Clinical Case Discussion
Cases from Detroit

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TB Clinical Intensive
September 10, 2013

Disclosures
• None relevant to this presentation

Objectives
Attendees will
1. Be able to recognize and efficiently diagnose asymptomatic early TB
2. Know when the diagnosis of latent TB infection is not applicable
3. Be able to recognize & timely treat TB even when MTb is not isolated
Applying Lessons Learned
In the Real World

Case 1: Begins in China

Case 1: International Student

- 23 year old Chinese man referred to IPH from Wayne State University Campus Health Center for a + T-Spot and abnormal chest x-ray.
- T-Spot results
  - Nil (control) 0 spots
  - Panel A 12 spots
  - Panel B 6 spots
  - + control >20 spots
  - Arrived in USA for the 1st time on 12/30/12

5, 6, or 7 borderline
Case 1: On Arrival

- Moved into student housing

Required TB Testing

- International students with J-1 or F-1 visas and who are from any of the 22 WHO designated high burden countries
- On arrival, or returning to US after ≥ 30 day absence

Why test incoming students?
Student from India 2008
Case 1: TB Testing
- T-Spot January 15, Chest X-ray January 18
- Asymptomatic, normal physical exam
- No past medical history
- Mother runs a pharmacy in China
  - Had TB infection 20 years prior, no treatment

8.7 Million New Cases
125/100,000
38% from India & China

TB In Detroit 2011*
- Cases 53
- Children 4 <22months old
- Incidence 7.4 per 100,000 population
- Alcohol abuse 30.2%
- Injection drug use 15.1%
- Non-injection drug 35.8%
- HIV + 3.7%
- Homeless 28.3%
- Black 77.4%
- Foreign Born 17.0% Bangladesh, Yemen, Mexico, students (Chinese, Indian)

* IPH jurisdiction
Where should you look?

Case 1 Question 1
What do you want to do now?
A. Outpatient CT scan to "confirm CXR findings"
B. Bronchoscopy
C. Admit the student to the hospital
D. Put him on home isolation (no classes)
E. Collect sputum for AFB smear and mycobacterial culture now and send him home to collect 1st morning sputum for 2 days

Prospective Study
Consecutive Subjects
- Subjects with chest x-ray consistent with TB, unable to expectorate sputum

<table>
<thead>
<tr>
<th>Day of study</th>
<th>Specimen obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>GW and 3 IS specimens</td>
</tr>
<tr>
<td>Day 2</td>
<td>GW and IS</td>
</tr>
<tr>
<td>Day 3</td>
<td>GW and IS, with or without BAL</td>
</tr>
</tbody>
</table>
- 30 mL 3% saline via a mouthpiece, using an ultrasonic nebulizer
- 1–20 mL (mean 4 mL) of sputum was obtained over 1–2 h

References
Proportion of subjects with cultures + for Mycobacterium tuberculosis, by diagnostic technique, for 73 subjects with results for all 5 sputum samples obtained by induction with nebulized hypertonic saline (IS) and all 3 gastric washing (GW) specimens.

Bronchoscopy vs. Sputum Induction

- BAL was performed for 21 subjects who had negative AFB smear results
- BAL cultures for 5 patients (24%) were positive for TB, and all were positive using the day 1 IS samples
- 2 subjects had positive culture results with day 1 IS specimens but negative results with BAL specimens
- Sputum trumps gastric washings & bronchoscopy

<table>
<thead>
<tr>
<th>Date</th>
<th>AFB Smear</th>
<th>NAAT</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 23</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>January 24</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>January 25</td>
<td>Few AFB</td>
<td>Positive for TB Complex</td>
<td></td>
</tr>
</tbody>
</table>
Case 1 Question 2
What do you want to do now?
A. Arrange for bronchoscopy
B. Perform CT Thorax
C. Start therapy for TB
D. Start therapy for LTBI
E. Wait for culture results

Case 1: Final Sputum Tests

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<tbody>
<tr>
<td>January 23</td>
<td>Negative</td>
<td>MTb, drug susceptible</td>
<td></td>
</tr>
<tr>
<td>January 24</td>
<td>Negative</td>
<td>MTb</td>
<td></td>
</tr>
<tr>
<td>January 25</td>
<td>Few AFB</td>
<td>Negative for TB</td>
<td>M gordonae</td>
</tr>
<tr>
<td>January 30</td>
<td>Negative</td>
<td>MTb</td>
<td></td>
</tr>
<tr>
<td>February 2</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>February 3</td>
<td>Negative</td>
<td>MTb</td>
<td></td>
</tr>
<tr>
<td>February 15</td>
<td>Negative</td>
<td>MTb</td>
<td></td>
</tr>
<tr>
<td>February 22</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>February 27</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>April 5</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>April 6</td>
<td>Negative</td>
<td>Negative</td>
<td></td>
</tr>
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TB Classification System

