OVERVIEW OF 2016 TB TREATMENT GUIDELINES

REACHING FOR PERFECTION IN AN IMPERFECT WORLD

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Disclosures

- None of the speakers or planners involved in this activity has any relevant conflict of interest.
- The use of trade names and commercial sources during this presentation is for identification only, and does not imply endorsement.
- No commercial support has been received for this program.

Objectives

- Introduce newly released guidelines for the treatment of drug-susceptible TB in adults and children.
- Highlight new recommendations and new content pertaining to case management and treatment regimens
- Give example of how to apply the new guidelines
- Discuss specific recommendations in new guidelines that may be difficult for local health departments to achieve
- Discuss strategies to maximize successful use of new guidelines

Outline

- Orientation to the 2016 guidelines
- Selected highlights from 2016 guidelines
- Emphasis on patient-centered care
- Need for programs to interpret guidelines
- Clinical Considerations
- Case example

ORIENTATION

Development

- Guidelines were written following GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methods
- Developed by: American Thoracic Society (ATS); Centers for Disease Control and Prevention (CDC); Infectious Disease Society of America (IDSA)
- Authors included representatives of: American Academy of Pediatrics; CDC; International Union Against TB and Lung Disease; World Health Organization
- Endorsed by: European Respiratory Society; US National TB Controllers Association

Orientation

- "It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment…Ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances"
- All recommendations are based on literature review, often citing studies conducted outside of the U.S.
- Recommendations emphasize patient values and costs, and trade-off between benefits and harms.
- Each program has to figure out how to implement the recommendations to achieve best possible care for each patient
- Balance optimal plan for patient with capacity of program to deliver the plan

SELECTED HIGHLIGHTS

Treatment Regimens for Drug-Susceptible Disease

	Intensive Phase		Continuation Phase			
Regimen	Drugs	Interval and Dose (min duration)	Drugs	Interval and Dose (min duration)	**Range of Total Doses**	**Comments**
1	INH, RIF, PZA, EMB	7 d/wk for 56 doses (8 wk) OR 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk) OR 5 d/wk for 90 doses (18 wk)	182 - 130	Preferred for newly diagnosed pulm TB
2	INH, RIF, PZA, EMB	7 d/wk for 56 doses (8 wk) OR 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110 – 94	Preferred when more frequent DOT is difficult to achieve
3	INH, RIF, PZA, EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	78	Caution in pts w HIV or cavitary; missed doses can lead to treatment failure
4	INH, RIF, PZA, EMB	7 d/wk for 14 doses, then twice weekly for 12 doses	INH RIF	2 times weekly for 36 doses (18 wk)	62	Do not use in pts w HIV; missed dose is inferior

Table 2. Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms.

Notes on Daily Treatment and DOT

- 2016 guidelines recognize 7 d/wk and 5 d/wk as **equivalent** for daily dosing.
- DOT remains the preferred routine treatment for all forms of TB
- Must **count the number of doses** to determine treatment completion. Weeks of treatment depend on dosing and whether doses are missed.

Examples of Priority Situations for DOT

- Table 5. Examples:
- Positive sputum smears
- Delayed culture conversion (sputum collected > 8 weeks of treatment is culture-positive)
- Homelessness
- Use of intermittent dosing
- HIV infection
- Children and adolescents

Practical Aspects of Treatment

(expanded discussions of…)

- Identifying & managing adverse effects
- Identifying & managing drug-drug interactions
- Therapeutic drug monitoring

Other important references:

- Recommended dosing for first and second line TB drugs (Tables 3, 10 & 11)
- Recommended baseline and follow-up evaluations (Figure 2)
- Drug-drug interactions involving the rifamycins (Table 8)
- Dosing recommendations for first and second line drugs in adults with reduced renal function (Table 12)

Treatment in Special Situations

(expanded discussions of…)

