Principles of TB Chemotherapy and Treatment

Overview

• TB treatment principles
• TB drugs and regimens
• Treatment implementation (and monitoring)
• Emerging concepts
• (extra slides) Special Situations

Milestones in TB Therapy

• 1860-1943 Sanitoria, rest, fresh air, lung collapse, ping-pong balls
• 1943 Schatz and Waksman discover streptomycin
• 1945 First drug-resistant strain isolated
• 1949 BMRC trial: streptomycin v streptomycin+PAS
• 1952 Development of INH
• 1960’s Ambulatory chemotherapy
• 1960’s INH preventive therapy
• 1970’s Introduction of RIF
• 1980’s Re-introduction of PZA in 6-mo. short-course regimens
• 2000’s Interest in Florquinolones and Linezolid for TB
• 2013 New TB drugs emerging: Bedaquiline, Delaminid
Antituberculosis Drugs Currently in Use

**First-Line Drugs**
- Isoniazid (INH)
- Rifampin (RIF)
- Pyrazinamide (PZA)
- Ethambutol (EMB)
- Rifabutin*
- Rifapentine

**Second-Line Drugs (not complete)**
- Streptomycin (SM)
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide
- Amikacin or kanamycin*
- Capreomycin
- Levofloxacin* Moxifloxacin*
- Bedaquiline

* Not approved by the U.S. Food and Drug Administration for use in the treatment of TB.

How did we get this regimen and approach?

- Why do we need multiple drugs?
- Why do we use these particular drugs?
- Why does the initial intensive phase treatment differ from continuation phase?
- Why do we treat for a total of 6 months?

Why do we need multiple drugs?

- Prevent drug resistance:
  - Tb must be treated with at least **two drugs** to which the organism is susceptible (**e.g., INH and Rifampin**)
  - Selection of drug resistance mutations with monotherapy
- Susceptibility is unknown:
  - Timeline from Drug Sensitivity testing is long
  - When population prevalence of INH resistance is >4%, we include Ethambutol (or Streptomycin) in the initial regimen
Preventing Drug resistance

- Resistance is conferred by genetic mutations
  - Spontaneous and random
  - Mutations are independent of each other

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Rate of mutation</th>
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<tbody>
<tr>
<td>INH resistance</td>
<td>1/1,000,000</td>
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<tr>
<td>Rifampin resistance</td>
<td>1/100,000,000</td>
</tr>
<tr>
<td>Both INH and rifampin resistance</td>
<td>1/100,000,000,000,000</td>
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2 drugs therefore likely to cover the entire population of bacteria

Multiple Drugs?

- Resistance mutations occur spontaneously within a replicating population of bacteria with a predictable frequency ($f$)
  - $f$ Rif-R mutation $10^{-8}$; INH-R $10^{-6}$
- Mutations appear independently of each other
- Among a population of $10^9$ AFB (e.g., intracavitary), 10 bacteria will be Rif-resistant; 1,000 will be INH-resistant
  - These resistant populations will be mutually exclusive
  - Therefore 2 drugs will cover the entire population

Multiple drugs have benefits

Any organism with mutations to both drugs will not be killed, but probability of one organism with both mutations is very small

Why these drugs: Objectives of TB Therapy

- Kill actively multiplying bacteria (Initial phase)
  - Improve symptoms & prevent death
  - Prevent transmission to others
  - Prevent emergence of resistance
- Sterilize disease sites (Continuation phase)
  - Cure the disease
- Drugs differ in their activity against TB
  - Bactericidal
  - Bacteriostatic
  - Sterilizing
Why do we use these drugs?

• Each drug has a special role in TB therapy
  – Isoniazid (H, INH): Early bactericidal activity (kill the dividing bacteria)
  – Rifampin (R, Rif): Sterilizing activity (prevents relapse)
  – Pyrazinamide (Z, PZA): special ‘shortening’ activity
  – Ethambutol (E, EMB): fortify the regimen to prevent drug resistance

Bacterial Targets of TB Therapy

• Rapidly multiplying bacteria (in cavities)
• Slowly multiplying bacteria (in acidic environment of macrophages or cavity wall)
• Sporadically multiplying bacteria (location?)

