A Practical Approach to Using IGRAs in Diagnosing Tuberculosis

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I have no conflicts of interest

Goals:

1. Describe and apply current recommendations for the use of Interferon Gamma Release Assays (IGRAs)
2. Integrate new information concerning the use of IGRAs into varying clinical situations
3. Disseminate programmatic experiences gained from clinical implementation of IGRA with other providers

Objectives

1. List the benefits and limitations of IGRAs in patients with different TB risks
   - Suspected active TB
   - Special populations
   - High vs. low risk for TB infection
2. Describe the operational advantages and disadvantages using IGRAs
3. Explain some of the cost issues associated with expanded use of IGRAs

Limitations of the TST

1. Subjective interpretation
2. Difficult to maintain proficiency
3. Requires 2 visits
4. Affected by prior BCG vaccination
5. Limited use by primary care providers
6. Despite > 100 years of use, there is no standard way to record and retrieve results

5

Interferon-gamma Release Assays (IGRAs)

1. Blood tests for detecting TB infection
2. Requires 1 visit
3. Results retrievable electronically
4. 2 FDA approved tests:

T-SPOT. *TB*
THE EASY TB TEST. REALLY EASY.
Oxford Immunotec

QFT®
QuantiFERON-TB Gold
QIAGEN®

QuantiFERON-TB (Cellestis)

- Originally developed in Australia to test cattle for *M. bovis* infection
- Measures IFN-γ in stimulated <u>whole blood</u> relative to a nil and mitogen control
1. QFT: PPD
2. QFT-Gold: ESAT-6 and CFP-10
3. QFT-Gold in tube (QFT-GIT): ESAT-6, CFP-10 and TB 7.7

T-SPOT.TB (Oxford Immunotec)

1. Developed in England
2. Uses a modified elispot platform
3. Measures IFN-γ production from effector T-cells after <u>separated PBMCs</u> are stimulated with ESAT-6 and CFP-10
4. Approved in Europe 2004 and in the U.S. 2008
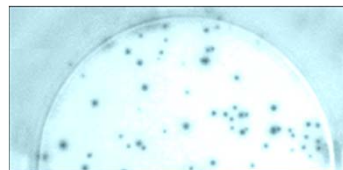
Each spot in the microtiter plate well corresponds to an individual T cell that has released interferon gamma due to challenge by TB antigens.

IGRAs –Basic similarities

- Single blood draw
- Incubate blood cells with antigens from the region of difference 1 (RD1)
  - not contained in BCG but present in *M.bovis*
  - Antigens present in *M. marinum, kansasii, szulgai, and flavescens*
- Results available in 1 day

Differences in QFT vs T-SPOT

QFT-GIT	T-SPOT.TB

QFT-GIT

- Positive ($\geq$ 0.35 IU/mL)
- Negative (< 0.35 IU/mL)
- Indeterminate
  - Low mitogen
  - High nil
- Failed
  - Inadequate blood volume
  - Broken tube
  - Delayed incubation

T-SPOT.TB

- Positive ($\geq$ 8 spots)
- Negative ($\leq$ 4 spots)
- Borderline (5-7 spots)
- Invalid
  - Low mitogen
  - High nil
- Failed
  - Inadequate blood volume
  - Broken tube
  - Delayed incubation

Indeterminate QFT

- Retrospective review; public chest clinics in NYC
- 28,864 tested → 522 (2%) indeterminate
  - 264 low mitogen (assoc. with age < 10, females, Asian, U.S. born)
  - 258 high nil (assoc. with foreign-born and Hispanic)
- Repeat test with a valid result (pos/neg) in 68%

Banach, IJTLD 2011; 15(12): 1623

New TB Diagnostics

The Problem

How do you evaluate a diagnostic test without a gold standard?

The Result

Hundreds of studies and dozens of meta-analyses

 ≠

IGRA Guidelines

33 guidelines from 25 countries
- Recommendations differ by country and patient risk

General Approaches:

1. Two step testing using TST followed by IGRA
2. IGRA only, replacing the TST
3. Both TST and IGRA
4. Either TST or IGRA, but not both (U.S.)

