Testing for TB Infection and Disease

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TB Clinical Intensive
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None

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None
Objectives

• Describe targeted testing strategies (CNTC)
• Explain how to interpret interferon-gamma release assay (IGRA) results
• Describe the differences between IGRAs and the TST
TB Diagnostics: Part 1

- Practical aspects of diagnosing active TB
  - Chest radiography
  - Defer discussion of microbiological techniques to next presentation

- Detecting latent TB infection (LTBI)
  - Tuberculin skin testing (TST)
  - Interferon-gamma release assays (IGRA)
Case 1

• 76 y/o man from China, smoker
• Arrived to US 2 months ago
• Class B1 (abnormal CXR, sputum sm/cx neg)
• Mild chronic cough, occasional blood streaking
• Levofloxacin x 7 days, cough maybe better
• Not ill: no weight loss, no fever
Case 1: next step?

1) Start INH 300mg qd x 9 months
2) Perform TB skin test
3) Perform QuantiFERON-TB Gold
4) Collect sputum x 3
5) Get sputum, start INH, RIF, PZA, EMB
What to do next?

• Sputum smears negative x 3

• Do we still suspect active TB?

• My answer: start RIPE, presume active TB
Clinical presentation of active TB

- Active TB can present like anything
- Symptoms less sensitive and specific
  - Chronicity is most helpful (re-activation)
  - Weight loss is a very sensitive sign
- Failure of outpatient pneumonia treatment
  - Beware of transient response to levofloxacin
First, what is the risk of infection with MTB?

• Consider *a priori* risk for MTB infection
  • Born in country with high endemicity
  • Contact to an active case
    • Even many years ago; ask the patient
  • Lived in congregate settings
  • High risk life-style
Next, why might MTB infection → disease?

- Consider co-morbidities, lifestyle
  - Immunosuppression
    - HIV
    - TNF-alpha inhibitors, chronic steroids
    - Other chronic illnesses
  - High risk life-style (poor nutrition?)
- Recent emigration = even higher risk

Cain et al, AJRCCM 175:75-79 2007
Cain et al, JAMA 300:4 2008
CXR manifestations of active TB disease

• Primary TB infection (Ghon complex)
• Mediastinal lymphadenopathy
• TB pneumonia

• Reactivation TB
• Pleural TB (extrapulmonary)
• Miliary TB

• Calcified granulomata = low risk for active TB
Chest radiography in tuberculosis

- Still the mainstay of screening and diagnosis
- Look at film with TB in mind (radiologist may not)
- Clearly see the apices bilaterally
  - Don’t hesitate to get apical lordotic views

- PA/lateral is standard of care for all kids w/TST+
  - Mediastinal adenopathy in kids = active TB
Role of CXR in empiric treatment

• Sometimes CXR + risk is all the data you have
  • Often enough for prudent initial management
  • Micro is key for drug susceptibility, treatment decisions, public health decision-making

• High-risk person, unexplained opacity = TB
  • Start 4-drug therapy
  • Assess for improvement at 6-8 weeks
    • If improved, treat as active TB (2-4 more months)
    • If not improved, you fully treated their LTBI
CXR and sputum in extra-pulmonary TB

• Why? They have no pulmonary symptoms!
• Case series: 72 XPTB patients, Seattle
  • CXR: 49% abnormal
  • 57 had sputum collected (15 couldn’t produce)
  • No signif. difference in sputum smear or culture + between abnormal CXR (23%) and normal CXR (19%)

• How did they get TB? They inhaled it

Active Tuberculosis Disease

• Primary infection or reactivation
• Pulmonary, extra-pulmonary, or both
• Clearly infectious or unlikely infectious
• Drug resistant or not (mono or multi)
• Clinical obstacles to effective treatment

• Real world obstacles to effective treatment
Public health department role

• Get them involved early, even if suspect case
  • Benefit from centralization of TB expertise
• DOT is the standard of care for every patient
• PH mission: reduce the barriers to TB treatment
  • Logistical
  • Financial (cost to patient = treatment failure)
  • Psychological (stigma)
  • Clinical (lack of expertise in community)
Testing for TB infection without disease: latent TB infection (LTBI)
Latent Tuberculosis Infection (LTBI)