Hypothetical Model of TB Chemotherapy
M. Iseman, D. Mitchison

3 anatomic/metabolic populations of bacilli in cavitary TB

A: rapidly multiplying, INH>RIF>EMB
B: slowly multiplying, acid pH, PZA>RIF>INH
C: sporadically multiplying, Rif>INH

Bactericidal

• Ability of drug to rapidly kill multiplying M. tb
• Drugs that have early bactericidal activity reduce the chance of resistance developing
  – INH/Moxifloxacin > EMB > RIF
  – PZA is poor in this regard

• “Intensive” phase: attempting to rapidly kill multiplying bacteria
  – (smear and culture conversion)
### Sterilizing

- Ability of drug to kill bacilli, mainly in the subpopulations of *M. tb*, that persist beyond the early months of therapy
  - RIF (and PZA) have the greatest sterilizing activity
- “Continuation” phase: attempting to sterilize/cure to prevent relapse

### The unique role of PZA

- PZA does not protect against the emergence of resistance in a companion drug
- It is essential in the first 2 months to allow a short course (i.e., 6 month) regimen (BMC trials)
- PZA works best in low pH environments

### Some general considerations: you can’t mix and match drugs

- 6 months (26 wks) is the minimum duration of treatment
  - Require a Rifamycin throughout
  - Requires PZA for the first 2 months
- 6 month regimens are effective without INH (RZE)
- Without PZA minimum duration is 9 months (39 wks)
- Without RIF, minimum duration is 12 months (up to 18+ mos)

### New guidelines prioritize daily therapy

- Accurate dose counting is required but difficult
- Studies have not evaluated 5 vs 7 days

Continuation phase increased to 7 months if initial film shows cavities and sputum is culture-positive at completion of 2 months of treatment.
Why do we dose the way we do?

- Drug half-lives is ~2-4 hours
  - Would indicate need for BID to TID dosing
- Bacteria multiplication rate is ~24 hours
  - Means daily dosing is adequate
- Most drugs have post-antibiotic effect
  - Allows for intermittent dosing (BIW, TIW, QWk)

Treatment Implementation and Monitoring and Duration

Initial Questions

Responsibility for Successful Treatment: Role of the Provider/Health Department

- Goal of treatment: Cure the individual patient and minimize transmission of M.tb
- Successful treatment benefits the individual patient and the community
- Responsibility lies with health care provider, not only for prescribing appropriate regimen, but for ensuring successful completion of therapy
Management Strategies

Treatment course can be challenging, potentially toxic, and LONG

Example of state regulations: Maryland

- “A health care provider shall place individuals with tuberculosis and suspected tuberculosis on a tuberculosis treatment regimen that is in accordance with current national and State standards of care, and that provide for direct observation by a trained health care worker of ingestion of each dose of medication.”

Management Strategies

- Circumstances surrounding each patient may affect their ability to complete treatment
- Individualized treatment and care plan for completion including management of special circumstances (HIV, liver disease, diabetes, transplant etc.)
- Case management, using a patient-centered approach to coordinate care
- Interventions using enablers to assist in completion of therapy (transportation, convenient clinic hours, bilingual staff)
- Interventions using incentives meaningful to the patient (movie passes, gift cards, meal vouchers, clothing)
Patient Centered Care:
DOT and individual treatment plans

- Direct observation of treatment (DOT) with individualized case management is approach of choice
  - Health care worker watches patient swallow each dose of medication
  - Usually done at the patient’s home or workplace
  - Allows clinician/program to KNOW when patient misses doses, allowing more intensive outreach/monitoring
  - Must consider individual circumstances

- Used with other measures to promote adherence
- Conducted for all patients

DOT Impact on Completion Rates

- Non-supervised therapy (n=9) 61%
- Modified DOT (n=2) 79%
- DOT (n=4) 86%
- Enhanced DOT (n=12) 91%

DOT = Directly Observed Therapy
Modified DOT = DOT given only for a portion of the treatment period, often while the patient was hospitalized
Enhanced DOT = Individualized incentives & enablers were provided in addition to DOT

Directly observed therapy (DOT) remains standard of care to promote successful completion of therapy

PICO Question 2: Does self-administered therapy (SAT) have similar outcomes compared to directly observed therapy (DOT) in patients with various forms of tuberculosis?
Recommendation 2: We suggest using DOT rather than SAT for routine treatment of patients with all forms of tuberculosis (conditional recommendation, low certainty in the evidence).

- Key principles outlined in new IDSA/CDC guidelines:
  - “To be consistent with principles of patient-centered care, decisions regarding use of DOT must be made in concert with the patient”
  - The “least restrictive public health interventions that are effective are used to achieve adherence”
  - “Implementation of DOT may not be readily feasible when resources are limited”
  - “DOT has expanded to other modalities such as web-based video and mobile phones which have been well received by both patients and health dept staff”

Treatment Monitoring

- How do you monitor treatment response?
- How do you determine treatment completion?

