Pitfalls in the Diagnosis and Management of Tuberculosis

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November 20th, 2013

Avoiding Pitfalls in Recognizing TB Disease

- Maintain a high index of suspicion
  - ‘Usual’ risk groups
  - Diabetes, Autoimmune disease, Transplant, CKD, Malnutrition
  - AFB smear negative ≠ no TB
- Settings where diagnostic delays commonly occur
  - HIV, Extrapulmonary TB, smear negative disease,
- Request a thorough microbiologic work-up in unusual cases
  - May require multiple or repeated diagnostic procedures
- Consult with local and regional public health authorities and TB experts
Diagnosis of TB

Risk Factors
Clinical Suspicion
Imaging
Microbiologic Tools

TB Diagnosis

Avoiding Pitfalls in Management of TB Disease

Drug – O - Gram
Case 1

- 29 year old Indian man who presents with right leg pain for 4 years
- Noted right ankle swelling about 1 year ago, and presented to Orthopedic clinic
- No cough, fevers, chills, night sweats or weight loss

Prior History

- 2006
  - Developed cough, fever and weight loss while visiting Denmark. Was treated for pneumonia without improvement
  - Tuberculin skin test positive
  - Returned to India with persistent symptoms and was started on a combination pill including INH, RIF and EMB for presumed pulmonary TB. Took all medications as directed for 6 months with clinical improvement.
- 2007 – Moved to US
- 2011 – Developed right ankle swelling
January 2012

- Underwent partial excision of fibula and deep biopsy of soft tissue and bone
- Findings – soft tissue mass and lateral malleolus erosion
- Frozen and final path – necrotizing granulomas

Microbiology

- Tissue and bone specimens – AFB smear neg
- Re-review of path specimen – solitary AFB
- MTB PCR + on tissue
- Tissue and bone specimens, MTB culture +
Extrapulmonary TB

- 21% of all TB cases in US
- Overall rates of TB declining, proportion of EPTB increasing
- Associated with women, foreign-birth, nonwhite race, immune compromise
- Not associated with MDR, incarceration, alcoholism, homelessness
- Meningeal and lymph node TB seen frequently in children
- GU and bone/joint in older adults
- Meningeal and pleural more commonly seen in US born

Trends in EPTB and PTB; 1993-2006
Extrapulmonary tuberculosis sites of disease, United States, 1993–2006 (N=47,293)

Table 2  Anatomical site of musculoskeletal TB

<table>
<thead>
<tr>
<th>Anatomical site</th>
<th>Patients (n)</th>
<th>Patients (%)</th>
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<tbody>
<tr>
<td>Spine</td>
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<td>Cervical</td>
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<td>Thoracic</td>
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<td>Not classified</td>
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<td>Humerus/elbow</td>
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<td>9.8</td>
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<tr>
<td>Knee</td>
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<td>8.2</td>
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<tr>
<td>Chest wall</td>
<td>5</td>
<td>8.2</td>
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<tr>
<td>Hip/femur</td>
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<td>6.6</td>
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<tr>
<td>Pelvis/SIJ</td>
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<td>6.6</td>
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<td>Wrist</td>
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<td>4.9</td>
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<tr>
<td>Fingers</td>
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<tr>
<td>Ankle</td>
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<td>1.6</td>
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EPTB Diagnosis

- Tends to be paucibacillary, and more difficult to detect microbiologically
- May require invasive/repeated procedures
  - Involves various sub-specialties
- Rapid Tests
  - Nucleic Acid Amplification Tests
  - GeneXpert MTB/RIF

