

Interferon Gamma Release Assays: What's new & How are IGRAs changing our programs

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Conflict of Interest

- Nothing to declare

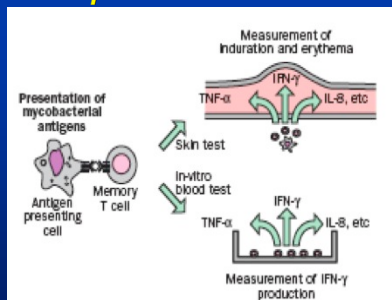
Objectives

- To provide an overview of the Assays
- To review the Canadian Tuberculosis Committee's new 2010 Advisory Statement regarding the use of IGRAs for tuberculosis infection
- To discuss select new studies and their implications
- To review how IGRAs are changing TB programs

Tuberculin Skin test

- False positive tests occur because of previous BCG vaccine or exposure to non tuberculous mycobacteria.
- False negatives occur because of T cell mediated immune deficiency due to drugs or disease.
- Up to 30% of patients with active TB will have a negative skin test making it poor for diagnostic purposes.
- Administered intradermally and then read in 48-72 hours requiring the patient to return for a reading.
- Both administration and the reading itself requires skill to be performed correctly.

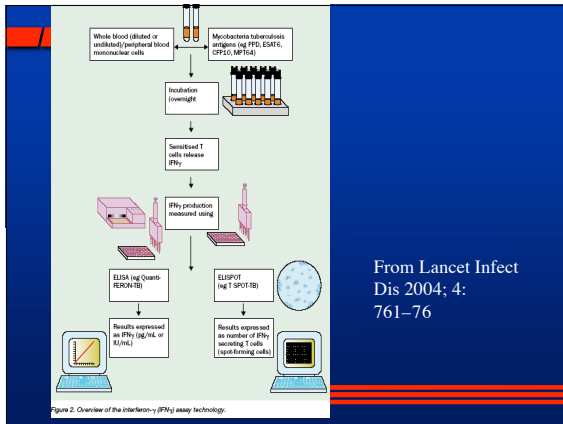
Principles of TB tests



Andersen, et al. Lancet 2000;356:1099

RD1 genes (ESAT6-, CFP-10)

- Present in *Mycobacterium tuberculosis* and *M. bovis* but not present in BCG
- Present in *Mycobacterium kansasii*, *Mycobacterium marinum* and *Mycobacterium szulgai* but not other atypicals



Comparison of Handling Requirements

	QuantIFERON® - TB Gold In-Tube	T-SPOT.TB
Need to process	Within 16 hours	Within 8 hours (Xtend kit=32 hrs)
Incubation time	16-24 hours	16-20 hours
Storage	Plasma samples can be stored for up to 8 weeks at 2°C to 8°C or below -20°C (preferably less than -70°C) for extended periods	no

Comparison of Cost

	QuantIFERON® - TB Gold In-Tube	T-SPOT.TB
Acquisition costs per test (based on 1000 test purchase)	C\$30	US\$24 + \$13 Cell prep tube \$37 ±Xtend @\$4.50
Hands on tech time	< 1 hour	< 3 hours (may reduce time somewhat with an automated plate reader)
Most cost effective # of patient tests per kit	28	24

Cost Effectiveness

Overall cost effectiveness studies not conclusive, but suggest TST followed by IGRA as a confirmatory test may be least costly.

Where rates of TST are high, IGRA alone most cost effective

Health Canada Advisory Statement Recommendations

1. IGRA may be performed in TST-positive, immunocompetent adults who are at relatively low risk of being infected with TB (including casual contacts) and of progressing to active disease if infected. Persons with a positive IGRA result may be considered for treatment of LTBI.
2. For close contacts or those individuals who have high or increased risk of progression to active disease if infected, a TST (or both TST and IGRA) should be used, and if either is positive the contact should be considered to have LTBI.
3. If both TST and IGRA testing will be used, it is recommended that blood be drawn for IGRA before or on the same day as reading the TST, whenever possible.

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Health Canada Advisory Statement Recommendations

IGRAs are not currently recommended :

1. For the diagnosis of active TB in adults (Sensitivity=rule out, specificity = rule in)
2. For serial testing such as in health care workers or prison staff and inmates.
3. In an immunocompromised person, TST is the preferred test. However, IGRA may be used in addition to the TST and if either is positive consider treatment for LTBI. However historical data suggests INH may not be as beneficial to HIV patients who are TST negative

Canada Communicable Disease Report: IN PRESS

Interpretation of results when both TST and IGRA results are available

Risk of developing disease if infected with <i>M. tuberculosis</i>						
High			Low			
	IGRA positive	IGRA negative	IGRA indeterminate	IGRA positive	IGRA negative	IGRA indeterminate
TST positive	Consider treatment for LTBI			Consider treatment for LTBI	Treatment for LTBI is not necessary	Repeat IGRA test or base interpretation on TST result
TST negative	Consider treatment for LTBI	Treatment for LTBI is not necessary if immunocompetent	Repeat IGRA test or base interpretation on TST result	Consult TB specialist	Treatment for LTBI is not necessary	

Health Canada Advisory Statement Recommendations

- For the diagnosis of active TB in children, IGRAs may be used as a supplementary diagnostic aid, in addition to symptoms, radiological abnormalities, history of exposure, and microbiological investigations such as microscopy and culture.

