Treatment of TB Disease

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Disclosures

• Grant Funding
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• Committees
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• Consulting
  — Consultant, Global TB Institute, New Jersey, USA
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• No financial relationship with a commercial entity producing health-care related products and/or services as well as no tobacco related associations.

Principles of Therapy

• In order to effect a cure, Tb must be treated with at least two drugs to which the organism is susceptible
  — Two drugs
  • It is the uncoupling of the drugs leads to drug resistance
  — Susceptibility
  • This is not known when the patient walks into the office
  • It takes time to obtain this information from the laboratory
    — Hours (Xpert testing)
    — Days (MDDR testing)
    — Weeks (Phenotypic testing)

Current recommendation for initiation of TB treatment:
  — Isoniazid (I or H)
  — Rifampin (R)
  — Pyrazinamide (Z)
  — Ethambutol (E)
• Why do we need four to start if two is curative?

Drug resistance

• Occurs by means of genetic mutations
• The genetic mutations conferring drug resistance will occur spontaneously and randomly in the environment
• These mutations occur at known rates for each of the drugs
• The mutations are independent of each other
Drug Mutations

<table>
<thead>
<tr>
<th></th>
<th>Rate of mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH resistance</td>
<td>1/1,000,000</td>
</tr>
<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>
</tr>
</tbody>
</table>

Principle of acquired drug resistance

- Drug A kills organisms susceptible to drug A and those resistant to drug B
- Drug B kills organisms susceptible to drug B and those resistant to drug A
- Any organisms that underwent both mutations would not be killed by this combination
  - But the probability of one organism undergoing both mutations is small

Organism burden in latent Tb versus cavitary reactivation disease

<table>
<thead>
<tr>
<th></th>
<th>Number of organisms present</th>
<th>Number of drugs required</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTBI</td>
<td>Only 10-100</td>
<td>1</td>
</tr>
<tr>
<td>Cavitary Tb disease</td>
<td>100,000,000,000</td>
<td>≥2 (start with 4)</td>
</tr>
</tbody>
</table>

We can treat latent Tb infection with only 1 drug (usually isoniazid x 9 months) but we need multiple drugs to treat Tb disease

TB Timeline

- Organism burden
  - 1 exposure
  - LTBI 10-100
  - Active Tb 100,000,000 (cavitary)

<table>
<thead>
<tr>
<th></th>
<th>History</th>
<th>TST</th>
<th>IGRA</th>
<th>AFB Smear</th>
<th>AFB Culture</th>
<th>PCR Based testing</th>
<th>Biopsy and Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Window Prophylaxis</td>
<td>One drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary one drug regimen</td>
<td>(INH or Rifampin)</td>
<td>2 drug -12 week regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial 4 drug regimen</td>
<td>Tailored if DST available</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Exposure to LTBI (test conversion) - 8-10 weeks
LTBI to Active Disease timeline depends on Host Immune System – weeks to years

Treatment

- Intensive phase: 4 drugs: isoniazid, rifampin, ethambutol, pyrazinamide
  - First two months
- Continuation phase: 2 drugs: isoniazid + rifampin
  - ≥4 months
  - Cure!
  - Obtain drug susceptibilities. Stop pyrazinamide after two months. Assess sputum culture at 2 months.

The “specialness” 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 regiment (BMC trials)
PZA is pH dependent

- Works best in low pH environments – such as in intracellular lysosomes (where IRE work poorly)
- It does not work well in neutral pH environments such as a cavity or lung parenchyma (where most of the organisms are)
- Compartmentalization of drugs = PZA is not very effective in the lung parenchyma
  - Therefore if the patient was INH Resistant, RX with HRZE is really RX with RZE and the lung is only “seeing” RE (2 effective drugs!)

