Treatment of MDR and XDR TB
An Overview -April 2009

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MDR TB – Definitions

TB resistant to INH and Rifampin

- TB - No Prior Therapy aka
- Primary MDR TB
  - Results from exposure to a patient with infectious MDR TB
- TB – Prior Therapy aka
- Acquired MDR TB
  - Results from inadequate treatment
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

PRE – XDR TB

- MDR TB
  - AND either resistance to a fluoroquinolone
  - OR resistance to one of the second line injectables.

- Not recognized by CDC or WHO as a definition but discussed widely by MDR experts and noted in recent publication
  - Extensively Drug Resistant TB in California 1993-2006. CID 2008 47; 450-7

Patients at Risk of Drug Resistant TB

- Birth or residence in country with high incidence of drug resistant TB
- History of prior treatment for TB
- Treatment failure
- Relapse in a patient not on DOT
- History of poor adherence
- Clinical deterioration during 4 drug therapy
- Exposure to patient with relapse or failure
TB in Foreign Born Patients

- Drug resistance more common in recent entrants
  - INH Resistance: Vietnam (20%), Peru (18%), Philippines (17%), China (16%)
  - MDR TB: China (6%), Peru (6%)

- Each year: smear-/culture + TB
  - About half from Vietnam and Philippines

CDC Data 2001 - 2006

NEW FACE OF TUBERCULOSIS

21 yr old Russian college student
Looking weight, tired x 6 mo
Fever, cough x 4-6 weeks
Abnormal CXR, Community acquired pneumonia
Continued to get worse

BAL + M Tuberculosis on culture, by now CXR and patient are worse

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

Current Bid $74.00
SOMETHING TO THINK ABOUT FOR YOUR TEEN?

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.

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 tests
  – 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

Isoniazid
Ethambutol
Rifampin

Streptomycin
Ethionamide
Ofloxacin

Rifabutin
Kanamycin
Capreomycin
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

Bad Bugs: Are There Drugs to Treat This Patient?

- 56 yr old male, TST positive, abnormal CXR
- Cough, fever, sweats, weight loss x 4 months
  - Culture positive M TB Resistant to:
    - INH
    - Rifampin, Rifabutin
    - PZA
    - Ethambutol
    - Streptomycin, Capreomycin, Amikacin
    - Levofloxacin
    - Ethionamide

Primary MDR TB  DOB:10-10-52, Date of film: 2-23-06
Inadequate Public Health Response from Past?

- 56 male, TST+ contact to father who died with MDR TB in 1994
  - Cough, fever, sweats, weight loss x 4 months
  - Culture positive M TB Resistant to:
    - INH
    - Rifampin, Rifabutin
    - PZA
    - Ethambutol
    - Streptomycin, Capreomycin, Amikacin
    - Levofloxacin
    - Ethionamide
  - Father was drug susceptible at first diagnosis!
  - Chronic, untreatable disease with transmission created by inadequate therapy, non-compliance and public health decisions

MDR (PRE-XDR) TB

- 24 yr old Indian graduate student
  - Flies to Texas to visit boyfriend
  - Sick on flight and goes right to the hospital
  - BAL positive smears for TB
  - Treatment started but patient is getting worse
  - Culture shows MDR TB
  - With resistance to everything but ethionamide and injectables
  - Pulse 150, respiratory rate 35
  - SOB at rest, 84 pounds, albumin 1.6, fever 103
  - Extensive cavitary TB on CXR

Chronic MDR TB

Extensive Drug Resistance

- 2005: Referred to Binational Project
  - Resistance: INH, Rifampin, Rifabutin, Strep, PZA, EMB, Ethionamide, Levofloxacin and Imipenem
  - Susceptible: Amikacin, Capreco, Cycloserine, PAS, Linezolid
  - Intermediate: Moxifloxacin 1.0 microgram/ml
- Treatment: Amikacin, Capreco, Moxifloxin 800mg, PAS and Linezolid 600mg
  - Culture conversion at 3 months
IF YOU DIAGNOSE XDR TB -

• THIS WOULD BE A GOOD TIME TO CONSIDER MEDICAL CONSULTATION!

BUT

• ANYTIME YOU HAVE A QUESTION IS A GREAT TIME

When Do You Start Treatment?

