complete adequate treatment for LTBI or TB disease
  - Failure to comply with treatment of other medical situations; diabetes, family planning, morbid obesity
  - Known or suspected drug resistant disease

DOT

- Is exactly what it says it is…"directly observed" and nothing else!

What DOT is Not

- Not leaving doses if the patient is not home
- Not letting family members or significant others be responsible for observing the patient taking medicines
- Not giving the patient pills to take unobserved–**Better to not give some patient's medicines at all, unless directly observed**
- Unobserved doses cannot be counted in the total dose count for completion of treatment

DOT Rules

- Once the patient is on DOT, do not take him/her off
- Make sure that the patient swallows pills and stay in patient's presence to make sure the pills go down
- Intermittent treatment is **always directly observed**
- There is always a way to get DOT to a patient. Brainstorm awhile and you will figure it out

More DOT Rules

- If the patient requires DOT twice a day, then he must receive it twice a day (as in treatment of drug resistance)
- Family members should only give meds under the direct observation of a healthcare worker
- Lay persons (non-licensed) do DOT very well. There should be an established safety net to protect both the supervisor and the lay worker

Field Worker Safety

- Ensure that the whereabouts of workers is known at all times; schedules and contacting information
- Maintain log with cell phone numbers of workers and patients (if available)
- Maintain communication link with case manager or person in charge
- Supply emergency phone numbers to field workers to maintain these links

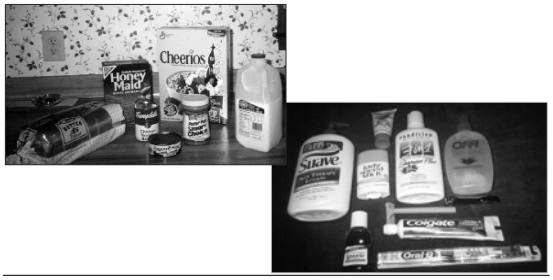
Field Worker Safety (2)

- Worker must make supervisor aware of patient/worker conflicts, threats, and other issues
- If threats are made with intent to harm the worker (weapons, violence), inform police according to agency policy
- If field visits are deemed not safe, change location of visit; have patient come into facility; provide transportation assistance
- Legal action should be the last resort, but not at expense of worker's safety

Using Incentives and Enablers to Enhance Adherence and Cooperation

- **Incentives**: small gifts that encourage the patient to complete treatment
  - Incentives are chosen by the caregiver and are special for each individual patient (*i.e.,* food items, treats, soft drinks, personal items, clothing, etc.)
- **Enablers**: things that enable a patient to complete treatment such as bus tokens, money for gas, money for baby sitter, pay for a driver's license fee

Incentives



Incentives (2)

Incentives (3)

Incentives (4)

Incentives (5)

How Do I Know That My Patient is Cured?

- Required number of doses have been ingested
- Strict DOT observed
- Patient has clinically improved
- Chest x-ray (CXR) has cleared to clinician's satisfaction (there may be a post treatment CXR)
- Sputum conversion has been documented

Can All TB Be Cured?

- In most cases, TB is curable
- MDR-TB can become incurable if not promptly diagnosed and appropriately treated
- May take years to cure MDR
- Very labor intensive; hard on the patient and the staff responsible for treatment

Can TB Be Prevented?

- If compliance with treatment for LTBI is assured, the prevention of TB disease is probably 90+%

Goals for Treatment of LTBI

- To prevent progression of LTBI to active disease
  - To prevent LTBI in persons who may be at high risk for developing TB infection and disease (primary prophylaxis)
  - Infants and young children exposed to contagious persons
  - Immune suppressed persons such as persons with HIV infection

Persons at Risk for Developing TB Disease

- Persons at high risk for developing TB disease fall into two categories:
  - Those who have been recently infected
  - Those with clinical conditions that increase their risk of progressing from LTBI to TB disease

Recent Infection as a Risk Factor

- Close contacts to persons with infectious TB
- Skin test converters (within past 2 years)
- Recent immigrants from TB-endemic regions of the world (within 5 years of arrival to the U.S.)