Denkinger, Clin Micro Infect, 2011; 17: 806

**Updated Guidelines for Using
Interferon Gamma Release Assays
to Detect *Mycobacterium tuberculosis*
Infection — United States, 2010**

IGRAs are preferred for:

1. BCG vaccinated

2. Groups with historically low return rates for TST readings

MMWR June 25,2010 Vol 59: RR-5

14

Case 1 - 52 y/o male

- Born in the Pacific Islands

- International travel in the U.S. military

- BCG as a child

- Cough for 1 month

Case 1 - 52 y/o male

- BCG-vaccinated

In addition to AFB smears and cultures, would you do
A. TST
B. IGRA
C. Both
D. Neither

Sensitivity for Active TB (1)

1. **Meta-analysis**
   - Data presented for the commercially available assays (QFT-GIT and T-SPOT)

2. **Results:**

	% (95% CI)
TST	70(67-72)
QFT-GIT	84 (81-87)
T-SPOT	90 (87-92)

Diel, Chest April 2010 137(4): 952

17

Sensitivity for Active TB (2)

- **Meta-analysis**
  - Low and middle income countries
  - Higher priority for studies of TB suspects over known active TB
- **Results:**

	Non-HIV % (95% CI)	HIV % (95% CI)
TST	78 (71-86)	45 (15-75)
QFT-GIT	84 (78-91)	60 (34-82)
T-SPOT	88 (81-95)	76 (45-92)

Metcalf, JID 2011 204 (Suppl 4): S1120

18

Case 1 - 52 y/o male

- Prior (+) TST
- QFT-GIT: negative
- Lung bx: granulomas, AFB smear (-)
- Rx with steroids for sarcoidosis
- Died 1 month later from progressive TB

Case 2 - 43y/o female with RA

- Born in MX
- BCG-vaccinated

- Meds:
  - Methotrexate
  - Prednisone 5 mg

- TST 23 mm (by report)
- QFT negative

20

Case 2 - 43y/o female with RA

- 23 mm TST (by report) : QFT negative
- Normal CXR

   What would you do?
A. Repeat the TST
B. Repeat the QFT
C. Do a T-SPOT
D. Treat for TB infection

21

BCG-vaccine and IGRAs (1)

- Numerous studies and meta-analyses of the performance of QFT-GIT and T-SPOT

- (+) TSTs associated with prior BCG vaccination regardless of TB exposure

- No association with BCG and (+) IGRA
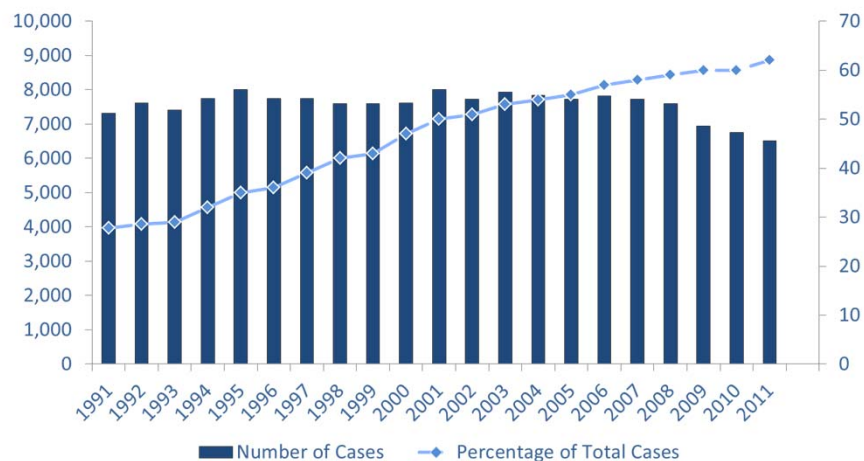
Diel Eur Resp J 2011; 37 (1): 88

BCG-vaccine and IGRAs (2)

- 316 BCG-vaccinated,TST (+)
- 137 (43%) QFT-GIT (+)

