Challenges of TB in the Elderly
Janice Louie, MD, MPH
November 22, 2019

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Today’s presenters, CME Committee, staff and planning committee have indicated they have no commercial affiliations to disclose.
Challenges of TB in the Elderly

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Disclosure:
I have no conflicts of interest in relation to this presentation
• Case Presentation
• Why this is an important topic
• Review of the literature
• Review of the article and what it adds
• Comparison to San Francisco data
• Conclusions/Discussion

**Case presentation**

90 year old male originally from China presented with 3 months of cough worse than baseline, weakness, dizziness and weight loss of 10 lbs over 6 months

Co-morbid illnesses:
- Aortic valve replacement with mechanical valve, on warfarin
- Atrial fibrillation
- Chronic obstructive pulmonary disease
- Chronic kidney disease (CrCl 35 ml/min)
- Gout, on allopurinol and colchicine
- Significantly hearing-impaired
- History of non-adherence
- History of LTBI in 1996 treated with INH, but patient recalls that he “felt terrible and tired and achey” and he decided to stop after a few months

Social History:
- Prior smoker, no ETOH
- In US since 1996, retired computer engineer, very articulate
- Lives alone (brothers in nearby apartments); main daily activities including reading and watching TV, visiting with family and going out for meals. Driving to the grocery store and post office.
Interpretation: Bilateral upper lobe nodules with large left upper lobe nodular mass

Chest CT: Bilateral upper lobe pulmonary masses/nodules, left greater than right. Bronchiectasis in the right lower lobe
IGRA negative
Microbiology: Sputa numerous AFB smear positive x 3 (NAAT positive, no Rif res)*
Treatment initiation

- Treatment with 4 anti-tuberculous drugs [INH, Rifabutin, Ethambutol (18.4 mg/kg qd) and Pyrazinamide] was initiated. Patient expresses understanding and agrees to home isolation. PCP informed of his TB meds.
- Within 7 days the patient was hospitalized for nausea, vomiting, and abdominal pain. He was found to have presumed drug-induced liver injury [aspartate transaminase/alanine transaminase to 600s]. TB meds held
- Patient was slowly re-challenged with INH, Rifabutin, EMB and Levoq (750 mg qd) with the liver function tests remaining within normal ranges.
- Discharged after 14 days to home with instructions to patient/family for patient to remain in isolation until smear negative x 3.

Treatment – Dose count #23

- The patient was hospitalized for complaints of new dizziness and black diarrhea [Hct 20% with INR not calculated (PT>100 seconds)].
  - After IV fluids and stabilization, treatment was eventually re-initiated with INH, Rifabutin, EMB and Levo qd.
  - Refused endoscopy
  - Ophthalmology screen: significant cataract OS. Patient noted to have difficulty following instructions
  - EKG: atrial fibrillation with calculated QTc 464
  - Abdominal US- fatty liver
- After Hct stable and patient therapeutic on coumadin (INR 2-2.5), he was discharged home to isolation.

Current regimen: INH, Rifabutin, EMB, Levo
First Two Months: Home Isolation with DOT

- Patient usually alone at DOT visit; often seems confused about the reason for the visit and does not recognize health worker
- Health worker reports calling patient he is coming, arriving for visit and seeing patient driving away in car
- TB staff request meeting with patient and family to discuss importance of need for isolation, treatment compliance and public health risk
- Patient provided specimen cups for sputum collection; returned 2 with sputa and 1 with urine
- Family conference requested by TB team to discuss concerns that patient is unable to care for self, and possibly has dementia which should be medically evaluated further. If he cannot stay in isolation, will need hospitalization and possible long-term care. Car keys taken away by family but later given back to patient on his insistence.

45 Days

- Health worker notes during DOT visit patient is scratching, and observes possible rash on patient’s neck.
- MD visit: Patient denies any itchiness; exam shows visible erythematous and excoriated rash on arms and neck. Meds held. LFTs normal
- Patient re-challenged with Rifabutin followed by Levo with daily cetirizine→ faint rash on arms. Meds held.
- Patient re-challenged again with a pre-dose cocktail of Prednisone 20 mg, Benadryl 25 mg followed 30 min later by Rifabutin 150 mg→ within 15 minutes, he develops hives on both arms.
- Rifabutin d/c ed. PCP informed to adjust coumadin dosing
Current regimen: INH, EMB, Levo
Two Month Visit

- Patient states “I’m okay but I don’t feel like eating because I might vomit”. Weight loss of 4 lbs.
  - Zofran started for nausea
- Patient unable to complete visual acuity exam; he is referred for Ophthalmology for monthly screening

