REFUGEE CASE REVIEW: Parasites and TB

“There is no greater sorrow on earth than the loss of one’s native land.”
—Euripides, 431 B.C.

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Dartmouth, Assoc Professor, ID Section
Consultant for Foundation for Innovative Diagnostics
Refugees and Infectious Diseases

- Refugees resettling in the US have a significant burden of infectious diseases.
  - Exposures in their countries of origin.
  - Circumstances of their migration.
- Overseas screening is required, but it is incomplete.
- US health assessment should test for tuberculosis, hepatitis B, intestinal/other parasites and update immunizations.
  - +/- Malaria screening.
- Testing for hepatitis C, HIV, STIs is performed on the basis of clinical signs and symptoms.
Guidelines for Refugees

• Protocol for medical screening of newly arrived refugees was published by the Office of Refugee Resettlement in 1995.

This protocol serves as an instrument to guide state and local programs in developing screening programs.

Immigrant and Refugee Health

Guidelines for the U.S. Domestic Medical Examination for Newly Arriving Refugees

The following guidelines were developed by CDC to assist State public health departments and medical professionals/clinicians in determining the best tests to perform based on evidence during routine post-arrival medical screening of refugees. These guidelines are intended as recommendations rather than as mandates.

On this Page
- Checklist and Guidelines for Medical Screening
- Information on Presumptive Therapy Received
- Development of the Guidelines

Checklist and Disease-Specific Guidelines for Medical Screening

Domestic Medical Screening Checklist
This checklist has been developed to summarize the guidelines. For more details about any specific task, click the links within the text to read specific sections of the complete guidelines.

Full Text of All Domestic Guidelines
Currently 12 guidelines are available.

- General Guidelines
- Guidelines for the History and Physical
- HIV Infection Screening Guidelines
- Immunizations Guidelines
- Intestinal Parasite Guidelines
- Lead Screening Guidelines
- Malaria Guidelines
- Mental Health Screening Guidelines
- Nutrition and Growth Guidelines
- Sexually Transmitted Disease Guidelines
- Mental Health Screening Guidelines
Outline

- Parasites
  - Initial screening
  - Evaluation
  - Case-based problems: worms, diarrhea, malaria
- Tuberculosis (TB)
  - Epidemiology update
    - Drug resistance
  - Refugee relevance
  - Case-based common scenarios: IGRAs, nontuberculous mycobacteria, drug resistance
Parasitic Diseases

- Caused by worms, protozoa or arthropods
- To screen newly-arrived refugees, there are state and federal guidelines
- To evaluate an ill patient from the tropics, you need to understand
  - Epidemiology
  - Parasite life cycles
  - Patient’s risk factors
SCREENING NEWLY-ARRIVED REFUGEES FOR
PARASITIC DISEASES
Intestinal Parasites are Common in Refugees

• Intestinal parasites identified from all refugee groups, with prevalence
  – 22% of 2,545 refugees to Minnesota during 1999
  – 56% of 1,254 African refugees screened in Massachusetts during 1995–2001
  – 22% of 252 refugees from Eastern Europe (including Bosnia, Russia, and Macedonia)

• Program of predeparture treatment with albendazole in certain refugees began 1997
Screening for Intestinal Parasites

- Evaluate using algorithm even if asymptomatic
- CBC with differential to assess eosinophilia
  - Recheck in 3-6 mos if elevated
- Confirm pre-departure treatments
  - If no pre-departure treatment: stool exams even if asymptomatic, serologies and CBC+diff
  - If albendazole only → strongyloides serology & schistosoma serology (if from SSA)
  - If albendazole + praziquantel → strongyloides serology only
Screening: No Predeparture Tx

- Stool ova and parasites examination x 2
  - CBC with differential
  - Serology for strongyloides (all refugees)
  - Serology for schistosomiasis (refugees from sub-Saharan Africa)

5. Treat positive potentially pathogenic parasites in stool sample and/or serologies (Table 2)

- Eosinophilia

If Yes:
- Re-check total eosinophil count in 3-6 months
- If Eosinophilia is Yes:
  - Further evaluation of etiology of eosinophilia

If No:
- Further evaluation only if symptomatic
Screening: Predeparture Albendazole

*CBC with differential
*Serology for strongyloides (all refugees)
*Serology for schistosomiasis if did not receive praziquantel (refugees from sub-Saharan Africa)

5. Treat if serologies positive for either strongyloides or schistosomiasis (Table 2)

4. Eosinophilia

Yes

Re-check total eosinophil count in 3-6 months

4. Eosinophilia

Yes

Further evaluation of etiology of absolute eosinophilia

No

Further evaluation only if symptomatic

No
Screening: Predeparture Albendazole and Praziquantel

- CBC with differential

  - Eosinophilia
    - Yes: Re-check total eosinophil count in 3-6 months
      - Eosinophilia
        - Yes: Further evaluation of etiology of eosinophilia
        - No: Further evaluation only if symptomatic
    - No: Further evaluation only if symptomatic
### Causes of Eosinophilia in Refugee

