Role of Nurses in Management of Drug-Resistant TB

Nurses play vital role:
- Guiding patients through long, difficult treatment
- Minimizing side effects
- Helping to prevent future cases

Case Presentation
- January 2014: 20 year old male with 3 months of cough, shortness of breath, and hemoptysis
- Admitted to community hospital via emergency department
- Cavitary chest x-ray and CT scan
- Sputum smear positive (3+)
- Specimen sent to state lab for molecular testing for possible drug resistance
Molecular Test Results

Pyrosequencing results from state lab

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of Administration</th>
<th>Isolates</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>oral</td>
<td>KatG (313-316) 315ACC mutation detected</td>
<td>Associated with INH resistance</td>
</tr>
<tr>
<td>ahpC</td>
<td>oral</td>
<td>No mutation detected</td>
<td></td>
</tr>
<tr>
<td>ahpC</td>
<td>oral</td>
<td>No mutations detected</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>oral</td>
<td>Rpob 531TTB mutation detected</td>
<td>Associated with rifampin resistance and rifabutin resistance</td>
</tr>
<tr>
<td>AMK, CAP, KM</td>
<td>oral</td>
<td>No mutation detected</td>
<td>Suggests susceptibility to amikacin, kanamycin and capreomycin</td>
</tr>
<tr>
<td>Quinolones</td>
<td>oral</td>
<td>No mutation detected</td>
<td>Suggests susceptibility to quinolones</td>
</tr>
</tbody>
</table>

Initial Treatment

Initial MDR treatment regimen
- RIPE + IV Amikacin and moxifloxacin
- INH and Rifampin discontinued after PSQ results
- Additional drugs added pending results from CDC
- Regimen: EMB, PZA, Amikacin, Moxifloxacin, Ethionamide, Linezolid, Cycloserine, and Vitamin B6

MDR Treatment Principles (1)
- Perform extensive patient evaluation prior to starting treatment
- Use at least 4-6 drugs to which isolate is susceptible (and preferably not used previously)
  - 1 bactericidal injectable
  - 1 fluoroquinolone
- Continue injectable for 6-12 months post culture conversion
MDR Treatment Principles (2)

- Continue at least 3 oral drugs for full treatment duration
- Treat at least 18 months-2 years after culture conversion
- Never add a single drug to a failing regimen

Additional Molecular Test Results

CDC Molecular Detection of Drug Resistance (Sanger Sequencing, embB and pncA only):

<table>
<thead>
<tr>
<th>Locus [region] examined*</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol</td>
<td>GAC&gt;GCC: Asp354Ala</td>
<td>Likely ethambutol resistant</td>
</tr>
<tr>
<td>pncA (promoter; coding region)</td>
<td>Silent mutation: GCC&gt;GCT: Ala178Ala</td>
<td>Cannot rule out PZA resistance. The mutation detected is synonymous (silent) single nucleotide polymorphism and does not result in an amino acid change and is not considered clinically significant</td>
</tr>
</tbody>
</table>

Social Situation and Discharge Planning

- Patient has own bedroom in apartment with family
- Family/Household:
  - Two adult brothers are both TST positive with CXRs pending
  - Father is TST positive
  - Mother is TST negative
  - No children under five or immunocompromised individuals
Discharge Home

- Patient discharged home with following plan to minimize transmission:
  - Avoid use of central heating
  - Pt to keep window open in his room
  - Pt to wear surgical mask when outside his room
  - Pt can meet with others outside
  - Mother to wear N-95 when in pt’s room

Criteria for Home Isolation*

Prior to meeting the criteria for non-infectiousness, TB patients may be placed in home isolation if following criteria met:

- the patient has started on a standard multidrug anti-TB treatment regimen;
- no infants, children <5 years or persons with other severely immunocompromising conditions are present in the household or—if present—are on appropriate LTBI treatment or window period treatment for presumed LTBI;
- all immunocompetent household members have been previously exposed to the patient; and
- the patient is willing to follow the restrictions imposed by the local TB control program.

* CDPH/CTCA, “Joint Guidelines for the Assessment of Tuberculosis Patient Infectiousness and Placement into High and Lower Risk Settings,” 2009

Case Update

- February 2014: Patient on MDR treatment for 5 weeks
- DSTs: R: INH, RIF, EMB
  - S: PZA, MFX, AK, CM, ETA
- Regimen:
  - PZA
  - Amikacin IV via PICC line
  - Moxifloxacin
  - Linezolid
  - Ethionamide
Provision of DOT

- DOT standard of care for MDR patients
- Benefits: close monitoring of side effects and ensure adherence
- Resource Intensive: program used team approach
  - Trained health educators to provide DOT
  - Initially twice daily
- Set up medisets:
  - One at patient’s home, one at health department

MDR Case: Managing Side Effects

- Patient initially tolerated treatment well
- Started experiencing nausea and vomiting about 10 minutes after medications

