TUBERCULOSIS IN THE NORMAL AND COMPROMISED HOSTS

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MAXIMED ASSOCIATES
MARYLAND

JULY 12, 2018
Speaker: The following speaker has nothing to disclose in relation to this activity: John I. McNeil, MD
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CME Disclosures:
Planning Committee And Speaker

AETC-Capitol Region Telehealth Project
Planning Committee: The following committee members have nothing to disclose in relation to this activity:

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John I. McNeil, MD
John Richards
Denise Bailey, MED

Speaker: The following speaker has nothing to disclose in relation to this activity: John I. McNeil, MD
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TEST YOUR KNOWLEDGE
Test Your Knowledge
Question #1

All but which of the following are considered risk factors for TB infection?

A. Homelessness
B. Healthcare or Correction Worker
C. Injection drug use
D. Multiple Transfusions
Test Your Knowledge
Question #2

First line treatment regimen for Active TB disease are:

A. Isoniazid, paritaprevir, capreomycin
B. Rifampin, ledipasvir-sofosbuvir, capreomycin
C. Isoniazid, rifampin, amikacin
D. All of the above
E. None of the above
Test Your Knowledge
Question #3

Some of the most common side effects of treatment for drug-resistant TB include - hearing loss, depression or psychosis, and kidney impairment.

A. True

B. False
Test Your Knowledge
Question #4

Diagnosis delay and non-completion of treatment are two central behavioral challenges for TB control:

A. True
B. False
LEARNING OBJECTIVES

Upon completion of this webinar, participating providers will have the enhanced ability to:

1. Describe the epidemiology of Tuberculosis
2. Describe the epidemiology of TB
3. Discuss risk factors for Infection and Progression to Disease
4. Describe Active TB disease: Clinical Presentations, diagnosis and treatment
5. Identify currently available medications
6. Identify risk factors for Drug resistant TB
REPORTED TUBERCULOSIS (TB) CASES
UNITED STATES, 1982–2016*

No. of cases

Year

*As of June 21, 2017.
TB DATA AND STATISTICS

- Tuberculosis (TB) is one of the world’s deadliest diseases:
- One fourth of the world’s population is infected with TB
- In 2016, 10.4 million people around the world became sick with TB disease. There were 1.7 million TB-related deaths worldwide
- TB is a leading killer of people who are HIV infected
- A total of 9,272 TB cases (a rate of 2.9 cases per 100,000 persons) were reported in the United States in 2016.

### REPORTED TB CASES BY RACE/ETHNICITY* UNITED STATES, 2016†

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Hispanic/Latin</td>
<td>28%</td>
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<tr>
<td>Asian</td>
<td>35%</td>
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<tr>
<td>Black/African American</td>
<td>21%</td>
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<tr>
<td>White</td>
<td>13%</td>
</tr>
<tr>
<td>Native Hawaiian/Pacific Islander</td>
<td>1%</td>
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<tr>
<td>American Indian/Alaskan Native</td>
<td>1%</td>
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<tr>
<td>Multiple race</td>
<td>1%</td>
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</tbody>
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*All races are non-Hispanic; multiple race indicates two or more races reported for a person, but does not include persons of Hispanic/Latino origin.

† Percentages are rounded; as of June 21, 2017.
Disparities in tuberculosis (TB) persist among members of racial and ethnic minority populations. In 2015, the majority (87%) of all reported TB cases in the United States (US) occurred in racial and ethnic minorities. Black, non-Hispanic persons, have a disproportionate share of TB in the United States.

In 2015, TB was reported in 1,995 black, non-Hispanic persons, nearly 21% of all persons reported with TB nationally. Also in 2015, the rate of TB in black, non-Hispanic persons was 5.0 cases per 100,000 population, which is over 8 times higher than the rate of TB in white, non-Hispanic persons (0.6 cases per 100,000 population).