Microbiology: Smear negative x 3 → isolation d/c’ed
Current regimen: INH, EMB, Levo

Interval decrease size of the left upper lobe consolidation. Other smaller area of nodular opacities have also decreased

Three Month Visit

- Patient not sure why he is in clinic, but then points to his knees and states “The TB pills are giving me pain”. Family thinks these were same symptoms patient had before with prior LTBI treatment
- Patient is unable to stand to be weighed.
  - On exam: mild swelling of right knee and foot; patient will not flex or extend right knee and both ankles fully due to pain; unable to comply with complete neurologic exam
- INH stopped
- Linezolid (600 mg) started
- Patient referred to Rheumatology, started on Prednisone taper for possible gout.

Microbiology: Pansusceptible, PSQ- no gyrA mutation. Culture conversion at 6 weeks.
Patient has two cultures growing NTM
Current regimen: Levo, Linezolid (600 mg), EMB
IMPRESSION:
Interval decrease in the size of the large left upper lobe mass/consolidation and some of the right upper lobe consolidation/nodules. However, there are new patchy areas of multiple nodules in the inferior right lower lobe. These findings are consistent with ongoing infection.

Four Month Visit
Patient states he is doing “fine”, but on exam has shallow lacerations of right leg, and family reports he fell in the bathroom. He is alert and oriented x 1. Right knee and foot swelling slightly improved with less tenderness. Gross neurologic exam is unchanged ➔ plain film of leg negative.
• Zofran stopped due to concerns of worsening mental status.
• Monthly CBC and CMP stable
Current regimen: Levo, Linezolid (600 mg), EMB
Six Month Visit

Brother states patient reports difficulty seeing the TV.
- Patient alert and oriented x 2, flat affect
- Patient unable to comply with visual acuity exam in clinic
- Meds held
- Ophthalmology exam – patient unable to follow instructions. Report notes no clear significant change, concluding: “Visual acuity deficit does not correlate with exam”.
- Head CT- multiple areas with small vessel ischemic disease. Focal encephalomalacia of right parietal lobe and left anterior insula (unable to determine if abnormalities are acute vs chronic)

Restarted on Levo, Linezolid (300 mg), EMB

6 month CXR- stable size of left upper lobe mass/opacity
Seven Month Visit

No complaints. Patient now homebound. Appetite +/-, weight stable.
– On exam patient is alert and oriented x 2.
– He has some cogwheeling of right arm and slight new contracture of right lower leg.
– Monthly CBC and CMP stable
– Family expresses concern that “TB treatment has made him worse”.

Patient unwilling to come in for chest CT

Current regimen: Levofloxacin, Linezolid (300 mg) and EMB

Microbiology Summary

<table>
<thead>
<tr>
<th></th>
<th>AFB smear</th>
<th>NAAT</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment initiation- Induced Sputum</td>
<td>Num Pos</td>
<td>Pos</td>
<td>+ MTB complex*</td>
</tr>
<tr>
<td>Day 2- Sputum</td>
<td>Num Pos</td>
<td>ND</td>
<td>+ MTB complex</td>
</tr>
<tr>
<td>Day 6- Sputum</td>
<td>Num Pos</td>
<td>ND</td>
<td>+ MTB complex</td>
</tr>
<tr>
<td>Day 21- Sputum</td>
<td>Few Pos</td>
<td>ND</td>
<td>+ Mycobacterium avium (no MTBC probe run)</td>
</tr>
<tr>
<td>Day 31- Sputum</td>
<td>Mod Pos</td>
<td>ND</td>
<td>+ MTB complex probe</td>
</tr>
<tr>
<td>Day 35- Sputum</td>
<td>Few Pos</td>
<td>ND</td>
<td>+ MTB complex probe</td>
</tr>
<tr>
<td>Day 42- Sputum</td>
<td>Rare Pos</td>
<td>ND</td>
<td>negative</td>
</tr>
<tr>
<td>Day 46 - Sputum</td>
<td>negative</td>
<td>ND</td>
<td>negative</td>
</tr>
<tr>
<td>Day 60- Sputum</td>
<td>Few Pos</td>
<td>ND</td>
<td>Mycobacterium abscessus#</td>
</tr>
<tr>
<td>Day 64- Sputum</td>
<td>Few Pos</td>
<td>neg</td>
<td>Mycobacterium abscessus</td>
</tr>
<tr>
<td>Day 80- Sputum</td>
<td>Rare Pos</td>
<td>ND</td>
<td>Mycobacterium abscessus</td>
</tr>
</tbody>
</table>

*MTBC Culture conversion at 6 weeks, pansusceptible including FQ
# M. abscessus: susceptibility results pending
The Problem

- The worldwide population is aging
- By 2030, estimates are that 20% of the US population will be over 65 years (US Census)
- Globally, young adults age 25-44 account for most TB cases (skewed by HIV in Africa)
- However, in Europe, US, Asia and South/Central America, the elderly have highest TB incidence rates


TB Case Rates* by Age Group, United States, 1993–2017

In the US (and other developed countries), TB incidence is highest in persons ≥65 years

*Cases per 100,000 population
Few Evidence-Based Studies of the TB in the Elderly to Date

Pulmonary tuberculosis in the elderly: a different disease?