- HIV
- Concurrent use of antiretrovirals and rifamycins
- Immune Reconstitution Inflammatory Syndrome
- Children
- Extrapulmonary TB
- Culture-Negative TB
- Pregnancy & breastfeeding
- Treating TB in context of renal disease
- Treating TB in context of hepatic disease

EMPHASIS ON PATIENT-CENTERED CARE

Many Facets of Patient-Centered Care

- DOT is critical – but often not sufficient – to promote treatment success
- Emphasize use of incentives & enablers
- Emphasize patient education, cultural and language competency (providing education and resources in patient's preferred language)
- Reminders for DOT and appointments
- Integrating/coordinating TB care with other conditions; inclusion of patient's primary care provider

Incentives and Enablers

Table 4. Possible Components of a Multifaceted, Patient-Centered Treatment Strategy

Incentive and Enabler Use in Michigan, FY 2016

- 14 health departments
- 554 people
- ~$47,800 total requested amount (highest to date; > 3X higher than FY 2015)
- Range per request $25 - $6,400
- 502 (91%) requests were for LTBI and/or contacts
- Major themes: homelessness; food, transportation, financial
- Kroger; Meijer; Walmart; rent/mortgage/hotel; utilities; car insurance
- Reimbursement of unusual health department costs

Observations From Cohort Reviews: Paradigm Shift?

- From Spring, 2015 through Spring, 2016, marked increase in numbers of barriers identified, and solutions attempted by using incentives and enablers
- Incentives and enablers tended to be used when health department staff "perceived a need"
- → Consider instead the "opportunity to assist"

Ask not [only] what your [patient needs from] you – ask what you can do for your [patient].

If your health department isn't using incentives and enablers, why not?

Patient Education

Themes in effective patient education

- Spend the time
- Be patient
- Be flexible – try multiple approaches
- Be willing to repeat or revisit topics often
- Learn how your patient learns best
- Invite questions

Language Competency

(more than just a translator)

- Medical interpreter is preferred, but using family members to interpret may be necessary
- If possible, vet and learn about interpretation services before using with a patient

Tips for effective use of interpreter

- Talk with and focus on your patient, not the interpreter
- Maintain the flow of conversation such that the interpreter can keep up smoothly. This may require prior planning w/ the interpreter.
- Support the interpreter to interject for clarification, but do not allow them to filter or steer the conversation

Cultural Competency

Culture

- Behaviors, beliefs, ways of living
- Can be learned (to some extent) through observation or polite inquiry
- Examples: gender roles; religious beliefs (some); non-verbal communications; personal space; shoes indoors; left vs right hand; food; gift-giving

Tips to pay attention to:

- Eye contact
- Smiling
- Tone of voice
- Gestures
- Cultural or religious holidays

PROGRAMMATIC INTERPRETATION OF GUIDELINES

Remember: Guidelines Are Not Protocols

- Programs should reference guidelines in their decision-making, but must choose the regimen they can best deliver and implement
- Interpret guidelines & recommendations in the context of each patient's needs **AND** programmatic capacity
- Programs should not attempt to use one treatment regimen for all patients; multiple regimens were given to provide choices
- Recognize that some patients may need daily dosing throughout treatment, but many can be treated appropriately with intermittent dosing
- Use the most-preferred regimen that your program can realistically perform
- If in doubt, call the MDHHS TB Program

CLINICAL CONSIDERATIONS

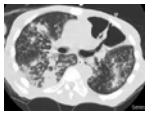
To What Situations the Guidelines Apply

- Settings where routine diagnostic tools are available
  - Culture
  - Drug susceptibility studies – phenotypic, molecular
  - X-rays
- TB disease: drug susceptible or **not** suspected of being resistant
  - Diagnosis of TB and decision to treat often occurs before diagnosis is confirmed and drug susceptibility is known
- Address clinical treatment & public health management