The proportion of TB in black, non-Hispanic persons, is even greater if only US-born (African–American) blacks reported with TB are examined. In 2015, among US-born persons reported with TB, almost 36% were African Americans (black, non-Hispanic).
In 2015, TB disease was reported in 1,995 non-Hispanic blacks in the United States, accounting for nearly 21% of all people reported with TB nationally.

Among U.S.-born people reported with TB disease, nearly 36% were non-Hispanic blacks.

The rate of TB disease was 5.0 cases per 100,000 population, which is over eight times higher than the rate of TB disease in white, non-Hispanic people (0.6 cases per 100,000 population).
REPORTED TB CASES BY ORIGIN AND RACE/ETHNICITY*, UNITED STATES, 2016†

U.S.-born persons

- Hispanic/Latino: 21%
- White: 31%
- Black/African American: 37%
- Native Hawaiian/Pacific Islander: 1%
- American Indian/Alaska Native: 4%
- Asian: 5%
- Multiple race: 1%

Non-U.S.–born persons $^$

- Asian: 48%
- Hispanic/Latino: 31%
- Black/African American: 14%
- Multiple race: 1%
- White: 5%
- Native Hawaiian/Pacific Islander: 1%

* All races are non-Hispanic; multiple race indicates two or more races reported for a person, but does not include persons of Hispanic/Latino origin.
† Percentages are rounded; as of June 21, 2017.
§ American Indian/Alaska Native accounted for <1% of cases among non-U.S.–born persons and are not shown.
PREVENTION CHALLENGES

- TB is a challenging disease to diagnose, treat, and control
- It is critical to reach those at highest risk for TB, and to identify and implement innovative strategies to improve testing and treatment
- TB rates are higher for some racial and ethnic groups. This relates to a greater proportion of people in these groups who have other risk factors for TB. Like other communities, blacks face a number of challenges that contribute to higher rates of TB

Challenges include:

- The duration of treatment for latent TB infection and TB disease is lengthy. Patients are often unable or reluctant to take medication for several months
PREVENTION CHALLENGES

- Socioeconomic factors impact health outcomes and are associated with poverty, including limited access to quality health care, unemployment, housing, and transportation.

- Language and cultural barriers, including health knowledge, stigma associated with the disease, values, and beliefs may also place certain populations at higher risk. Stigma may deter people from seeking medical care or follow up care.
TB remains a serious threat, especially for people who are infected with human immunodeficiency virus (HIV). People infected with HIV are more likely than uninfected people to get sick with other infections and diseases, including TB.

In addition to HIV, other underlying medical conditions may increase the risk that latent TB infection will progress to TB disease. For example, the risk is higher in people with diabetes, substance abuse (including injection of illegal drugs), silicosis, or those undergoing medical treatments with corticosteroids.

Delayed detection and diagnosis of TB disease, as well as delayed reporting of TB disease remains a challenge in TB prevention and treatment. Because the number of TB cases in the United States is declining, there is decreased awareness of TB signs and symptoms among
TB MORBIDITY UNITED STATES, 2011–2016

<table>
<thead>
<tr>
<th>Year</th>
<th>No.</th>
<th>Rate*</th>
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<tr>
<td>2011</td>
<td>10,509</td>
<td>3.4</td>
</tr>
<tr>
<td>2012</td>
<td>9,940</td>
<td>3.2</td>
</tr>
<tr>
<td>2013</td>
<td>9,561</td>
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<tr>
<td>2015</td>
<td>9,547</td>
<td>3.0</td>
</tr>
<tr>
<td>2016</td>
<td>9,272</td>
<td>2.9</td>
</tr>
</tbody>
</table>

* Cases per 100,000 population; as of June 21, 2017.
TB CASE RATES,* UNITED STATES, 2016

*Cases per 100,000; as of June 21, 2017.