- (+) QFT-GIT associated with
  - Age, TST-size, birth in a high-burden country for TB, less time in the U.S., male gender
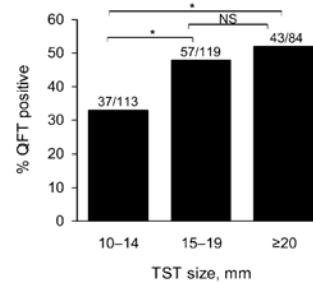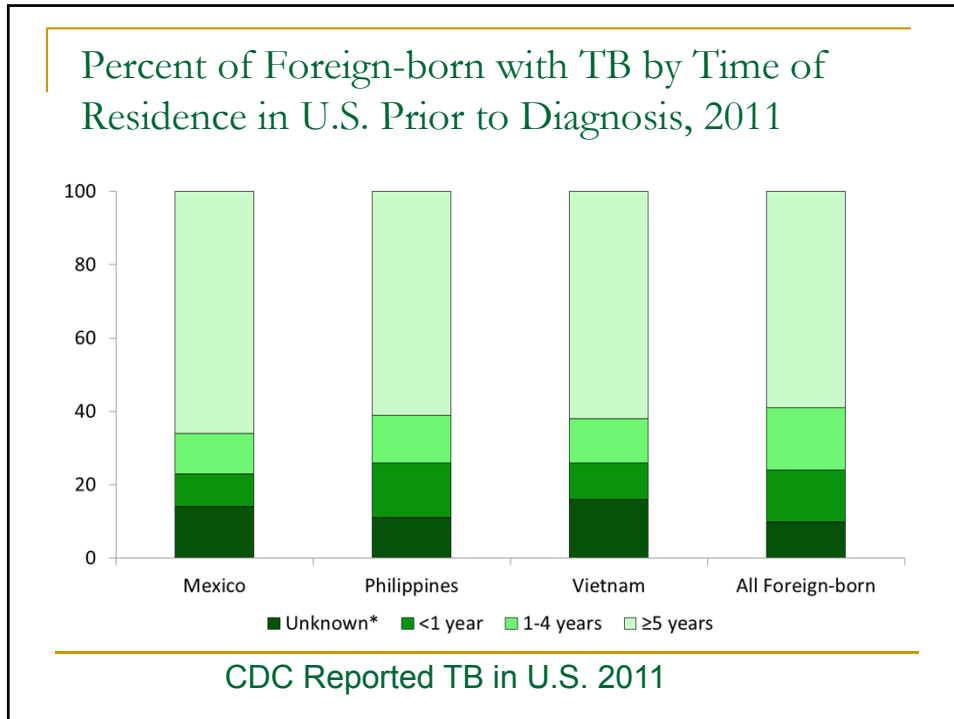

Mahan et al IJTLD 2011 15 (2): 174

Trends in TB Cases in Foreign-born Persons United States, 1991 – 2011

CDC Reported TB in U.S. 2011

Percent of Foreign-born with TB by Time of Residence in U.S. Prior to Diagnosis, 2011

CDC Reported TB in U.S. 2011

Case 2 - 43y/o female with RA

1. QFT negative (TB-nil = 0.09)
2. Repeat TST is 27mm

Risk for infection ✔
Risk for progression ✔

I recommended latent TB treatment

Case 3 – Family from Nepal

- Father, mother and 3 children (2, 4, and 7)
- All BCG vaccinated at birth
- How would you test for TB infection?
    1. TST for all
    2. IGRA for all
    3. IGRA for adults and TST for children
    4. IGRA for adults and older child, TST for the young children
    5. Something else

TST vs T-SPOT

- Prospective study:193 children w/ both tests
- Stratified by: no risk for TB exposure, risk but no known contact, contact with a known TB case, and active TB
- Median age 8.6y (range 1 mo to 18y)

Results: multivariate analysis

- (+) TST associated with BCG
- (+) T-SPOT associated with exposure risk

Cruz Pediatrics 2011 127(1): e31

TST vs IGRA in BCG-vaccinated Children

- 2,521 children
  - 970 (38%) Mexico
  - 953 (38%) Philippines
  - 598 (24%) Vietnam

Association Between Age and Test Positivity

Age Category	TST+ n(%)	RR (95% CI)	QFT+ n(%)	RR (95% CI)
2–5 years	103 (20%)	Reference	13 (3%)	Reference
6–9 years	173 (25%)	1.2 (1.0, 1.5)	27 (4%)	1.5 (0.8, 3.0)
10–14 years	397 (30%)	1.5 (1.3, 1.8)	105 (8%)	3.2 (1.8, 5.6)

Howley, poster IUATLD 2011, Lille, France

Meta-analysis of IGRAs in Children

- Association between test results and exposure risk were similar for TST and IGRAs
- Sensitivity and specificity for active TB were slightly higher for IGRAs but not statistically different
- Overall the accuracy appears similar

Mandalakas IJTLD 2011; 15: 1018

Case 3 – Family from Nepal

- Father, mother and 3 children (2, 4, and 7)
- All BCG vaccinated at birth

- In Denver, we test them all with an IGRA

Case 4 - 20 y/o student (1)