Primary Drug Resistance

- The latent stage of TB allows the host to carry organisms far from their origin – both in time and in space. A patient may be infected in his youth, but not develop disease for decades
  - Susan is born in Vietnam, where there is significant inh drug resistance
  - She is infected in childhood
  - Susan moves to USA. At age 50 she becomes ill with TB and infects her friend George
  - George was not found in the contact investigation as he had changed addresses and moved to Rhode Island
  - 2 years later he is ill
  - The history cannot find these links to discover he has INH resistance before his DST returns
  - Thus we start 4 drug regimen until his DST returns
- This 4 drug regimen prevents emergence of MDR TB in this case
  - If he has INH resistance, his 4 drug regimen means that he is an effective RX with RZE 

Secondary Drug Resistance

- Drug uncoupling has occurred through out the world in multiple ways
  - First treatment regimens were with monotherapy, then sequential addition of monotherapy
  - Patient nonadherence
    - Side effects, misunderstanding, cost
  - Physician nonadherence
    - Lack of recognition of disease
    - Inadvertent nonadherence
      - Malabsorption (DM, HIV, malnutrition)
      - Poor drug formulation
  - Inadvertent drug interactions
  - Drug resistance

Therapeutic implications

<table>
<thead>
<tr>
<th></th>
<th>Length of treatment</th>
<th># of drugs</th>
<th>Cure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pansusceptible</td>
<td>6 months</td>
<td>4 (H/R/Z)</td>
<td>99%</td>
</tr>
<tr>
<td>INH resistance</td>
<td>12 months</td>
<td>2 (H/R/E)</td>
<td>85%</td>
</tr>
<tr>
<td>Rifampin resistance</td>
<td>18 months</td>
<td>2 (H/E)</td>
<td>85%</td>
</tr>
<tr>
<td>INH and Rifampin resistance</td>
<td>18-24 months</td>
<td>4 to include amikacin and a quinolone</td>
<td>50%</td>
</tr>
<tr>
<td>INH and Rifampin plus</td>
<td>18 months or greater sputum culture conversion</td>
<td>5 to include an injectable</td>
<td>70%</td>
</tr>
</tbody>
</table>

Definitions

- **Primary resistance**
  - Resistance appearing on the initial specimen of the patient
- **Secondary resistance**
  - Resistance that appears during the course of therapy for TB
  - Uncoupling of drugs during the course

Treatment: two drugs to which the organism is susceptible

- We do not know this when the patient walks in
- In the past assume susceptible until resistance proven
  - Interviewed the patient for risk factors for resistance
- Assume resistance until proven susceptible
  - Modify the regimen after that is known
  - Begin with 4 drugs in all areas where the rate of INH mono-resistance >4%
Primary Anti-TB Drug Resistance, United States, 1993 – 2014*

*Updated as of June 5, 2015.
Based on initial isolates from persons with no prior history of TB. Multidrug-resistant TB (MDR TB) is defined as resistance to at least isoniazid and rifampin.

Treatment for Tuberculosis in the 21st Century

- Emphasis on provider/program responsibility
- Focus on individual case management with DOT
- Tailoring treatment regimens to circumstances
- Importance of evaluating response
- Increasingly complicated patients

Risk Factors for Relapse

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Factor</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td>Increasing age</td>
<td>Hong Kong</td>
</tr>
<tr>
<td>Clinical</td>
<td>White race</td>
<td>Study 22</td>
</tr>
<tr>
<td></td>
<td>Underweight</td>
<td>Study 22</td>
</tr>
<tr>
<td></td>
<td>Concomitant disease</td>
<td>Poland</td>
</tr>
<tr>
<td>Social</td>
<td>Alcohol use</td>
<td>Poland</td>
</tr>
<tr>
<td>Radiographic</td>
<td>Extent of disease</td>
<td>Poland, Study 22</td>
</tr>
<tr>
<td></td>
<td>Cavitation</td>
<td>East Africa, Poland, Study 22</td>
</tr>
</tbody>
</table>

Risk of Relapse (Study22)

Continuation phase, Control, (I/R 2x/wk)

<table>
<thead>
<tr>
<th>Cavity</th>
<th>Culture positive at 2 months</th>
<th>Culture negative at 2 months</th>
</tr>
</thead>
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<tr>
<td>Yes</td>
<td>21.8%</td>
<td>6.2%</td>
</tr>
<tr>
<td>No</td>
<td>5.0%</td>
<td>2.1%</td>
</tr>
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</table>
DOTS

- Does not ensure adherence
- Ensures that the physician KNOWS as soon as a patient is not adherent
- DOT - an outreach worker observes each dose to be swallowed
  - Twice or thrice weekly dosing
  - Stop as soon as cure is reached
  - Cure is guaranteed

We know the drugs, but....