Strategies for Managing Nausea (1)

- Interventions which don’t require additional medications
  - Eat a light snack before taking meds
  - Adjust timing of drug dosing without lowering overall dose
  - Mask medication odor
  - Have patient keep symptom diary to better identify time and pattern of symptoms
Strategies for Managing Nausea (2)

- Use an anti-emetic (e.g., Compazine or Zofran)
  - TIP: try a different anti-emetic if first one doesn’t work
- Provide drug holiday
- Other considerations:
  - If anticipatory nausea or anxiety—try small dose anti-anxiety drug
  - Assess for other causes (e.g., pregnancy, hepatitis)
  - SEA-band or suppository

Case switched timing of ethionamide from split dose of 500 mg. in am and 250mg in pm to taking 250 mg in am and 500 mg in pm

Case Update: Mild Neuropathy

- 10 months of treatment, good bacteriologic and radiographic response to treatment, injectable discontinued in September
- October 2014 (all medications taken at same time)
  - PZA 2000 mg po daily
  - Moxifloxacin 400 mg po daily
  - Ethionamide 750 mg po daily
  - Linezolid 600 mg po daily
- Reports intermittent numbness of lower extremities

Management of Peripheral Neuropathy

- Assess other potential causes of neuropathy
- Increase Vitamin B6 to maximum daily dose of 200mg
- Consider lowering the dose of likely offending drug if possible
- Gabapentin may help alleviate symptoms
- Neuropathy associated with linezolid is common after prolonged use and can be permanent
Case Update: Management of Neuropathy

- Increased Vitamin B6 to 150 mg daily
- Linezolid dosage decreased to 300 mg po daily
- No further episodes of neuropathy noted

Case Update: Nausea and Elevation of LFTs

- Later in October 2014 patient reported vomiting 30-60 minutes after medications, LFTs mildly elevated

<table>
<thead>
<tr>
<th>Date</th>
<th>AST</th>
<th>ALT</th>
<th>Alk Phos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct 16, 2014</td>
<td>34</td>
<td>44</td>
<td>61</td>
</tr>
<tr>
<td>Nov 30, 2014</td>
<td>27</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td>Dec 18, 2015</td>
<td>36</td>
<td>67</td>
<td>55</td>
</tr>
</tbody>
</table>

Zofran prescribed and taken 30 mins before medications with good results; PZA kept in the regimen.

Management of Elevated LFTs

- PZA-related hepatitis can be seen later in treatment, important to monitor closely
- If enzymes are >3 times upper limit and symptoms—stop all medications
- Evaluate and treat other causes of hepatitis (check for Hep A, B, C viruses, alcoholism)
- Drug-related hepatitis generally resolves after offending medication discontinued
**Common Side Effects of Second Line TB Medications**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable agents</td>
<td>Tinnitus, hearing loss, serum electrolyte abnormalities, renal toxicity</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Nausea, dizziness, insomnia, arthralgia, QT prolongation</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Nausea, GI upset, anorexia, metallic taste, hypothyroidism</td>
</tr>
<tr>
<td>PAS</td>
<td>Diarrhea, gas, hypothyroidism</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Inability to concentrate/lethargy, depression, psychosis</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Myelosuppression, Peripheral neuropathy, diarrhea, nausea, optic neuropathy</td>
</tr>
</tbody>
</table>

**Toxicity Monitoring**

- Most 2nd & 3rd line TB drugs cause significant toxicity
- Help your patient understand:
  - They will feel worse before they feel better
  - The toxicity symptoms will improve
  - There are ways to minimize toxicity symptoms
- Develop an individualized monitoring plan
- Use drug ramping for PAS, ETA, & CS
- Vitamin B6 used with CS and LNZ

**Contact Investigation**

- Friends
- School
- Home/Family
- Hospital
- Work
Infectiousness of Patients with MDR TB

- Drug-resistant TB similar in transmissibility to drug-susceptible TB
- Most transmission occurs before treatment initiated
- Smear-positive cases transmit more efficiently than smear-negative cases, but variability
- Patients with MDR not more infectious, but duration of infectiousness may be prolonged if not started on effective regimen promptly

Contact Investigation Sites (1)

- Household (4) / Family (2)
  - 1 clinical case (patient 1)
  - 3 converters (mother, brother 2)
  - 2 new positives (father and uncle)
  - 1 TST

- Friends (28)
  - 23 Girlfriend's Family:
    - 3 converters (girlfriend and nephew)
    - 13 TST
  - 2 not evaluated
  - 5 Friends: TST

Contact Investigation Sites (2)

- Worksite (16)
  - 16 TST: first round testing; 14 TST - second round testing

- Hospital (15)
  - 15 IGRA negative
  - 3 initial QFT converters

- College (34)
  - 34 students identified as contacts; 16 tested
  - 13 TST
  - 3 TST + (all foreign born, 1 prior positive, 1 neighbor)
Contact Investigation Continued: Interpreting results when using QFT (2)

