MDR TB Guidelines
Progress to date and the way forward

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Disclosures

- No financial disclosures
Weno Island, Chuuk
Typical Chuukese Residence
Patient Example (TT)

- 11 y/o F, neighbor and close contact of index case #1 (confirmed MDR TB inhA + rpoB)
- Cough, fever, night sweats and right cervical LAD x several months
- CXR in May, 2008: suspicious for active TB
- Dx: clinical TB case in May, 2008
- Started on 4 drug therapy
- Improvement of symptoms
- LAD unchanged (+ draining sites)
- Repeat CXR: next slide
Treatment Course

- Treated with Amikacin, EMB, PZA, Levofloxacin and PAS x 9 months as an inpatient
- Treated with EMB, PZA, Levofloxacin for an additional 9 months as an outpatient
- Cured!
Objectives

- Overview of MDR TB Guidelines Process and Objectives
- Next Steps
- Systematic Review on Pregnancy and MDR TB Outcomes
- Systematic Review of MDR TB Contact Treatment Outcomes
Formation of workgroup

- CDC
- American Thoracic Society
- Infectious Disease Society of America
- European Respiratory Society
- In collaboration with WHO
Collaboration with WHO

- Objectives
  - To minimize redundancy and maximize efficiency
  - To ensure that recommendations are aligned and seamless wherever possible
- Share PICO questions
- Share literature reviews
- One or two members participate on both workgroups for monthly meetings
- Prepare guidelines as quickly as possible
PICO/GRADE approach

- Population
- Intervention
- Comparator
- Outcome
Define PICO Questions

Treatment Regimen and Duration – Adult MDR TB Patients

- Should at least 5 effective drugs (including a parenteral agent) rather than 4 effective drugs (including a parenteral agent) be given daily rather than intermittently during the intensive phase in all adult patients with MDR TB?

- Should treatment be given for 8 months or longer rather than for less than 8 months during intensive phase and for 12 months or longer rather than less than 12 months after completion of the intensive phase in all adult patients with MDR TB?

- Should treatment during the intensive phase include both an injectable agent and a newer generation FQ as rather than a standard MDR TB regimen without one or both of these drugs in all adult patients with MDR TB?
Define PICO Questions

Treatment Regimen and Duration – Adult MDR TB Patients

- Should treatment during the intensive phase include at least one of the newer, more potent drugs such as linezolid, bedaquiline, or delamanid, rather than a standard MDR TB regimen with an older drug such as ethionamide, PAS, or cycloserine in adult patients with MDR TB?
- Should clofazimine, or meropenem/imipenem plus clavulanate be used as part of the MDR TB regimen when at least 4 active drugs are not available due to resistance or toxicity in adult patients with MDR TB?
Define PICO Questions

Treatment Regimen and Duration – Rifampin and INH mono-resistant TB

- Should INH/EMB/FQ/PZA daily be given for **at least 12 months** rather than INH/EMB/FQ/PZA + 2 months of intravenous agent **for 9-12 months** be used in adult patients infected with **rifampin resistant but INH susceptible** TB?
- Should RIF/PZA/EMB or RIF/PZA/EMB/FQ daily be given for longer than 6 months rather than for 6 months in adults with **INH mono-resistant** TB?
Define PICO Questions

Children with MDR TB

- Should treatment duration be **12 months or less** rather than **longer than 12 months** in children with MDR TB who respond well to treatment (clinically, radiographically, and if available bacteriologically)?

- Should an injectable, fluoroquinolone or linezolid be used along with a background MDR TB regimen in children?
Define PICO Questions

**Pregnant MDR Patients**
- Should treatment with a tailored MDR regimen be offered to pregnant women versus first line drugs or observation alone in pregnant women with MDR TB?

**HIV Patients with MDR TB**
- Should anti-retroviral therapy be provided within the first 2 months of MDR TB treatment versus waiting after 2 months in patients with MDR TB and HIV co-infection?
Define PICO Questions

Surgical Intervention for MDR TB

- Should lung resection surgery (i.e., lobectomy or pneumonectomy) rather than no surgery be used in selected patients with MDR TB receiving antimicrobial treatment?
- Should treatment with an MDR TB regimen be given for 12 months or less after surgery rather than the standard 18 – 24 month in patients who have surgery?
Define PICO Questions

Treatment of Contacts

- Among contacts to infectious MDR TB patients, is LTBI treatment associated with lower TB incidence, compared with no medical treatment?
- Among contacts to infectious MDR TB patients, should LTBI treatment be given for longer than 9 months versus 9 months or less?
- Should children < 5 and other vulnerable persons (HIV+, TNF alpha antagonist recipients, transplants, etc.) who are contacts of MDR TB be evaluated with a CXR even when TST or IGRA negative rather than without one?
Define PICO Questions

Infection Control
- Should respiratory isolation be continued until sputum culture consistently negative in 2 or 3 sequential AFB cultures versus respiratory isolation until sputum AFB smear consistently negative in 3 sequential specimens among MDR TB patients?