Laraque, CID, 2009
Hillemann JCM, 2011
Tortoli, ERJ, 2012

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EPTB Treatment

<table>
<thead>
<tr>
<th>Site</th>
<th>Length of Therapy (mo)</th>
<th>Rating (duration)</th>
<th>Corticosteroids</th>
<th>Rating (corticosteroids)</th>
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<td>Lymph node</td>
<td>6</td>
<td>AI</td>
<td>Not recommended</td>
<td>DH</td>
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<tr>
<td>Serosal and joint</td>
<td>6–9</td>
<td>AI</td>
<td>Not recommended</td>
<td>DH</td>
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<tr>
<td>Pleural disease</td>
<td>6</td>
<td>AI</td>
<td>Not recommended</td>
<td>DH</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>6</td>
<td>AI</td>
<td>Strongly recommend</td>
<td>AI</td>
</tr>
<tr>
<td>CNS tuberculosis including meningitis</td>
<td>9–12</td>
<td>BI</td>
<td>Strongly recommend</td>
<td>AI</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>6</td>
<td>BI</td>
<td>Not recommended</td>
<td>DH</td>
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<tr>
<td>Gastrointestinal</td>
<td>6</td>
<td>AI</td>
<td>Not recommended</td>
<td>DH</td>
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<tr>
<td>Peritoneal</td>
<td>6</td>
<td>AI</td>
<td>Not recommended</td>
<td>DH</td>
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</tbody>
</table>

* For rating system, see Table 1.
* Duration of therapy for extrapulmonary tuberculosis caused by drug-resistant organisms is not known.
* Corticosteroid preparations vary among studies. See Section 8.3 for specific recommendations.
Challenges in EPTB

- Fewer TB cases has likely led to lowered suspicion for TB
- Public health focus is primarily on PTB
- Differing risk factors
- Diagnosis often more difficult and delayed
- Treatment efficacy and culture conversion can be difficult to detect
- Multidisciplinary approach often involving surgery, pathology, radiology etc.

Case 2

- 29 y.o. physician from Pakistan with dry cough x 2 months
- No fever, night sweats or weight loss
- TST negative 6 months previously
Case 2

- Induced sputum – AFB smear negative
- Quantiferon Gold positive
- Started on multidrug therapy
- Cultures MTB positive 4 weeks later
Smear-Negative TB

- Sputum smear microscopy sensitivity ~ 50%
  - Lower in HIV and children
- Leads to diagnostic and treatment delays
- Increasingly common, especially in high HIV settings
  - 35 – 40% of US cases
- Smear negative TB accounts for 10-20% of TB transmission
- Leads to one-quarter the number of cases as smear positive index cases

Shah, IJTLID, 2012
Tostmann, CID, 2008

Smear-Negative TB

- Is common and transmissible
  - Infection control measures are necessary
- Often entails treatment delays
- Contact tracing is essential, but is often delayed
- Rapid diagnostic tests are moderately sensitive and may help mitigate above
- Treatment similar to smear positive TB
- Empiric therapy may be needed
Case 3

- 45 y.o. woman currently incarcerated with history of injection drug use.
- Complains of cough, fevers, sweats and weight loss for 2 months.

- No old CXR to compare with
Case 3

- AFB smear negative
- Started on antitubercular therapy
- Cultures remained negative with minimal improvement in CXR, but resolution of symptoms

Culture Negative Pulmonary Tuberculosis

- Clinical and radiologic picture of active TB
- Cultures remain negative
  - Paucibacillary
  - Incorrect specimen processing
  - Temporal variation in bacteria shedding
- Perform at least 3 quality sputum exams
- Consider other diagnostics such as bronchoscopy
- Up to 15-20% of reported TB cases in US
Culture negative TB

- 4 month regimen of isoniazid and rifampin has been shown to have a 1.2% relapse rate
- GeneXpert MTB/RIF may have some utility

Dutt, 1989
Marlowe, 2011
Zeka, 2011
Atypical Radiographic Presentations

- Lower lobe infiltrates
- Predominant adenopathy
- Miliary or disseminated
- Pleural effusion
- Mass-like opacities
- Pneumothorax

More common in children with ‘primary’ TB

"Classic" Cavitary Tuberculosis

- 31 y.o. man from Ecuador with cough, night sweats, fevers and weight loss
Non-cavitary Tuberculosis