- Born in India
- Required to get TB testing for college enrollment
- TST = 11 mm   CXR = normal

    "It's due to my BCG"

Case 4 - 20 y/o student (2)

- Born in India
- Required to get TB testing for college enrollment
- TST = 11 mm   CXR = normal
    "It's due to my BCG"
- QFT positive (TB-nil = 1.15)
    "It's boosting from the TST"

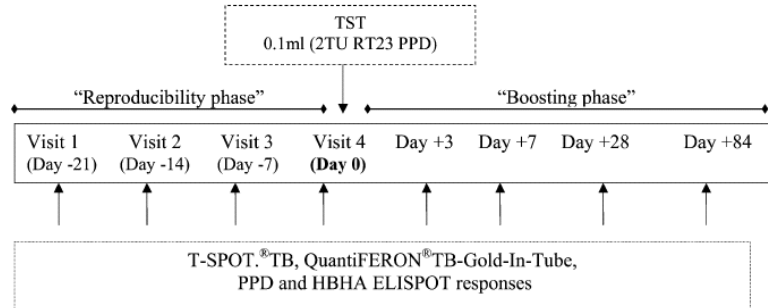## Case 4 - 20 y/o student (3)

- TST = 11 mm   CXR = normal
    "It's due to my BCG"
- QFT positive (TB-nil = 1.15)
    "It's boosting from the TST"

What would you do?

A. Repeat the QFT
B. Do a T-SPOT
C. Treat for LTBI

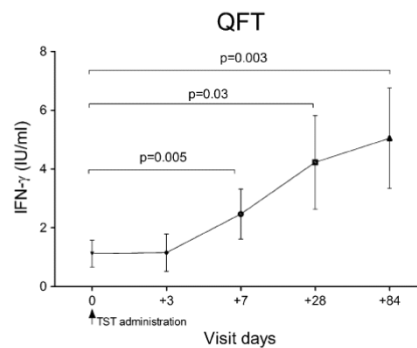## TST and boosting IGRAs (1)

- 26 healthy volunteers from South Africa

van Zyl-Smit, AJRCCM 2009; 180:49

TST and boosting IGRAs (2)

- Boosting occurred

- most pronounced in those with a (+) test at baseline

- 3 patients changed from (-) to (+) and all were TST (+)

van Zyl-Smit, AJRCCM 2009; 180:49

TST and boosting IGRAs (3)

A. TST negative   B. TST positive
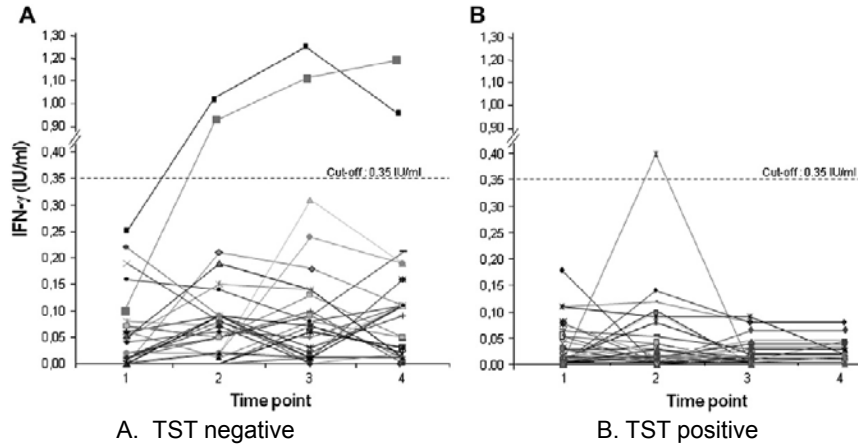
• 102 HCWs in Italy

Sauzullo, Tuberculosis 2011; 91 322

Case 4 - 20 y/o student (4)

• Born in India
• Required to get TB testing for college
  enrollment
• TST = 11 mm   CXR = normal
        "It's due to my BCG"
• QFT positive (TB-nil = 1.15)
        "It's boosting from the TST"
• Repeat QFT negative (TB-nil = 0.34)
        "Finally we agree"

Case 5 – 35 y/o male

- HIV-infected, CD4 350 on HAART

- U.S. born, living in Denver

- No travel outside the U.S.