Case Management
- Should patient centered case management be utilized rather than no case management in patients with MDR TB in order to minimize AEs and maximize treatment success?
- Should hospitalization during the initiation phase of treatment or until culture conversion versus initial community based case management be used in patients with MDR TB?
Define PICO Questions

Monitoring

- Should sputum monitoring (at least one sputum specimen for AFB smear and culture) be performed monthly rather than less often in patients with MDR pulmonary TB?

- Should patients with MDR TB be followed annually with a clinical assessment, CXR and sputum at 6 month intervals after treatment completion for MDR TB versus only when clinically indicated?
Define PICO Questions

Monitoring

- Should monitoring for drugs with significant toxicity (injectable medications, cycloserine, linezolid), or with recognized concentration dependent killing (injectable medications, FQ) be monitored with initial serum therapeutic drug monitoring and dose adjustment made based on results rather than with clinical monitoring alone?

- Should clinical monitoring include formal documentation of audiology testing (injectable medications), vision testing (ethambutol and/or linezolid), neuropathy screen (linezolid or ethionamide, FQ), and psychological assessment (cycloserine) rather than no specific required testing or documentation?
Define PICO Questions

Palliative Care

- Should persons with untreatable MDR be offered palliative care including some infection control measures (to decrease respiratory transmission) versus returned to their homes in the community without these measures?
Prioritize PICO Questions

- Should at least 5 effective drugs (including a parenteral agent) rather than 4 effective drugs (including a parenteral agent) be given daily rather than intermittently during the intensive phase in all adult patients with MDR TB?

- Should treatment be given for 8 months or longer rather than for less than 8 months during intensive phase and for 12 months or longer rather than less than 12 months after completion of the intensive phase in all adult patients with MDR TB?

- Should treatment during the intensive phase include both an injectable agent and a newer generation FQ as rather than a standard MDR TB regimen without one or both of these drugs in all adult patients with MDR TB?

- Should treatment during the intensive phase include at least one of the newer, more potent drugs such as linezolid, bedaquiline, or delamanid, rather than a standard MDR TB regimen with an older drug such as ethionamide, PAS, or cycloserine in adult patients with MDR TB?
Prioritize PICO Questions

- Should INH/EMB/FQ/PZA daily be given for at least 12 months rather than INH/EMB/FQ/PZA + 2 months of intravenous agent for 9-12 months be used in adult patients infected with rifampin resistant but INH susceptible TB?
- Should RIF/PZA/EMB or RIF/PZA/EMB/FQ daily be given for longer than 6 months rather than for 6 months in adults with INH mono-resistant TB?
- Should treatment with a tailored MDR regimen be offered to pregnant women versus first line drugs or observation alone in pregnant women with MDR TB?
- Among contacts to infectious MDR TB patients, is LTBI treatment associated with lower TB incidence, compared with no medical treatment?
Define Outcome Measures

- cure
- treatment failure
- relapse-free cure
- completion of treatment
- death
- time to culture-conversion
- adverse effects
- quality of life

- development of resistance
- school/work-days lost
- fetal outcomes (in pregnant women)
- progression to active disease (in LTBI)
- Transmission
- Cost
Literature Reviews

- Literature review performed
  - Treatment of contacts
  - Pregnancy and MDR TB
  - Community vs. Hospital-based care
  - HIV and MDR TB
  - Case management and DOT
Next Steps

- Dick Menzies group has been contracted to perform an individual patient data meta-analysis of MDR TB treatment outcomes
  - MDR TB - Number of drugs, duration of treatment, use of injectable and FQ, use of newer drugs
  - Short course regimens
  - INH and RIF mono-resistant TB treatment
- Summarize data and present to workgroup
- Group discussion and formulation of recommendations
- Writing of guidelines
- Clearance
Acknowledgments

- CDC
- ATS
- IDSA
- ERS
Thank You!