• Who to test for LTBI

• Tuberculin skin testing (TST)

• Interferon-gamma release assays (IGRA)
Case 2

- 45 y/o woman from Nigeria, emigrated 3 yr ago
- Type 2 diabetes
- TST 12mm induration
- QFT: NEGATIVE (TB Ag – nil = 0.32)
Case 2

- 45 y/o woman from Nigeria, emigrated 3 yr ago
- Type 2 diabetes
- TST 12mm induration
- QFT: NEGATIVE (TB Ag – nil = 0.32)
- CXR: scattered calcified granulomata

- What to do next?
Case 2: next step?

1) Offer LTBI treatment
2) Clear the patient as not TB infected
3) Start INH/RIF/PZA/EMB
4) Repeat QFT
5) Repeat TST
My answer

1) Offer LTBI treatment
Latent TB Infection in context

• One-third of world has LTBI
  • NHANES 1999-2000: 4.2% TST>10mm US population

• Risk of progression to active TB: 10% lifetime
  • 5% in the first year after infection

Characteristics:
15X: <2y after infection
6-19X: abnormal CXR
2-5X: children

Co-morbidities:
50-110X: HIV
20-75X: transplant
10-25X: CKD
2-9X: TNF-α inhibitors
2-4X: DM

Bennett, et al, AJRCCM 177:2008
Lobue and Menzies, Respirology 15: 2010
What is the goal of LTBI screening?

- 70% of those with TST+ start LTBI treatment
  - Only 60% of people who start LTBI tx finish
- Target highest risk of truly being infected
  - Recent contacts to active TB, esp. kids
  - Born in/exposed to high-incidence countries
  - Prison, homeless, substance abusing, HCW
- Target highest risk of reactivating
  - Children
  - Recent immigration
  - Immunocompromised
    - HIV+, immunosuppressive meds, chronically ill

Bennett, *et al*, AJRCCM 177:2008
Lobue and Menzies, *Respirology* 15: 2010
Pathogenesis of MTB infection → LTBI

- *Mycobacterium tuberculosis* (MTB) bacilli inhaled
- Phagocytosis by macrophages (Mφ), dendritic cells
- MTB proliferates in Mφ and within lesion
  - Inhibits apoptosis (early) of infected cells
- After a lag, specific CMI kicks in to break cycle
  - Infected Mφ produce pro-inflammatory cytokines
    - Mφ activated to present MTB (with MHCII)
    - CD4 (Th1)/CD8/NK cells activated to produce INF-γ
- Caseating granuloma is formed, then resolves
- Hearty bacilli enter dormant state but *MAY* survive in Mφ to establish latent infection

Paradigm of 2 different microenvironments

Caseous granuloma in TB disease

Fibrotic granuloma in latent TB

What is LTBI exactly? A continuum

• Does positive T-cell response reflect persistent infection or immune response?
  • No easy way to know in an individual
• Risk of reactivation TB based on epi data
  • Complicated by risk of re-infection in high incidence settings (primed immune system?)
• Higher risk = higher suspicion of viable MTB

Mack et al. *Euro Resp J* 33:5 2009
Testing for past/present MTB infection

- Active TB disease: testing fairly definitive
  - Smear, direct PCR, culture
  - Biopsy
  - Clinical response to therapy
- Latent TB infection (ie, without disease)
  - Indirect evidence of T-cell recognition of MTB
    - TST or IGRA
LTBI test characteristics

- No gold standard test for latent TB infection
- Sensitivity: approximated by false negative rate in patients with culture-confirmed TB
- Specificity: approximated by false positive rate in persons with no known risk factors for TB infection

*Cellestis, QFT-GIT package insert, 2011
MMWR, 59 (RR-5) 2010*
Tuberculin Skin Test (TST)