Since the early 1980s there has been concern at the increasing incidence of pulmonary tuberculosis in people over 65. Part of the concern has been the difficulty in making the diagnosis in this population and the ease with which, in enclosed environments such as institutions and homes for the elderly, the disease may reach epidemic proportions among the susceptible aged. The predisposition to develop tuberculosis in those immunocompromised by age, drugs, disease, or malnutrition is well recognized.

The basic classification of tuberculosis into primary infection (and disease) and postprimary (or reactivated) disease is well established. The radiological features of the primary infection (small mid zone peripheral lesion or segmental inflammatory lesion, or both, with hilar adenopathy) and of postprimary disease (apical fibrosis, pulmonary opacities, cavitation, and apical pleural thickening) are well known. Why then is there difficulty in diagnosing the disease in the elderly? It is because it presents differently in obvious cause should alert clinicians to the possibility of tuberculosis.

The means of acquiring the disease may also be different in elderly people, as not all postprimary disease in the elderly is due to reactivation. When clusters of cases occur, as in homes for the aged, an index case has caused either an exogenous initial primary infection or, importantly, re-infection. In the latter case previous acquired immunity would be presumed to have waned, that individual thus becoming vulnerable to reinfection and disease. Possibly endogenous acquired infection may play a part. Today's elderly people contracted the disease at a time when not only was tuberculosis more prevalent but effective treatment was non-existent. Most people born in the early twentieth century became infected and are therefore liable to reactivation of infection. It is postulated that with decreasing immunity breakdown of a dormant (apical) lesion precipitating sickness. It would appear that the organism may be present for years in the elderly...
Korea

Retrospective cohort study
• N=470, comparing < 65 to ≥ 65 years
• Standard 4-drug therapy, all self-administered
• Outcomes (success, failure, relapse) measured by radiographic improvement and culture

Elderly patients:
– More likely to have comorbid illness
– More likely to have positive culture (81% vs 68%; p=0.002)
– Less likely to have cavity (16% vs 34%; p<0.001)
• No difference in proportion with adverse events or mortality

Kwon et al. BMC Infectious Diseases 2013, 13:121

Africa/Nigeria

Retrospective cohort study
• N=1668 (<60 compared to ≥ 60 years); 30% HIV positive
• Treated with 4-drug regimen with modified DOT (family or community member)
• Outcomes (success, failure, relapse) measured by smear positivity

Elderly patients:
• Less likely to be smear positive (40.7% vs 65.8%; p <0.001)
• Trend toward more likely to default (more elderly lived in rural area) (12.3% vs 9.0%, p=0.07)
• Trend toward death (all-cause) during treatment (12.3% vs 9.5%, p=0.1)

Oshi et al. PLOS ONE Nov 2014;9 (11):e111910
India

Retrospective cohort study
- N=2436 (<60 compared to ≥ 60 years); ~85% HIV status not documented
- Treated with 4-drug regimen (SA) three times weekly
- Outcomes (success, failure, relapse) measured by smear positivity

Elderly patients:
- More likely to be smear positive (56% vs 47.4%; P<0.001)
- More likely to report adverse events (24.0 vs 13.1; p<0.001)
- More likely to default (9.9% vs 6.5%; p=0.002)
- More likely to die (all-cause) during treatment (7.6% vs 1.5%; p<0.001)

U.S.