My part of talk

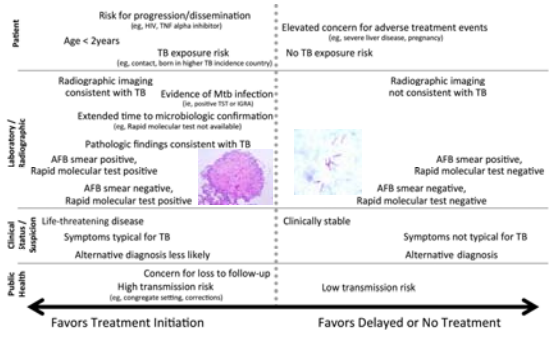
Initial Decision to Treat for TB Disease

- Before TB disease is confirmed or drug susceptibility is known, the decision to treat is based on
  - Clinical factors
  - Radiographic findings
  - Laboratory data
  - Patient factors
  - Public health issues



- "In addition, clinical judgment and the index of suspicion for TB are critical in making a decision to initiate treatment." In "…patients who have a "high likelihood of having TB or are seriously ill with a disorder suspicious for TB, empiric treatment with a 4-drug regimen…should be initiated promptly even before the results of …AFB smear microscopy, molecular tests, &…culture are known."

Decision to Treat for Tuberculosis Disease



Treatment Regimens

- 4 regimens
  - 8 week intensive phase INH, Rifampin, PZA & Ethambutol
  - Ethambutol not needed when the TB is documented to be sensitive to INH and Rifampin
  - 18 weeks continuation phase, INH and Rifampin
  - Daily therapy considered most effective, preferred
  - 5 days a week by directly observed therapy (DOT) considered equivalent to 7 days a week by self administered therapy (SAT)

Dosing

- Adult dosing begins at age 15
- For dosing by weight
  - Consider obese to be >20% above ideal body weight (IBW)
  - Use actual weight for non-obese patients
  - Can use IBW for obese patients
  - Alternatively use this formula for weight to use:

Weight =
IBW + 0.4(actual BW-IBW)

	Intensive Phase		Continuation Phase		
Regimen	**Drugs**	**# Doses**	**Drugs**	**#Doses**	**Comments**
1	INH RIF PZA EMB	Daily 8 weeks 56 doses if given 7 days/week 40 doses if given 5 days/week DOT if 5 days/week	INH RIF	Daily for 18 weeks 126 doses 7 days/week 90 doses 5 days/week	Most effective regimen. EMB not needed if TB is sensitive to INH & RIF. Use DOT for < 7 doses/week. Add Pyridoxine 25-50 mg. if risk for neuropathy.
2	Same	Same as above	Same	3 times a week 18 weeks 54 doses	
3	Same	3 times a week 8 weeks 24 doses	Same	Same as above	Caution with HIV or cavitary disease. Missed doses => Rx failure, relapse, drug resistance
4	Same	7 days a week for 14 doses Followed by 2 times/week for 12 doses	Same	2 times a week 18 weeks 36 doses	Do not use in HIV, AFB smear+ disease, cavitary disease

When to Extend Treatment Length: 9 months instead of 6

- Cavitation on chest x-ray **and** sputum collected at 8 weeks is still culture positive
  - You won't have those results until up to 8 weeks later
- Consider extension of therapy for **either** cavitation **or** positive cultures at 8 weeks **and**:
  - HIV or other immune suppression
  - >10% below ideal body weight
  - Active smoking
  - Diabetes
  - Extensive disease on chest x-ray

Managing interruptions in therapy

Time Point of Interruption	Details of Interruption	Approach
During intensive phase	Lapse is <14 d in duration	Continue treatment to complete planned total number of doses (as long a all doses are completed within 3 mo)
	Lapse is ≥14 d in duration	Restart treatment from the beginning
During continuation phase	Received ≥80% of doses and sputum was AFB smear negative on initial testing	Further therapy may not be necessary
	Received ≥80% of doses and sputum was AFB smear positive on initial testing	Continue therapy until all doses are completed
	Received <80% of doses and accumulative lapse is <3 mo in duration	Continue therapy until all doses are completed (full course), unless consecutive lapse is >2 mo If treatment cannot be completed within recommended time frame for regimen, restart therapy from the beginning (ie, restart intensive phase to be followed by continuation phase)[b]
	Received <80% of doses and lapse is ≥3 mo in duration	Restart therapy from the beginning, new intensive and continuation phase (ie, restart intensive phase, to be followed by continuation phase)

Abbreviation: AFB, acid-fast bacilli.