- Intradermal injection of Purified Protein Derivative (PPD)
  - Mantoux technique (since 1907)
  - Crude mixture of 200 antigens (MTB, BCG, NTM)
- DTH reaction present 2-8 weeks post infection
- Reaction size considered positive based on probability of true + and risk of being wrong
  - $\geq 5\text{mm}$ is +: highest risk of developing active TB
    - HIV+, recent contacts, abnormal CXR, strongly immunosuppressed (transplant)
  - $\geq 10\text{mm}$ is +: increased probability of true positive
    - Recent immigration, kids$<4$, IVDA, living in congregate settings, relatively immunosuppressed (steroids, ETOH, DM)
  - $\geq 15\text{mm}$: everyone else

Carter and Lee. *PIDJ* 21 2002
TST Limitations

- Need for follow-up visit
- Operator error: 18% read >15mm as negative
- Boosting phenomenon (reason for 2-step)
- TST is far from 100% sensitive
  - 20-25% confirmed active TB cases have neg. TST
- TST is far from 100% specific
  - BCG vaccine and NTMs may cause positive TST

Carter and Lee, *PIDJ* 21 2002
TST limitations in children

- False positives in BCG recipients, esp. recent
  - Subject to booster phenomenon
- High false negative rate in kids with TB disease
  - ~10% of culture confirmed children TST negative
  - Higher in paucibacillary cases (more common)
  - 38% of TB meningitis cases TST negative (HIV-)
  - Even worse in HIV infection

Van der Weert, et al. PIDJ 25(1) 2006
Effect of BCG vaccination on TST

- BCG 80% effective in preventing disseminated TB in children
  - Variation in # of vaccinations, solution used
- ~50% of vaccinated infants have neg TST
  - Botswana: 70% TST neg 3-60 months post-BCG
- Extent of boosting unknown, but occurs
- Guidelines: ignore BCG vis-à-vis TST result

Orme, *Tuberculosis* 2010
Lockman, *et al. IJTBLD* 3 1999
Sepulveda, *et al. PIDJ* 7 1988
TST Performance

• 2007 meta-analysis
• Pooled sensitivity (confirmed active TB)
  • 71% sensitive
• Pooled specificity (low-risk of LTBI)
  • Non-BCG: 98% specific
  • BCG: 56% specific
• Inter-test variability: +/- 6 mm
Interferon-γ Release Assays (IGRA)

• Incubate PBMC with MTB-specific antigens and positive/negative controls
• Measure level of IFN-γ release from T-cells
• Compare IFN-γ produced in response to MTB-specific antigens compared to controls
Test details for 3 licensed tests

- **QuantiFERON-TB Gold (QFT-G, Cellestis, 2005)**
  - Incubate whole blood with ESAT-6 and CFP-10, and pos/neg controls
  - Measure IFN-γ in supernatant with ELISA vs. controls
  - Need to process blood within 12 hours

- **QuantiFERON-TB Gold In-Tube (QFT-GIT, Cellestis, 2007)**
  - Adds TB 7.7 Ag with other 2 antigens in one tube
  - Incubation in collection tubes

- **T-SPOT. TB (Oxford Immunotec, 2008)**
  - Isolate and incubate PBMCs with ESAT-6 and CFP-10 (2-8ml)
  - Stain IFN producing cells (“spots”) using ELISpot immunospot test
  - Accounts for low CD4 counts
QuantiFERON-TB Gold In-Tube (QFT-GIT)

Don’t overfill, shake, incubate 37°C x 16-24 hours

Centrifuge, take off supernatant

Perform ELISA in 96-well plate with duplicate wells

Measure level of IFN-Ɣ in supernatant of each tube

Calculate net reaction in tube coated with MTB antigens
How QFT-GIT is reported

• Amount of IFN-γ in each tube measured (IU/ml)
  • Nil control
  • Mitogen (+) control (PHA)
  • Tube coated with 3 MTB antigens

• Important value is TB Ag minus nil (net IFN-γ reaction)
  • ≥ 0.35 IU/ml = positive test result
  • (if nil≤8.0 IU/ml, Ag-nil≥25%nil)

• Indeterminate result = not interpretable
  • Not an intermediate result
  • Usually low mitogen response (<0.5 IU/ml)
    • Sometimes because of high nil response >8.0 IU/ml)
  • Usually about 1% (5% in HIV +, 15% kids)
T-SPOT. TB