Retrospective cohort study
- National TB Surveillance System Data 1993-2006
- N=250,784 (<65 compared to ≥ 65 years)

Elderly were:
- Less likely to have a positive TST (68% vs 82%; p<0.001)
- Less likely to have cavitary disease (18% vs 28%; p<0.001)
- More likely to die (all cause) during therapy (21% vs 7%; p<0.001)
Background/Methods

Retrospective Cohort Study of cases seen in King County, WA (population ~2.2 million) over a 5-year period (2009-2014)

- Incidence of TB in King County is 7.0 per 100,000
- Pulmonary cases only
- Excluded: MDR and patients dead at diagnosis
- Categorical comparisons of outcomes [(completion, failure, relapse and adverse events due to TB drug (treatment interruption)]
  - Age <65 years vs ≥ 65 years
  - Age <75 years vs ≥ 75 years for adverse events only
- PZA started based on provider discretion in patients ≥ 75 years
Elderly more likely to be Asian (79 vs 51%) and have multiple co-morbidities (46 vs 25%)

Elderly less likely to have a cavity on chest X-ray (14 vs 24%).
Elderly more likely to die (all-cause) during therapy (19 vs 2%)
Elderly >75 yrs more likely to require >12 months of treatment (25 vs 8%)
Elderly more likely to have treatment interruption due to a TB medication adverse event (32 vs 7%) (liver injury, hypersensitivity, musculoskeletal, GI intolerance). PZA accounted for ~50% of adverse events, followed by RIF, INH, EMB.

**Table 3. Characteristics of Adverse Reactions Related to Tuberculosis Medication by Different Age Groups Among the Abstracted Population**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>18-44 Years (n = 51)</th>
<th>45-64 Years (n = 38)</th>
<th>65-74 Years (n = 54)</th>
<th>&gt;75 Years (n = 67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reactions**</td>
<td>17</td>
<td>12</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>Adverse reactions related to TB medications**</td>
<td>12</td>
<td>9</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Multiple adverse reactions**</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Magnitude of adverse reaction</td>
<td>Moderate</td>
<td>11 (21.7)</td>
<td>8 (21.1)</td>
<td>11 (20.8)</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>Type of first adverse event</td>
<td>Gastrointestinal intolerance</td>
<td>2 (3.9)</td>
<td>0 (0.0)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity</td>
<td>4 (3.3)</td>
<td>2 (5.3)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td></td>
<td>Liver injury</td>
<td>4 (3.3)</td>
<td>1 (11.1)</td>
<td>6 (11.1)</td>
</tr>
<tr>
<td></td>
<td>Musculoskeletal</td>
<td>0 (0.0)</td>
<td>3 (3.3)</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td></td>
<td>Other*</td>
<td>1 (1.9)</td>
<td>2 (5.3)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td></td>
<td>Multiple</td>
<td>1 (1.9)</td>
<td>1 (11.1)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Drug responsible for first medication held</td>
<td>EMB</td>
<td>0 (0.0)</td>
<td>1 (11.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td></td>
<td>INH</td>
<td>1 (1.9)</td>
<td>0 (0.0)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>10 (16.3)</td>
<td>5 (13.2)</td>
<td>8 (15.1)</td>
</tr>
<tr>
<td></td>
<td>Rif</td>
<td>0 (0.0)</td>
<td>2 (5.3)</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td></td>
<td>Other TB drug</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Drug level of toxicity</td>
<td>Confirmed</td>
<td>0 (0.0)</td>
<td>1 (11.1)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>12 (100)</td>
<td>8 (21.1)</td>
<td>13 (24.1)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) unless otherwise indicated. N = 205.
* Abbreviations: EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide.
**P < .05 comparing those aged ≥65 y with those aged 18-64 y.
***P < .05 comparing those aged ≥75 y with those aged 18–64 y.
* Other includes acute, drug interaction, neurologic, hematologic...

**Figure 1.** Kaplan–Meier curve depicting time to last adverse event by age categories (18–44, 45–64, 65–74, and ≥75 years). Abbreviation: TB, tuberculosis.

Elderly >75 years more likely to have multiple and late adverse events (P < 0.02)
Limitations

• Retrospective review
• Not all patients over 75 years of age systematically started on PZA: non-random assignment based on clinician judgment
• Inter-clinician variability on definition of an adverse event; adverse events due to TB drugs did not assess whether medications held due to medication or “overall condition of the patient”
• Cause of death not reviewed

Conclusions (Narita et al)

Elderly patients ≥65 years:
• More likely to have co-morbid illness (DM, ESRD, immunosuppression)
• Less likely to have cavity on chest radiograph
• More likely to have adverse events due to TB meds (PZA>RIF>INH>EMB)
• Less likely to complete TB treatment, because
• More likely to die during treatment (all-cause)

Additionally, elderly patients ≥75 years:
• Require 12 months or more to complete treatment (regardless of whether PZA used or not)
• Trend toward decreased sputum smear positivity and culture positivity
San Francisco TB Cases: 2018

- Incidence rate of 13.2 per 100,000 (n=118)
- Non-US Born: 86%; >80% have been in US over 5 years
- Most common countries of origin outside of the US: China, Philippines, Vietnam
- Median age: 64 years (range 3-95)
- 49% were ≥65 years of age
- The median age of TB cases in San Francisco is increasing.