• Wait to identify enough drugs to constitute a regimen with a chance of cure
• Empirically using enough drugs to cover for unsuspected additional resistance
• Must consider how sick patient is as well as risk to community
  – Treat HIV TB now – there is no time to wait
  • If suspect MDR TB augment regimen and back off later
• At all costs avoid creating an untreatable patient who can transmit this bug
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

Amplification of Drug Resistance

- Development of additional drug resistance during treatment of TB.
- MDR TB develops sequentially.
- The risk of INH and rifampin resistance developing by chance alone is 1 in $10^{14}$
  - Bacterial populations in cavities $10^9$

Management Should Avoid Amplification of Resistance

- Standard Therapy is designed to protect against monotherapy until drug resistant patterns known.
  - Ethambutol is especially beneficial for protecting rifampin if there is INH resistance
- Management of drug resistance
  - Always plan to protect against further resistance developing
    - *Never add a single drug to a failing regimen*
Protecting Rifampin
Preventing Amplified Drug Resistance
Initial RX: INH, Rifampin, EMB, & PZA.
– If INH resistance is present:
  • EMB will protect rifampin during initial phase of treatment
• Culture and susceptibility tests detect INH resistance and allows change in treatment

Protecting Rifampin
Preventing Amplified Drug Resistance
Initial RX: INH, Rifampin, & PZA
– If INH resistance is present:
  • PZA is not active in cavities and rapidly growing lesions so it does not protect rifampin in both the initiation and continuation phase → rifampin monotherapy
• Culture and susceptibility tests detect INH resistance and allows change in treatment

Diagnosis by Smear is Standard of Care in Most of the World

Cultures or susceptibility tests rarely done
Clinical Pearls

- Suspect drug resistance when relapse in patient from country with high incidence of TB who is treated without cultures & sensitivity tests
- When report of drug resistance received
  - Stop treatment
  - Evaluate carefully
  - Three new sputums with new susceptibility
    - Tell lab about case and ask them to do quickly

Management of INH Resistance

- INH resistance
  - Rifampin, ethambutol, PZA (+/- INH)
  - Treatment should be daily 6 – 9 months
  - Add fluoroquinolone if extensive disease or underlying immunosuppression
- Contacts should have rifampin

Rifampin Resistant Tuberculosis

- Treatment outcomes poor
- Rifampin the most important drug in the treatment.
- Respond with as much concern as you would with MDR TB
**Treatment of Rifampin Resistant TB**

- INH, EMB, PZA, Levofoxacin x 12 months; +/- Injectable x 2 months
  - INH, EMB, PZA and Strep x 2 months then INH,PZA and Strep x 7-10 months
    » OR
  - INH, PZA and EMB x 18-24 months

**DX and Management of Treatment Failure**

- Treatment failure: "Patients whose sputum cultures remain positive after 4 months of treatment are considered to have failed treatment"
- "Patients with treatment failure should be assumed, until proven otherwise, to have drug-resistant organisms and be treated with multiple agents that they have not received before.
- A single drug should never be added to failing RX
- It is "prudent to add at least 3 new drugs"
  » MMWR Treatment of Tuberculosis 2003; 52

**Fluoroquinolone resistance**

- Susceptibility testing performed on isolates of all culture-confirmed TB cases between 1/98-3/02
  - 19/55 patients received fluoroquinolone monotherapy prior to initiation of anti-TB drugs
  - 2/19 had some resistance to fluoroquinolones;
    » both were HIV infected with CD4 < 50
- Conclusion: Incidence of fluoroquinolone resistance high, particularly among patients previously treated with fluoroquinolones
  
Fluoroquinolone resistance

• Mice infected with *M. tb* complex and treated with four concentrations of moxifloxacin (0.125, 0.25, 0.5, 1.0%).
• Selection of fluoroquinolone resistant mutants occurred in all surviving mice
• Conclusion: Fluoroquinolone resistance in tuberculosis may rapidly emerge


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Fluoroquinolone resistance

• Susceptibility testing performed on isolates of all culture-confirmed TB cases between 1/98-3/02
  – 55 patients; 19 received fluoroquinolone monotherapy prior to initiation of anti-TB drugs
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Fluoroquinolone Resistance

