Complex TB Cases – The Triathlon

Objectives

Participants will:
- be able to identify situations that may require treatment regimens different than the standard 4-drug regimens.
- be able to state circumstances that may change the presentation of TB disease.
- recognize when additional assessment is needed for failure to clinically improve, or when clinical condition declines.
- identify when to initiate interventions utilizing options in the “TB Control Law Guidebook”, based on state code and regulation.

Case 1

Baby J
May 23 - Memorial day weekend

The phone rings, it’s 1:30 PM

- A local pediatrician office calls to inform you of TB infection in an 8 month old infant. The TST is 7mm

What sort of questions you would ask?

Discussion

- Why was the TST done?
- Is there any risk of being infected?
- Is the baby healthy? Does the baby have symptoms?
- What is the doctor’s plan?
- Do you need assistance with providing treatment?
- Is this TB infection or TB disease?
- Has a CXR been done, and if so, what are the results?
- Collect demographics
May 23 - Memorial day is this weekend

15 minutes later
The phone rings, it's 2 PM
- As soon as you hang up the phone you receive a call from the mother of baby J
- She is worried about baby J and has questions about TB

What sort of questions you would ask? What are the teaching points?

Discussion

- Emphasize the importance of asking questions and digging deeper
- Answer the mother’s questions first
- How has baby J been feeling lately?
- Why did the baby go to the doctor?
- Ask about the family. Is there anyone else in the house who is ill?
- Is the baby adopted or foreign born?
- Teach about the difference between TB and LTBI
- Plan to keep in touch

Going back in time to May 20th

Now for the rest of the story
Baby J status/ 8 mos old

- Delayed Growth
- Unable to roll over
- Lethargic/ listless
- Not interested in play
- Low grade fevers
- Persistent weak cough
- Supraclavicular adenopathy
- Lymphadenopathy is the most common clinical sign in pediatric patients

Baby J/ Visit to pediatrician/ May 20, 2013

- Inspiratory wheezing, upper and mid lung
- Initial diagnosis: r/o bacterial pneumonia
- Treatment: Bactrim pediatric
- TST placed
- CXR today, CT if indicated
- Scheduled I&D of lymph node in two days
- Atypical infections, such as M. bovis can look identical to M. tb

Findings - May 22, 2013

- CXR done – Hilar lymphadenopathy
- PPD read: 4mm (theoretically negative)
- Not feeding
- I & D results pending, gram stain and AFB ordered
- Infant increasingly lethargic – stat head CT ordered
- Hospitalized
Imaging – Chest: PA and lateral

**CXR: PA view**
Hilar lymphadenopathy.

**CXR: Lateral view**
Rounded lymph node

Do a PA and lateral film for pediatric patients to get a better view of the hilar lymph node.

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**Imaging – Head CT or MRI**

Tuberculoma is most common form of localized disease

Ring Enhancing lesions

Cerebral Hemisphere most common site

Asymmetrical Vascular Enhancement

Usually 2 – 6 months after infection and most common in children under 2 yrs of age.

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**Miliary Pattern**

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THIS IS WHEN YOUR PHONE RINGS

Would your approach be different now?

Be more aggressive and dig deeper

- Is treatment being started?
- How long has the baby been ill?
- What has the mother told you?
- Request medical records
- Do a home visit. The source of a young child’s illness is likely in the home, over 75% are.

Diagnostic Challenges

- Otherwise healthy infants
  - Known contact with an adult case of TB
  - Positive TST
  - Suggestive signs on a chest x-ray
- ‘Typical’ TB symptoms are often not present
  - Change in behavior
  - Failure to thrive (growth delay)
  - Unexplained lymphadenopathy (firm, nontender)
  - Shallow, weak, dry cough (children are poor TB transmitters)
  - They often do not improve long term with ‘common’ antibiotics
- Age is the most important risk factor for progression to disease
Risk of progression to TB disease in untreated pediatric patients with LTBI

- The lung focus may resolve without detection in primary disease
- The CXR appearance of primary TB typically includes enlargement of regional lymph nodes
- Lymphohematogenous spread is typical and can result in disseminated disease