DC, District of Columbia; NYC, New York City (excluded from New York state)
TB CASE RATES* BY AGE GROUP, UNITED STATES, 1993–2016

*Cases per 100,000 population; as of June 21, 2017.
REPORTED TB CASES BY AGE GROUP, UNITED STATES, 2016*

*Cases per 100,000 population; as of June 21, 2017.
TB CASE RATES BY AGE GROUP AND SEX, UNITED STATES, 2016*

*Cases per 100,000 population; as of June 21, 2017.
TB CASE RATES BY AGE GROUP AND RACE/ETHNICITY, *UNITED STATES, 2016†

* All races are non-Hispanic; multiple race indicates two or more races reported for a person, but does not include persons of Hispanic/Latino origin.
† As of June 21, 2017.
PERCENTAGE OF NON-U.S.–BORN PERSONS AMONG TB CASES, UNITED STATES, *
2006 AND 2016

*As of June 21, 2017.

DC, District of Columbia; NYC, New York City (excluded from New York state)
PRIMARY ANTI-TB DRUG RESISTANCE,
UNITED STATES, 1993–2016*

* As of June 21, 2017. **Note**: Based on initial isolates from persons with no prior history of TB; multidrug-resistant TB (MDR-TB) is defined as resistance to at least isoniazid and rifampin.
REPORTING OF HIV TEST RESULTS AMONG PERSONS WITH TB, BY AGE GROUP
UNITED STATES, 1993–2016*

* As of June 21, 2017.

Note: Includes persons with positive, negative, or indeterminate human immunodeficiency virus (HIV) test results and persons from California with co-diagnosis of TB and acquired immunodeficiency syndrome (AIDS). Rhode Island did not report HIV test results for years 1993–1997. HIV test results for Vermont are not included for years 2007–2013. HIV test results for California are not included for years 2005–2010.
ESTIMATED HIV COINFECTION AMONG PERSONS REPORTED WITH TB, UNITED STATES, 1993–2016*

* As of June 21, 2017.

Note: Minimum estimates are based on reported HIV-positive status among all TB patients in the age group.
TB CASES AMONG PERSONS AGED ≥15 YEARS RESIDING IN CORRECTIONAL FACILITIES, UNITED STATES, 1993–2016*

No. of cases

Year

Percentage

* As of June 21, 2017.

Note: Resident of correctional facility at time of TB diagnosis.
COMPLETION OF TB TREATMENT THERAPY,
UNITED STATES, 1993–2014*

* As of June 21, 2017; data available through 2014 only.

Note: Includes persons alive at diagnosis, with initial drug regimen of one or more drugs prescribed, who did not die within one year of initiating treatment; excludes persons with initial rifampin-resistant isolate, patients with bone and joint disease, meningeal disease, or disease of the central nervous system, or pediatric patients (ages 0–14 years) with military disease or positive blood culture or a positive nucleic acid amplification test on a blood specimen, and those who moved out of the country within one year of initiating treatment.
Exposure

Infection (TST or IGRA pos)

No Infection

Latent TB Infection

HIV-neg
5-10% lifetime

HIV-pos
5-10%/Year

Active TB Disease

HIV –neg: 5% in first 1-2yrs
HIV-pos: much more likely

Overview of TB Epidemiology
RISK FACTORS

For TB Infection
- Exposure to TB case
- From TB endemic area
- Homelessness
- Works in healthcare or corrections
- Injection drug use

For Progression to TB Disease
- Recent TB infection
- HIV infection
- TNF – alpha inhibitors
- Immunosuppression
- End stage renal disease
- Diabetes
- Silicosis
- CXR fibrotic lesions c/w prior TB
- Intestinal bypass
- CA head or neck, Hodgkin’s leukemia
ACTIVE TB DISEASE: CLINICAL PRESENTATIONS

- Fever, sweats, wt. loss
- Cough if pulmonary
- Usually subacute to chronic (wks. to months)
- Can be acute in immunocompromised
- Upper lobe/apical cavity typical
  - With surrounding infiltrates
  - Usually adenopathy
IMAGING CONSIDERATION