- 1 tube of blood collected (2 in HIV)
- No lab processing on sending side
- Shipped Fed Ex to Oxford Immunotec
- Results in 36 hours
- More expensive than QFT
- No laboratory variation
- 3 results: positive, negative, equivocal

Oxford Immunotec website: http://www.tspot.com/
Accessed 11/11/2013
Pros and cons of IGRA

• Pros
  • More specific for MTB infection than TST
    • Infection with BCG and most NTM do not cause positive results (exceptions: *M. kansasii, szulgai, marinum*)
  • One blood draw, no return visit
  • No boosting effect

• Cons
  • **Cost**, phlebotomy and lab both must be equipped and trained, quality control
  • Not validated in children <5 years of age
  • Interpretation controversies
Performance of IGRA testing
Sensitivity of IGRA: setting of active TB

- Meta-analysis: 2008
  - Gold standard: confirmed TB disease
- Sensitivity (false negative rate)
  - Pooled sensitivity:
    - QFT-Gold: 78%
    - QFT-GIT: 70%
    - T-Spot: 90%
- 2011 meta-analysis:
  - Sensitivity: QFT 80%
    - Body fluids: 48% sensitive

Metcalfe et al. AJRCCM 187 2013
Sester et al. Euro Resp J 2011
2008 meta-analysis: TST vs IGRA

- TST: pooled sensitivity: 76%

- QFT-GIT: pooled sensitivity: 70% (QFT-G=78%)

- T-Spot: pooled sensitivity: 90%

Sensitivity of IGRA in kids with active TB

• Cambodia: 405 cases of pediatric TB disease
  • 91 (23%) micro confirmed
  • 81 of these had IGRA
  • Only 43 were + (53% sensitivity)
  • Unaffected by age, sex, clinical presentation

• Not as sensitive in active pediatric TB

HIV and effect on TST/IGRA (active TB) - 1

- Might expect lower sensitivity of all tests
  - Not consistently seen
- 160 adults, all 3 tests, S Africa (46% HIV+)
  - 43% QFT+ (HIV+) vs 46% QFT+ (HIV-)
  - 52% T-SPOT+ (HIV+) vs 59% T-SPOT+ (HIV-)
  - 35% TST+ (HIV+) vs 66% (HIV-)
  - Indeterminate: QTF 5%, T-spot 1%
- T-Spot and QFT sensitivity similar in HIV+ and –
- Both more sensitive than TST
- 64 adults, Switzerland (all HIV+)
  - TST and T-Spot similar sensitivity
HIV and effect on TST/IGRA (active TB) - 2

• Zambia: 112 active TB patients (53% HIV+)
  • QFT: sensitivity 84% (HIV-) but 63% (HIV+)
  • TST: sensitivity 81% (HIV-) but 55% (HIV+)
  • Increasing false negative with lower CD4 cells
  • Both TST and QFT were less sensitive in HIV+ patients

TST/IGRA not definitive data in context of suspected active TB disease

- Positive (either) is helpful to support dx of TB
- Negative (either) does not r/o TB
  - If TB is suspected clinically, ignore negative TST and/or IGRA result
- Measure of the immune response
  - Same immune defect leading to reactivation of LTBI might produce negative TST/IGRA
- Yet most data in setting of active TB disease
IGRA in setting of (suspected) latent TB infection
Performance of IGRA re: LTBI - Sensitivity

• Sensitivity (false negative rate) is difficult to estimate in suspected LTBI
  • No gold standard test for LTBI
• Definitive measurement: of those tested, who eventually develops active TB
  • Would require longitudinal follow-up x years
  • Ethically, can’t disregard +IGRA
• Crude estimates extrapolated from active TB

Cellestis, package insert 2011
Mack et al. *Euro Resp J* 33:5 2009
Performance of IGRA re: LTBI - Specificity

- Specificity (false positive rate) also difficult to estimate in suspected LTBI
  - How can you ever know if not really LTBI?
  - Many fewer data than with sensitivity
- Rate of positivity in persons with no known risk factors for MTB infection
  - Cellestis data/CDC guidelines: 99% specific
  - 180 German nursing students: 99% specific

Cellestis, package insert 2011
2007 Meta-analyses: TST vs IGRA

• TST: pooled specificity: 66%
  • Non-BCG: specificity: 98%
  • BCG: specificity: 56%

