“I think we have an ISSUE”
Background

- 72 year old adult patient
- Foreign born
- History of diabetes
- Cepheid MTB /rifampin resistance detected from specimen collected in March
What testing should be performed if resistance is detected/suspected?

a. Immediately either refer or perform additional testing for additional molecular markers on the processed sputum.

b. You have heard about silent mutations so report the results of the Cepheid assay but wait for an isolate to perform additional testing.
What testing should be performed if resistance is detected/suspected?

If rifampin resistance and/or MDR-TB is suspected, molecular testing for resistance markers should be pursued rather than wait for culture isolation for susceptibility.

CDC offers Molecular Detection of Drug Resistance (MDDR) testing to public health laboratories and clinical providers.

Additional resources are provided through National Public Health Laboratory Drug Susceptibility Reference Centers for MDDR.
Molecular detection of resistance

Initial specimen had mutations in the following genes:

- rpoB
- katG
- embB
- pncA

No mutations were identified in:

- gyrA
- rrs (1400 region)
- eis (promoter)
- thyA (entire ORF)
Molecular detection of resistance markers

Resistance would be predicted for which of the following drugs:

a) rifampin, clofazimine, pyrazinamide and amikacin  
b) isoniazid, pyrazinamide, streptomycin, and rifampin  
c) isoniazid, rifampin, fluoroquinolones, and ethambutol  
d) isoniazid, rifampin, ethambutol, and pyrazinamide
Molecular detection of resistance markers

Initial specimen had mutations associated with resistance in the following genes:

- *rpoB* - rifampin
- *katG* - isoniazid
- *embB* - ethambutol
- *pncA* - pyrazinamide

No mutations were identified in:

- *gyrA* - fluoroquinolone
- *rrs* (1400 region) - amikacin
- *eis* (promoter) - kanamycin
- *thyA* (entire ORF) - capreomycin
Which drugs are included in the WHO Group A recommendations for treatment of MDR-TB?

a) levofloxacin, amikacin, pyrazinamide  
b) bedaquiline, levofloxacin, linezolid  
c) clofazimine, meropenem, delamanid  
d) moxifloxacin, linezolid, ethambutol
WHO longer MDR-TB treatment regimen

<table>
<thead>
<tr>
<th>Groups &amp; steps</th>
<th>Medicine</th>
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</thead>
<tbody>
<tr>
<td><strong>Group A:</strong> Include all three medicines</td>
<td>levofloxacin OR Lfx</td>
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<tr>
<td></td>
<td>moxifloxacin Mfx</td>
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<tr>
<td></td>
<td>bedaquiline²³ Bdq</td>
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<td></td>
<td>linezolid Lzd</td>
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<tr>
<td><strong>Group B:</strong> Add one or both medicines</td>
<td>clofazimine Ctz</td>
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<td></td>
<td>cycloserine OR Cs</td>
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<td></td>
<td>terizidone Trd</td>
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<tr>
<td><strong>Group C:</strong> Add to complete the regimen and when medicines from Groups A and B cannot be used</td>
<td>ethambutol E</td>
</tr>
<tr>
<td></td>
<td>delamanid³³ Dlm</td>
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<tr>
<td></td>
<td>pyrazinamide⁶ Z</td>
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<td></td>
<td>imipenem–cilastatin OR Ipm–Cin</td>
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<td></td>
<td>meropenem⁷ Mpm</td>
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<td></td>
<td>amikacin Am</td>
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<td></td>
<td>(OR streptomycin⁸ (S)</td>
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<td></td>
<td>ethionamide OR Rto</td>
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<tr>
<td></td>
<td>prothionamide Pto</td>
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<tr>
<td></td>
<td>p-aminosalicylic acid⁹ PAS</td>
</tr>
</tbody>
</table>

WHO consolidated guidelines on drug-resistant tuberculosis treatment

https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf?ua=1
Impact of MDR-TB

- Patient started on amikacin, cycloserine, ethionamide, linezolid, and moxifloxacin. Follow up cultures were collected every week in March with multiple positive cultures.

- In April, specimen collection switched to 2x month.

- Patient remained negative through April/May/June but in July became culture positive.
What testing should be performed on this isolate?

a) Repeat susceptibility testing is not indicated, the patient can still be culture positive for several months after the start of therapy

b) Repeat susceptibility testing for just first line drugs. If resistant, then refer out for second line drug susceptibility.

c) Repeat susceptibility testing for both first and second line drugs at the same time.

d) Repeat susceptibility testing but just for the second line drugs included in the patient treatment regimen. That way we can look for new resistance.
What testing should be performed on this isolate?

- Repeat susceptibility testing should be performed if the patient is culture-positive after three months of therapy or shows clinical evidence of failure to respond to therapy.
- Initiation of second line drug susceptibility testing should be performed at the same time as repeat testing.
- Second line drug testing should include amikacin and/or kanamycin, capreomycin, quinolone (e.g., levofloxacin), and ethionamide.
- Detection of new resistance should be treated as a critical value and reported as soon as possible.

Back on track?

- Results of MDDR detected no new resistance mechanisms
- Susceptibility panel showed the same resistance profile with the exception of new resistance to ethionamide
- Cultures continued to be collected through the months of August, September, October, and November
- All specimens were smear and culture negative
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- December 2018 sputum is smear negative
- January 2019, TB is cultured from December specimen
- That same week, District TB Director reports patient is coughing. A sputum specimen is collected and the patient scheduled for Chest X-Ray.
- He also reports that Clofazimine had been added to the treatment regimen 2 months ago
- The GPHL TB unit reports the January 2019 sputum specimen as 2+ smear positive.
What testing would you perform?

a) Perform conventional susceptibility testing for clofazimine. The patient must be resistant.  
b) Refer specimen for MDDR molecular testing.  
c) Wait and perform conventional susceptibility testing. The patient is already a known MDR-TB.  
d) Refer the isolate for NGS the patient must have been re-infected.
What testing would you perform?

• MDDR panel was performed on the positive specimen.
• No new resistance although the isolate is reported as susceptible to ethionamide again.
• Additional MDDR and susceptibility testing was performed by Florida Bureau of Public Health Laboratories on the specimen from January and from the original April specimen.
• No new mechanisms of resistance are detected and the susceptibility patterns remain exactly the same between the new isolate and the initial isolate in April.
• MIC panels do not indicate any resistance to the current drug treatment regimen.
What are factors that may be associated with increased risk for recurrent TB?

- Diabetes Mellitus
- HIV
- Smoking
- Age (15-44)
- Positive sputum culture at 2 months of treatment


Impact of MDR-TB

- MDR-TB has a significant impact on a patient’s life.
- Coordination and communication between the laboratory, public health, physician and patient is required when treating a patient with MDR-TB.
- Recognizing alert values, using MDDR resources for timely resistance data from clinical specimens, and communicating susceptibility results in a timely manner can impact treatment regimens and reduce the need for additional drugs.
Acknowledgements

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