TB for the Intensivist-Update on the Diagnosis and Management of the TB Patient in the ICU

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Case

- 28 yo Honduran male (came to US in 2000) who worked as a landscaper-presented to a Palm Beach Hospital in Dec 2012 with a 6 month hx of diarrhea (watery diarrhea 6-7/day) no N/V (-) BRBPR Occ epigastric and periumbilical pain but denied RLQ pain
- Patient also gave a history of low grade fever for ~ 3 months, anorexia, and generalized weakness
- The patient had a colonoscopy and was diagnosed with Crohn's Dx by biopsy on pathology
Case

- The patient was started on Prednisone 60mg po qD and sulfasalazine without improvement.
- In March 2013, due to continued symptoms the patient was started on Humira and Steroids (40mg SQ q 2 weeks-received 3 doses total). The patient does not remember if a PPD was performed or if he received an Interferon Gamma Release Assay (IGRA).
- The patient initially improved symptomatically.
Case

- In May 2013 (two weeks after getting his last Humira injection) he developed worsening diarrhea, cough and fevers (102 to 103) and gave a history of losing 30 lbs over 6 mths
- Denied History of prior TB exposure
Case

- The patient was admitted to another Palm Beach Hospital on 5/22/2013
- 5/22/13 CXR bilateral infiltrates
- 5/23/13 CT showed bilateral upper lobe infiltrates and LUL cavity
- 5/23/13 CT of Abd-Significant wall thickening of colon from cecum to left colon with pericolonic inflammatory changes-c/w diffuse colitis.
- 5/24/13-MRI Abd-narrowing in central intrahepatic biliary tree w/o dilation or obstruction.
Thickened Bowel wall
Narrowing of bile ducts
Case

○ 5/24 Sputum AFB 3+
○ 5/31 colon bx AFB (+), subsequently Culture (+) TB
○ HAINS no mutations subsequently pansusceptible
○ Started on INH/Rif/Ethambutol/PZA orally daily on 5/25/13
Transmission of Tuberculosis

Dissemination of Tuberculosis

**Expulsion**
- Droplets containing *M. tuberculosis* coughed or sneezed into air
- Droplets remain suspended in air for an hour or two
- Sterilized by sunlight and/or dispersed by winds

**Introduction into host**
- Inhalation
- Ingestion (infected milk)

**Implantation**
- **Lungs** (initial infection anywhere in lung). Drainage to hilar lymph nodes
- **Tonsil** Drainage to cervical lymph nodes
- **Lymph nodes**
- **Intestine** (most commonly in lower ileum and cecum). Drainage to mesenteric lymph nodes
- **Finger** Drainage to axillary lymph nodes

**Secondary dissemination to other organs**

Infectious mycobacteria preserved in darkness and moisture from hours to months.

Laboratory accident
Pathogenesis of Tuberculosis
Tuberculosis Infection – No Disease

- Cannot spread to others
- Not considered a TB case
- Positive skin test reaction
- X-ray negative
- No symptoms
- Potential for active disease
Progression from Infection to Disease is Increased by . . .

- HIV infection
- X-ray evidence of old, untreated TB
- Substance abuse, injecting drug use
- Silicosis, diabetes
- Certain therapies (eg TNF blockers)
- Certain cancers
- Underweight by 10% or more
Overexpression of TNF-\(\alpha\)

- Inflammation and tissue destruction
- Immune-mediated inflammatory diseases (IMID)
  - Rheumatoid arthritis, inflammatory bowel disease, psoriasis, ankylosing spondylitis, others

- Rewards of TNF-\(\alpha\) blockade
  - Highly successful in treatment of these conditions
TB Diagnosis

- Smear
  - Cheap & rapid
  - Only 40-60% positive in cases of active TB
TB Diagnosis

- **Culture**
  - Positive ~80% of active TB cases
  - Takes 6-8 weeks by conventional
  - Takes 1-3 weeks by liquid media

- **Sensitivity**
  - Takes 1-2 weeks after positive culture
TB Diagnosis
Nucleic Acid Amplification