Table 3. Causes of eosinophilia

<table>
<thead>
<tr>
<th>Parasites that cause eosinophilia commonly found in stool examination</th>
<th>Parasites commonly found in the stool NOT typically associated with eosinophilia</th>
<th>Common non-parasitic causes of eosinophilia</th>
<th>Tropical infections NOT associated with eosinophilia</th>
<th>Other tropical infections commonly associated with eosinophilia but less likely to be found in stool specimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascaris lumbricoides</td>
<td>Entameoba histolytica, Entameoba dispar, other Entamoeba spp.</td>
<td>Asthma</td>
<td>Arboviral infections</td>
<td>Angiostrongylus</td>
</tr>
<tr>
<td>Hookworm (Ancylostoma spp, Necator spp)</td>
<td>Cryptosporidium spp.</td>
<td>Atopy</td>
<td>Brucellosis</td>
<td>Anasaciasis</td>
</tr>
<tr>
<td>Trichuris trichiura</td>
<td>Giardia intestinalis (lambia)</td>
<td>Drug allergy</td>
<td>Enteric fever</td>
<td>Capillaria spp.</td>
</tr>
<tr>
<td>Strongyloides stercoralis*</td>
<td>Hodgkin’s lymphoma</td>
<td>Eosinophilic leukemia</td>
<td>Leishmaniasis</td>
<td>Cysticercosis (Taenia solium)</td>
</tr>
<tr>
<td>Tapeworm (Taenia solium and T. saginatum)</td>
<td>Hyper-eosinophilic syndrome</td>
<td>Pemphigoid</td>
<td>Leprosy</td>
<td>Echinococcus spp.</td>
</tr>
<tr>
<td>Ophisthorchis spp.</td>
<td>Pemphigus</td>
<td>Malaria</td>
<td>Trypanosomiasis</td>
<td>Fasciola spp.</td>
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<tr>
<td>Fasciola spp.</td>
<td>Polyarteritis nodosa</td>
<td>Tuberculosis</td>
<td></td>
<td>Filariasis (Wuchereria bancrofti, Brugia spp, Mansonella spp, Onchocerca volvulus, Dracunculus medinensis. Loa loa)</td>
</tr>
<tr>
<td>Schistosoma (S. mansoni*, S. haematobium*, S. japonicum)</td>
<td></td>
<td></td>
<td></td>
<td>Gnathostoma spp.</td>
</tr>
<tr>
<td>Toxocara spp.</td>
<td></td>
<td></td>
<td></td>
<td>Paragonimus spp.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Schistosoma (S. mansoni*, S. haematobium*, S. japonicum) *</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Strongyloides stercoralis*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Toxocara spp. Trichinella spiralis</td>
</tr>
</tbody>
</table>
CARING FOR ILL REFUGEE PATIENT

PARASITIC DISEASES
Epidemiology Integral to Differential Diagnosis

Table 1: Predominant intestinal parasites in specific populations

<table>
<thead>
<tr>
<th>Global</th>
<th>Middle East*</th>
<th>Eastern Europe*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascaris lumbricoides</td>
<td></td>
<td>Diphyllobothrium latum</td>
</tr>
<tr>
<td>Trichuris trichiura</td>
<td></td>
<td>Opisthorchis felineus</td>
</tr>
<tr>
<td>Hookworm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strongyloides stercoralis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobius vermicularis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasciola</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hymenolepis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most protozoa, especially <em>Giardia intestinalis</em> (lamblia)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Organisms either unique to or highly prevalent in the specified region.
Worms

- Roundworms
  - Intestinal Roundworms
  - Tissue Roundworms
- Flatworms
  - Tapeworms
  - Flukes

Containers for Ova & Parasite examination
Roundworms

- Simple tubular structure
  - Outer impermeable cuticle
  - Inner structures:
    - Intestines
    - Gonads
- Adults either
  - Lay eggs
  - Release larvae
- Do not multiply in host
  - *S. stercoralis* is exception
Lifecycles of Intestinal Nematodes are Simple and Suggest Prognosis

- Transmitted to humans by
  - Ingestion of soil contaminated with eggs
  - Penetration of skin with infective larvae
- Rarely associated with disease after migration
- Most pathology related to parasite load, which decreases rapidly after migration
  - *S. stercoralis* is exception, because of autoinfective cycle and long-lived adults
Initial Health Screen for Family From Dem Rep of Congo

- Refugee family of 7 seeing you for initial screen
  - Received pre-departure albendazole
  - Complex catch-up immunizations
  - Embarrassed concern of anal itching
- Family well, afebrile
- Labs normal
- Perianal exam
  - Slight erythema
  - One child shows:
What is this (and why did this happen in spite of having received albendazole)?
Enterobiasis (Pinworm)

- Infection common worldwide: ~30% of children, 15% of adults are infected
- Causes perianal itching
  - Rare complications
    - e.g., pinworm neurosis
- Eggs remain infectious 2 weeks in environment
  - Eradicating eggs in home difficult
  - Reinfection is common
- Need to coordinate repeated treatments
1. Embryonated eggs ingested by human

2. Eggs on perianal folds
   Larvae inside the eggs mature within 4 to 6 hours.

3. Larvae hatch in small intestine

4. Adults in lumen of cecum

5. Gravid female migrates to perianal region at night to lay eggs

△ = Infective Stage
△ = Diagnostic Stage

http://www.dpd.cdc.gov/dpdx
Another Worm!