Case #1: TB treatment

- 17 year old girl admitted with pneumonia
- Started on Ceftriaxone and Azithro: not improving 7 days later
- HIV test: negative
- Started on Moxifloxacin
- Improves and is discharged
- 3 days after discharge
  - AFB smear result: 3+ positive
  - Mycobacterial culture grows TB at 14 days

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<thead>
<tr>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
<th>Extension</th>
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<tbody>
<tr>
<td>4 Drugs: Rifampin, Isoniazid, Pyrazinamide, Ethambutol</td>
<td>2 Drugs: Isoniazid, Rifampin</td>
<td>Consider Prolong therapy for cavitary TB, slow culture conversion, TB meningitis, TB osteomyelitis</td>
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<tr>
<td>8 WEEKS</td>
<td>18 weeks</td>
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Baseline Evaluations

1. Collect specimens for microscopy and culture:
   - Helps to determine infectiousness, and microbiological response
2. Perform susceptibility testing for INH, Rif, PZA and EMB on an initial positive culture
   - Allows determination of appropriate therapy
3. Perform HIV counseling and testing for all patients/suspects
   - CD4, viral load if HIV positive
4. LFT’s (Hepatitis screening), Chemistry: baseline and at least monthly
5. Imaging
6. Diabetes screening
7. Baseline visual acuity and color monitoring (if EMB is used longer than 2 months)
8. Clinical Assessment: Weight, symptoms, physical findings

Treatment Monitoring – components

- Monitoring Needed:
  - Microbiologic: sputa monthly until culture negative for two consecutive months
  - Clinical: weekly
  - Laboratory: monthly
  - Radiographic: consider at two months and at conclusion
- Treatment assessment

TB Treatment Timeline:

- Obtain drug susceptibilities.
- DST results: pan sensitive
- Stop EMB
- Assess culture conversion
- Complete Target Doses for intensive phase (e.g. 56 daily DOT)
- Stop PZA
- Complete Target Doses for continuation phase (INH + Rifampin) (e.g. 126 daily DOT)
- Missed doses are made up
- Assessing clinical, microbiological, radiographic response
Treatment Monitoring – Microbiology

- Serial sputum smears (weekly) to assess early response
  - Target: Smear Conversion (smear positive to negative)
- Monthly sputum for AFB smear and culture (until consecutive cultures negative for 2 months)
  - Target: Culture Conversion (Cx positive to negative)
  - 2 month culture conversion is an important benchmark
  - Persistent Culture positivity (e.g. 3 mo) requires further investigation

Example: TB treatment review (weekly, monthly)

- 17 year old girl with Smear positive Pulmonary TB:
  - Started on RHZE daily → IR in continuation phase thrice/weekly
- Microbiologic assessment:
  - Smear conversion: 12 days
  - Culture Conversion: 45 days
- Clinical/Lab assessment:
  - Fevers resolved; Gained 10lbs at 2 months
  - Baseline LFT’s normal, HIV-negative
- Radiologic assessment:
  - CXR at 3 months: Normal
- Treatment assessment and progress:
  - Example: “Currently at 30 verified doses out of a target of 40 doses (5 doses/wk x 8 weeks)”;
  - “has completed 6 (30/5 doses per wk) out of 8 weeks of DOT doses”
  - Document # of missed doses and overall adherence to DOT

Drug level monitoring?

- After 2 months of therapy, if cultures are positive or symptoms/radiology do not resolve, reevaluate for:
  - Drug resistance
  - Non-adherence
  - Malabsorption
- Repeat Drug Susceptibility Testing
- Therapeutic Drug Level Monitoring
  - May consider even earlier in some patients (diabetics, abnormal gut anatomy)

Heysell et al. TDM for slow responders to TB treatment in a State Control Program. CID 2010 Oct
Treatment Monitoring – clinical/laboratory/radiology

• Clinical Monitoring: (minimum monthly) evaluation to assess adherence and identify adverse reactions
• Repeat chest x-ray:
  – At completion of initial treatment phase for patients with initial negative cultures
  – At end of treatment for patients with culture-negative TB
  – Generally not necessary for patients with culture positive TB
  – A significant proportion will have persistent radiographic abnormalities even at treatment completion
• Liver Function Tests (LFT’s) for high risk individuals (hepatitis, HIV, pregnancy, elderly)
• Visual acuity and color vision monthly if EMB used > 2 months or doses > 15-20 mg/kg

Principles: Determining Treatment Completion

• Document (daily/weekly) treatment progress
  – Completed/verified doses and Target Doses
  – Example: Continuation phase (18weeks x 3time/wk=54 doses)
• Continue treatment until you verify completion of target number of doses (document treatment adherence)
  – Not bound by strictly ‘calendar’ time (e.g. 8 weeks)
  – General rule: If <50% of doses are missed, add them on to the end if >=50%, restart.
• Specified doses must be administered
  1) Within 3 months for initial phase
  2) Within 6 months for 4-month continuation phase

Completion of Therapy

• Completion of treatment primarily defined by number of ingested doses within specified time frame (not solely on duration of therapy)
• For example:
  1. 6-month daily regimen (7 days/wk) = at least 182 doses of INH and RIF, and 56 doses of PZA
  2. 6-month daily regimen (5 days/wk) = at least 130 doses

Treatment Interruptions
When to Extend Continuation-Phase Treatment for 3 Months?

