MDR TB – XDR TB
The Laboratory -
A Clinician’s Perspective

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Areas of Coverage

Legend
Area of Coverage
Region 1  San Francisco, CA
Region 2  San Antonio, TX
Region 3  Newark, NJ
Region 4  Gainesville, FL

Center Location
Partnership with the TB laboratory provides an essential resource for successful treatment outcomes.
Clinicians Really Want to Know

- Is it TB?
- Drug susceptible?
- What drugs can I use?

AND WE NEED TO KNOW IT NOW!
IF YOU SUSPECT RESISTANCE
- I WANT TO KNOW - PLEASE CALL
Rapid Diagnosis of MDR TB

• Allows us to treat patient appropriately
  – Prevent clinical deterioration
  – Limit toxicity

• Public health benefits
  – Prevent further drug resistance
  – Prevent transmission
  – Identify treatment regimen for contacts
MDR TB – Definitions

TB resistant to INH and Rifampin

- TB - No Prior Therapy
  aka
  • Primary MDR TB
    – Results from exposure to a person with infectious MDR TB
    – Can catch you by surprise

- TB – Prior Therapy
  aka
  • Acquired MDR TB
    – Results from inadequate treatment
    – Usually harder to treat
XDR TB

- MDR TB Plus
  - Resistance to one of the fluoroquinolones
    - Ofloxacin
    - Levofloxacin
    - Moxifloxacin

  AND

- Resistance to one of the second line injectables
  - Amikacin
  - Capreomycin
  - Kanamycin
Initial Encounter With Patient

• Ask about factors that increase their risk of drug resistance

• Decide whether treatment should be augmented to cover for possible drug resistance
  – Unfortunately in the community they are adding moxifloxacin alone if they are worried
  • THIS RISKS FLUROQUINOLONE RESISTANCE
Patients at Risk of Drug Resistant TB

- History of prior treatment for TB
- Treatment failure
- History of poor adherence
- Clinical deterioration during 4 drug therapy
- Exposure to a patient with relapse or failure
- Birth or residence in country with high incidence of drug resistant TB
Estimated Number of MDR TB Cases*

*Zignol et al., JID 2006

- More than 50,000 cases
- From 10,000 to 50,000 cases
- From 1,000 to 9,999 cases
- From 100 to 999 cases
- Less than 100 cases
WHO estimates 40,000 cases emerge each year

49 countries
World Health Organization

TUBERCULOSIS

MDR-TB & XDR-TB

THE 2008 REPORT

ANTI-TUBERCULOSIS DRUG RESISTANCE IN THE WORLD
Case Study

- 26 year old Vietnamese female diagnosed with smear and culture + M TB June 2008
  - Weight loss, bloody sputum, fever, short of breath, rapid heart rate
  - Extensive bilateral cavitary infiltrates
  - Started on standard TB treatment “RIPE”
    - Cough, fever, and shortness of breath worsen
    - Admitted to ICU end of July
Case Study

• Patient deteriorating, impending respiratory failure
• From an area of the world with not only MDR TB but XDR TB
• Physician adds moxifloxacin alone 7/27/08
• 8/1/08 nurse calls lab and they report possible “resistance to everything”
  – I asked her to clarify what that meant
No Time to Wait For Lab Results

• “We have preliminary MTB drug susceptibility test results for patient --. specimen # --, DOC=06-13-08. We have repeated the test a second time. The test results indicate MDR TB to include resistance to INH, Streptomycin, Ethambutol and Rifampin. We are checking to determine if the culture is pure before we report out a preliminary report. The culture will be sent to -- this week for extended susceptibility testing and genotyping”

Sent 8/4/08
COMMUNICATION AND PARTNERSHIP BETWEEN THE LABORATORY AND PROVIDERS IS ESSENTIAL

The healthcare providers knew the patient was getting worse

The laboratory knew the specimen did not look like drug susceptible TB
Management of Contacts of MDR TB

• Use 2 drugs to which the infecting organism has demonstrated susceptibility
  (Ethambutol, levofloxacin, Moxifloxin and PZA)

5 month old baby and 3 year old at home
Delay In Reporting Suspected Resistance Can Be Costly

• Treatment has not been modified
• Second line drug susceptibility studies not yet set up
• Treatment must be empiric
  – More drugs, more toxicity, more expensive
• We don’t have any drugs to offer the childhood contacts that we are sure will be susceptible
NEW FACE OF TUBERCULOSIS

21 yr old Russian college student
Loosing weight, tired x 6 mo
Fever, cough x 4-6 weeks
Abnormal CXR,
Smear positive
Started 4 drug therapy 2/3/08
Mycobacteria on culture 3/4/08
M TB identified (Reference lab)
Referred to state lab 3/10/08

Contact Investigation
College campus
Hookah bar
Model Club
Face Book
hose Sahara stem
Sahara Subzero Wide Vase
3 Washable Synthetic Leather Hose
Hookah Carrying Bag
Charcoal Ash Tray (attaches to stem)
3 Instant lite Charcoal Rolls
1 Ceramic Hookah Bowl
Metal Charcoal Tongs
1 Metal Charcoal Screen
10 Plastic Mouthpieces
Rubber Hose, Bowl & Vase
Grommets
Cleaning Brush
18" x 24" Hookah Poster
Set-up Instructions
With all of the adults howling about teens wreaking havoc and making trouble, it makes no sense to me that we wouldn't be seeking viable alternatives for them. Give teens a safe place to hang out with friends, allow them to express themselves on live mic night, and offer those who are of legal age a non-alcoholic way to socialize, and we might be surprised at what could happen. Provide teens with a solution to their boredom and we just might see them enjoying themselves in ways other than vandalizing property, partying without adult supervision, and generally causing mayhem.