- Mother newly arrived from Burma calls you concerned that her 5 year old son has passed a worm
  - Received albendazole
  - Child well
What is this?
Ascaris lumbricoides

Lumbricus terrestris
(earthworm)

Ascaris
Aberrant Ascaris Migration
Vietnamese Immigrant with Cough

- 62yo Vietnamese man with dry cough and bloody sputum several months
- PMH: 6 yrs as farmer in reeducation camp in North Vietnam
  - Arrived in US <1 year before with h/o blood per rectum and eosinophilia
    - No diagnosis reached
- PE: afebrile, mild wheezing, no rash
- CXR parenchymal opacity at right base
- Labs show anemia and eosinophilia 1,870 per mm$^3$
What is this?
Hookworms

*Necator americanus*
New world
*Ancylostoma duodenale*
Old world
Ancylostoma
(Old World Hookworm)

• Symptoms according to events of lifecycle:
  • Dermatitis when larvae penetrate skin
  • Cough, wheezing and pulmonary infiltrates when larvae pass from tissues through lungs
  • GI discomfort when larvae are coughed up, swallowed and become adults in small intestine, where they attach and suck blood
  • Eosinophilia, iron deficient anemia
  • Single dose albendazole or 3 days mebendazole
Hookworm Prevalence

From WHO
Febrile III Returning Traveler

• Former refugee from Liberia through Cote d’Ivoire sees you for fatigue, low grade temps
  – Arrived 6 months before
  – Not sure if received malaria pre-departure prophylaxis
• PMH ‘malaria’, known TST positive, got usual childhood vaccines (??)
• PE 100°, 110bpm, 110/70, unwell appearing, ?scleral icterus, pale, ?spleen
• Labs normal WBC, low platelets and hgb (7.4), high INR, creatinine, AST/ALT and bilirubin
In this patient, this illness is:

1. Not likely malaria because he has baseline malaria immunity and may have received pre-departure prophylaxis
2. Not likely malaria because incubation is too long
3. Less likely malaria and more likely dengue because his platelets are low
4. Is potentially an emergency = complicated malaria and needs iv antimalarials

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<table>
<thead>
<tr>
<th>Region</th>
<th>Presumptive Pre-departure Treatment</th>
<th>Malaria Regimen [ACT]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MMR Vaccine *</td>
<td>Intestinal Parasites†</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td></td>
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<tr>
<td>Nairobi</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Kakuma</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Dadaab</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Tanzania</td>
<td></td>
<td></td>
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<tr>
<td>Ethiopia</td>
<td></td>
<td></td>
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<tr>
<td>Addis Ababa</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Shimelba</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Malaria

- Five species: *falciparum, vivax, ovale, malariae, knowlesi*
- 3rd leading cause of death in world
  - 1500 cases/yr in US with foreign-born overrepresented
- Fever, headache, endorgan damage:
  - CNS, lungs, kidney, liver
- Labs reflect hemolysis, low platelets, renal and hepatic abnormalities
  - Normal WBC, including CSF
  - Slight coagulation abnormalities
Dengue

- Short incubation
- Rash usual
- Myalgias severe
- Low WBC
- Low platelets
- Elevated LFTs
- RARE hemorrhagic complications

Malaria

- Med-long incubation
- Rash unusual
- Myalgias uncommon
- Normal WBC
- Low platelets
- Elevated LFTs
- Evidence of hemolysis, including anemia
Malaria in Refugees

• Refugees may arrive in US with asymptomatic or sub-clinical malaria
  – 1997-9: 60% of Liberian refugees from 4 asylum countries in West Africa were parasitemic 4w after arrival
  – 18% of refugees from Tanzania

• Infected but asymptomatic refugees may develop clinical malaria
  – Average ~3 months after arrival
Preventing Malaria in Refugees

• Lack of knowledge of malaria among US clinicians may lead to delay in diagnosis and inappropriate treatment
• May 1999: CDC recommended refugees from malaria endemic areas in sub-Saharan Africa receive presumptive therapy for malaria
• Artemisinin-based combo therapy (ACT)
  – If not, presumptive treatment on arrival (preferred) or have laboratory screening
Detecting Malaria in Refugees

• **Who** should be evaluated for malaria?
  – Any symptomatic or anemic refugee from malaria endemic setting
  – Any asymptomatic refugee from malaria epidemic setting

• **How** should they be evaluated?
  – For symptomatic refugees, test using
    • 3 thick and thin blood smears
    • Rapid antigen test
  – For asymptomatic refugees, PCR more sensitive and is test of choice
WHO Management of Severe Malaria
http://mosquito.who.int/docs/hbsm_toc.htm