- Adherence
- Adherence
- Adherence
- Adherence
- Adherence
- DOT – Directly Observed Therapy

Adherence

- Not determined by socioeconomic status, education status, severity of illness
  - Accuracy in predicting adherence 50%
- Only accurate predictors of non-adherence are untreated mental illness and active drug abuse
- Adherence is a major barrier to Tb care
  - Long treatment regimens (at minimum 6 months)
  - Patients feel better long before cure completed.

DOT-Directly Observed Therapy

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- Ensures that the physician KNOWS as soon as a patient is not adherent
- DOT - an outreach worker observes each dose to be swallowed
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Fundamental Responsibility and Approach

- The provider (or program) is responsible for prescribing an appropriate regimen AND ensuring that treatment is completed successfully
- Direct observation of treatment (DOT) with individualized case-management is the approach of choice

Components of Patient Centered Care
Initiation of Therapy

- Often is based on high index of suspicion
  - Do not delay treatment waiting for smear and culture results, especially in ill patients
  - Absence of AFB on smear or granulomas on biopsy does not rule out tuberculosis, nor does negative TB culture
  - A positive TST is only supportive, may be negative in 25% of cases

Drugs in Current Use

**First-line**
- Isoniazid (INH)
- Ethambutol (EMB)
- Rifampin (RIF)
- Rifabutin* (RBT)
- Rifapentine (RPT)
- Pyrazinamide (PZA)

**Second-line**
- Cycloserine
- Levofloxacin*
- Ethionamide
- Moxifloxacin*
- p-Aminosalicylic acid (PAS)
- (Gatifloxacin*)
- Amikacin/Kanamycin*
- Capreomycin
- Streptomycin (SM)

**xxx-line**
- Bedaquiline

*Not approved by FDA for use in tuberculosis 2016

Roles of “Newer” Agents

- **Rifabutin**: May be used as a primary drug for patients receiving medications having unacceptable interactions with rifampin, especially for patients with HIV infection
- **Rifapentine**: May be used as a primary drug by DOT in a twice-weekly initial phase (FDA 2010) and once-weekly continuation phase for highly-selected (HIV-neg) patients; prevention (FDA 2015)
- **Levofloxacin, Moxifloxacin (Gatifloxacin – not in US)**: Oral agents that can be used when first line drugs are not tolerated or the organism is resistant

Bedaquiline (TMC 207)

- Accelerated FDA approval, November 2012
  - 2 studies involving a total of 440 patients with MDR-TB: time to culture conversion
  - Safety concerns
- Unique mechanism
  - ATP synthase proton pump inhibitor
- Indication
  - as part of combination therapy for the treatment of MDR pulmonary TB in adults
- Phase 3 trial planned for 2013
  - double-blind study: 9 months bedaquiline versus placebo, with background regimen

Sirturo® Janssen Therapeutics

Treatment of Culture-positive Pulmonary Tuberculosis

**General Conclusions from the Literature**

- 6 months (26 wks) is the minimum duration of treatment
- 6 month regimens require a rifamycin throughout and PZA for the first 2 months
- 6 month regimens are effective without INH

**General Conclusions from the Literature**

- Without PZA minimum duration is 9 months (39 wks)
- Without RIF, minimum duration is 12 months (up to 18+ mos)
- SM and EMB are approximately equivalent in effect
Drug Susceptible TB Drug Regimens

Treatment of Culture-positive Pulmonary Tuberculosis

Regimens Rated A-I (HIV Uninfected)

2 mos - I, R, Z, E daily (56 doses, 8 wks) then
4 mos - I, R daily (126 doses, 18 wks) or
4 mos - I, R 2X / wk (36 doses, 18 wks)

Continuation phase increased to 7 months if initial film shows cavities and sputum is culture-positive at completion of 2 months of treatment.

