I declare that there are no conflicts of interest, nor a financial interest, arrangement or affiliation with any organization that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

*Pamela B. Hackert, MD, JD, MPH*
Goals of Talk

1. Identify how the traditional patterns of extrapulmonary vs. pulmonary TB are changing
2. Challenges in diagnosis with extrapulmonary disease
3. Challenges in case management of extrapulmonary disease
Remember the Giant Cell?

- Hallmark of extrapulmonary histopathology
- Paucity of bacilli is typical
- Constitutional symptoms may mimic a malignancy
Extrapulmonary Tuberculosis

• The overall decline in TB cases since 1953 has been almost exclusively due to a reduction in pulmonary TB, with extra-pulmonary TB remaining relatively constant.

• Explanations that have been proposed include:
  • The increased burden of chronic diseases*
  • Immigration patterns*
  • The increase in the use of immune suppressant medications*
  • Certain phenotypes of the tubercle bacilli may be linked to a higher risk of extrapulmonary dissemination^"}

*Epidemiology of extra-pulmonary tuberculosis in the United States: high rates persist in the post-HIV era, Adada,* M. A. Valley,† S. A. Nour,* J. Mehta,* R. P. Byrd, Jr.,* J. L. Anderson,† T. Roy,* INT J TUBERC LUNG DIS 18(12):1516–1521 Q 2014 The Union http://dx.doi.org/10.5588/ijtld.14.0319

^Different strains of Mycobacterium tuberculosis cause various spectrums of disease in the rabbit model of tuberculosis, Manabe YC, Dannenberg AM Jr, Tyagi SK, Hatem CL, Yoder M, Woolwine SC, Zook BC, Pitt ML, Bishai WR, 2003. Infect Immun 71: 6004 – 6011.
“The basic principles that underlie the treatment of pulmonary tuberculosis (TB) also apply to extrapulmonary forms of the disease. As a general rule, regimens that are adequate for treating pulmonary TB in adults and children are also effective for treating extrapulmonary disease since, in most cases, the mycobacterial burden is considerably smaller in this form.”

CLINICAL POLICIES

AND PROTOCOLS

Bureau of Tuberculosis Control

New York City Department of Health and Mental Hygiene
Differences for Extrapulmonary Tuberculosis:

**Length of Treatment**
- CNS tuberculosis
- Spine and joint
- Disseminated
Evaluation of Long Term Outcomes of Standard Extrapulmonary TB Treatment

• Retrospective cohort study of all patients treated for EPTB in the state of Texas between January 2000 and December 2005, who had no pulmonary disease.

• Survival compared to persons with latent infection as well as between different types of extrapulmonary TB

• Significant predictors of poor long-term outcome were:
  • Age (hazard ratio for each year of age-at-diagnosis was 1.05; CI: 1.04-1.06)
  • Treatment duration
  • Type of EPTB
  • HIV-infection (HR = 2.16; CI: 1.22, 3.83)

Therapy duration and long-term outcomes in extra-pulmonary tuberculosis. T. Pusch, J. Pasipanodya, R Hall, and T. Gumbo, BMC Infectious Diseases. 14:115, March 1, 2014.
Table 1 Demographic and clinical characteristics at the time of starting therapy for the 438 study patients
Pusch et al. BMC Infectious Diseases 2014, 14:115
http://www.biomedcentral.com/1471-2334/14/115