- Never homeless or incarcerated

Case 5 – 35 y/o male

- HIV-infected, CD4 350 on HAART
- No identified risk for TB exposure
- QFT positive;TB antigen minus nil = 0.85

What would you do?

A. Treat for LTBI if the CXR is normal
B. Repeat the QFT
C. Do a confirmatory TST or T-SPOT

High Risk Populations - HIV-infected (1)

- Enrollment: 830 consecutive HIV-infected patients tested using QFT-GIT
- all QFT-GIT (+) declined LTBI treatment

Results: bivariate analysis
- Indeterminate result associated with low CD4
- (+) QFT - Black ethnicity, birth in Africa and birth in a country with a high burden of TB

Aichelburg, CID 2009; 48

High Risk Populations - HIV-infected (2)

Results Continued:

QFT	Baseline Active TB	Follow-up Active TB
Positive (n=44)	7	3
Negative (n=739)	1	0
Indeterminate (n=47)	0	0

Aichelburg, CID 2009; 48

High Risk Populations - HIV-infected (3)

- Cross-sectional study
- Enrollment: Sept '05 to July '06

- Patient population: 336 HIV-infected patients at 2 clinics in Atlanta

- Test: TST, T-SPOT and QFT-GIT

Talati, BMC Infect Dis 2009; 9:15

High Risk Populations - HIV-infected (4)

Results:
- Any (+) Test   27 (8.0%)
- All 3 (+)   1 (0.3%)
- TST (+)   7 (2.5%)
- QFT-GIT (+)   9 (2.7%)
- T-SPOT (+)   14 (4.2%)

Conclusion: Poor concordance among tests

Talati, BMC Infect Dis 2009; 9:15

High Risk Populations - HIV-infected (5)

Background

- – Less than 50% of HIV patients completed a TST
- – QFT-GIT replaced the TST in 2009
- – LTBI testing improved to > 90%
- – Higher than expected rate of (+) tests among U.S.-born with no risk for TB exposure
- – Instituted a policy of repeating all (+) QFTs in patients with no TB exposure risk

Gray CID 2012; 54: e20

High Risk Populations - HIV-infected (6)

Methods:

- – retrospective review of QFT-GIT at 2 HIV clinics in Denver, July 2009-June 2010

Results:

	Overall N= 1364	Repeat Test – No TB Risk N = 41
Positive	94 (7%)	6 (15%)
Negative	1243 (91%)	**33 (80%)**
Indeterminate	27 (2%)	2 (5%)

Gray CID 2012; 54: e20

High Risk Populations - HIV-infected (7)

1. **Meta-analysis**
   - commercially available QFT-GIT and T-SPOT
   - 37 studies (23 concurrent TST)
   - 5,736 patients

2. **Results:**
   - modest predictability and suboptimal sensitivity
   - similar performance between TST and IGRAs

Cattamanchi, JAIDS 2011; 56: 230

Case 5 – 35 y/o male

- HIV-infected, CD4 350 on HAART
- No identified risk for TB exposure
- QFT-GIT positive
  - TB antigen minus nil = 0.85

- Repeat QFT-GIT negative
  - TB antigen minus nil = 0.05

IGRAs and Immune Mediated Inflammatory Disorders

- Literature review
- No evidence that IGRAs are better than TST
- Consider the clinical and epidemiologic risk

- With a high clinical suspicion (eg. foreign-born with known prior contact) consider doing both a TST and IGRA

Smith, Curr Opin Rheum 2011; 23: 377

High Risk Populations – Other Immunosuppression

1. Rheumatoid Arthritis
   - QFT-G (+) similar in patients and healthy controls
        Inanc J Rheum 2009; 36:12

1. Hemodialysis
   - TST correlated with BCG vaccination
   - QFT-GIT and T-SPOT correlated with exposure risk
        Chung Clin Micro Infect 2009

Case 6 – 25 y/o pregnant female

- 10 weeks pregnant, HIV negative
- Born in Mexico - BCG as a child
- TST 12mm, asymptomatic

What would you do?