[a] According to expert opinion, patients who are lost to follow-up (on treatment) and brought back to therapy, with interim treatment interruption, should have sputum resent for AFB smear culture, and drug susceptibility testing.

[b] The recommended time frame for regimen, in tuberculosis control programs in the United States and in several European countries, is to administer all of the specified number of doses for the intensive phase within 3 months and those for the 4-month continuation phase within 6 months, so that the 6-month regimen is completed within 9 months.

DOT or SAT?: GRADE Methodology

- PICO Question 2: Does SAT have similar outcomes compared to DOT?
- Recommendation 2: We suggest using DOT rather than SAT for routine treatment of patients with ***all forms of tuberculosis***
- *Conditional recommendation; Low certainty in the evidence*

Strong vs. Conditional Recommendation

STAKE HOLDERS	STRONG RECOMMENDATION	CONDITIONAL RECOMMENDATION
PATIENTS	Most patients would want this. A small number would not.	A majority of patients would want this. Many would not.
CLINICIANS	Most patients should receive this. Adherence to this recommendations could be used as a quality criterion or performance indicator. Decision aids may not be needed.	Different choices may be appropriate for individual patients. You must help each patient reach decision based on his/her values & preferences. Decision aids may be useful.
POLICY	Recommendation can be adopted as policy in most situations.	Policy making may require debate & involvement of stakeholders.

Special Circumstances: HIV and TB
Unique issues with TB and HIV

- Drug drug interactions between rifamycins and ART
  - Table 8 – drug interactions
- Paradoxical reactions that might suggest patient is worse
  - Immune Reconstitution Inflammatory Syndrome (IRIS)
- Greater potential for developing resistance to rifamycins when using intermittent regimens

Special Circumstances: HIV and TB
Recommendations on regimen & duration

- TB/HIV patients already receiving antiretroviral (ART) therapy
  - Use regimen #1 for 6 months (unless meet criteria for 9 months)
    - Recommendation 5a
- TB/HIV patients NOT expected to receive ART during TB therapy
  - Extend therapy to 9 months
    - Recommendation 5b
- Recommendations 5a and b are conditional with very low certainty in the evidence

Special Circumstances: HIV and TB Recommendations on when to start ART

- TB/HIV patients not on ART when TB diagnosed should start ART
  - If CD4 is <50, begin ART within 2 weeks a of starting TB Rx
  - If CD4 is >50 begin ART by 8-12 weeks after starting TB Rx
  - For TB meningitis do not start ART until 8-10 weeks after TB Rx is completed no matter what CD4 count is
    - IRIS reactions can be severe
- Recommendation 6 is **strong** with **high** in the evidence

Special Circumstances: Meningitis & Pericarditis

- TB Meningitis
  - Add corticosteroids in the form of Dexamethasone for 6 weeks at the start of TB treatment
  - Extend therapy to 9 months (greater chance of relapse)
- TB Pericarditis
  - Corticosteroids should not be routinely given
  - In selected cases corticosteroids may be appropriate
    - Large pericardial effusions
    - High levels of inflammatory cells or markers in fluid
    - Early signs of constriction