• All QFT: pooled specificity: 97%
  • Non-BCG: specificity: 100%
  • BCG: specificity: 96%

• T-Spot: pooled specificity: 92%

Meta-analyses: TST vs IGRA

- **TST**
  - 2007: pooled sensitivity 71%
  - 2008: pooled sensitivity 76%

- **QFT-GIT**
  - 2007: pooled sensitivity 76%
  - 2008: pooled sensitivity 70% (QFT: 78%)

- **T-Spot**
  - 2007: pooled sensitivity: 88%
  - 2008: pooled sensitivity 90%

MMWR: IGRA sensitivity/specificity (adults)

• Sensitivity (in active TB): indistinguishable
  • Average sensitivity:
    • TST = 77%, QFT-GIT = 70%, T-Spot = 90%
    • 11 studies: TST vs QFT-GIT (any active TB)
      • No diff (6), TST>QFT-GIT (3), QFT-GIT>TST (2)

• Sensitivity (by correlation with predictors of LTBI)
  • IGRAs marginally better than TST

• Specificity (low TB prevalence): IGRA better
  • QFT=96%, T-Spot=93%, TST=59%
Performance of IGRA in kids - 1

- Children <5 y/o secrete less IFN-γ
  - Adult data should not be extrapolated to kids
- More data on T-SPOT than QFT-GIT
- Active TB: specificity 95% but ↓ sensitivity
  - QFT-GIT: 52-93%; T-SPOT: 40-100%
  - TST more sensitive
- LTBI: concordance 60-90% with TST
  - Discordant mostly +TST/-IGRA; higher w/BCG
  - Correlate better than TST with exposure to TB

Starke, J. presentation, NTCA 2009
Haustein, et al. PIDJ 28(8) 2009
Lewinsohn, et al. Curr Opin Peds 22 2010
Performance of IGRA in kids - 2

- High rate of indeterminate results (>15%)
  - Positive control failure most often
  - Indeterminate rate: QFT-GIT > T-SPOT
    - Most indeterminate QFT samples were negative by T-SPOT
  - Indeterminate rate highest in youngest (<4)
    - For QFT-G, QFT-IT and T-SPOT
- IGRA clearly less reliable in kids than in adults

Haustein, et al. PIDJ 28(8) 2009
2010 CDC recommendations

- TST and IGRA equally valid (not both usually)
  - Use either for contact investigations, screening
- IGRA preferred: when BCG confuses issue
  - Most foreign-born people (assume hx of BCG)
  - Low likelihood of returning for TST reading
- TST preferred: when IGRA is not validated
  - Children under 5 y/o
    - Risk of future TB disease outweighs risk of LTBI treatment from possible false + TST
Practical aspects of IGRA in LTBI

• Always consider the patient’s situation
• Consider a positive result proof of LTBI
• Negative result must be viewed in context
  • *A priori* risk of having been exposed
  • Distance from the cutoff
  • Can expect up to 20% discordance with TST
TST vs IGRA discordance - 1

- **High risk of LTBI**: contacts to active cases
  - Diel 2006: 315 contacts (Germany) (50% BCG)
    - 10% QFT+ vs 44% TST >5mm
    - Overall concordance = 64%
    - BCG: 39% concordance; No BCG: 90%
  - Diel 2011: 1417 contacts (Germany) (52% BCG)
    - 22% QTF-GIT+ vs 65% TST >5mm (67% had BCG)
    - Overall concordance = 56%
    - BCG: 34% concordance; No BCG: 80%
  - Arend: 785 contacts (Holland) (no BCG)
    - 89.6% concordance
    - TST corr with age, IGRA corr with time in contact
    - 56% of 29 QFT+/TST- contacts converted TST within 1 year

Arend et al. *AJRCCM* 175 2007
Diel et al., *AJRCCM* 2011
Franken et al. *Clin Vac Imm* 14:9 2007
TST vs IGRA discordance - 2