CDC 2003, 2016

Risk Factors for Relapse: Study 22

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Tuberculosis Trials Consortium. Lancet. 2002; 360

Tailoring Tuberculosis Treatment Regimens

Rationale for Extending Treatment by 3 Mos

- Continuation of PZA for additional 2 months does not improve outcome
- Prolongation of continuation phase by 2 months decreased relapses in silicotuberculosis from 20% to 3%

Preventing Complications: Drug Selection and Dosing

- Select individual treatment regimen based on individual risk factors for toxicity, clinical, and life conditions
  - Understand specific toxicities of TB medications
    - e.g., Avoid hepatotoxic medications in patients with active hepatitis
  - Tailor regimen to accommodate lifestyle of patient
  - Case management DOT → SAT?
- Adjust doses of specific drugs as necessary
  - Use weight-based dosing
  - Reduce doses of specific drugs if metabolism is impaired
    - e.g., Increase dosing interval of EMB in renal failure (3x/wk, with dialysis)
  - Consider drug level testing/monitoring in specific circumstances
    - Malabsorption?

Sputum Monitoring Simply Stated

- Obtain sputum every month until culture-negative for at least 2 consecutive months
- For those with either delayed culture conversion (beyond 2 months) or cavitation on plain CXR, clinicians may extend treatment to 9 months, although 6 mos is acceptable
- For those with both cavitation and delayed culture conversion, 9 months is recommended
- Patients with sputum cultures that remain positive at 3 months require further investigation

Simply Stated

- Understand specific toxicities of TB medications
Baseline Evaluations

- Collect appropriate specimens for microscopy and culture
  - 3 sputum samples, 8-24 hr apart
  - Sputum induction or bronchoscopy
- Perform susceptibility testing for INH, Rif, EMB on an initial positive culture (each site of disease)
- Perform HIV counseling and testing for all patients/suspects
  - CD4, viral load if HIV-positive

Monitoring for Drug Toxicity

- At baseline
  - ALT, bilirubin, alkaline phosphatase, serum creatinine, and platelet count
  - Eye examination (Va, color*) for all patients receiving EMB
- Education
- Education!
- At least MONTHLY
  - Clinical evaluations usually are sufficient, unless abnormal baseline values are found or other risk factors for toxicity exist
    - e.g., Risk factors for hepatitis: chronic hepatitis (hep. C), use of hepatotoxic drugs (including acetaminophen, EtOH, lipid lowering drugs), age (>35), postpartum, young black or Hispanic women
  - Eye examinations (EMB) – monthly testing of Va and color* is recommended for patients receiving EMB >15-20 mg/kg/d and if on drug for >2 mos.
- For second and third-line medications, seek expert consultation

Follow-up Evaluations

- For pulmonary TB
  - Sputum smear/culture monthly until 2 consecutive samples are culture negative
    - Repeat drug susceptibility testing, other investigations, if culture-positive still at 3 mos
  - If initial culture positive – perform 2 mos CXR to assess response; CXR at completion of therapy
  - Frequency and types of evaluations depend on site

Response to Treatment

- May be rapid (days)
  - Signs/symptoms
- Weight gain is an excellent early marker of effective treatment.
- Expect > 90% sputum culture conversion by 3 months
  - If slow conversion – evaluate and consider longer treatment
- Allow return to home/work environment based on individual considerations
  - Infectiousness of case: look for clinical response, declining organisms on smear
  - Risk of others becoming infected (contacts)

Clinical Hepatitis in Persons Taking INH and Rif

<table>
<thead>
<tr>
<th>Drug</th>
<th>Studies</th>
<th>Patients</th>
<th>% Clinical Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>6</td>
<td>38,257</td>
<td>0.6</td>
</tr>
<tr>
<td>INH + other drugs (NOT Rif)</td>
<td>10</td>
<td>2,053</td>
<td>1.6</td>
</tr>
<tr>
<td>INH + Rif</td>
<td>19</td>
<td>6,155</td>
<td>2.7</td>
</tr>
<tr>
<td>Rif + other drugs (NOT INH)</td>
<td>5</td>
<td>1,264</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Serum Drug Level Monitoring