| Variable                  | Total | Lymph nodes | Bone and joint | GUS | Meninges | Peritoneum | Other | p-value |
|---------------------------|-------|-------------|----------------|-----|----------|------------|-------|---------|
| Age (years)               | 49(18)| 47(18)      | 52(19)         | 48(17)| 43(15)  | 49(16)     | 52(19)| 0.02    |
| Male                      | 224(51)| 76(47)      | 46(50)         | 15(63)| 31(56)  | 23(54)     | 33(54)| 0.63    |
| Race                      |       |             |                |     |          |            |       |         |
| White                     | 216(49)| 73(45)      | 46(50)         | 20(83)| 24(44)  | 21(49)     | 32(53)| 0.02    |
| Black                     | 213(49)| 85(52)      | 45(49)         | 3(13)| 31(56)  | 22(51)     | 27(44)|         |
| Other                     | 9(2)  | 5(3)        | 1(1)           | 1(4)| 0        | 0          | 2(3)  |         |
| Hispanic                  | 123(28)| 42(26)      | 25(27)         | 11(46)| 14(25)  | 11(26)     | 20(33)| 0.39    |
| Non-Hispanic              | 315(72)| 121(74)     | 67(73)         | 13(54)| 41(75)  | 32(74)     | 41(67)|         |
| Residence                 |       |             |                |     |          |            |       |         |
| Jail                      | 29(7) | 14(9)       | 5(5)           | 1(4)| 2(4)    | 2(5)       | 5(8)  | 0.83    |
| Nursing home              | 18(4) | 8(5)        | 2(2)           | 1(4)| 3(5)    | 1(2)       | 3(5)  | 0.86    |
| Homeless                  | 13(3) | 3(2)        | 1(1)           | 1(4)| 4(7)    | 1(2)       | 3(5)  | 0.19    |
| Substance abuse           |       |             |                |     |          |            |       |         |
| Alcohol                   | 48(11)| 17(10)      | 8(9)           | 2(8)| 3(5)    | 11(26)     | 7(11) | 0.07    |
| Injection                 | 15(3) | 4(2)        | 6(7)           | 0  | 1(2)    | 4(9)       | 0     | 0.06    |
| Other non-injection       | 35(8) | 18(11)      | 5(5)           | 2(8)| 2(4)    | 5(12)      | 3(5)  | 0.33    |
| HIV-infected              | 93(21)| 52(32)      | 5(5)           | 1(4)| 16(29)  | 6(14)      | 13(21)| <0.001  |
| Prior TB                  | 15(3) | 3(2)        | 4(4)           | 3(13)| 1(2)    | 2(5)       | 2(3)  | 0.15    |
| Acid-fast bacilli stain   | 74(17)| 37(23)      | 11(12)         | 6(25)| 4(7)    | 6(14)      | 10(16)| <0.001  |
| *Mtb* culture             | 308(70)| 131(80)     | 72(78)         | 16(67)| 22(40)  | 30(70)     | 37(61)| <0.001  |
| Completion of therapy     |       |             |                |     |          |            |       |         |
| Completed                 | 346(79)| 133(82)     | 74(80)         | 21(88)| 36(65)  | 33(77)     | 49(80)| 0.08    |
| Not completed             | 53(12)| 15(9)       | 12(13)         | 3(13)| 8(15)   | 5(12)      | 10(16)|         |
Detail of the Impact of Age on Mortality

- Table A is men, B is women
- The black line is mortality in the extrapulmonary TB group
- Red line is LTBI group
- Blue line is general non-TB Texas population
- Hazard ratio for each year of age-at-diagnosis was 1.05
- Age of 65 or older at time of diagnosis most significant factor predicting mortality
Survival Curves of Different EPTB Types for Patients with Microbiologically Proven Disease
“For all disease syndromes, mortality decreased with longer treatment duration until a nadir, which was the treatment duration associated with lowest proportion of patients with adverse long-term outcomes. Thereafter, mortality increased with longer duration of therapy.”
What Does All This Mean?

• Five year mortality of adequately treated meningitis (46%) and peritonitis (42%) TB is similar to that of untreated, smear positive pulmonary TB (42-70%)
  • May reflect TB’s damage to different organs in the body
  • May reflect different antibiotic penetration of different organs in the body
  • May indicate that Mtb genotypes that preferentially cause meningitis or peritonitis are more difficult to kill and have a higher propensity to fail or develop drug resistance

• Implies that there is a treatment length duration point associated with a best long-term outcome, and that therapy duration beyond this point leads to poorer survival.

• This was a retrospective study, and findings must be tested in prospective studies.
Differences for Extrapulmonary Tuberculosis:

Adjunctive Corticosteroids

- CNS tuberculosis
- Disseminated tuberculosis with refractory hypoxemia
- Tuberculous pericarditis?
  - 2014 NEJM study of pericardial TB and the use of glucocorticoids
Pericardial Tuberculosis and Steroids?

- Did not reduce the risk of death, cardiac tamponade, or constrictive pericarditis.
- Increase seen in HIV associated cancer
- Decrease seen in pericardial constriction and hospitalization

Prednisolone and Mycobacterium indicus pranii in Tuberculous Pericarditis. Bongani M. Mayosi, M.B., Ch.B., D.Phil., Mpiko Ntsekhe, M.D., Ph.D., Jackie Bosch, Ph.D., et al., N Engl J Med Volume 371(12):1121-1130, September 18, 2014.
HIV—Unique Features of AIDS Associated Tuberculosis

- Higher rate of disseminated disease
- Higher rate of extrapulmonary tuberculosis
- Rapid progression
- Visceral lymphadenopathy
- Tissue abscesses
- Negative TST

1. Diagnosis and management of miliary tuberculosis: current state and future perspectives. S. Ray, A. Talukdar, S. Kundu, et al., *Therapeutics and Clinical Risk Management*, 9, 9–26, 2013.
2. An Updated Systematic Review and Meta-analysis on the Treatment of Active Tuberculosis in Patients with HIV Infection. F. Khan, J. Minion, A. Al-Motairi, A. Benedetti, A. Harries, D. Menzies, *Clin Infect Dis.* 55 (8): 1154-1163, 2012.
Clinical Clues for Suspicion of Extrapulmonary Tuberculosis

- Ascites with lymphocyte predominance and negative bacterial cultures
- Chronic lymphadenopathy (especially cervical)
- Exudative pleural effusion with lymphocyte predominance, negative bacterial cultures, and pleural thickening
- HIV infection
- Joint inflammation (monoarticular) with negative bacterial cultures
- Persistent sterile pyuria
- Unexplained pericardial effusion, constrictive pericarditis, or pericardial calcification
- Vertebral osteomyelitis involving the thoracic spine