A. IGRA
B. CXR
C. Both
D. Neither

IGRAs and Pregnancy

140 pregnant patients
- Mean age 18.5
- 9 (6.4%) indeterminate

■ 28 (20%) TST (+)

■ 15 (11%) QFT (+)

no difference by trimester
correlated with:
- increase exposure risk
- size of TST

Table 2. Assay Response in Pregnant Patients With Different Likelihoods and Risks of *Mycobacterium tuberculosis* Exposure

Exposure Risk	n	% Interferon-Gamma Release Assay–Positive
Minimal*		
No known risk, tuberculin skin test-negative	12	0
No known risk, tuberculin skin test-positive	0	0
Low to moderate†		
Positive risk factors, tuberculin skin test-negative	91	3
Positive risk factors, tuberculin skin test-positive	26	38
High‡		
Known direct contact with TB index case, tuberculin skin test-negative	0	0
Known direct contact with TB index case, tuberculin skin test-positive	2	100

Lighter-Fisher, Ob & Gyn 2012; 119 (6): 1088

Case 6 – 25 y/o pregnant female

- 10 weeks pregnant, HIV negative
- Born in Mexico - BCG as a child
- TST 12mm, asymptomatic

- We would get an IGRA and only do a CXR if it was positive
- Our OB clinics now use QFT-GIT to screen pregnant women at risk for TB exposure and refer patients with a (+) result

Case 7 - 48 y/o U.S. born nurse

- No travel risks
- Multiple prior negative TSTs
- T-SPOT positive (11 spots)
- CXR normal

Now what do you do?
1. Recommend LTBI treatment
2. Check a TST
3. Check a QFT-GIT
4. Repeat the T-SPOT

54

TST and IGRAs in Healthcare Workers (1)

- CDC-funded, longitudinal study
- 4 sites: Denver, Houston, Baltimore, NYC
- Population:
  - ❏ 2,418 adult HCWs undergoing routine LTBI testing

- Intervention: TST, QFT and, T-SPOT at baseline, 6, 12 and 18 months

TST and IGRAs in Healthcare Workers (2)

- **Results**

	TST n(%)	QFT n(%)	T-SPOT n(%)
Baseline (+)	126 (5.2)	118 (4.9)	144 (6.0)
Conversion	21 (0.9)	138 (6.1)	177 (8.3)
Reversion*	11/12 (92)	81/106 (76)	91/118 (77)

* Not all converters had a repeat test

- 11 TST-positive HCWs treated for LTBI
- No cases of active TB

Case 7 - 48 y/o U.S. born nurse

- No travel risks
- Multiple prior negative TSTs
- T-SPOT positive (11 spots)
- CXR normal

- I would repeat the T-SPOT

57

Case 8 – 24 y/o student

- U.S. born
- PMHx: benign brain tumor and seizures
- Meds: Oxcarbazepine, folic acid and OCPs

Baseline
- TST 15 mm
- QFT-GIT negative

1 year later
- QFT-GIT positive
- Normal CXR and no symptoms

What would you do?
A. TST
B. Repeat QFT
C. Treat for latent TB

Predictability for Future TB (1)

1. **Meta-analysis**
   - commercial and in-house assays
   - Median follow-up 4years (IQR 2-6)
2. **Results**
   - Incidence in IGRA (+) was 4-48/ 1,000 person-yrs
   - Incidence Rate Ratio for test (+) vs test (-)
     - IGRAs   2.11 [95% CI 1.29-3.46]
     - TST   1.60 [0.94-2.72]

Rangaka, Lancet ID Jan 2012 12: 45

59

Predictability for Future TB (2)

1. **Meta-analysis**
   - commercial and in-house assays
2. **Results –** limited to commercial IGRAs, % (95% CI)

	PPV –All	PPV - High Risk	NPV
IGRA	2.7 (2.3-3.2)	6.8 (5.6-8.3)	99.7 (99.5-99.8)
TST	1.5 (1.2-1.7)	2.4 (1.9-2.9)	99.4 (99.2-99.5)

Diel, Chest July 2012 142: 63

60

Case 8 – 24 y/o student

- U.S. born
- PMHx: benign brain tumor and seizures
- Meds: Oxcarbazepine, folic acid and OCPs

Baseline
- TST 15 mm, QFT-GIT negative

1 year later
- (+) QFT-GIT (1.21 IU/mL)
- (+) Repeat QFT-GIT (2.02 IU/mL)

High Risk Populations – Contacts to Active TB (1)

1. Supermarket employee with smear (+) pulm TB
2. > 15,000 TSTs on 2 separate days
3. 785 BCG-unvaccinated had QFT-GIT and T-SPOT

Results:
- ❑ TST was correlated with age but not exposure time
- ❑ QFT-G and T-SPOT.TB correlated with exposure time