CDC Malaria Consultation
770-488-7788
Fever and Cough in Bhutanese Refugee

• 31yo refugee from Bhutan through Nepal 5 years ago evaluated for
  – One month fever and productive cough
  – Reports concurrent exacerbation of his baseline “irritable bowel syndrome” characterized by loose stool

• PMH
  – Treated LTBI
  – Episodic asthma with recent exacerbation started on steroids 1mo before
  – Prone to hives
Fulminant Course

- Febrile, hypotensive, rapid respiratory decompensation in ED
- Rash noted
- Labs remarkable for 12% eosinophilia
- Mixed GNRs
  - Sputum GS and culture
  - Blood culture
- Expires
Diffuse, bilateral, patchy infiltrates
What is this?
**Strongyloides Stercoralis**

- Worldwide nematode
- Refugee populations have very high prevalence rates, with more than 40% of certain populations having serologic evidence of strongyloides infection
Strongyloides Lifecycles

1. Eggs are produced by fertilized female worms.
2. Development into free-living adult worms.
3. Rhabditiform larvae hatch from embryonated eggs.
5. The rhabditiform larvae develop into infective filariform.
6. Infective filariform larvae penetrate the intact skin initiating the infection.
7. The filariform larvae enter the circulatory system, are transported to the lungs, and penetrate the alveolar spaces. They are carried to the trachea and pharynx, swallowed, and reach the small intestine where they become adults.
8. Adult female worm in the intestine.
9. Eggs deposited in intestinal mucosa, hatch, and migrate to lumen.
10. Autoinfection: Rhabditiform larvae in large intestine, become filariform larvae, penetrate intestinal mucosa or perianal skin, and follow the normal infective cycle.
Strongyloidoses Hyperinfection

- Lifecycle markedly accelerates under some conditions
  - Esp associated with high dose steroids
- Symptoms related to
  - Invasion: itchy rash
  - Migration: Loeffler syndrome through lungs and serpiginous urticaria
  - Intestinal penetration: N/V/D/abd pain
- Eosinophilia in 40-80% of patients
- Complicated by gram negative meningitis and sepsis
Diagnosis and Treatment

- **Diagnosis by**
  - Stool microscopy
  - Sputum microscopy
  - Serology
  - Stool ELISA for antigen

- **Treatment**
  - Thiabendazole 25 mg/kg 7 days
  - Ivermectin 200 mcg/kg once
  - Albendazole 400 mg po bid 3 days
Prolonged Diarrhea in a Former Sudanese Refugee

• 53M evaluated for diarrhea
  – From Sudan in 2003 with diarrhea
  – On arrival,
    • Screened negative for strongyloides and schistosomiasis
    • Treated empirically with albendazole and metronidazole
  – Improved but never completely resolved
• Symptoms are mild cramping, soft stool, embarrassing gas, no fever or weight loss
How do you manage this?
Diarrhea: Acute vs Persistent

• Acute causes identified in ~50%
  – Campylobacter, Enterotoxigenic E. coli, Shigella, Salmonella, Vibrio, Pleisiomonas, Aeromonas, viruses
• Persistent (>2 wks) more challenging
• 3% of those with acute diarrhea have symptoms >4 weeks
  – Protozoans: Giardia, E. histolytica
  – Bacteria: C. difficile, bacterial overgrowth
  – Parasites: strongyloidies, schistosomiasis
  – Noninfectious such as inflammatory or irritable bowel syndromes
Persistent Diarrhea Management

• Empiric metronidazole (not antibiotic)
• Empiric trimethoprim sulfamethoxazole
  – For coccidian pathogens
• O+P, special stains for coccidians
• Endoscopic evaluation?
• Use Manning or Rome criteria for irritable bowel syndrome (IBS)
  – Reassurance and symptomatic mgt
Itchy Foot Rash

• 14F had this intensely itchy rash on initial health evaluation
What is this?
Cutaneous Larva Migrans

Dog and Cat Hookworm
Migrates up to a centimeter a day, leaving an itchy painful track.
TUBERCULOSIS
Human → Human
TB: Major Cause of Suffering and Death

- First human case 3400 BC
- Consumption, White Plague, scrofula, King’s Evil, pthisis
- England 1815: 1 in 4 deaths
- France 1918: 1 in 6 deaths
- During 20thC, TB killed ~100 million
- In 2009, estimated 9.4 million incident cases, and 1.68 million deaths
TB Changed Course of Human History

• Bronte Family
• Cardinal Richelieu
• Katherine Mansfield
• Luigi Boccherini
• Amedeo Modigliani
• Sir Walter Scott
• Franz Kafka
• Fyodor Dostoyevsky
• Eleanor Roosevelt
• Jimmie Rogers
• Robert Louis Stevenson

• Anton Chekov
• Doc Holiday
• Igor Stravinsky
• D H Lawrence
• Eugene O’Neill
• Johann von Goethe
• Freidrich Schiller
• Tom Fogerty
• George Orwell
• Christy Mathewson
• Gavrilo Princip
“It was the fashion to suffer from the lungs; everybody was consumptive, poets especially; it was good form to spit blood after each emotion and to die before the age of thirty.”