• NO PERFECT MARKERS FOR CURE
• Cavitary pulmonary disease and positive sputum cultures at end of initial phase
• HIV+ pt. with positive 2-month sputum culture – “Disseminated TB”
• Initial phase excluded PZA
• Other special clinical circumstances: example TB meningitis

Among the goals: Cure the patient and prevent relapse

Cultures become and remain negative on TB therapy, but after completion of therapy:

1) patient develops culture-positive TB disease again, or
2) patient experiences clinical or radiographic deterioration consistent with active TB

Most relapses occur in the first 12 months after completion of therapy

Treatment of Tuberculosis
Risk Factors for Relapse

<table>
<thead>
<tr>
<th>Cavity?</th>
<th>Culture (+) at 2 months?</th>
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<tbody>
<tr>
<td>Yes</td>
<td>21.8%</td>
</tr>
<tr>
<td>No</td>
<td>5.0%</td>
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Extend therapy to 9 months for pts with cavitary TB and positive cultures at 2 months

Treatment of Tuberculosis
Extending Therapy

- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol

Initial Phase Continuation Phase

0 1 2 3 4 5 6 7 8 9 months
Special Situations: Drug Interactions or Toxicity

- Consult with an expert
- **HIV:**
  - Many anti-retroviral agents for HIV interact with TB medications
  - Rifampin leads to reduced protease inhibitor levels
  - *Rifabutin* often used if patient is on an HIV protease inhibitor (or INSTI)
- **Organ transplantation:**
  - Rifampin interacts with immunosuppressive agents (Tacrolimus)
- **Hepatitis C:**
  - All Rifamycins interact with new treatments (Sofosbuvir/Simeprevir)
  - May need ‘liver sparing regimen’
- **Anticoagulation**
  - Rifampin decreases warfarin efficacy (may need dose adjustment)
  - Rifampin decreases dabigratran AUC by 66%


Emerging Concepts/Drugs: Can we do better?

- For the first time in over 40 years, there are new TB drugs in clinical development
- Pre-clinical and early clinical results suggest they have potential to dramatically improve treatment of TB and DR-TB
- New information on drug dosing/drug levels is emerging

Therapeutic Intensification?

- RCT showed improved CSF concentrations and reduced mortality (HR 0.42 [0.2-0.9]):
  - High dose IV Rifampin +/- Moxifloxacin with HZE (with steroids)
  - Standard RHZE (with steroids)

Ruslami et al. Lancet ID 2013

Exposure-response for Rifampin

Dose-response in mouse model

Early Bactericidal Activity in smear-positive pulmonary TB patients

Jayaram et al, AAC (2003); 47:2118; Diacon et al, AAC 2007; 51(8)
**Effects of Replacing Ethambutol with a FQ* in the First-line Therapy for TB**

*FQ = fluoroquinolone

**Emerging drugs: Linezolid**

- Linezolid is an oxazolidinone with good activity against MDR-TB in vitro
- California cohort of 30 M(X)DR-TB patients from 2003-2007 received 600mg once daily
  - 22/30 completed therapy with median culture conversion at 7 weeks.
  - Only 3 discontinued treatment due to side effects

**Trials to Assess Role of Moxifloxacin in TB Regimens**

- ReMOX TB Trial:
  - Randomized, double-blind, non-inferiority trial
  - 25 sites in Africa, Asia, Mexico
  - Comparing standard regimen (2RHZE/4RH) to:
    - 2RHZM/2RHM
    - 2RMZE/2RM
- RIFAQUIN Trial:
  - randomized controlled non-inferiority trial examining rifapentine plus moxifloxacin

**Emerging Drugs: Linezolid**

- South Korea Phase 2 Randomized trial
  - 41 patients with refractory culture positive XDR-TB without treatment response
Conclusions

• TB treatment is complex and requires a multi-disciplinary team

• Standardized regimens exist and have improved TB cure when high levels of adherence can be assured (i.e. D.O.T)

• New drugs and regimens are forthcoming!

• Specialized circumstances exist that require individualized assessments/plans (extra slides)

Questions