SOMETHING TO THINK ABOUT FOR YOUR TEEN?

In Egypt

At least 17% of TB is transmitted through smoking at a hookah bar.
Case Study

• Initial culture referred to state lab for susceptibility
  – 3/26/08 Ken and Denise from Texas review “very preliminary DST results” and note it “appears clearly resistant by BACTEC 460 to INH, rifampin, ethambutol, PZA, strep, ethionamide, rifabutin, ofloxacin, and kanamycin”
  – They note problems with the control but notified CDC and physician while repeating results
  – They consulted with colleagues to obtain further tests
  – 4/2/08 patient admitted for XDR TB care

They knew this did not appear to be drug susceptible TB
XDR-TB
Extensively Drug Resistant Tuberculosis

control

Isoniazid
Ethambutol
Rifampin

control

Streptomycin
Ethionamide
Ofloxacin

control

Capreomycin
Rifabutin
Kanamycin
• Pathogenesis of Drug Resistance
Pathogenesis of Drug Resistant Tuberculosis

• Because of the natural occurrence of spontaneous mutations, if treatment is given with only one drug (or one effective drug) resistance will ultimately develop in the whole population of mycobacteria.
  – Drug susceptible bacteria will be killed but drug resistant bacteria will survive and eventually replace the susceptible population.
Drug-resistant mutants in large bacterial population

Monotherapy: INH-resistant bacteria proliferate

Multidrug therapy: No bacteria resistant to all 3 drugs

INH
RIF
PZA

INH
INH resistant bacteria multiply to large numbers.

Spontaneous mutations develop as bacilli proliferate to $>10^8$.

INH mono-resist. mutants killed, RIF-resist. mutants proliferate $\rightarrow$ MDR TB.
MDR TB Case History

• Prior treatment in Mexico
• Started on Study 28 4/30/07
  – Moxi, EMB, PZA, Rifampin
• Clinical improvement
• 5/28/07 resistant: INH & RIF
• New cultures and susceptibility tests requested
• Three new drugs added
  – Amikacin-ethionamide-PAS
MDR TB Case History (3)

• Resistance to ethionamide (initial culture) 6/4/07
• Resistance to PZA (initial culture) 6/14/07
• New cultures show resistance to ethambutol and ofloxacin (repeat culture from 5/28) several days later
• Moxi, EMB, PZA, Amikacin, Ethionamide, PAS
  – Did I create further resistance?
  – What can I add now so that I am not chasing resistance
    • NEVER ADD A SINGLE DRUG TO A FAILING REGIMEN
When MDR TB is Diagnosed

- Stop first line therapy
- Repeat drug susceptibility studies to ensure that further resistance has not occurred
  - There is no mechanism for this to occur
  - Must be requested & many don’t think of it
  - Request whenever there is a risk that the regimen was compromised.
- Start a new regimen with at least 6 drugs
Case History

• 50 year old female, smoker's cough x years
  – Treated with multiple courses of antibiotics
    • Fluoroquinolones among them
  – Gradual deterioration
  – Bronchoscopy grows M TB sensitive to 1st line
• Treatment with standard regimen
  – Culture still positive at 31/2 months
    • Concerned about treatment failure
    • Concerned about fluoroquinolone resistance ---
    • Later this was documented by laboratory.
Clinical Needs for Adequate Patient Care

• Better and faster initial diagnosis of TB

• Point of care rifampin susceptibility
  – Ideally on all patients
  – Imperative for those at high risk.

• Rapid rifampin susceptibility in those who fail therapy

• Rapid knowledge of fluoroquinolone susceptibility
  – I want to know moxifloxacin or at least levofloxacin
Can a Fluoroquinolone Be Part of the Initial Panel?

- They are increasingly used to treat a variety of respiratory infections
  - Resistance can develop after several weeks
- It is the most important drug in the treatment of MDR TB or treatment failure
- A fluoroquinolone is the primary substitute drug for toxicity, intolerance & INH resistance

Counting on a drug that is not susceptible is a grave mistake but many don’t think to test for resistance.
Clinical Needs for Adequate Patient Care

• But when I have rapid diagnosis of rifampin drug resistance I will want to know
  – What can I treat with?
  – Especially true in those at risk of XDR TB
  – Rapid fluoroquinolone, amikacin, capreomycin, and Linezolid

• Last, but not least, what does
  – Ethambutol susceptibility at 10ugm/ml really mean?
  – What does susceptible in broth; resistant in agar really mean?

Can I trust it?