<table>
<thead>
<tr>
<th>Age of infection</th>
<th>Risk of TB disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth – 12 months</td>
<td>43 - 50%</td>
</tr>
<tr>
<td>1 – 5 years</td>
<td>20 – 25%</td>
</tr>
<tr>
<td>6 – 10 years</td>
<td>2%</td>
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<tr>
<td>11 – 15 years</td>
<td>16%</td>
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</tbody>
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Proving TB disease with a + M.tb culture

- Sputum
  - Generally better yield than Gastric Aspirates (GA)
  - Difficult for those under 5 years, limited experience with induction
  - Induced sputum (IS) can be attempted if no active cough
    - Consider albuterol for 5 minutes
    - 15 minute induction with 5% hypertonic solution
    - Wheezing, Vomiting
    - Increased coughing, Epistaxis
  - Often move forward without culture confirmation if
    - Abnormal CXR, TST +, and if reported as a known contact to TB (classic diagnostic picture for suspicion of TB in pediatric patients)

- Gastric Aspirate
  - Hospitalization generally required over three days
    - Early morning
    - NG tube inserted upon waking
    - Invasive and frightening
    - Expensive
  - Study 2005 – compared yield between IS and GA
    - 3 GA = one IS (64-66%)
    - 3 IS yield much better results (87%)
  
  **Bottom Line – IS have better yield than GA**
Baby J family / Today is 5/24/13

- Born in the United States, September 13, 2012
- January 2012 - Parents arrive from Libya
  - TB evaluation upon entrance, both IGRA positive
    - Mother: CXR nodular densities LLL (stable), asymptomatic
    - Sputum X3 smear and culture negative, INH 6 months
    - Father: CXR negative, asymptomatic, INH 9 months
- Maternal grandmother arrives in U.S. late July 2012
  - No medical evaluation – Visitors visa
  - Overs stays visa

From a public health perspective....

- Is this a source or contact investigation?
- What level priority is it? Not as high as a smear positive, culture positive case
- What are your first steps?
  - Thorough s/s review of immediate family
  - Always be suspicious of those you don’t ‘see’ present at the time of the visit
  - Grandmother was the source case

Case management challenges

- Treatment regimen
- DOT
- Assessing for side effects
- Allaying fear and suspicion
- Observing and documenting improvement
# Treatment Regimens and DOT

**RIPE**
- Normally well tolerated
- May exclude EMB if resistance is not a concern
- Give 1 hour before or 2 hours after a meal
- Do monthly weights and adjust dosages as weight changes
- Crush as fine as possible before mixing
- Don’t mix ahead of time
- Expect to change strategies frequently

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## Rifampin and Isoniazid

**Rifampin**
- Mix thoroughly in very small amount of food
- 150 mg capsule
- Rif suspension is stable 4 weeks, shake before using, not refrigerated, capsules are preferred
- 600 mg reconstituted in 10ml of sterile water for infusion

**INH**
- Rarely requires B6, unless breastfed
- 100 mg tablet
- INH solution, 50mg/5ml, not refrigerated; can cause gastric upset, crushed tablets are preferred
- INH 100mg/ml for infusion

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## Pyrazinamide and Ethambutol

**Pyrazinamide**
- Crushed tablets only
- Lower frequency of side effects than with adults

**Ethambutol**
- No widely standardized test available to test visual acuity
- Weigh risk/benefit for use
- Be alert for changes in developmentally appropriate visual response
Allaying fear and suspicion

Mr. S
Case 2

Resource
Mr. S, 32 yr., from Vietnam, IT employee

- Single, multiple sexual partners
- Past substance abuse, current alcohol use
- PCP seen for
  - Weight loss, 17 lbs. in 2 months
  - Fever, 99° to 101° F
  - Nagging cough, productive in A.M.
- Chest x-ray abnormal, not consistent with TB (RLL infiltrate)
- Treated with 10 days of levquin
- Return in 2 ½ weeks scheduled