Increased Risk for Progression to TB Disease

- HIV infection
- Prior untreated TB
- Those with fibrotic lesions on CXR
- Underweight or malnourished persons
- Injection drug users
- Those receiving tumor necrosis factor-alpha (TNF-α) antagonists for treatment of RA or Crohn's Disease

Increased Risk for Progression to TB Disease (2)

- Medical conditions such as:
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure or on hemodialysis
  - Solid organ transplantation (*i.e.,* heart, kidney)
  - Carcinoma of head or neck
  - Gastrectomy or jejunoileal bypass

Treatment of LTBI

- Treatment can be done with just one drug (INH drug of choice)
- Regimens vary in presence of exposure to drug-resistant smear positive cases
- Number of TB organisms are much less than in TB disease
- Non-adherence to INH treatment of LTBI rarely causes drug-resistant disease

Initiating Treatment of LTBI

- Rule out TB disease
  - Get CXR
  - Wait for culture result if specimen obtained
  - Determine prior history of treatment for LTBI or TB disease
  - Assess risks and benefits of treatment
  - Determine current and previous drug therapy
  - Assess potential compliance issues

INH Regimen

- 9 months preferred
- 6 months less effective, but may be used if unable to complete 9 months
- May be given daily or intermittently (biw)
- Must be on DOT for intermittent regimen

RIF Regimen

- If possible, with exposure to drug resistant organisms or intolerance to INH, RIF for four months daily may be used
- Rifabutin may be used instead of RIF for person with HIV on protease inhibitors

Monitoring in LTBI Treatment

- Baseline liver function tests (LFTs), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin are not necessary except for patients with the following risk factors:
  - HIV infection
  - History of liver disease
  - Alcoholism
  - Pregnancy or in early postpartum period

Clinical Monitoring for LTBI Treatment

- Monthly assessment for symptoms of liver toxicity and other adverse events such as rash, gastric distress
- For self-administered treatment (SAT) of LTBI, never dispense more than 30 days supply of medication, due to potential liver toxicity
- DOT visits for person at high risk of developing TB (close contacts) and children are opportune times to assess for side effects

Completion of Therapy

- Completion of therapy based on the total number of doses administered, not on duration alone

Working With Private Providers

- The name of this game is **cooperation and communication**
- The health department has overall responsibility to see that TB cases have adequate treatment and are treated to cure
- If the private provider assumes treatment responsibility, he or she must have the same goal of providing adequate treatment to cure

Working With Private Providers: Private Physician's Responsibility

- Report suspected and confirmed cases to the health department
- In California, submit discharge plans for review and approval by the health department (Gotch Law)
- Discuss treatment plans with the health department's responsible person
- Ensure that treatment regimen is adequate

Working With Private Providers: Private Physician's Responsibility (2)

- Information for report of verified case of TB (RVCT) is provided
- Issue order for DOT
- Ongoing medical assessment
- Management of other illnesses and any reported problems with medications

Working With Private Providers: Private Physician's Responsibility (3)

- Maintains communication with TB Control:
  - Updates clinical, radiographic, and bacteriological information when it becomes available
  - Provides clinical update at least quarterly and as requested by health department
  - Compliance issues arise (if DOT has been previously refused)
  - Patient completes treatment

Working with Private Providers: Private Physician's Responsibility (4)

- Maintains communication with TB Control if:
  - Patient fails to keep appointments
  - Patient relocates without notice
  - Patient discontinues care

Co-management of TB Patients

- Health department responsibilities
  - Assigns case manager
  - Conducts risk assessment for non-adherence; provides DOT
  - Maintains ongoing surveillance
  - Ensures that contact investigation is completed (not the physician's responsibility)
  - Carries out all mandated responsibilities of protecting the public's health

Co-management of TB Patients (2)

- Ensure that private provider has current information on the diagnosis, treatment, and management of TB
  - Maintain TB register
  - Obtain patient update every 1–3 months or more often as necessary
  - Monitor follow-up sputum collection to document conversion
  - Provide DOT, incentives, and enablers to ensure compliance and completion of RX

The Last Word

- Confidentiality
  - Take care to remember that the patient's confidentiality must be maintained at all times and in **all** that we have talked about today
  - The health department must maintain its trustworthiness in the community to benefit our work with future patients

References

- ATS/CDC. **Treatment of Tuberculosis and Tuberculosis Infection in Adults and Children**. *American Journal of Respiratory and Critical Care Medicine.* 1994. 149;1359-1374.
- CDC. **Treating Tuberculosis–A Clinical Guide**. 1994.