- Chest CT Scan
- Chest X-ray
ACTIVE TB DISEASE: CLINICAL PRESENTATIONS

Extrapulmonary (dx eval should include biopsy for AFB smear, mycobacterial culture, histopathology)

- CNS (meningitis, focal tuberculomas)
- Lymphadenitis (cervical, thoracic, abdominal)
- Bone and joint
  - Vertebral (thoracic, lumbar, anterior wedging, +/- psoas abscess)
  - Consider TB in DDX of chronic osteomyelitis, arthritis
- Pleural
- Abdominal/Pelvic
  - GU (sterile pyuria, obtain multiple cultures, can be associated with infertility)
  - GI (can mimic inflammatory bowel disease, obtain cultures, histopathology)

Disseminated

- Advanced HIV, significant iatrogenic immunosuppression
- Can present as sepsis
- Mycobacterial blood cultures, obtain respiratory specimens
Smear microscopy for acid fast bacilli

- Low sensitivity takes a lot of bacilli to make a smear positive (sputum 10,000 cfu/ml)
- Overall around 50-60% sensitive for pulmonary TB
- Much less sensitive in advanced HIV (30-50%)
- **IMPORTANT POINT:** a negative smear does not exclude dx of active disease
- In pulmonary TB, the yield of smear microscopy increases if multiple specimens are obtained
- Not specific for M. tb (most mycobacteria look alike)
- Good PPV in TB endemic settings
**ACTIVE TB DISEASE: DIAGNOSIS**

**Nucleic Acid Amplification Tests**

- E.g. ‘Xpert MTB/RIF
- Sensitivity between that of smear and culture
- A negative test does not rule out TB
- High specificity for M. tuberculosis (by design)
- Xpert MTB/RIF detects M. tuberculosis and also rifampin resistance (No information about INH)
- Procedures designed for sputum
  - Can be used for other specimens but the test can be false negative due to inhibitors of amplification rxn
ACTIVE TB DISEASE: DIAGNOSIS

Mycobacterial Culture

- The most sensitive method
- SLOW (3-6 weeks)
- Once growth observed, the lab performs additional tests to identify species (e.g. M. tuberculosis)
- Considered the gold standard, but not 100% sensitive
  - Pulmonary TB around 90-95% sensitive
  - Extrapulmonary TB much less sensitive
ACTIVE TB DISEASE: TREATMENT

- First line treatment
  - Rifampin, Isoniazid, Pyrazinamide, Ethambutol x 2 months, then
  - Rifampin plus isoniazid x 4 months (continuation phase)
  - Use pyridoxine (vitamin B6) to prevent neuro toxicity to INH

- Always start with daily treatment
  - Daily more efficacious than intermittent
  - In HIV-positive, intermittent tx associated with emergence of RIF resistance
ACTIVE TB DISEASE: TREATMENT

Extend continuation phase therapy for

- Pulmonary dx if cavitation and cx positive at the end of tx month 2 (9 months total)
- CNS TB (usually 9-12 months total duration)
- Bone and joint TB (6-9 months total duration)

Corticosteroids indicated for TB meningitis

- Pericardial TB: previously universally recommended, but recent placebo controlled randomized trial showed no difference in outcomes overall
Drug adverse effects

- **Hepatotoxicity:** Isoniazid, PZA, rifampin
- **Peripheral neuropathy:** Isoniazid (use pyridoxine)
- **Retrobulbar neuritis:** ethambutol (color vision first affected)
- **Arthralgias:** PZA
- **Vestibular/ototoxicity:** streptomycin > amikacin, kanamycin
- **Nephrotoxicity:** amikacin, kanamycin > streptomycin
DRUG RESISTANT TB

Risk factors for

- Contact with drug resistant TB case
- From (or prolonged travel to) eastern Europe, former Soviet Union
- Prior h/o TB treatment, especially if non-adherent with hx

MDR = resistance to isoniazid plus rifampin

XDR = MDR plus resistance to fluoroquinolones plus a at least one of the injectable second line drugs (amikacin, kanamycin, capreomycin)