- Results within eight hours
  99% specificity on smear (+) cases
- Up to 80% sensitivity on three samples
- $30 to $50 per test
- Approved by the FDA for smear-positive and –negative, untreated cases
- May have a rule in non-pulmonary samples
# CDC MDDR Performance Data:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td>RIF</td>
<td><em>rpoB</em></td>
<td>96.1%</td>
<td>97%</td>
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<tr>
<td>INH</td>
<td><em>inhA</em> + <em>katG</em></td>
<td>88.6</td>
<td>98.7</td>
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<tr>
<td>FQ</td>
<td><em>gyrA</em></td>
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<td>97</td>
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<tr>
<td>KAN</td>
<td><em>rrs</em> + <em>eis</em></td>
<td>86.8</td>
<td>96.9</td>
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<tr>
<td>AMK</td>
<td><em>rrs</em></td>
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<td>99</td>
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<tr>
<td>CAP</td>
<td><em>rrs</em> + <em>tlyA</em></td>
<td>44.6</td>
<td>85.9</td>
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<tr>
<td>PZA</td>
<td><em>pncA</em></td>
<td>86%</td>
<td>98%</td>
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GenExpert
Thanks to a Partnership Grant from the Virginia TB Foundation, the SNTC offers NAA and/or HAIN Testing when Determined to be Necessary
Figure 2: Standard “MYCOTB” Microtiter 96-well Plate

<table>
<thead>
<tr>
<th>OFL</th>
<th>MXF</th>
<th>RIF</th>
<th>AMI</th>
<th>STR</th>
<th>RFB</th>
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<th>ETH</th>
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<td>32</td>
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</tbody>
</table>

OFL – Ofloxacin; MXF – Moxifloxacin; RIF – Rifampin; AMI – Amikacin; STR – Streptomycin; RFB – Rifabutin; PAS – p-Aminosalicylic Acid; ETH – Ethionamide; CYC – Cycloserine; INH – Isoniazid; KAN – Kanamycin; EMB – Ethambutol

Vision plate-reader image of isolate with resistance to Streptomycin

Vision plate-reader image of isolate with multi-drug resistance – resistance to Rifampin, Rifabutin, Isoniazid
CDC Pathology Lab

- CDC can do PCR (and if positive Molecular Detection of Drug Resistance-MDDR) on fixed tissue and specimens in formalin
- Call 1-800-4TB-INFO and arranged through FL State Lab
Case

- QFT indeterminate
- Nil=7.21
- Mitogen – Nil 0.36 (>0.5) no mitogen response)
- TB minus nil 0.15 (0-0.34),
Diagnosis of TB Infection – Tuberculin Skin Test (TST) Formerly PPD
Sensitivity and Specificity of the Tuberculin Skin Test (TST)

- Depending on prevalence of disease in population you are testing and geographical area
  - Up to 20% of positive reactions might be false positives
    - Infected with Mycobacteria other than TB (e.g. MAC)
    - BCG vaccine
  - Up to 20% of individuals with active TB may be false negative
    - Critically ill TB patient
    - Immunosuppressed person
    - Recently vaccinated with live virus
    - Recent TB infection
Interferon Gamma Release Assays (IGRAs) for LTBI

- IGRAs recently approved by FDA (Quantiferon© Cellestis, T-Spot© Oxford Immunotec)
- Guidelines from the CDC now recommend that the use of such interferon-γ release assays for MTB (IGRA) may be used in all circumstances in which the TST is currently used, including contact investigations, the evaluation of recent immigrants, and sequential testing surveillance programs for infection control (eg, those for healthcare workers)
- May be able to discern reaction to BCG and NTM
- More studies needed to discern role in LTBI diagnosis (especially performance in certain populations eg, young children and immunosuppressed persons)
FDA Approved IGRAs

- **QuantiFERON®-TB Gold In-Tube (QFT-GIT)**
  - FDA approved Oct 2007

- **T-Spot®. TB (T-Spot)**
  - FDA approved July 2008
How to Interpret QFT?