<table>
<thead>
<tr>
<th>Class</th>
<th>Stage of Disease</th>
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<tr>
<td>0</td>
<td>No exposure, no infection</td>
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<td>4</td>
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<tr>
<td>5</td>
<td>TB suspect</td>
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Initial Management TB Suspect

• Collect 3 sputum samples (mycobacteria, AFB) at least 8 hours apart
  • include at least 1 first morning sample
  • Induce if needed
• TST or IGRA
• AFB smear
  • 45-80% sensitivity in culture + TB
  • 50-80% + predictive value due to non-tuberculous mycobacteria

NAAT*

• Detects >95% TB in smear + specimens
• Detects 50-80% TB in smear – specimens
• Perform on at least 1 respiratory specimen from patients suspected of having TB when the result would influence TB control activities or case management. Includes smear – specimens
  • Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis. MMWR January 16, 2009 / 58(01);7-10

*Amplification of specific target sequences of nucleic acids (RNA or DNA), detection via nucleic acid probe.

Lessons

• Suspicion for TB should be high in high risk individuals
  • Know your local population
  • TB does not have to be symptomatic
  • Chest x-ray findings may be very subtle
• Morning & induced sputum for AFB, mycobacteria culture are the procedures of choice
• Decisions must be made before all the data is in
  • This must be individualized
• If suspicion for TB is high, treatment should be initiated promptly
Case 2: Begins Here

India 2.25 million
China 1.00 million
SAfrica 500,000
Indonesia 450,000
Pakistan 400,000

Case 2: Background

• 11/14/2012 - 15 year old girl, referred to the IPH for "follow-up and treatment with INH" because of a 13 mm. TB skin test result
• Born in the USA, parents Bangladeshi
• Never received BCG
• 2005 spent 3 months in Bangladesh
• Healthy until June, 2012
Case 2: Initial Course
• 6/15/12 – Slipped on watery surface, hit knee, felt patella move out of place and then back
  • ED
  • X-ray - ?chip fracture medial femoral condyle & joint effusion, MRI recommended
  • Multiple orthopedics visits; knee immobilizer, crutches, hinged knee brace, physical therapy
  • Ortho diagnosis - ? MCL tear
  • Knee improved a little

Case 2: Now Sick
• 10/12/12 – ED with cough, chest pain, difficulty breathing for 4 days
  • Chest x-ray normal
  • Treated with Azithromycin
• 10/19/12 – ED fever, cough, shaking chills, vomiting, diarrhea, headache
  • Crackles on physical exam
  • Temperature 38.5
  • Rx: Ceftriaxone, Prednisone, Ibuprofen, home on Amoxicillin

Case 2: Sicker
• 11/2/13 – ED fever, abdominal pain, vomiting
  • Temperature 104.3
  • Rx: Ketorolac, Ondansetron, fluids
  • Diagnosis: mononucleosis
• 11/7/13 – ED fevers, headache, nausea, vomiting, abdominal pain, body aches, weight loss
  • T 39.5, HR 148, BP 105/55, knee swollen
  • TB mentioned in ED & TB skin test placed there
  • Admitted to PICU
  • Ceftriaxone, fluids, lots of labs & imaging studies
Case 2
• 11/13/12 discharged
“Patient might be a convertor as she has visitors from the endemic country **though she is not symptomatic.** We sent IGRA and still pending and she will probably need INH with vit B6 for 9 months to be supplied by the health department.”

Case 2: 1st IPH Visit
• 11/14/12 Wednesday afternoon
  • Weight 110# (8 pound weight loss)
  • Chronically ill appearing, coughing

Case 2 Question 1
What would be the wrong thing to do?
A. Collect sputum for AFB, mycobacterial culture, including early morning samples
B. Start treatment for LTBI
C. Start treatment for TB
D. Order an MRI knee
E. Order a chest x-ray

• This cannot be "Latent TB Infection," which is defined as a condition without signs or symptoms of TB
• **Beware of a diagnosis of LTBI made by others**
Case 2: Final Hospitalization

- 11/14 & 15 sputum collected
- 11/15 & 16 RIPE was begun
- Weekend – no medication given
- 11/18/12 (Monday) – ED
  - Severe body pain, persistent vomiting, chest pain, difficulty breathing, fevers
  - Admitted to PICU in shock
Septic Shock: 1991 Definition*

- Documented / suspected infection
- Persistent hypotension requiring vasopressors
  - She was persistently hypotensive after IV fluids and was started on Dopamine, BP 88/45
- 2/4 of the following
  - HR ≥90 beats/minute 130
  - RR ≥20 or pCO2 ≤32 mm. Hg. 24-28; 26.9
  - Core temperature ≤36 or >38 38.3

* Society Critical Care Medicine,
* American College Chest Physicians

Case 2 Question 2
What should you do immediately?