Return visit to PCP 6 weeks later

- Respiratory symptoms improve x 6 weeks, then recur
- Returns to PCP
- Phlegm now blood streaked
- Repeat chest x-ray unchanged
- Respiratory culture with gram stain collected
- Azithromycin prescribed
- Told to call if symptoms don’t improve

2 Weeks Later

- Cough persists
- Calls to PCP
- Office visit
  - Gram stain/respiratory culture negative
  - Referred to a pulmonologist
- Appointment scheduled 1 month later
At the pulmonologist…

- Symptoms
  - Worsening cough
  - Fevers
  - Continued weight loss; 3 more lbs
  - Decreased appetite
  - Night sweats
  - Missing days at work
- MD looks at 2 prior chest x-rays and orders a CT scan
- Client refuses bronch due to fear and poor insurance
- Referral to health dept. as TB suspect

Call to refer to health department

- When do you plan to see the client? Within 3 days, or that day.
  - TB risk assessment, get medical record, sputum for AFB, explain role of the HD, discuss infection control measures
- What are the additional tests needed? HIV, TST, CXR?
- What other risk factors do you think the client might have? HIV?
- The client is worried about his poor insurance coverage; what do you tell him about potential charges? Don’t worry about anything; eligibility will be done and a sliding scale applied.

Discussion

- See ASAP – this looks like TB! Contact same day; see in 1-3 business days per nursing guidelines for TB case management
- Get demographic/contact information
- Explain health department role
- Encourage to stay home
- TB risk assessment
- Arrange testing
  - Sputa x 3 for AFB and culture, etc.
  - HIV
  - TST or IGRA
  - LFTs because of current alcohol use
  - Chest x-ray (obtain prior films)
- Obtain medical records
- Who are the sexual partners?
- No charge for evaluation of TB suspects or contacts per Code of Virginia and Eligibility Guidelines
### Visit with client the next day

- Take everything needed
- TST / IGRA done
- Sputa collected
- Weighed – 140 lbs
- History completed
  - Identify past heroin use
  - Identify sexual preference, MSM, name of partners unknown
  - Gay bar rendezvous weekly
- TB education done
- HIV drawn

### Results – 2 days later

- 1st smear 1+
- TST negative/0 mm
- Chest x-ray with ground glass appearance throughout lung fields; RLL infiltrate resolved
- Results sent to pulmonologist and office called/message left
- Co-worker suggests an IGRA, given Hx of BCG

### Discussion

- What does the 0 mm TST reveal?
  - TST might only reflect poor immune function
- Is this chest x-ray improved?
  - no
- Is this chest x-ray consistent with TB?
  - For immune suppressed, yes
- Would an IGRA be a good idea?
  - No, all signs point to immunosuppression (chest x-ray, TST, risk factors for HIV)
Additional information and orders

- Subsequent 2 sputa
  - Smear negative and +/-
- MTD positive
- Pulmonologist returns call after MTD positive results faxed
  - TB meds ordered
    - INH 300 mg po daily
    - RIF 600 mg po daily
    - PZA 1500 mg po daily
    - EMB 1000 mg po daily

Any comments?

- What should be in the discussion with the pulmonologist?

Discussion

- Dosing of EMB; EMB dosing corrected to 1200 mg po daily
- Share risk factors for HIV, and that results are pending
- Ask what the MD has told the client
- Isolation needed
  - Negotiate treatment plan / who will do what?
    - Clinical evaluations
    - Labs – baseline and ongoing
    - Sputa
    - Ensure HIV done if not previously performed
- Advise of HD services
  - DOT [no order needed/don't need to ask unless medical Hx concern]
  - Vision monitoring
  - Home isolation
  - Contact investigation
HIV results positive

Resources

How will case-management change?