Alexander Dumas (1802-1870)
“I look pale . . . I should like to die of consumption – because the ladies would say ‘Look at poor Byron, how interesting he looks in dying’.”

Lord Byron (1788-1824)
In 2011, ~8.7 million new cases
- India+China 40%, Africa 24%
- 13% co-infected with HIV

1.4 million people died from TB
- 430,000 among HIV-positive

15% of TB is in children

Multi-drug resistant (MDR)* TB
- 3.7% among new cases
- 20% among previously treated
- 9% of MDR is XDRTB*

*MDR is resistance to H+R;
XDR is MDR+resistance to FQ+injectable
Number of TB Cases in USB vs. FB Persons

No. of Cases

1993 1995 1997 1999 2001 2003 2005 2007 2009

U.S.-born Foreign-born
Trends in TB Cases in FB Persons in US

In NH, 87% over 10 years
Countries of Birth of FB Persons Reported with TB

- Mexico (23%)
- Philippines (12%)
- India (8%)
- Vietnam (8%)
- China (5%)
- Guatemala (3%)
- Haiti (3%)
- Other Countries (38%)
310,000 MDR TB cases annually
60% in India, China, Russian Federation
1 in 10 TB patients in China has MDR
Primary MDR TB in USB vs FB Persons
US 1993–2009*

MDR TB has decreased in FB and USB, but more in USB
1993–2009, proportion of primary MDR TB in FB increased
from 25% to 88% of US MDR cases.

*Updated as of July 1, 2010.
Note: Based on initial isolates from persons with no prior history of TB.
MDR TB defined as resistance to at least isoniazid and rifampin.
TB Among Refugees

- Estimated TB rate among refugees in DeKalb County, GA 1995-99
  - 83/100,000 for refugees
  - 12/100,000 for US-born
- 1997-99 TB risk among refugees
  - 7x higher than US-born
  - 2x higher than other non-US-born
- High rates despite overseas screening therefore screen in US

Hadzibegovic et al, Int J TB & Lung Dis, 2005
Overseas Screening for TB in US-Bound Immigrants and Refugees

• In 378,506 US-bound refugees 1999-2005
  – 3,923 had smear-negative TB (1,036/100,000)
  – 10,743 had inactive TB (2,838/100,000)
• After US arrival, active TB diagnosed in
  – 7% of those with “smear-negative TB”
  – 1.6% of those with “inactive TB”
• Follow up evaluation after arrival in US is high-yield intervention to identify active TB
• Since 2007, overseas culture and DST now required if suspect TB

Liu et al, NEJM, June 2009
SCREENING NEWLY-ARRIVED REFUGEES FOR TUBERCULOSIS
## TB Classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Chest radiograph</th>
<th>Sputum Smear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A (TB infectious, “non-</td>
<td>Abnormal, suggestive of active pulmonary TB</td>
<td>Positive for acid-fast bacilli initially. When</td>
</tr>
<tr>
<td>communicable for travel purposes”)</td>
<td></td>
<td>negative they are cleared for travel.</td>
</tr>
<tr>
<td>This person should be currently on</td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class B1 (TB, clinically active, not</td>
<td>Abnormal, suggestive of active pulmonary TB</td>
<td>Negative for acid-fast bacilli.</td>
</tr>
<tr>
<td>infectious)</td>
<td></td>
<td>TB, clinically active, not infectious.</td>
</tr>
<tr>
<td>This person might be on anti-TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>medications.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons with radiographic or other</td>
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<td></td>
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<tr>
<td>evidence of extra-pulmonary TB,</td>
<td></td>
<td></td>
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<tr>
<td>clinically active, also are classified</td>
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<tr>
<td>as B1</td>
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</tr>
<tr>
<td>Class B2 (TB, not clinically</td>
<td>Abnormal, suggestive of pulmonary TB, not clinically</td>
<td>Not required</td>
</tr>
<tr>
<td>active)</td>
<td>active</td>
<td></td>
</tr>
<tr>
<td>This person may be on or recently</td>
<td></td>
<td></td>
</tr>
<tr>
<td>finished anti-TB medications when</td>
<td></td>
<td></td>
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<tr>
<td>entering the U.S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class B3 (Consistent with TB, old or</td>
<td>Abnormal, only because calcified hilar lymph node, a</td>
<td>Not required</td>
</tr>
<tr>
<td>healed)</td>
<td>calcified primary complex, or a calcified granuloma</td>
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<tr>
<td>Other chest condition (B)</td>
<td>Abnormal, not consistent with TB</td>
<td>Not required</td>
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</tbody>
</table>
Initial US Health Assessment for TB