- 29 y.o. physician from Pakistan with dry cough for 2 months

Disseminated TB + HIV

- 45 y.o. woman with HIV with cough and fever for 1 week.
  - Treated for LLL pneumonia & parapneumonic effusion without improvement
  - QFT – G negative
  - AFB smears from sputum negative
- Sputum, pleural fluid, blood cultures ultimately grew MTB
Miliary TB

59 y.o. woman with dermatomyositis, on corticosteroids with shoulder pain and ulcerated tongue mass

Pneumothorax
Take Home Points

- TB disease can present in a myriad of ways
- Keep a high index of suspicion especially in certain risk groups
- Utilize infection control measures appropriately
- Become familiar with rapid tests offered in your region and recognize their limitations
- Collaborate closely with primary care, specialists, microbiologist, public health authorities and experts
Diagnosis of TB Meningitis
A Case From New Hampshire

Elizabeth A. Talbot, MD
Deputy State Epidemiologist, NH DHHS
Associate Professor, ID Section,
Dartmouth Medical School

Routine Report of Suspect Bacterial Meningitis

- Feb 27: suspect bacterial meningitis reported to NH DHHS
- 19yo male from China with F, HA, weakness, photophobia, N/V and suggestive CSF
  - Student at UNH
- Question regarding N. meningitidis prophylaxis for girlfriend and at school
History Prior to Suspect Bacterial Meningitis

- Dec 13-17 (2m PTA) hospitalized for RLL pneumonia and effusion
  - Thoracentesis done (neg AFB smear)
  - HIV test negative
  - Received 14 days of levaquin: cough improved
- Dec 2012-Jan 2013 (1m PTA) hospitalized in China for pneumonia
  - Told “not TB” (TST neg)
  - Received 10 days of unknown antibiotic: cough improved

HPI (This Episode)

- Feb 14 (10d PTA): Nonspecific symptoms
- Feb 18 and 20 ED “not feeling well”
  - Azithromycin given
- Feb 24 presented to ED (3rd time) with HA, F, weakness and photophobia
  - Admitted
  - HCT: no acute intracranial abnormality
  - Feb 28 LP glu 25, pro 169, WBC 370 with 70% PMNs. No bacterial growth; AFB not done
- Started on IV cipro and "improving"
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“Could This be TB Meningitis (TBM)?”

- Navigated first CSF to probe and AFB
- Patient became confused, weak: seizures
  - Normal sodium throughout
  - Transferred to ICU
- Mar 4 second CSF collected: AFB sm pos
  - Isolate sent to CDC for sensitivity testing
- Mar 6 first CSF positive Gen Probe for MTBC; AFB sm/cx negative
  - Started RIPE, steroid, antiepileptic
- Mar 16: transferred to MGH for worsening

17d after presentation
11d after admission
Complicated Course

- Mar 19 (d13 tx) neuro status worse
  - Added moxi + amikacin to RIPE
- Third LP AFB sm pos
- Mar 21 second CSF isolate pansensitive
- Mar 29 (d23 tx) CN deficits result in double vision and balance problems
- Aug 1 family took him back to China
- Eventually returned to normal neurologic function
NH’s Clinical Summary

- Two unexplained pneumonias in otherwise healthy young adult from China
- Presented with nonspecific (but perceived urgent symptoms) over 10 days
- Presentation and CSF suggested TBM
- RIPE started 17 days after presentation
  - Aminoglycoside and fluoroquinolone added two weeks later when deteriorated
- TBM diagnosis confirmed by probe, smear, culture

TB Meningitis Diagnosis
TBM Pathogenesis

TB bacteremia occurs in primary or reactivation disease and establishes subependymal tubercles (Rich foci) which rupture into subarachnoid space → meningitis

- At base of brain
  - Dense gelatinous exudate develops
  - Surrounds arteries and CNs