Extrapulmonary TB: Conditions in which to extend Rx to 9 months

- Meningitis
- Bone
- Joint
- Spine

Culture Negative, Paucibacillary TB in Adults

- Therapy **can be** shortened to 4 months

Baseline & Follow-up Evaluations

Shaded boxes optional, or contingent on other information

Activity	Baseline	Month of Treatment Completed 1	2	3	4	5	6	7	8	End of Treatment Visit
MICROBIOLOGY										
Sputum smears and culture[1]	☐	☐	☐	☐	☐					☐
Drug susceptibility testing[2]	☐			☐						
IMAGING										
Chest radiograph or other imaging[3]	☐		☐							☐
CLINICAL ASSESSMENT										
Weight[4]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Symptom and adherence review[5]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Vision assessment[6]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
LABORATORY TESTING										
AST, ALT, bilirubin, alkaline phosphate[7]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Platelet count[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Creatinine[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
HIV[9]	☐									
Hepatitis B and C screen[10]	☐									
Diabetes Screen[11]	☐									

3 sputum at baseline, 1 rapid molecular test

Monthly until 2 consecutive ones negative

Other Issues Addressed by Guidelines Without PICO Questions

- Treatment failure
- Adverse effects of TB medications
- Drug drug interactions
- Therapeutic drug monitoring
- Children
- Pregnant and nursing women
- Kidney disease
- Hepatic disease

PICO Questions
9 were addressed in the guidelines

- Population
  - Patients with or suspected of having drug susceptible TB
  - Special circumstances (HIV, culture negative TB, certain forms of extra-pulmonary TB, pregnant or nursing women, children, renal & hepatic disease)
- Intervention
  - Example given in this talk is DOT(slide 11)
- Comparators
  - DOT versus SAT, for example or intermittent therapy versus daily
- Outcomes
  - Percent who relapse, for example

PICO Questions

- 1. Do case management interventions improve outcomes?
  - Conditional recommendation; very low certainty in the evidence
- 2. Does SAT have similar outcomes compared to DOT?
  - Conditional recommendation; very low certainty in the evidence
- 3. Does intermittent dosing in intensive phase have similar outcomes compared to daily dosing?
- 4. Does intermittent dosing in continuation phase have similar outcomes compared to daily dosing?
- 5. Does extending treatment beyond 6 months improve outcomes in patients co-infected with HIV and TB
  - 5a and 5b Conditional recommendation; very low certainty in the evidence

For 3 and 4 refer to the guidelines.

PICO Questions

- 6. Does ART during TB Rx improve outcomes in patients with HIV?
  - Strong recommendation; high certainty in the evidence
- 7. Do adjuvant corticosteroids in pericarditis provide mortality and morbidity benefits?
  - Conditional recommendation; very low certainty in the evidence
- 8. Do adjuvant corticosteroids in meningitis provide mortality and morbidity benefits?
  - Conditional recommendation; moderate certainty in the evidence
- 9. Does a shorter duration of treatment in HIV negative individuals with paucibacillary TB (AFB smear negative, culture negative) have similar outcomes compared to 6 month treatment?
  - Conditional recommendation; very low certainty in the evidence

CONSIDERATIONS FOR CHOOSING REGIMENS

Patient Factors

- Severity of disease (smear positive; cavitary)
- Immune status & comorbidities
- General health & nutrition
- Substance use
- Living arrangements
- Desired frequency & location for DOT
- Tolerance of meds / adverse effects
- Ability to drive and/or meet staff for DOT
- Work schedule
- Ability & willingness to use video DOT
- Diligence and investment in treatment

Health Department Factors

- Staff availability & time
- Number of other patients currently receiving DOT
- Feasible frequency & location for DOT
- Ability to use video DOT
- Other parties who could assist with DOT (private doc; home health; dialysis center; parole officer; social worker)

Synergize and Maximize

- Identify ways to maximize mutual convenience and frequency of DOT
- Work as a team (patient and health department), using each others' strengths and abilities
- Be flexible

Grand Goal – use the regimen that:

- Provides maximum frequency of dosing, AND
- Is most desirable and best tolerated by patient, AND
- Is most feasible and practical for health department

Questions?