- Useful in selected circumstances
  - e.g., inadequate response to treatment, severe disease where malabsorption is questioned
- Helps determine therapeutic concentrations
  - Allows adjustments for variable drug absorptions
- Documents adherence to treatment
- May reduce toxicities

Serum Drug Level Monitoring

- Aminoglycosides
  - To reduce toxicity, achieve therapeutic levels
  - In-house (Amikacin) vs send-out (Kanamycin)
- Ethambutol
  - May be useful in renal insufficiency to reduce toxicity
- Rifampin
  - To determine malabsorption (e.g., in severe HIV)
- Cycloserine
  - To determine therapeutic levels

Legal Considerations

- Throughout the US, there are quarantine laws to protect the public
- Slight variability between states
- RI: Intention to Cure Law
  - All other measures must have been tried and have been documented to fail
- Most patients want to be well. The challenge is finding out the why of what they are doing to fix the peripheral issues that are hindering compliance.

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

Completion of Therapy

- In cases of drug toxicity or non-adherence to regimen, all specified number of doses must be administered within:
  - 3 months for initial phase
  - 6 months for 4-month continuation phase
- If the specified number of doses is not administered within the targeted time period, patient is considered to have interrupted therapy

Therapy Deviations

- Treatment interruptions: Significance varies with
  - Bacillary load at time of interruption
  - Time in course when interruption occurred (initial or continuation phase)
  - Duration and intermittency of interruption
- Split dosing of first line agents
  - Lowers peak serum concentrations – may encourage emergence of resistance
Management of Treatment interruptions

Renal Disease

• Consider increasing dosing interval of renally excreted anti-TB drugs (rather than lower dose) if Creatinine clearance decreased (<30 ml/min)
  – EMB, PZA, FQN, aminoglycosides, Capreomycin (CS
• Consult experts for dosing of patients on dialysis
  – No adjustment for INH & RIF
  – Lengthen interval for EMB & PZA (generally 3x/wk, following dialysis)

Fluoroquinolones and Drug-Resistant TB

• Use of a fluoroquinolone-class drug alone in patients with unsuspected tuberculosis has been shown to delay diagnosis and induce resistance to this class of drug (Wang, Thorac, 2006; Ginsberg, NEJM, 2003; Ginsberg, CID, 2003)
  – Potential contribution to JDR
• Up to 1/3 of patients with pulmonary TB will have “atypical” radiographic presentations
• TB risk history should be performed before empiric use of these drugs is initiated for CAP
  – Persons at risk for TB should not be treated with fluoroquinolone empirically
  – EDUCATE YOUR COLLEAGUES !!!

IDSA / ATS: Empirical Antibiotics for Community Acquired Pneumonia

• Outpatient
  – I. Previously healthy and no use of antimicrobials within the previous 3 months
    • A macrolide (strong recommendation; level I evidence)
    • Doxycycline (weak recommendation; level II evidence)
  – II. Presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; nephrosis; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)
    • A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]; strong recommendation; level I evidence)
    • A β-lactam plus a macrolide (strong recommendation; level I evidence)
• Inpatients, non-ICU
  – A Respiratory fluoroquinolone (strong recommendation; level I evidence)
• Inpatients, ICU
  – β-lactam + azithromycin or respiratory fluoroquinolone

Summary

• Patient-centered case management is standard of care
• When prescribing treatment:
  – Use preferred regimens
  – Extend treatment for cavitation and/or + sputum cultures at 2 mos
    • Consider extension in other patient specific instances
  – Calculate # doses within prescribed time frame
  – Use DOT as a tool to ensure treatment adherence
• Special situations
  – Be mindful of additional guidelines for pregnant or breastfeeding women, HIV (+) persons, patients with renal or liver disease


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Join today!