Extrapulmonary tuberculosis: an overview. MP Golden, HP Vikram, Am Family Physician, 2005 Nov 1;72(9):1761-8.
Lymphadenopathy—Most Common Form of Extrapulmonary TB

- **Infection?**
  - Granulomatous causes
  - Reactive adenopathy/non-granulomatous
    - EBV – mononucleosis
    - CMV

- **Non-infectious process?**
  - Lymphoma
  - Head/neck neoplasia

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Fig. 186.—A summary of the natural history of tuberculous lymphadenitis.
• 15 y.o. boy, originally from Vietnam
• Presented to primary care provider with R cervical swelling
• 7/04 CXR for positive TST “Linear opacity in the right mid-lung. Atelectasis or scar are both considered.”
• 8/27 CT of neck shows “pathologic nodes, with low attenuation areas within, near fluid density”
• 10/17 Excision of R Neck mass, showing extensive necrotizing granulomatous inflammation. Smear negative
• 11/20 Tissue culture positive for M tb—Physician and hospital notified by lab
• 11/28 CXR now done for dyspnea. Read as “area of streak atelectasis in the right mid-lung. Summary: Normal Chest”
• 11/28 Referral made to Oakland County Health Division (OCHD)
Oakland County Health Division

- 11/28 Notified of patient with +Mtb lymph node
- 11/28 Patient seen by TB Case Manager. First sputum collected
- 11/29 second sputum collected, RIPE started with 14 daily doses
- 11/30 third sputum
- 12/18 OCHD notified that first and second sputum +Mtb
Skeletal Tuberculosis

• Symptoms of skeletal TB may include the following:
  • Back pain or stiffness
  • Lower-extremity paralysis, which can be seen in as many as half of patients with undiagnosed Pott’s Disease

• Tuberculous arthritis, usually involving only 1 joint

• Bones involved in order of frequency:
  • Vertebrae > knee > hip > elbow > wrist > shoulder
82 Year Old Man With SOB

- Worked up for pulmonary embolism
- History of emphysema with bilateral calcified and noncalcified pleural plaques
- A new perivertebral mass was found with this admission that eroded through the T3 and T4 vertebral bodies
Pott’s Disease

• Spinal tuberculosis
• Most commonly involving the thoracic spine
• Infection begins in anterior/inferior aspect of vertebral body
• Destruction of intervertebral disc and adjacent vertebrae
• Creates anterior wedging and angulation of adjacent vertebral bodies
Pott’s Disease
46 y.o. Man with Painful Rib Lesion

- Healthy, no TB risk, public relations professional
- Presented with pain on right side, specific area on anterior right chest
- Initially no other signs or symptoms
- After 4 months developed slight lump at the site of the pain.
- No history of trauma, no radiation of pain
Where Did He Get This?

- CT of chest showed axillary, hilar and mediastinal adenopathy
- 3.6 x 2.6 cm destructive lesion of the 8th right rib
- Working diagnosis was malignancy
- Biopsy grew Mtb
Genitourinary Tuberculosis

- Predominantly affects men (40-50 years of age), with a prevalence twice that which is seen in women
- 75% of women with GUTB are aged 20-45 years
- GUTB is strongly associated with infertility in women and rates of successful pregnancy remain low even after treatment
- May account for up to 1% of postmenopausal bleeding
- Patients with renal TB can present with flank or suprapubic pain, nocturia or hematuria as well as constitutional symptoms
54 y.o. Woman Evaluated for Abdominal Pain and Cramping

- U/S on Dec 10\textsuperscript{th} read as multiple hypoechoic solid myometrial masses, largest measuring 9 cm.
- Likely exposed during childhood in Central America
- TST in 2001 positive-not offered treatment
- S/S included night sweats, +history of fibroids
Further Studies

CT of Abdomen May 5-Large heterogeneous uterus measures 16.8 cm in its greatest dimension, with smaller adjacent satellite masses.

The CT report said that a large degenerating fibroid/neoplasm was a consideration, but less likely given that the path report had already said granulomatous endometritis.
Extrapulmonary Disease Does Not Exclude Pulmonary Disease

- LPH not contacted by infectious disease specialist as this was “extrapulmonary and not contagious.”

- No address had been put on lab specimens, so lab report of positive findings was sent to the county where the lab was located, not the county of residence.

- Three sputums submitted by Oakland County after two weeks of treatment. One positive for Mtb.

- It’s not excessive, it’s precaution!
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It is critical for HIV+ patients with pericardial tuberculosis that corticosteroids are used to reduce morbidity and mortality.

A. True
B. False
With treatment of endometrial tuberculosis, more than half of women have fertility restored.

A. True
B. False
For immuno-competent, otherwise healthy adults, with a normal chest x-ray, sputums are not necessary in extrapulmonary tuberculosis.

A. True
B. False