- Nil = 7.21
- Mitogen – Nil 0.36 (>0.5) no mitogen response
- TB minus nil 0.15 (0-0.34),

Sample Result

<table>
<thead>
<tr>
<th>TABLE 1. Interpretation criteria for the QuantIFERON-TB Gold Test (QFT-G)</th>
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</thead>
<tbody>
<tr>
<td><strong>Interpretation</strong></td>
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<td>Positive</td>
</tr>
<tr>
<td>Negative</td>
</tr>
<tr>
<td>Indeterminate</td>
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<tr>
<td>TB minus</td>
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</table>


* The interferon gamma (IFN-γ) concentration in plasma from blood incubated with saline.
† The higher IFN-γ concentration in plasma from blood stimulated with a cocktail of peptides representing early secretory antigenic target-6 (ESAT-6) or a cocktail of peptides representing culture filtrate protein 10 (CFP-10) minus Nil.
‡ The IFN-γ concentration in plasma from blood stimulated with mitogen minus Nil.
§ Interpretation indicating that Mycobacterium tuberculosis infection is likely.
** Interpretation indicating that M. tuberculosis infection is not likely.
†† Interpretation indicating an uncertain likelihood of M. tuberculosis infection.

MMWR 6/25/10
IGRAs-Not the Total Answer

• Not for diagnosing active disease but to support TB exposure
• More Specific in BCG pts
• ? Sensitivity in Immunosuppressed and Children
• “Wobble” effect in Serially Tested Low Prevalence Populations
Bayes Theorem

“Accuracy of a Test is Based on the Prevalence of the Disease In the Population”
  - PreTest Probability is Important!!
LTBI testing in High Risk Individuals (eg TNF pts, immunosuppression and HIV)

- May consider using both PPD and QFT and if both neg or indeterminate consider treating in high risk pts eg foreign born, hx of TB exposure
Case

- After 15 days of TB treatment pt developed BP 80/60 P=90 RR=16 T=103.2 SaO2 on RA 96% Abd Soft (-) HSM (-) rebound or guarding no masses Chest Clear

- WBC 12.8 Hct 28.8 plt 404 MCV 75 PT 12.8 INR 1.2 BUN 5 Cr 0.6 Na 120 K 5.6 Cl 86 and CO2 21 AST 400 ALT 475 Alk Phos 2230 Glu 63 C Diff (-) Bld Cx (-) HIV (-)

- Placed on Liver Sparing regimen but meds continued due to probable TB of Liver
  - Usually involves biliary tract with Alk Phos elevation out of proportion to LFTs
  - Don’t stop TB drugs-use FQs, Aminoglycosides, EMB
Case-Addisons Dx

- Baseline Cortisol level 6
- Post cortrosyn 11
  - Studies have shown 5-55% of TB patients may have evidence of hypoadrenalism (controversy how to test)
  - Most asymptomatic
  - Some had clinical evidence of hypoadrenalism esp in pts with disseminated dx
Case

- Admitted to ICU for continued fevers and further therapy 6/11/13
- MRI of Brain (-)
- MRI of T/L/S spine (-)
- CXR 7/4 Increasing upper lobe infiltrates L>R
Tuberculosis immune reconstitution inflammatory syndrome “IRIS”

- 2 forms
  - “Paradoxical TB-IRIS”-Immune reconstitution with inflammatory response in patients on therapy for TB associated with improved immune function (commonly associated with the initiation of ARV therapy)
  - “unmasking TB-IRIS”-patients on ARV therapy who are recognized to have active TB disease within 3 months of initiating ARV therapy

- ARV associated TB is the development of TB anytime after starting ARV therapy

Manabe et al JID 2009:199;437-444
Airborne Isolation Infx (AII) Control Precautions

THINK TB!!