- Hospital investigation had 3 initial converters
  - RN who did respiratory evaluation: exposed to patient on 1/4/14
  - Initial QFT on 1/17/14: positive (0.80)
  - Repeat QFT on 1/21/14: positive (1.6), CXR nl
  - RN declined treatment for LTBI due to concern about side effects
  - A third QFT done on 3/07/14 was negative (0.02), TST negative
- Repeat QFT for 2 other “converters” were negative

Contact Investigation Continued: Interpreting results when using QFT (3)

- Use of IGRA in contact investigations recommended and beneficial among individuals with prior BCG history
- Caution: false conversions at follow up testing may occur due to test variability
- Consider reviewing quantitative results and interpret in context of exposure and evidence of transmission

Strategies to Get Contacts Evaluated

- Use incentives and Enablers
- Health Officer Orders in California:
  - Health and Safety Code Sections 120142 and 121364: both the state [public health] director and each local health officer may order examinations for TB infection for the purposes of directing preventive measures and for persons for whom the local health officer has reasonable grounds to determine are at heightened risk of tuberculosis exposure.
  - However, these HSC sections don’t specify an enforcement procedure should the person fail to adhere to the order.
- Perform testing in the field
Treatment of Contacts to MDR

LTBI Treatment for Family Contacts

- Brother 1: clinical case, treated with MDR regimen
- Brother 2: TST converter, treated with moxifloxacin
- Father: new positive TST, treated with moxifloxacin
- Mother: TST converter on second round testing, treated with moxifloxacin
- Uncle: new positive TST, started treatment but stopped due to "intolerable" side effects

Considerations in Treatment of Contacts to MDR TB

- Thorough TB history of contacts critical to assess whether recent infection
- Consider treatment thought to be due to infection with drug-resistant TB
- Use caution to lessen the risk of toxicity from treatment regimens
Drug-Resistant LTBI Treatment Options (1)

- Treatment based on resistance pattern of the source case isolate
- 1992 CDC guidelines advise:
  - treatment of MDR-LTBI with 2 drugs to which isolate is susceptible (e.g. EMB and quinolone, PZA and quinolone or ethionamide and quinolone)
- No randomized clinical trials to show clear efficacy of regimens

Drug-Resistant LTBI Treatment Options (2)

- Published case series show poor tolerability of multidrug regimens for MDR LTBI, especially those including PZA
- Small studies show use of moxifloxacin or levofloxacin alone might be effective in preventing progression
- No treatment also an option given lack of efficacy data
  - Monitor for 2 years with symptom review every 3-6 months and chest x-ray as clinically indicated

Recent Report on Management of LTBI in Child Contacts

- Exposure to teacher with MDR in California (R: INH, Rif, EMB)
- 118 children (ages 6-13) with significant contact
  - 31 children developed LTBI
  - 26 treated with levofloxacin and PZA (per CDC guidelines)
  - 12 required a change of therapy due to adverse effects (abdominal pain, arthralgia/myalgia and elevated transaminases)
  - 15 children completed LTBI treatment—no progression to active disease during 24 months of follow-up

Contact Investigation Continued: Addressing Side effects to LTBI Treatment

- Close Friends:
  - Girlfriend’s nephew: 11 years old TST positive
  - Started on levofloxacin
  - Began experiencing knee pain and “walking funny”
  - Mom became distraught

Contact Investigation Continued: Addressing Side effects to LTBI Treatment (2)

- Nephew evaluated by pediatrician
  - Levofloxacin discontinued
  - Plan to follow every 6 months
- Lower threshold for tolerating side effects with LTBI treatment since benefits are not well established

Use of Fluoroquinolones in Children

- Fluoroquinolones commonly used in children for other infections and is well tolerated
- Black box warning highlights concern for musculoskeletal adverse effects
- Lack of data on effect of long-term use of fluoroquinolones
- Despite limited data in children, fluoroquinolones are recommended as part of multidrug regimen for treatment of MDR TB and MDR LTBI
Managing Side Effects to LTBI Treatment

Benefits:
- Potential Decrease Disease Risk

Risk:
- Possible Significant Side Effects

Summary: Positive Outcomes and Nurse Case Management

- Patient doing well on treatment, no permanent side effects
  - Careful monitoring of response to treatment, side effects and signs of toxicity
  - Team approach for DOT
- Brother (clinical case) completed 15 month regimen without complications
  - Early identification of contacts (good rapport with case)
  - Effective communication with patient and family
- 3 family members and 2 friends completed MDR LTBI
  - Thorough contact investigation
  - Case management of contacts to help them get through LTBI
Acknowledgements

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- Gayle Schack
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