- What other resources would be helpful?
- How do you tell the client of HIV results?
- Is there a change needed in the TB regimen?
Discussion

- **Resources**
  - HIV/STD program
  - DIS
    - For visit with TB PHN to share results with client
    - For HIV contact investigation/partner notification
    - Eventually for ADAP program

- Connect to ID clinic at local teaching hospital
- No change in treatment now/not on ART

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**HIV management**

- Client with appointment in ID clinic in 2 weeks
- CD4, viral load and other related tests planned for this week
- Because of the delay in ID appt. the PCP questions starting ART now
- All other case management activities continue

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**Discussion**

- ART should wait until HIV labs are known; the timing of start of ART depends on client evaluation and HIV labs, especially the CD4 count
ART in the management of TB disease

- Complicated by
  - ART interactions with rifamycins, especially
    - Protease inhibitors (PI)
    - Non-nucleoside reverse transcriptase inhibitors (NNRTI)
  - Overlapping toxicities
  - Review of other medication interactions complex
- Rifabutin usually substituted for rifampin
- Review with TB Medical Consultant

IRIS - Immune Reconstitution Syndrome

- IRD – Immune Restoration Disease
- After ART is started there may be an exuberant immune system response to TB bacilli
  - Paradoxical reaction - Worsening of clinical symptoms of TB
  - Unmasking – Initial clinical symptoms related to TB
- Predictors of IRIS
  - More common with CD4 <50 and high viral load
  - Improvement of CD4 and viral load once ART is initiated
  - IF ART is initiated less than 30 days after TB treatment began
  - High burden of TB disease
- Explains the importance of ruling out TB before HIV treatment is initiated

Symptoms of IRIS

- Within 3 months of starting ART
- Initial TB symptoms worsen
  - Large adenopathies, including abdominal
  - Cold Abscess
  - Return of night sweats, fever, poor appetite
  - Worsening CXR with new or worsening respiratory symptoms, cavity formation
  - New or worsening CNS
  - Miliary TB with large nodules
  - Sputa remain negative if conversion has occurred
Treatment

Do Not Stop TB or ART meds
- Corticosteroids
- NSAIDS
- Drainage?
- Additional interventions dependent upon site involved
- Can be life threatening

Client states “you’re killing me”
- Client refuses all medication
- What do you tell the client?
- How do you discuss the refusal?
- Stops being available for DOT

Discussion
- Review Sx
- Give opportunity to vent
- Education; re: IRIS, signifies an immune system being restored
- Discuss options
  - TB drugs not negotiable
  - Encourage
  - Offer some hope; 2 TB drugs can be stopped after 8 weeks
- Work with ID clinic
  - Discuss options for side effects
  - Treatment of IRIS
  - Collaborate with HIV case manager to assure consistent message
Client no longer available for DOT

- Three doses of DOT missed
- Refuses to provide sputa
- Also not adhering to home isolation
- What can be done?

Discussion

- Talk with the client
  - Address concerns
  - Reinforce need for isolation, potential for drug resistance
  - Review agreements that were signed (DOT and Isolation)
  - Document, document, document
- Code of Virginia
- TB Law Guidebook – letter templates available
  - Counseling Order Letter
  - Examination Request Letter
  - Outpatient treatment Order
  - Emergency Detention Order
  - Work with health director and TB Control Program

Contact investigation unfolds...

- IT workplace; 300 employees
- Gay bar weekly
  - Multiple partners
  - One regular weekly partner – only nickname is known
- Hookah bar weekly – the Crystal Cathedral
Discussion

- How to approach contact investigation in uncomfortable or unsafe places
  - Partnership with DIS or Community Based Organizations
  - Approach management/evaluate each setting
    - Provide education
    - Get their input on how to best reach regular customers
  - Prioritize the locations and the people at those places
    - Attempt to identify any symptomatic
- TB elimination will require reaching out to non-traditional sites of transmission

The Outcome

- A counseling letter is delivered
- Face to face counseling preferable, or mail to last known address
- Consider certified mail and regular delivery together
- Client returns to treatment after 1 week missed therapy
- Rest of treatment course uneventful
  - IRIS resolved
  - Treated for 26 weeks
  - Contact investigation continues

Ms. K
Case 3
Ms. K, female, age 71, today is 5/31/13, 4:00 P.M.

What topics might be covered in this phone call?