- **Low risk of LTBI**: Cellestis data: 98.7% QTF-TST agreement

- **Low risk of LTBI**: healthcare workers (HCW)
  - Cohort of 388 Canadian HCW (McGill)
  - Relatively low incidence setting
    - 36% BCG vaccinated
  - 5.7% TST+, 6.2% QFT+
  - But 8.3% were discordant
    - 4.4% TST-/QTF+
    - QTF+ associated with working as HCW abroad

Cellestis, *QTF package insert* 2011
Zwerling et al *PLoS One* 2012
TST vs IGRA discordance – HIV+

- 160 adults, all 3 tests, 46% HIV+ (S Africa)
  - Good agreement in HIV+, poor in HIV-
- 196 adults, no active TB, all HIV+ (SF, US)
  - 8.5% QFT +, 19% TST+ (none CD4<100)
  - 89.3% concordant but only 8/29 + on both tests
  - Only 6% got BCG (only 1 of the TST+)

Rangaka et al. AJRCCM 2007
Luetkemeyer et al. AJRCCM 2007
Which is better, TST or IGRA?

- Suspected active TB: doesn’t matter
- LTBI: depends on context (what do we want?)
  - Persons with high risk of exposure (e.g., contacts)
    - Want high sensitivity (either test is good)
  - Persons at low risk of exposure and reactivation
    - Want high specificity (really know who has true LTBI)
  - Persons with high risk of reactivation
    - Any positive should be interpreted as true LTBI
    - If one negative, do the other?
There is no gold standard test for latent TB infection
Back to Case 2

• 45 y/o woman from Nigeria, emigrated 3 yr ago
• TST 12mm induration
• QFT: NEGATIVE (TB Ag – nil = 0.32)
• CXR: scattered calcified granulomata

• CXR c/w remote primary TB infection
• Probably got BCG, but QFT is just under cut-off
• High risk of TB exposure: offer LTBI treatment
Open questions about IGRA
Other questions being addressed

• How to interpret QFT numerical results?
• How to view IGRA within-subject variability?
• What is boosting effect of TST on IGRA?
• Does TST stay + longer than IGRA? Relevance?
• Can IGRA help as measure of treatment success?
• Best protocol for TNF-α inhibitor patients?
• Is reliance on IGRA cost-effective?
  • Serial screening for health care workers
Does QFT numerical result matter?

• Reported as positive or negative
  • Numerical result above or below cut-point
  • What about results right near the cut-point?
• Very small variation can “convert” test
  • “Wobble” = conversion or reversion
• Repeatability: same sample
• Reproducibility: same person different sample
IGRA variability in same sample

- Cellestis data: CV = 8.7% (average variability of numeric test result, 27 runs on same sample)

- 2012: 366 low-risk subjects: retested same sample
  - Inter-test variability: ±0.6 IU/mL
  - 28/366 (8%) discordant results (0.35 cut-point)
    - 15 pos then neg; 13 neg then pos
  - 86% had initial test in borderline range
    - 0.25 to 0.8 considered borderline in either direction

*Metcalfe et al. AJRCCM 2012*
Within-subject IGRA variability - Not bad?

• Same person, draw on different day
  • Biological variation plus inherent test variability

• Cellestis data: 98.5% repeatability
  • 530 subjects, draws 4-5 weeks apart

• Serial testing, 14 subjects (India)
  • 16% variability (values), no discordance (+/-)

• 2009 meta-analysis: 4 studies, wobble seen
Within-subject IGRA variability - A problem?

- 26 HCW, S Africa
  - 80% variability in QFT value 1 week apart
  - 7/26 (27%) converted/reverted (most near 0.35)

- 250 contacts, rural India
  - 54% QFT +; 12 months later, 6.4% reverted to neg

- 182 HCW, serial testing, Germany
  - Of 18 QFT+, 6 (33%) reverted; 2% converted

Van Zyl-Smit et al. *AJRCCM* 180 2009
Pai et al. *IJBTLD* 13(1) 2009
Ringhausen et al. *BMC ID* 10: 220 2010
Diurnal variation of IGRA results

- 158 Air Force recruits
- Compared am vs pm collection times (same person)
- 25% + for pm collection vs 21% + for am (p=0.03)

Mazurek et al. NTCA abstract 2012
Inter-lab variation of IGRA results

- 103 Air Force recruits and CDC staff (Texas)
  - Prior +TST
  - Same sample, 3 different labs ran QFT-GIT
  - 7/91 (7.7%) discordant results from different labs
  - 86% were <0.25 IU/ml from cutoff

Implications

• Should there be an “gray zone” QFT result?
  • T-Spot does report borderline positive value

• Serial screening of >2000 HCW (Cleve. Clinic)
  • 2.8% converted using 0.35 IU/mL as cut-off
  • Using gray zone <1.0 IU/mL (71%), <1% converted

Fong et al. Chest 2012
Does TST boost IGRA result?