- Start standard treatment with oral INH, Rifampin, PZA, Ethambutol
- Start treatment with IV Levofloxacin*, Rifampin*, Amikacin*, & Linezolid*
- Arrange for an open lung biopsy
- Bronchoscopy, lymph node biopsy, and BAL
- Start Vancomycin & Meropenem

* Not FDA approved for TB

Case 2: Final Hospital Course

- Symptoms – pain, fever, persistent vomiting & inability to eat; hypotensive & requiring Dopamine for 4 days
- TB treated with IV Levofloxacin, Amikacin (once daily dose, aiming for Peak 60-80, trough <1 mcg/mL), Rifampin, and oral Ethambutol
  - Rifampin changed to oral form in 1 week, Levofloxacin changed to oral form next, Amikacin stopped the day prior to discharge
Case 2: Final Hospital Course
- Methylprednisolone 80 mg was given day 1 after an ACTH test was done (normal).
- A short course of low dose prednisone was given later during the admission.
- Ondansetron and Metoclopramide were given for nausea and vomiting.
- Total parenteral nutrition was given.
- She gradually improved & was discharged after an 11 day hospitalization.

Case 2: Final Evaluation in Hospital
- Multiple imaging studies were done.
- Lumbar puncture, bronchoscopy with BAL, EGD, early morning urine for mycobacteria culture – no MTb was identified.
- Multiple labs – HIV negative, hyponatremia, CRP 191, ESR 72, WBC 22K with immature neutrophils, anemia, low albumin.
- Persistent fevers up to 39.4.

May 20, 2013
MRI: T1 with Magnevist Contrast
Case 2 Question 3
Which statement is true?

- The diagnosis is uncertain
- This case should not be reported as a case of TB
- The diagnosis is *Mycobacterium tuberculosis* septic shock
- Amikacin, Rifampin, & Levofloxacin all have activity against bacteria, including methicillin resistant staph aureus, so if she improves, sepsis due to such organisms is more likely than TB
- Time to initiation of appropriate therapy is unlikely to affect outcome in hypotensive TB cases

*Mycobacterium tuberculosis* Septic Shock

- Retrospective review, adults ≥ 18 with septic shock 1996-2007
- Consecutive patients from 28 medical centers in Canada, USA, Saudi Arabia
  - Cooperative Antimicrobial Therapy of Septic Shock (CATS) database – 8,670 subjects
- 53 cases determined to have septic shock from MTB
  - 1% of cases that had culture + septic shock


Septic Shock from TB vs. Other Bacteria

- TB cases – average 10 years younger
- TB cases had lower BMI
- APACHE II scores underestimated mortality in TB cases
Relationship between APACHE II score and survival in MTB and bacterial septic shock.

APACHE = Acute Physiology and Chronic Health Evaluation; MTB = Mycobacterium tuberculosis.

**Figure Legend:**

TB Cases vs. Others

<table>
<thead>
<tr>
<th>Feature</th>
<th>TB</th>
<th>Other bacteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV/AIDS</td>
<td>15%</td>
<td>2.8%</td>
</tr>
<tr>
<td>BMI</td>
<td>22.2 kg/m²</td>
<td>27.3 kg/m²</td>
</tr>
<tr>
<td>Mortality</td>
<td>79.2%</td>
<td>49.7%</td>
</tr>
<tr>
<td>Inappropriate initial Rx</td>
<td>52.8%</td>
<td>16.6%</td>
</tr>
<tr>
<td>Median time to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>appropriate Rx</td>
<td>31 hours</td>
<td>4.8 hours</td>
</tr>
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Relationship between antimicrobial delay and survival in MTB and bacterial septic shock. No. survivors/No. total for each group: < 24 h MTB shock, 6/11; < 24 h bacterial shock, 1,992/3,527; > 24 h MTB shock, 1/24; > 24 h bacterial shock, 47/478. See Figure 1 legend for expansion of abbreviation.
TB Cases

- No TB patient with BMI ≤ 20 kg/m² survived
- 7/53 TB patients had bacteremia
- For TB, cases survival was 7.1% for those with inappropriate initial therapy, and 36% for those with appropriate therapy
- For TB patients, median time to appropriate therapy was 10.2 hours for survivors and 35.2 hours for non-survivors
Laboratory Criteria for Diagnosis

• Isolation of MTB Complex from a clinical specimen —
  • OR
• Demonstration of MTB Complex from a clinical specimen by NAAT —
  • OR
• Demonstration of acid-fast bacilli in a clinical specimen when a culture has not been or cannot be obtained or is falsely negative or contaminated

Clinical Case Definition

All criteria must be met
Diagnostic evaluation must be completed

• A + TB skin test or IGRA
  • AND
• Signs, symptoms, x-ray / CT, other evidence of current disease
  • AND
• Treatment with 2 or more anti-TB medications

Lessons Learned

• Suspicion for TB should be high in high risk individuals
• LTBI cannot be diagnosed in patients with clinical evidence of TB
• TB can be a cause of sepsis / septic shock
• Time to treatment with appropriate medications is as important for sepsis due to TB as it is for sepsis due to other bacteria
• A diagnosis of TB can be made and should be made in some individuals without laboratory evidence of disease
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MRI Before & After TB Treatment

- November 21, 2012
- May 20, 2013
Questions & Discussion