- Infection Preventionist from local hospital calls with a referral on TB suspect, Ms. K
- AFB smears are 4+, and 3+ twice
- Other diagnoses
  - End-stage renal disease
  - Insulin dependent diabetes mellitus

What topics might be covered in this phone call?

- Airborne isolation (Aii), a.k.a. “negative pressure”
- Need for “TB Treatment/Discharge Plan” completion
- All pertinent information available on TB intake form
- Treatment plan for the TB drug regimen; TB drug start date
- Is the person on dialysis?
- Hx of prior TB, prior + TST or IGRA, Tx for LTBI, NTM diagnosis?
- Arrange hospital visit if possible
- Potential discharge date
This information is discovered in the call; what is your input or concern now?

☐ Suspect was in airborne isolation
☐ HIV had not been done due to client’s age
☐ Wt. is 52 kg
☑ Patient is on dialysis, and has been “for months”
☐ TB medication was started on 5/15/13
  ☐ INH 300 mg. tablet, po, daily
  ☐ Rifampin 300 mg. capsule, po, twice daily
  ☐ Pyrazinamide 500 mg. tablet, po, twice daily
  ☐ Ethambutol 400 mg. tablet, po, twice daily

Discussion

☐ What about the TB drug regimen?
  ☐ Doses should be given once daily, all simultaneously
  ☐ And in this case?
  ☐ Encourage HIV testing
  ☐ Was airborne isolation in place from first contact forward, or after positive AFB smears found?
  ☐ May address delay in health department notification

Renal Insufficiency Considerations, page 63-64 (1)

☐ Related to Toxicity:
  ☐ Dependant on creatinine clearance of individual
    ☐ < 30 ml/minute – dosing adjustment recommended
    ☐ >30 ml/minute – no recommendation for dosing adjustment, but measurement of serum drug concentrations recommended to detect potential toxicity
  ☐ INH and RIF are metabolized by the liver; no dosing adjustment needed
  ☐ PZA also metabolized by liver, but metabolites excreted by kidneys
  ☐ EMB cleared by kidneys
  ☐ The recommendation is to alter the dosing interval for EMB and PZA
Renal Insufficiency Considerations (2)

- Effect of Dialysis:
  - PZA removed significantly,
  - INH and EMB to a lesser degree (not significant)
  - RIF not affected
- Recommendation: Dose TB meds AFTER dialysis

“Treatment of Tuberculosis,” page 64, Table 15

“Treatment of Tuberculosis,” TB Drug Regimens, pg. 3
How should the current treatment regimen be addressed?

- The infection preventionist is reluctant to discuss the regimen with the physician prescriber
- The client has been on this TB treatment regimen daily for 11 days, with no reduction in clinical symptoms or sputum smear positivity (still 3+ and 4+)
- Hospital discharge is not expected in the near future because family says they can’t care for the client at home

Discussion

- Call the prescribing physician and discuss the regimen
- Discuss with your health director or health department TB clinician
- Ask for all labs and review the creatinine clearance or glomerular filtration rate
- Call TB Control Program and ask advice
- Call TB Control Program and request to speak to a TB medical consultant

Importance of Interviewing

- This person is still in the hospital
- The interview:
  - Builds rapport
  - Opportunity for education and gain more TB exposure and past treatment information directly
  - Elicits solid information to pursue a contact investigation in a setting with high risk persons (dialysis)
  - Provides a more complete contact list outside of dialysis
  - Provides information to assist in determining infectious period
  - Elevates the importance of health department involvement
Client progress over the next 10 days; what might be suspected/why no improvement?

- Sputa remain at 3+
- The regimen has been changed to the recommended three times a week dosing intervals, with the recommended doses and no split dose administration
- The clinical picture is essentially unchanged after 3 weeks of treatment

Discussion

- The client has an NTM, not TB (but wouldn't growth and ID occurred by now with a rapid grower?)
- The client has drug resistance issues
- The client may have absorption issues due to the DM
- The client may have absorption issues due to food, other medications, or other clinical conditions
- Non-adherence

Interventions

- Call the lab and check culture growth
- Were serum drug levels done at 2 weeks (DM)? If not, suggest they be done now
- Evaluate TB medication administration –
  - On empty stomach?
  - Drug interactions?
  - Calcium containing products?
- Evaluate medication administration practice (DOT?)
- Review co-morbidities, diarrhea, vomiting, etc.
What is discovered; what should be recommended?