- Refugees ≥6 weeks should have tuberculin skin test (5 TU PPD, read at 48–72 h)
- Results should be recorded as mm of induration, perpendicular to long axis of arm
- ≥10 mm is positive result for most refugees
  - ≥5 mm is considered positive for refugees who
    - Known contact with active TB
    - Abnormal chest radiograph finding
    - With signs or symptoms suggestive of TB
    - Immunocompromised
TB Screening Miscellaneous

- Exempt from screening if h/o prior positive skin test or prior TB
- BCG vaccination *not* a contraindication:
  - Disregard BCG history when reading TST
- Refugees with LTBI are candidates for treatment
- LTBI and active TB are reportable in NH
- Consider country of origin and risk for drug resistant TB
COMMON SCENARIOS AMONG REFUGEES RE: TUBERCULOSIS
Case 1: Refugee with Abnormal CXR

- 51W referred to your outpatient clinic for evaluation for active TB
- She immigrated from Dukwe, Botswana, 1 mo ago
  - No symptoms of TB
  - No h/o of TB or significant PMH
- TST 13 mm (no previous TST)
- Abnormal CXR
Right upper lobe fibronodular opacities with volume loss and hilar retraction. Right apical pleural thickening.
Will an IGRA help you diagnose TB?
Sensitivity of IGRAs in Active TB: Independent Studies

- Pooled study data
  - QFT-G 55-88% (weighted pooled mean 75%), TST 77%\(^1\), TSpot 83-97%, QFT-G 70-89%\(^2\)
- Comparison TSpot vs QFT-G in S. Korea\(^3\)
  - TSpot 96.6%, QFT-G 70.1%, TST 66.7%
- Conclusion: IGRAs should not be used to exclude active TB
  - Sensitivity in question for extra-pulmonary TB\(^4\)

IGRAs are NOT for Diagnosis of Active TB

- CDC: IGRAs “cannot differentiate infection associated with TB disease from LTBI”
- If positive: no surprise and still can’t conclude has active TB
  - Botswana TB rate >600/100,000
- If negative: doubt sensitivity of IGRA test
- Need specimens for smear and culture for TB diagnosis
Patient’s Course

• Induced three sputa:
  – AFB smears negative

• At 8 weeks:
  – Mycobacterial cultures negative
  – Remained asymptomatic
  – CXR unchanged

• How would you treat this?
LTBI in Refugee With Evidence of Past TB

- Old fibrotic lesions can represent previous TB
  - High risk for development of TB
  - Should be treated for LTBI
- Calcified solitary pulmonary nodules, calcified hilar lymph nodes, and apical pleural capping represent healed primary M. tuberculosis infection
  - Same risk and treatment as with normal CXR
- Treatment options
  - INH 9 months
  - Rifampin 4 months
  - Rifapentine + INH weekly x 3 months (12 doses)
Dukwe Refugee with Cough and Abnormal CXR

• 31W outpatient who (was born in and) immigrated from Dukwe, Botswana, 1 mo ago
  – Symptoms of TB: dry cough and weight loss
  – No h/o of TB or significant PMH
• TST 13 mm (no previous TST)
• Abnormal CXR
Parenchymal consolidation in right lower lobe with loculated right-sided effusion
Patient’s Course (1)

• Induced three sputa
• All three are scant positive, culture pending

• Would you start this patient on INH, RIF, EMB, PZA?
Pulmonary pathogens
- TB
- Nontuberculous mycobacteria (e.g., MAC)
- Nocardia species
- Actinomycoses

Some gi parasites are weakly acid fast, so modified acid fast stain (sulfuric acid instead of acid alcohol)
- Cryptosporidium oocysts
- Sarcocystis spp
- Isospora belli
Empiric TB Treatment

• Decision to initiate empiric 4-drugs therapy based on
  – Epidemiology
  – Signs compatible with TB
  – AFB smear status
  – Seriously ill (e.g., miliary TB)
  – High risk of transmission
• Most of world uses empiric or smear-only diagnosis to initiate treatment
Patient’s Course (2)

- Started on INH, RIF, EMB, and PZA
- Within 1-2 weeks, cough worse, fevers develop, new SOB, new cervical lymphadenopathy
- Repeat CXR much worse with bilateral infiltrates and mediastinal lymphadenopathy
- What has happened?
Paradoxical Reaction

- Exacerbation of TB symptoms after beginning antiretroviral (ART) or TB therapy
  - More common among HIV-pos patients
  - In HIV-neg, especially when treat TB lymphadenitis
- Reconstitution of immune responsiveness
- Incidence uncertain
  - Narita et al\(^1\): in HIV+ patients on ART, 36% developed paradoxical worsening after beginning TB treatment compared with 7% of those not taking ARTs
  - Wendel et al\(^2\): only 7% of HIV+ TB patients developed paradoxical worsening, not associated with ART

Paradoxical Reaction: Diagnosis and Treatment

• Signs: high fevers, lymphadenopathy, expanding CNS lesions, worse pulmonary infiltrations, and increasing pleural effusions
• Diagnosis of exclusion
• Treatment*
  – Mild: symptomatic, no change in antiTB or ART
  – Severe (e.g., airway compromise from lymph nodes, effusions, sepsis): steroid taper

*CDC. Treatment of Tuberculosis, ATS, CDC, and IDSA. MMWR 2003; 52 (No. RR-11)
Immigrant from FSU with Cough and Abnormal CXR

- 71W outpatient who immigrated from rural Ivanova Oblask Russia 1 mo ago
  - Dry cough and weight loss
  - TST unknown
  - Abnormal CXR consistent with active TB
- PMH only significant for prolonged cough illness which was treated “for a long time”
- What are helpful questions toward a diagnosis of relapsed TB?
Relapsed TB?