• Cellestis says no in package insert

• 2009 meta-analysis: 13 studies suggest yes
  • More pronounced in QFT + at baseline
  • Effect most documented 3 days post-TST
  • Wanes by 3 months

• If doing both, the optimal time to collect blood is at same time as TST placed
Duration of positivity: TST vs. IGRA

- TST and IGRA may not measure exact same components of immune response
  - IGRA measuring effector T-cell activity
  - TST measuring memory T-cell activity (less IFN-γ)
- Does TST reactivity reflect older infection?
- Does IGRA measure ongoing immune activity?
- May be relevant in recent contacts

IGRA to monitor treatment success

- Serial QFT-GIT testing on 149 active TB cases
  - Montreal: 93% foreign-born
  - QFT at start of tx, 2 months, and end of tx
  - 89% + pre-treatment, 87% + at 2 months
  - 81% + at end of tx (7 converted/13 reverted)
  - Substantial within-subject variability
- QFT also stays + after LTBI treatment
  - 82 subjects s/p INHx6m: no change in QFT

Johnson et al. *Chest* 2013 (online)
Immunosuppressive treatments and effect on TST/IGRA

• RA patients 2-4x risk after starting TNF-α inhibitors
  • Baseline screening prior to starting now standard

• 248 IBD patients: QFT-GIT and TST (Denmark)
  • Prednisone ↑ rate of indeterminate QFT, neg TST
  • MTX, AZA and 5-ASA did not

• 109 autoimmune pts: QFT/TS/TST (Finland)
  • Low rate indeterminate; IGRAs>TST corr. LTBI RF

• 56 autoimmune pts: QFT/TST (Holland):
  • 9/56 (16%) +TST and/or +IGRA; 6 discordant

Belard et al. *Inflamm Bowel Dis* 17 (11) 2011
Tavast et al. *Int J Rheum* 2012
Kwakernaak et al. *Clin Rheum* 30 2011
IGRA before TNF-alpha therapy

- High risk of reactivation after starting
- Easy to implement routine screen
- Treating positive result will prevent cases
- Reduced sensitivity: falsely reassuring
  - Already on immunosuppressive meds
  - If high *a priori* risk of LTBI, low threshold to treat
  - Consider TST also; if either is +, then treat LTBI
Cost effectiveness of TST vs IGRA

- Public health context (contact investigations)
- Ill inpatient (are either really necessary?)
- Ill outpatient (are either really necessary?)
- Healthy outpatient
- Occupational screening
Quality control issues

- Stanford report: QFT+ rate from 10 to 31%
- Single 2011 lot of tubes identified and recalled
- Recent increase in indeterminate results
  - Lower mitogen (+) response for some users
  - Sept 2013 memo from Qiagen

“As with any diagnostic test for TB infection, QFT is an aid to assist clinicians in their diagnosis and should be used in conjunction with risk assessment, radiography, and other medical and diagnostic evaluations.”

Slater et al, *JCM* 50(9) 2012
Qiagen, Memo to Customers, September 23, 2013
Question 3

• Patient has a “negative” TST and QFT result

• Is infection with MTB ruled out?

• 1) Yes
• 2) No
• 3) Need more information
Last word: negative QFT±TST

• Is TB infection ruled out? Not necessarily
  • Consider all risk factors for infection
    • Esp if ever a known contact to active TB
    • Calcifications on CXR are always suggestive
  • Don’t assume small TST in kids is from BCG
  • Consider all risk factors for reactivation
    • Immunosuppression
• Risk of assuming neg > cost of false positive
Discussion

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