  – MDR TB  8.5%
  – XDR TB:  89%
  – MDR TB  8%
  – XDR TB  100%
• South Korea (1995-2004): CID 2008
  – MDR and XDR TB  42%
Principals of Treatment and Management of MDR TB

- Treat patients with likely drug resistant disease with an **adequate number** of drugs to prevent emergence of further resistance (amplification of resistance).
  - Use more drugs if susceptibility tests pending
    - Often will start with at least 6 drugs in this case

**Principals of Treatment and Management of MDR TB**

- **Drug selection**
  - Treatment should include 5 to 6 drugs
  - **At least 3 New drugs** not previously used
  - Those with **proven or suspected** susceptibility
  - **As many bactericidal** drugs as possible
  - Any first line drugs with proven susceptibility
    - Even if part of prior failing regimens
  - **Limit toxicity as much as possible**

**Step 1**

- Begin with any **available** agents to which the isolate is **susceptible**
- Add 1 Fluoroquinolone and an injectable drug to **susceptibilities**
- **First line drugs**
  - Pyrazinamide
  - Ethambutol
- **Fluoroquinolones**
  - Levofloxacin
  - Moxifloxacin
- **Injectable agents**
  - Amikacin
  - Capreomycin
  - Streptomycin
  - Kanamycin
  - **PLUS One of these**

**Step 2**

- Add 2nd line drugs until you have 4-6 drugs to which the isolate is susceptible
  - **Oral second line drugs**
    - Cytoxin
    - Ethionamide
    - **PAS**
- **Third line drugs**
  - Imipenem
  - Linezolid
  - Macrolides
  - Amoxicillin/Clavulanate
Principals of Treatment and Management of MDR TB

- Treat at least **18-24 months after conversion of the culture to negative**
- Continue injectable at least 6 - 12 months after conversion of culture to negative
- Shorter therapy for limited, primary or early disease
  - Consistent with the International Standards for TB Control released 3-24-06

Principals of Treatment and Management of MDR TB

- Never add a single drug to a failing regimen
- However a single drug can be added:
  - To augment a weak regimen in the first 2 – 3 wks
  - After conversion of cultures
  - To augment an oral regimen after stopping an injectable or another drug if patient is responding and cultures are negative
- If culture still positive, add 2 drugs

New Immigrant from Nepal

- History of TB treated for one year with one drug, unknown type
- Reported normal exit CXR and cleared for immigration to US
- Coughing extensively all during flight
Recent Immigrant from Nepal

Evaluation in US

• Chronically ill
• Weight loss, malnutrition, (76 lbs)
• Abnormal CXR
• Sputum + for AFB
• Treatment: RIPE plus Moxifloxacin

Was this a good idea?

Evaluation in US

• Treatment: RIPE plus Moxifloxacin

If You Suspect Drug Resistance, Especially MDR TB

Never Augment a Regimen With Only One New Drug!
Recent Immigrant From Nepal

- Culture positive for M TB
  - 1st culture resistant to
    - INH, rifampin, EMB(5ug/ml), rifabutin,
    - Sensitive to Ethion, Levo, Amikacin, EMB (7.5 ug/ml)
  - Treatment changed to:
    - Amikacin, Moxi, EMB, Cycloserine

Should we worry about fluoroquinolone resistance?

Recent Immigrant From Nepal

- Culture positive for M TB
  - Initial: resistant to INH, rifampin, ethambutol (5.0 ug/ml), rifabutin, and PZA
  - Several weeks later treatment: Amikacin, Moxi, EMB, Cycloserine
  - Susceptible to ethionamide, levofloxacin, amikacin, ethambutol (7.5 ug/ml)

Should we worry about fluoroquinolone resistance?