- Was he told it was TB?
  - No.
- How many pills (any injections)? Names?
  - One but doesn’t know name.
- Did he have to go to the clinic to get everyday?
  - Maybe once a week.
- How long did he take them?
  - Months
- Did secretions turn red?
  - Doesn’t recall reddish secretions while taking
- Did he take all prescribed?
  - Thinks so.
What is the significance of “one pill for months”?
Fixed Dose Combinations (FDCs)

- WHO recommends FDCs for new TB cases
- Justification includes simplicity, improved compliance, prevention of drug resistance
- Two FDCs available for use in US
  - Combination of INH and RIF (Rifamate®)
    - 2 Rifamate® provide daily doses of INH (300 mg) and RIF (600 mg)
  - Combination of INH, RIF, and PZA (Rifater®)
    - Rifater® = INH (50 mg), RIF (120 mg), PZA (300 mg)
    - 6 Rifater® = INH (300 mg) RIF (720 mg), PZA (1,800 mg)
      - RIF dose higher than typical because RIF is less bioavailable
<table>
<thead>
<tr>
<th>Drug (abbreviation)</th>
<th>Dose form</th>
<th>Strength for daily use</th>
<th>Strength for intermittent use 3 times weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td>rifampicin + isoniazid (RH)</td>
<td>Tablet</td>
<td>150 mg + 75 mg 300 mg + 150 mg 60 mg + 30 mg</td>
<td>150 mg + 150 mg 60 mg + 60 mg</td>
</tr>
<tr>
<td></td>
<td>Tablet or pack of granules</td>
<td>60 mg + 30 mg</td>
<td></td>
</tr>
<tr>
<td>ethambutol + isoniazid (EH)</td>
<td>Tablet</td>
<td>400 mg + 150 mg</td>
<td></td>
</tr>
<tr>
<td>rifampicin + isoniazid + pyrazinamide (RHZ)</td>
<td>Tablet</td>
<td>150 mg + 75 mg + 400 mg</td>
<td>150 mg + 150 mg + 500 mg</td>
</tr>
<tr>
<td></td>
<td>Tablet or pack of granules</td>
<td>60 mg + 30 mg + 150 mg</td>
<td></td>
</tr>
<tr>
<td>rifampicin + isoniazid + pyrazinamide + ethambutol (RHZE)</td>
<td>Tablet</td>
<td>150 mg + 75 mg + 400 mg + 275 mg</td>
<td></td>
</tr>
</tbody>
</table>

*The fixed-dose combination R 150 mg + H 75 mg + E 275 mg is currently available from the Global Drug Facility. The process of including this drug combination in the WHO model list of essential medicines has been recently initiated.*

*For paediatric use.*
Patient’s Course

• Induced three sputa
• All three are 1+ positive, culture pending

• Would you start this patient on INH, RIF, EMB, PZA?
High Suspicion for TB Drug Resistance

- Previous TB as evidenced by possible use of FDC
  - Relapse due to initial drug resistance or noncompliance
- Rate of retreatment MDR TB in Ivanovo 58%
  - Even if not previous TB, primary MDR high 12.3%
- Excellent on-line source for regional and national drug resistance rates
310,000 MDR TB cases annually
60% in India, China, Russian Federation
1 in 10 TB patients in China has MDR
Drug Resistant TB

- Drug resistant TB is created by
  - Patient: Not completing treatment
  - Clinicians: Not prescribing right drugs
  - Health system: Can’t afford steady supply of drugs or sold sham drugs

- Drug resistant TB creates challenges
  - Patient: Longer, more toxic treatment
  - Clinician: Complicated regimens
  - Health system: Cost/case increased
Empiric Treatment for Relapsed TB

- In US, for patients with relapsed TB*:
  - If TB known to be initially drug-susceptible and treated by DOT
    - Standard four-drug initial phase regimen until results of susceptibility tests are known
  - If not DOT or had irregular treatment
    - Infer risk of acquired drug resistance
    - “Expanded regimen”, especially in patients with impaired immunity, limited respiratory reserve, CNS involvement, or other life-threatening circumstances

- Global: std 4 drug+1... but “never add one drug to a failing (failed?) regimen”

*CDC. Treatment of Tuberculosis, ATS, CDC, and IDSA. MMWR 2003; 52 (No. RR-11)
Empiric Expanded Regimen Possible Drug Resistant TB