Arend, Am J Resp Crit Care 2007; 175: 618-27

High Risk Populations – Contacts to Active TB (2)

Conclusions:

- ❑ TST appears more sensitive but may be identifying remote infection

- ❑ IGRAs appear more specific and may better identify recent infection

- ❑ Varying the cutoffs used for interpreting the IGRAs resulted in better agreement between the tests

Arend, Am J Resp Crit Care 2007; 175: 618-27

High Risk Populations – Contacts to Active TB (3)

December 2011
- Local high school student with pulmonary TB

Contact Investigation
- QFT-GIT for close contacts
- ≥ 2 classes = 10/19 (53%)
- 1 class = 50/140 (36%)

Expanded to > 1200 at school

TB rate high at metro school

All 1,200 students and 120 faculty at Longmont High in the fall term will be tested.

By Karen Augé The Denver Post

Some 40 percent of 140 students and staff exposed to tuberculosis at Longmont High School have tested positive for latent TB, a rate that one expert called "absolutely astounding." The unexpectedly high rate of positive tests

High Risk Populations – Contacts to Active TB (4)

<u>Operational challenges using IGRAs</u>

- Need to pre-register patients to generate labels for the lab reporting purposes
- Blood draws require more time than TST
- Vasovagal syncope a greater risk than with TST
- Time constraints for delivering specimens to the lab
- Max laboratory capacity per week
- Increased cost for testing the "worried well"

High Risk Populations – Contacts to Active TB (5)

<u>Contact Investigation</u> – 1200 school contacts

- QFT-GIT for foreign-born or BCG vaccinated
- TST for everyone else

- **Majority of testing completed in less than a month**

Estimated Cost of IGRAs vs TST (1)

1. **Methods**
   - ❑ Markov model to estimate the cost of screening using TST vs IGRAs in risk groups targeted for LTBI testing in the guidelines
2. **Results**
   - ❑ IGRAs are more cost effective than TST when LTBI testing is prioritized toward close contacts, HIV-infected, and foreign-born (regardless of time in the U.S.)

Linas, AJRCCM 2011; 184 (5): 590

Estimated Cost of IGRAs vs TST (2)

Important considerations for cost

- Who is paying and what are they paying for?
  - – laboratory costs vs. person time (patients and HCWs)
  - – real current costs vs. potential future costs

- Cost avoidance
  - – Unnecessary CXRs and LTBI treatment (including toxicity)

Objective 1 (1)

List the benefits of using IGRAs in different populations at risk for TB

- ❑ May be slightly better for detecting active TB
- ❑ More specific in BCG-vaccinated (large population at highest risk in U.S.)
- ❑ Comparable or slightly better in HIV and other immunosuppressed patients
- ❑ Ability to know when the test failed

Objective 1 (2)

List some challenges using IGRAs in different populations at risk for TB

- ❑ Not sensitive enough for active TB
- ❑ Only modest ability to predict future TB cases during short term follow-up (limited data)
- ❑ Higher rate of false positive tests in lower risk populations than originally recognized

Objective 2 (1)

Describe the operational advantages

- ❑ One visit
- ❑ Less subjective
- ❑ Results reported electronically
  - ◾ Retrievable
  - ◾ Easier to analyze epidemiologic data

Objective 2 (2)

Describe the operational disadvantages using IGRAs

- ❑ Need to register patients in the lab (generally)
- ❑ Potential limitations from the lab
  - ◾ number of tests and the times of the day
- ❑ Greater risk for vasovagal syncope
- ❑ More time to draw blood and look up tests

Objective 3 (1)

Explain some of the cost implications associated with expanded use

- ❑ Lab costs vs. time lost
- ❑ Who pays
  - ▪ for the testing vs. the follow-up
- ❑ What is the risk in the population being tested
  - ▪ Affects the rate of false positives and
  - ▪ Future risk of active TB if undiagnosed

My Recommendations:

- • **Test people at risk for infection**
  - – 1º people born or lived in a high-burden country
  - – focus on those with risk for exposure AND progression **(**HIV, DM, ESRD etc.)
- • **Prefer IGRAs if available**
  - – Better in BCG-vaccinated people
  - – Results are easily retrieved
- • **Repeat all (+) IGRAs in lower risk people**
  - – U.S. born homeless and healthcare workers
  - – Consider for those with risk of progression (HIV, DM etc.) but no risk for exposure