- Lab reports M.tb positive culture
- Nausea was an issue, so TUMS were being given immediately before each dose
- Increasing joint pain reported

Recommendations

- Stop the TUMS administration
  Calcium products may interfere with absorption!
- Serum drug levels drawn
- Suggest uric acid be drawn
- Suggest use of aspirin or other NSAID for joint pain

Joint pain and PZA

- Uric acid level part of baseline TB lab panel
- Increase in uric acid expected with PZA, though usually asymptomatic
- Renal insufficiency can contribute to uric acid rise
- Allopurinol Rx an option
- May require that PZA be discontinued
- If initial phase not complete with PZA, requires treatment for 39 wks. (9 months)
Discoveries and follow-up; thrice weekly

- **Pansensitive**
- **INH level 4.8 mcg/ml (9-18 mcg/ml expected)**
  - Dose adjustment ↑ INH to 1200 mg, po three x a week
- **RIF level 3.0 mcg/ml (8-24 mcg/ml expected)**
  - Dose adjustment ↑ RIF to 900 mg, po three x a week
- Improvement in smear positivity to 1+ within a week
- Repeat serum drug levels both within expected range
- Joint pain relieved with ibuprofen

Slow Response – 4 to 6 weeks of treatment

- **Definition:**
  - **Sputum smear (+) not decreasing**
    - adequate decrease is:
      - 4+ to 2+
      - 2+ to 1+
      - 2+ or 1+ to smear negative
  - **No improvement in TB symptoms**
    - no weight gain
    - no reduction in cough
    - persistent fever, or
    - worsening of chest x-ray if performed

Medically ready for hospital discharge; planning for dialysis and release from isolation

- Still smear positive, but +/- and 1+
- Symptoms are improved —
  - Decreased cough
  - Weight gain of 3 lbs.
  - Resolution of fever and night sweats
- On treatment for 5 weeks
- What is the criteria for release from isolation?
- What is the plan for dialysis?
- Does the dialysis plan effect the discharge plan?
Isolation and congregate settings

- "Controlling Tuberculosis in the United States," Nov. 4, 2005, pg. 9, Box 3
  - 3 consecutive negative AFB smears
  - Collected at least 8 hrs. apart
  - Dialysis could still be arranged at the hospital with appropriate Aii until release from isolation

The course is uneventful, until.../
What's up? What to do?

- Smear conversion occurs by 6 weeks (2 weeks after dose adjustment and correction of administration practices)
- Dialysis is now at the regular dialysis center (no Aii)
- Sputa continue to be collected to document culture conversion
- One sputa in week 10 returns AFB smear 1+

Interventions and Possibilities

- Revert dialysis to hospital Aii facility
- Possibilities
  - Treatment failure
  - + smear reflects dead organisms
  - Non-tuberculous mycobacterium (NTM)
- Collect series of 3 sputa, 8 hrs. apart, HCW observed
- Would an MTD "rapid test" be helpful?
Discussion

- Have to assume the worst and move to Aii
- Evaluate clinically; is clinical progress still evident?
- Won’t know if dead organisms until culture final
- NTM ID likely back much sooner
- If 3 sputa all smear negative, move to regular dialysis if clinical improvement still clear
- MTD not helpful; already know it is M.tb

Uneventful course going forward ...

- Cultures converted by day 55 of treatment
- The sample with 1+ smear was identified as M. gordonae, a common NTM contaminant
- Completed 26 weeks of treatment...is that right?

...the end of the story

Discussion

- Extend treatment due to absence of clinical improvement and poor serum drug levels
- In other situations, if clinical improvement has occurred, extension of treatment might not be needed
Questions?