- Treat with multiple agents against which the isolate is susceptible
- Never add a single drug to a failing regimen
ACTIVE TB DISEASE: HIV CONSIDERATIONS

Clinical Presentation

- Lung cavitation may be absent in advanced immunosuppression
- Negative CXR does not exclude TB
- With advancing immunosuppression, risk for
  - Smear-negative pulmonary TB
  - Extrapulmonary TB (with or without pulmonary disease)
  - CNS TB
  - Widely disseminated disease
- Immune reconstitution inflammatory syndromes
Transplantation associated immunosuppression increases the risk of active TB disease if the person is infected.

Atypical presentations leading to delayed disease:
- 1/3 to ½ is disseminated or extrapulmonary
- 4% of cases thought to be donor derived

High mortality

DDI between rifampin and calcineurin inhibitors (cyclosporine, tacrolimus), mammalian target of rapamycin inhibitors (sirolimus/everolimus), corticosteroids. At risk for graft rejection:
- Monitor drug levels
- Use rifabutin
ACTIVE TB DISEASE: TNF-ALPHA INHIBITORS

- TNF-alpha inhibitors markedly increases the risk of active TB if infected
  - Risk greater with anti-TNF antibodies (infliximab) than with TNF receptor fusion protein (etanercept)
  - Can present with atypical TB (non-cavity pulmonary disease, extrapulmonary, disseminated)
  - Increased TB mortality and morbidity
- Test for latent TB infection (TST or IGRA) prior to starting anti-TNF agents
  - If LTBI, then initiate LTBI tx prior to starting anti-TNF
  - Optimal duration of delay between initiating LTBI treatment and initiating anti-TNF treatment not known (some say 2-8 weeks)
LATENT TB INFECTION (LTBI): DIAGNOSIS

Tuberculin skin test
- A mix of antigens; can have false-positive test due to prior BCG vaccination, NTM
- Intradermal inoculation, measure induration at 48-72 hours (a positive reaction lasts a few days)
- Cut-offs based on the likelihood of true exposure, risk of progression to active TB if infected
  - 5 mm
  - 10 mm
  - 15 mm
- Adjunctive in diagnosis eval of active TB
LATENT TB INFECTION (LTBI): DIAGNOSIS

Interferon gamma release assays
- QFT Gold in-tube: T-SPOT TB
- Blood-based: in vitro stimulation of WBC with protein antigens specific for M. tuberculosis
- SPECIFIC for M. tb infection: no cross-reactivity with BCG
- Sensitivity in approximately the same as TST
- Can be negative immunosuppressed
- Lots of issues around performance in clinical care
- As for TST adjunctive in diagnoses eval for active TB
BACILLE CALMETTE-GUERIN (BCG)

- Attenuated live vaccine (from M. bovis)
- Neonatal vaccination
  - Decreases incidence of severe forms of childhood TB
  - No impact on adult TB
  - Regional lymphadenitis can occur after vaccination: typically no treatment needed
  - Disseminated infection can occur in immunocompromised (treatment indicated)
THANK YOU!
TEST YOUR KNOWLEDGE
Test Your Knowledge
Question #5

All but which of the following are considered risk factors for TB infection?

A. Homelessness
B. Healthcare or Correction Worker
C. Injection drug use
D. Multiple Transfusions
Test Your Knowledge
Question #6

First line treatment regimen for Active TB disease are:

A. Isoniazid, paritaprevir, capreomycin
B. Rifampin, ledipasvir-sofosbuvir, capreomycin
C. Isoniazid, rifampin, amikacin
D. All of the above
E. None of the above
Some of the most common side effects of treatment for drug-resistant TB include - hearing loss, depression or psychosis, and kidney impairment.

A. True
B. False
Test Your Knowledge
Question #8

Diagnosis delay and non-completion of treatment are two central behavioral challenges for TB control:

A. True
B. False
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