- Results in
  - Hydrocephalus
  - Vasculitis → infarction, hemiplegia, quadriplegia

neuropathology.neoucom.edu

Tuberculous Meningitis. Donald and Shoerman, NEJM. 351:17, 10/21/2004
TBM Outcomes

- 3 Stages:
  - Lucid: insidious HA/F; 2-3 wks
    - 19% mortality
  - Meningitic phase: meningismus, N/V, CN palsies
    - 69% mortality
  - Paralytic phase: stupor, coma, seizure, pareses
- 1/3 - 1/2 patients complete neuro recovery
- 1/3 have residual severe neurologic deficits such as hemiparesis, blindness, seizure disorder

Prognosis Study

- University Hosp in Taiwan
- 41 adults in retrospective cohort
  - Age 16-80 (med 41)
  - 41% with immunocompromise
- Mortality 10%; morbidity 56%
  - AFB+ CSF worse prognosis
  - 19 patients got worse during therapy
Another Prognosis Study


• Among 49 adults/children with TBM, most significant predictors of outcome
  - Age
  - Stage of disease
  - Focal weakness
  - Cranial nerve palsy
  - Hydrocephalus
  - Delayed treatment

Diagnosis:

CSF Examination

• Usually lymphocytic pleocytosis, elevated protein, depressed glucose
• AFB stain: sensitivity 10-60%
  - Median time to see 10 minutes
• MTB culture: sens 25-75% 2-6 weeks
  - Better with increased volume, up to 6 mL
• GeneXpert MTB/RIF: automated realtime PCR
• Adenosine deaminase (ADA) level
Studies of Gene Xpert MTB/RIF on Extrapulmonary Specimens

- Pre-2011 metanalysis found sens 80% [95% CI 75-85]**
- Systematic review of 18 studies of 10,224 pulmonary and EP patients
  - Sens med 77% (range 25-97%)
  - Specificity 98% [98-99]*
  - Variation between populations, selection, type of EPTB, sample processing, ref standard . . .


Selected* (Mixed) EPTB Studies
*=>100 patients, non-urine, control group

<table>
<thead>
<tr>
<th>Author</th>
<th># Pts</th>
<th>Sample(s)</th>
<th>Sens</th>
<th>Spec</th>
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<td>340</td>
<td>Tissue, gastric aspirate, pleural fluid, pus</td>
<td>95</td>
<td>100</td>
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<td>Hillermann</td>
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<td>Tissue, gastric aspirate</td>
<td>77</td>
<td>98</td>
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<td>Moure</td>
<td>149</td>
<td>SMEAR NEG pleural fluid, lymph node, pus, tissue</td>
<td>58</td>
<td>100</td>
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<tr>
<td>Vadwai</td>
<td>533</td>
<td>Tissue, pus, body fluids</td>
<td>81</td>
<td>100</td>
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<td>Zeka</td>
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<td>Pleural fluid, lymph node, CSF, pericardial fluid, tissue</td>
<td>54</td>
<td>100</td>
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<tr>
<td>Tortoli</td>
<td>1474</td>
<td>Mixed</td>
<td>81</td>
<td>100</td>
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Xpert as a “Rule-in Test”?
Adenosine Deaminase
ADA Reflects Immune Cell Activity

Having phagocytosed Mycobacterium, macrophages secrete a panel of cytokines (e.g., IL-12 and IL-16) which interact with various cell populations including natural killer (NK) cells and CD4+ T cells. This leads to the activation of these cells and the stimulation of interferon gamma (IFN-γ) release. IFN-γ induces macrophage bactericidal mechnisms. Activated macrophages release adenosine deaminase (ADA2), whereas ADA1 is released from macrophages and lymphocytes as well.