Canada Communicable Disease Report: IN PRESS

Other National Guidelines

- CDC Recommendations QFT-Gold**
December 16, 2005 / Vol. 54 / No. RR-15
QFT-G may be used in all circumstances in which the TST is currently used.
- National Institute for Health and Clinical Excellence**
Clinical Guideline 33 London 2006 (For use in the National Health Service in England and Wales)
Those with positive TST should be considered for testing; if IGRA negative-no action

What's NEW!

Sensitivity Based on Patients with Active TB compared to TST

	QFT Intube	T-SPOT.TB	TST
Number of studies	5	7	
Number positive/ total	108/130	219/243	81/130 166/243
Pooled sensitivity	83%	91%	62% 68%

Adapted from Diehl et al, published ahead of print December 18, 2009

Sensitivity Based on Head to Head Studies with Patients with Active TB

	QFT Intube	T-SPOT.TB
Number of studies =4		
Number positive/ total	91/108	84/108
Pooled sensitivity	84%	62%

Adapted from Diehl et al, published ahead of print December 18, 2009

IGRA Specificity

	QFT Intube	T-SPOT.TB
Number of studies	5	3
Number positive/ total	508/512	220/255
Pooled sensitivity	99%	86%

Adapted from Diel et al, published ahead of print December 18, 2009

IGRA Indeterminate Rates

	QFT Intube	T-SPOT.TB
Number of studies	72	59
Number positive/ total	469/21,922	462/12,168
Pooled results	2.14%	3.80%

Adapted from Diel et al, published ahead of print December 18, 2009

IGRA Indeterminate Rates in Immunocompromised

	QFT Intube	T-SPOT.TB
Number of studies	24	18
Number positive/ total	242/5473	168/2681
Pooled results	4.42 %	6.12%

Adapted from Diel et al, published ahead of print December 18, 2009

IGRA Indeterminate Rates: Head to Head

	QFT Intube	T-SPOT.TB
Number of studies =11		
Number positive/ total	76/3057	133/3057
Pooled results	2.47%	4.33%

Adapted from Diel et al, published ahead of print December 18, 2009

A statistical method for the meta-analysis of tests for LTBI

	QFT	T-Spot.TB	TST
Sensitivity	0.642	0.500	0.709
Specificity	0.996	0.906	0.683

Sadatsafavi et al.(BC) J Clin Epi, 2009

FDA Approval July 2008 T-spot.TB

- FDA required a borderline category of 5-7 spots which requires retesting
- This reduced sensitivity by 5% and increase specificity by 2%.

Serial Testing: Abstract Daley et al

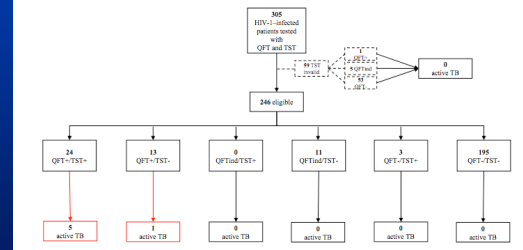
Outcomes Using Standard and Proposed Criteria

Method		Baseline Positive (%)	Baseline Borderline (%)	6 month Conversion (%)	6 month Reversion (%)	Conversion Criteria
Standard	TST	8.9	-	0.6	45.7	Increase > 10 mm
	QFT	6.9	-	3.6	32.8	Value above 0.35
	T-Spot	8.0	4.1	3.8	28.6	8 or more spots
Proposed ¹	QFT	4.6	5.3	1.9	11.1	Increase from <0.35 to >0.70
	T-Spot	6.6	9.0	3.5	35.9	Increase from <6 spots to >9 spots

¹ van Zyl-Smit Am J Resp Crit Care Med, April 2009
 - proposed Borderline Ranges: QFT-GIT 0.2 to 0.7, T-SPOT 4 to 8

Prediction of Active TB

Active TB Within the Follow-Up Period



Diel et al, CID 2009-48 (1 April)

TST(+), QFT(-) Prediction of Active TB

1851 QFT tests on 1750 patients were reviewed.

1430 were TST positive.

823 of these also had a negative QFT test (57.6%). 97 received LTBI treatment, leaving 724 untreated.

1849 patient-years of follow-up were obtained, the minimum follow-up being one year, and the mean and median being 2.5 years.

No cases of active tuberculosis were identified in these 724 patients during this follow-up period.

Chan et al abstract ICC 2009

The Canadian Tuberculosis Committee (CTC) recommends that all provincial and territorial governments fund the use of IGRAs for use according to the current CTC recommendations.

How are IGRA's Changing Our TB Programs

Decreasing number of LTBI treatments

- Edmonton Zone, 62 % of patients eligible for TB preventative therapy based on the TST, are QFT negative and likely do not require preventive TB therapy

Increases Acceptance and Completion Rates?

TABLE. Data on Isoniazid Therapy Among Healthcare Workers (HCWs) With Latent Tuberculosis Infection (LTBI), Before and After Implementation of Interferon- γ Release Assay Screening

No. (%) of HCWs with LTBI	Before implementation	After implementation	OR (95% CI)	P
	(n = 45)	(n = 62)		
Who accepted a prescription for isoniazid	11 (24)	32 (52)	3.3 (1.3-8.0)	.008
Who took isoniazid	5 (11)	32 (52)	8.8 (3.1- 23)	.001

Sahni et al, infectioncontrolandhospital epidemiology february 2009, vol. 30, no. 2

Conclusion

- IGRA's increased specificity decreases the number of patients treated for LTBI
- Their optimal use in some situations still needs to be defined through further research

END TB