• No clinical trials to guide choice of agents for empiric expanded regimens
• Expert opinion* indicates
  – INH, RIF, and PZA
  – PLUS 3 drugs
    • EMB
    • Fluoroquinolone
    • Injectable agent
      – e.g., SM, amikacin, kanamycin or capreomycin

*CDC. Treatment of Tuberculosis, ATS, CDC, and IDSA. MMWR 2003; 52 (No. RR-11)
Can you find out whether this isolate is drug resistant quickly?
**Molecular Detection of Drug Resistance (MDDR) DNA Sequencing**

- Sept 09, CDC offers DNA sequencing for id of drug resistance-associated mutations
- First, RIF and INH
- Then if resistant,  
  - Fluoroquinolone (FQ), amikacin (AMK), kanamycin (KAN), and capreomycin (CAP)
- Isolates on solid media or MGIT cultures

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mutation</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIF</td>
<td>rpoB</td>
<td>96.1</td>
<td>97</td>
</tr>
<tr>
<td>INH</td>
<td>inhA/katG</td>
<td>88.6</td>
<td>98.7</td>
</tr>
<tr>
<td>FQ</td>
<td>gyrA</td>
<td>82.2</td>
<td>97</td>
</tr>
<tr>
<td>KAN</td>
<td>rrs + eis</td>
<td>86.8</td>
<td>96.9</td>
</tr>
<tr>
<td>AMK</td>
<td>rrs</td>
<td>87.9</td>
<td>99</td>
</tr>
<tr>
<td>CAP</td>
<td>rrs + tlyA</td>
<td>44.6</td>
<td>85.9</td>
</tr>
</tbody>
</table>
MDDR Submission Criteria

- High-risk of RIF resistance or MDR-TB
  - Previously treated TB case
  - Drug resistant TB contact
  - Foreign-born from area with high rates of MDR TB
- Known RIF resistant isolates
- High profile patients
  - e.g., daycare workers, nurses
- Adverse reactions
  - e.g., patient allergic to RIF
- Mixed or non-viable cultures
- Other situations on case by case basis
Initial MDDR results in days, and final results when conventional DST results are available!
Fever, Cough, Weight Loss in Smoker From Iran

- 71 yo man from Iran admitted for SOB
  - 1 m fever especially night sweats
  - Increasingly productive cough with slight hemoptysis
  - Worrisome weight loss 20 lbs
- 50 pack-year history of smoking
  - Vague h/o COPD but no treatment
- TST 5mm on US entry
  - No known TB contact (“BCG!”)
• TST 7mm
• CT scan multiple small nodules
Your Differential Diagnosis?
Differential Dx for Pulmonary Nodules

• Malignancy
  – Metastatic solid organ malignancies
    • Usually lung bases
  – Lymphoma
  – Kaposi’s sarcoma in HIV+
• Rheumatologic and autoimmune: Wegeners
• Other: AVM, pneumoconiosis, silicosis
• Infectious
  – Bacteria: abscesses and septic emboli
  – Fungi (histoplasmosis, coccidiomycosis)
  – TB and nontuberculous mycobacteria (NTM)
Nontuberculosis Mycobacteria (NTM)

- Many mycobacterial species affect lungs: *avium, intracellulare, xenopi, abscessus, kansas*, etc.
- Distinguishing between TB and NTM aided by:
  - Epidemiology: more common in
    - Male smokers
    - Middle-aged female nonsmokers (RML)
  - Rarely radiographic features
  - Growth characteristics and biochemicals
    - Microscopic appearance
    - Genetic probes
Clinical Spectrum of MAC

- Asymptomatic infection: 30-40%
- Symptomatic disease
  - Localized cervical adenitis age 1-5
  - Disseminated disease in AIDS
  - Pulmonary disease
    - Mimics TB, but slower and less virulent
Groups at Risk for Pulmonary MAC

• Preexisting lung disease
  – Acquired bronchiectasis
  – Cigarette smokers
  – Cystic Fibrosis

• Chest wall abnormalities
  – Thin, elderly women, no previous lung disease
    • “Lady Windemere’s Syndrome”
  – Pectus excavatum
  – Scoliosis

• Hot tub users: hypersensitivity pneumonitis
Summary

- TB is a great and formidable disease
- There are many resources out there to aid management
  - ATS Guidelines
  - Drug-o-gram
  - State Health Department TB Medical Consultant
  - Regional Training and Med Consultation Ctr
- Fill out your reviews carefully
Refugee Health References

- NH DHHS:
  - [http://www.dhhs.nh.gov/omh/refugee/facts.htm](http://www.dhhs.nh.gov/omh/refugee/facts.htm)

- State of NH Guidelines for Initial Medical Screening and Care of Refugees Resettled in New Hampshire:
  - [http://128.121.25.104:8080/awweb/awarchive?item=39232&type=meta](http://128.121.25.104:8080/awweb/awarchive?item=39232&type=meta)

- CDC:
Acknowledgements

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