- Negative pressure isolation
- N95 masks
- 6-12 air exchanges/hr
- Try to intubate (as well as other droplet producing procedures) in All Room
Airborne Isolation Infx (AII) Control Precautions

- Ventilators
  - in-line suctioning to maintain the ventilator circuit as a closed system.
  - Humidification should be done via heat-moisture exchangers with viral-bacterial filter properties rather than heated humidifiers.
  - Each ventilator should have two filters: one between the inspiratory port and ventilator circuit and the other between the expiratory port and ventilator circuit, to provide additional protection from exhaust gases and minimize ventilator contamination.
Case

- Started on Steroids (for IRIS and hypoadrenal) - Solumedrol 60 q 6 hours
  - No randomized placebo control studies to support use of steroids in TB pts
    - Recommended for TB meningitis in children, pericarditis, ? Endobronchial TB and IRIS when inflammatory complications are present
  - No dosing schedule shown to be superior
Case

- Due to severity of disease and continued positive smears and cultures-transferred to Jackson Memorial Hosp RCU on 7/11/13 for continued therapy
  - 2 contracted hospitals-JMH and Shands at Jaxville
- Started on IV meds due to concerns for malabsorption due to GI involvement
- Started IV INH/RIF/Levo/Amik
- Clinically responded and became smear and culture negative on 8/4/13
- Switched to oral meds
IV TB Meds

Need for patients unable to take oral meds (e.g., ileus or concerns for GI dysfunction, unable to use NGT tube)

- INH
- Rifampin
- Aminoglycosides
- Fluoroquinolones
- Linezolid
Serum Drug Levels

Serum Drug levels (2hr and 6hr (expected))

- RIF 600mg 2.1 and 2.8 (8-24)
- INH 300mg 1.58 and .57 (3-5)
- PZA 1000mg 21 and 13 (20-60)
- EMB 1200mg 0.83 and 0.46 (2-8)

Dosages adjusted-eventually needed INH 1500mg po TIW and Rifampin 1200mg po TIW to achieve expected levels
## Drug Levels

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<th>DRUG</th>
<th>ABOVE</th>
<th>EXPECTED</th>
<th>BELOW</th>
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<tbody>
<tr>
<td>INH</td>
<td>4</td>
<td>22</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>6%</td>
<td>34%</td>
<td>59%</td>
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<tr>
<td>RIF</td>
<td>0</td>
<td>17</td>
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<tr>
<td></td>
<td>0%</td>
<td>27%</td>
<td>73%</td>
</tr>
<tr>
<td>PZA</td>
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</tr>
<tr>
<td></td>
<td>0%</td>
<td>95%</td>
<td>5%</td>
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<tr>
<td>EMB</td>
<td>1</td>
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</tr>
<tr>
<td></td>
<td>2%</td>
<td>58%</td>
<td>41%</td>
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<tr>
<td>TOTALS</td>
<td>5</td>
<td>136</td>
<td>115</td>
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<tr>
<td>n = 256</td>
<td>2%</td>
<td>53%</td>
<td>45%</td>
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</table>
Who should have TDM?

UF Pharmacokinetics Lab

- Patients failing treatment
- Resistant patients
- Patients with possible toxic side effects
- Patients with renal, GI or hepatic dysfunction
- Drug interactions
- Compliance checks
Case

- Wt 69 (adm 55.9) Tapered off Prednisone
- Discharged 10/2/13 on TIW DOT
- Rx until 2/4/14 (6 months after culture negative-prolonged therapy due to positive TB cultures after 2 months of treatment)
- Remains disease free
“DOT THERAPY WORKS!”

- 95% of patients with TB will be cured by DOT
  - Decreases Morbidity & Mortality and cost (~$1500/pt)
  - Decreases Spread of Disease
    - Average patient with TB infects 30 other individuals
  - Decreases resistance
    - MDR costs~$250,000 to cure with only ~80% success
- 5% of patients with Active TB will be unable to complete therapy; requiring legal interventions and facilities to cure them
  - In S.F. one non-compliant patient with MDR-TB was responsible for 40 other cases
THANK YOU!!

1-800-4TB-INFO

Southeast National TB Center/FL DOH
TB HOTLINE