San Francisco Data (2016-17)

N=201

Elderly ≥65 years (n=75):
- Asian predominance (92% vs 70%; p <0.001)
- **More likely to have co-morbidities (93 vs 48%; p <0.00001)**, including diabetes (34.7 vs 19%), chronic lung disease (28 vs 4%), chronic heart disease (17.4 vs 1.6%), immunosuppression (22.7 vs 8%), and dementia (13.4 vs 3.2%)
- Less likely to have HIV, ETOH or drug use
San Francisco Data (2016-17)

Elderly ≥65 years (n=75)
• For pulmonary cases:
  – No difference in proportion that were smear positive, GeneXp positive, culture positive or time to culture conversion
  – Elderly much less likely to have cavitary disease on chest X-ray (14.7 vs 36.9%; p<0.05)
• No difference in proportion with adverse events necessitating drug cessation, but trend toward increased intolerance to PZA (28 vs 16.8%; p=0.05)
• Elderly less likely to receive 60 doses of PZA (56 vs 74.6%; p<0.01)

<table>
<thead>
<tr>
<th></th>
<th>Total (n=201)</th>
<th>&lt;65 years (n=126)</th>
<th>≥65 years (n=75)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>22 (11)</td>
<td>2 (1.6)</td>
<td>20 (26.7)</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>TB related</td>
<td>10 (5)</td>
<td>1 (&lt;1)</td>
<td>10 (13.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>268/246</td>
<td>259/235</td>
<td>290/273</td>
<td>0.063</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Elderly more likely to die due to TB disease while on treatment (13.4 vs <1%)
Median duration of treatment in elderly is longer than younger patients (approaches significance)
Conclusions

• As our general population in the US ages, TB in the elderly is becoming more common.

• Difficult to recognize and diagnose:
  – Less likely to be part of a cluster/outbreak; more likely reactivation
  – In the setting of co-morbid illness (DM, chronic lung, cardiac or kidney disease, malignancy), symptoms can be non-specific and difficult to recognize
    • Weight loss often leads to malignancy workup first
    • Dementia can be unrecognized, and may affect report of symptoms
    • NTM infection in the setting if chronic lung disease can confuse diagnosis
  – TB testing (TST, IGRA) may have a lower predictive value due to waning immunity (T cell)
  – Less likely to have cavitary disease (why)

Conclusions

• Treatment of TB in the elderly is difficult due to increased likelihood of adverse events (hepatotoxicity, rash, GI distress, polyarthralgias) and interactions with other medications (e.g. anti-hypertensives, anticoagulants, chemotherapies). Dementia can make it challenging to monitor treatment response and adherence. This may all contribute to longer duration of treatment.

• The elderly may be more likely to die due to TB disease.

• We need more data:
  - Better study of TB drugs, including second line agents, for use in the elderly (e.g., many agents are QT prolonging, or cause adverse events difficult for the elderly to tolerate (joint pain/arthritis, neuropathies, cytopenias, altered mental status, nausea)
  - Associated costs and resources, including catastrophic costs to family/support networks and management of psychosocial issues
Questions/Discussion
Increased Hepatotoxicity in the Elderly

Meta-analysis of 38 studies (40,034 participants; 1208 cases of hepatotoxicity)

- Comparing <60 compared to ≥ 60 years
- Risk of hepatotoxicity (defined as elevated LFTS >2–5 times the upper reference level and/or symptoms of hepatitis)

Results:
- For active TB, odds ratio of 1.32 (95% CI: 1.04–1.68).
- For LTBI (mostly INH monotherapy, odds ratio of 4.14 (95% CI: 2.21 –7.74).

Conclusions: Recommend enhanced monitoring for hepatotoxicity in patients ≥60 who are undergoing treatment for either latent or active TB.

- Careful review of the medical record to minimize other co-morbidities, choose effective, yet potentially more “liver sparing” drug regimens to reduce toxicity as much as possible, and more frequent symptom and biochemical monitoring (e.g., every two weeks symptom and liver function monitoring)

Increased Hepatotoxicity in the Elderly

- N=926, all on active TB treatment in Taiwan
- Hepatotoxicity defined by symptomatic elevation of liver transaminases $\geq$3 times the upper limit of normal, or $\geq$5 times if asymptomatic
- 12.0% developed hepatotoxicity after a median 38 days; PZA most likely culprit
- Age $>67.5$ years associated with increased incidence, earlier onset of hepatotoxicity