Metanalyses of ADA
Krenke R et al. Use of Plural Fluid Levels of ADA. Current Opinion in Pulm Med 2010: 16

- Pleural effusion, ascites, CSF
- Most show sens/spec 90/<90
- (Our patient did not have it done)

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients studied</th>
<th>Tuberculous (n)</th>
<th>Malignant (n)</th>
<th>PPE/parapneumonia (n)</th>
<th>Other (n)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<td>Sharma and Banga [65]</td>
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<td>Dholki et al. [59,51**]</td>
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<td>13</td>
<td>3</td>
<td>3</td>
<td>90.0</td>
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<tr>
<td>Total (number mean ± SD)</td>
<td>739</td>
<td>305</td>
<td>302</td>
<td>69</td>
<td>32</td>
<td>88.5 ± 8.7</td>
<td>90.1 ± 9.6</td>
</tr>
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AUC: area under curve; na, data not available; PPE, parapneumonic effusion.
Diagnosis: Imaging

- CXR shows
  - Primary, miliary or old TB
  - Normal
- CT/MRI demonstrates
  - Hydrocephalus, basilar exudates and inflammation
  - Tuberculomas
  - Infarctions

Thwaites Score
Thwaites GE, Chau TT, Stepniewska K, Phu NH, Chuong LV, Sinh DX, et al.
Diagnosis of adult TBM by use of clin and lab features. Lancet
2002;360(9342):1287-1292

- 5 variables predictive in Vietnam adults
  - Max score 13
  - ≤ 4 TBM
  - > 4 bacterial
- Sens/spec 97/91%
- NH case score
  - 0+0-5+0+0=-5
**Thwaites Team Validation**

- 205 inpatients in same hospital in Vietnam
- TBM sens 99%

**Algorithm Extensions**

- 508 adults admitted to ICU in Morocco who satisfied criteria for TBM ($n = 274$) or bacterial meningitis ($n = 234$)
- Retrospective MVA and classification and regression tree (CART) without CNS radiology available
- For score >7
  - Sens 87% and 88%
  - Spec 96% and 95%
Lancet Consensus Scoring System

- 20 parameters in 4 categories
  - Clinical
  - CSF
  - CNS imaging
  - Evidence of TB elsewhere
- Max score 20

Definite TBM: micro id or evidence from commercial NAAT of CNS
Probable TBM: imaging available, >12; imaging not available, >10
Possible TBM: imaging available, 6–11, imaging not available, 6–9

Our case: 15
Summary

• Diagnosing TBM requires high clinical suspicion
  – Poor prognosis linked to delays
• Health departments retain TB diagnostic vigilance and can facilitate
• Clinical scores/algorithms are available
• Rely on presentation, risk factors, imaging, routine CSF exams +/- ADA
  – GeneXpert may be useful “rule in test”
Pitfalls in Dx TB: Diagnosis Delayed

25 year old male

- 25 yo American born Cambodian male
- Father had Tuberculosis 1 year previously (parents had lived in Vietnam and traveled back and forth frequently)
- Contact investigation by public health:
  - Patient not screened as he was unavailable (going to college and had a catering job on the side)
  - All other family members were TST negative
25 year old male

- 1/2013: experienced flu-like symptoms with a dry cough
- Cough attributed to smoking cessation
- No weight loss but by 4/2013: developed fevers, drenching night sweats, continued cough
- 5/2013: noted headache and sister felt his head “looked funny” and convinced him to go for assessment. Went to ED

ED

- Seen in ED
- Scalp mass palpated
- Physician orders plain films
Patient started on INH/Rifampin/PZA/EMB plus Moxifloxacin, Amikacin and Cycloserine

Sputum grew pansensitive TB
Treatment Course

- Patient received 2 months of IV Capreomycin with resolution of the cold abscess of the head
- Thoracic and cervical pain much improved
- Headache continues
- Cycloserine d/c’d at 5 months
- Headache resolves

Despite significant improvement, patient unable to return to work as a caterer. He had dropped out of community college as well.