Recent Immigrant from Nepal

- Patient improves clinically
  - Gains 25 pounds
  - Cough nearly resolves, fever and night sweats gone
  - Smears and cultures convert at 12 weeks
  - Last positive culture now Moxifloxacin resistance and resistant to ethambutol at 7.5ug/ml

Repeat sensitivity on last positive culture to look for further resistance!
Clinical Pearls

• Suspect drug resistance when relapse in patient from country with high incidence of TB who is treated without cultures & sensitivity tests
• When report of drug resistance received
  – Stop treatment
  – Evaluate carefully

Repeat Susceptibility Tests

• Always repeat susceptibility at least every two months if culture is still positive
• At the time MDR TB is identified and standard regimen stopped
• Anytime new resistance is identified and there is a question as to whether treatment is effective
• Try not to chase the culture/susceptibility

Can a Fluroquinolone 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.
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 contacts that we are sure the isolate will be susceptible to

MDR TB Case History

• 47 yr old diabetic
• Started Trial 28 (4/30/07)
  – Moxi, Rif, EMB, PZA,
• Clinical improvement
• 5/28/07 Resist. INH & RIF
• Three new drugs added
  – Amikacin-ethionamide-PAS

Three years ago she was Rx in Mexico x 6 months

Resistance to PZA on initial culture reported 6/15/07

MDR TB Case History (3)

• New culture and susceptibility one month later
  – New resistance to ethambutol and ofloxacin (5/28)
  – Resistance to ethionamide (6/4) also reported
• Clinical improvement
  – 3 lb weight gain, cough and fever
  – AFB + < 1/hpf
• Moxi, EMB, PZA, Amikacin, Ethionamide, PAS
• Current therapy
  – Moxi, EMB, PZA, Amikacin, Ethion, PAS

Moxifloxacin possibly resistant
Only active drugs may be Amikacin and PAS
These results 3 ½ weeks old
Possibility of further resistance now

Initial treatment only included two active drugs; ethambutol and moxifloxacin

• More costly to treat
• Treatment less effective
• Some cases not treatable and become chronic transmitters
• Drug resistant disease is as infectious as drug susceptible
• Treatment of contacts with LTBI more expensive and toxic; outcomes uncertain

“Fall and Rise” phenomenon
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

Fluoroquinolone resistance

- TBTC 1995-2001:
  - 1373 isolates from clinical trials
    - 96% susceptible to INH and RIF
    - 0.15% resistant to ciprofloxacin
- Referral sample of isolates sent to CDC 1996-2000 due to drug resistance
  - 1852 referral sample isolates
    - 32.6% MDR,
    - 1.8% resistant to ciprofloxacin (75.8% MDR)
- Conclusion: Despite widespread use of fluoroquinolones, resistance remains rare, occurring primarily among MDR strains

Fluoroquinolone resistance

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Fluoroquinolone resistance
• Russia: Of 251 MDR-TB isolates, 4.3% were ciprofloxacin resistant
• Taiwan: Of 33 MDR-TB isolates, 7-20% fluoroquinolone resistant (depending on year tested)
• California 1995-2001: 20/272 (7%) were fluoroquinolone resistant
• California MDR-TB service 2002-present: 3/30 (10%) fluoroquinolone resistant

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**Management of Contacts of MDR TB**

- Treat for 6 months or observe without treatment
  - Use drugs source case is sensitive to
    - Choose 2: EMB, FQN, PZA
  - HIV positive and immunocompromised persons should be encouraged to accept treatment
    - Treat HIV-positive persons for 12 months
- Follow for 2 years regardless of treatment
  - CXR and clinical evaluation

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**TREATMENT OUTCOMES**

**Culture Conversion**

- California: (1993-2006)
  - XDR TB - 46.7%  MDR TB – 87.3%
  - XDR TB - 195 days  MDR TB – 98.5 days
- Germany: (2004-2006)
  - XDR TB – 80%  MDR TB 87.2%
- Latvia: (2000)
  - MDR TB 77%  - median time 60 days
- South Korea: (1995-2004)
  - XDR TB - 66%  MDR TB – 67%
Factors Associated with Good Treatment Outcomes for MDR TB

- Younger age
- Absence of cavities
- HIV negative
- Primary disease
- Hospitalization
- Culture conversion by 3 months
- ? Surgery
- Sensitivity to ofloxacin
- No prior therapy with ofloxacin
- Fewer # drugs MTB is resistant to
- More effective drugs in regimen
- Appropriate therapy

Summary

- Preventing MDR TB must be the goal
- Current treatment options can be successful in > 90% of patients but are costly and time consuming
- Successful therapy requires DOT, case management & expert consultation
- Current MDR patients have increasing drug resistance
- New therapies are needed