No money

Described by sister as "a recluse"

Admits to depression but unwilling to see a therapist

Started on Zoloft
Visit 11/8/2013

- Spirits markedly improved on Zoloft
- Mass on head gone
- No side effects from meds
- Currently on boosted Isoniazid, boosted Rifampin, Ethambutol and Pyrazinamide (off Cycloserine, Capreomycin and Moxifloxacin)

21 year old female

- Born in China
- Came to US in 2009 to attend U Mass
- Positive TST 16 mm
- CXR negative
- Declined LTBI therapy
- Well until 12/12
12/7/12 symptoms

- Developed cough
- Went to student health
- No chest x-ray
- Treated with azythromycin x two
- Perhaps slight improvement
- Leaves on Christmas break for China

12/25/12

- Developed cough
- Went to student health
- No chest x-ray
- Treated with azythromycin x two
- Perhaps slight improvement
- Leaves on Christmas break for China

While in China

- Parents note coughing
- Brought to local hospital
- CXR and CT accomplished
- Both abnormal
- AFB smear negative
- Told OK to return to US
- Dx pneumonia, not TB
CT continued

CT China
Back in Boston

- Continues to cough over the next 5 months
- Multiple visits with midlevel HCP at PCP office who does multiple CXRs as well as CTs
- Multiple courses of antibiotics including fluoroquinolones, Augmentin, azithromycin as well as inhaled corticosteroids
Cough/Cough

- By June, patient is no better
- Patient requests consult with pulmonary physician
- Told this was an abuse of her insurance policy

Pulmonary Evaluation

- CT worse
- AFB smear +
- Pulmonologist makes presumptive dx of TB
- Started on RIPE 6/27/2013
- Over ensuing month, smears remain +
- Moxifloxacin started 8/8/2013
Smear Conversion

- Two weeks after initiation of Moxifloxacin, AFB smears become negative
- Cultures growing MAC and MTB
- Difficulty obtaining sensitivities secondary to MAC overgrowth
- CXR worse
- Low serum drug levels (Rifampin and Ethambutol)
- Referred to LSH Outpatient Department on September 8th

Seen in OPD not anxious for admission to LSH

- Should we treat MAC?
- Should we add additional drugs or await sensitivities?
LSH

- 9/17/2013 sensitivities return:
  - Resistance to INH (at all levels), Rifampin, Ethambutol, Ethionamide
  - PZA pending
  - Sensitive to Cycloserine, Capreomycin and Ciprofloxacin
- How do we treat at this point?

LSH Rx

- Rx Capreomycin 12 mg/kg IV (S)
- Continued Moxifloxacin (S initially)
- Continued PZA pending sensitivities
- Added Cycloserine 500 mg daily (S)
- Added Linezolid 600 mg daily (no testing)
- Patient feels much better on medications and tolerates meds well
LSH Admission

- Hospitalized for 1 week to initiate IV therapy
- Then discharged to home
- But returned for daily IV infusion M-Friday for 10 days
- Now receiving IV infusion of Capreomycin at home

TB Treatment

- 2 weeks into new TB treatment, CXR unchanged
- Additional information: initial sputum culture PZA resistant as well
- ? Rx changes
Treatment course

- Started PASER (no testing for S yet)
- Isolate subsequently found to be Linezolid sensitive (send out)
- Capreomycin, Cycloserine, Linezolid, Moxifloxacin and PASER continued
- AFB culture growing from 9/9/2013
- Awaiting Moxifloxacin sensitivity from this later culture. Awaiting PASER sensitivity from initial culture
- Of 5 drugs, we know definitively she is sensitive to 3

MAC/MTb

- Cultures consistently growing 2 organisms
- Presence of MAC on 9/10 culture makes sensitivities difficult. Colonies on initial culture hand picked for accuracy
- Cultures taken from shower head in apt and kitchen faucet
- Both grow MAC after 7 days!
Do we treat MAC?

- Change shower head and filter on faucet
- Is the MAC a pathogen?
- Do we eliminate exposure to MAC, or do we treat MAC?
- Should we do MAC sensitivity?

New Problem

- Platelets fall to 110. Previously nl. Related to Linezolid?
- What to do?